Final Report

DRUG-RESISTANT INFECTIONS

A Threat to Our Economic Future

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Table of Contents

Boxes

Tables

Figures

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Abbreviations and Acronyms

AGAR	Australian Group on Antimicrobial Resistance
AGP	Antimicrobial Growth Promoters
AIDS	Acquired Immune Deficiency Syndrome
AM	Antimicrobial (drug or agent designed to kill microbes)
AMPs	Antimicrobial peptides
AMR	Antimicrobial resistance (resistance of microbes to antimicrobials)
ANSORP	Asian Network for Surveillance of Resistant Pathogens
API	Active pharmaceutical ingredient
ARSP	Philippines Antimicrobial Resistance Surveillance Program
ASP	Antibiotic stewardship program
AST	Antimicrobial susceptibility testing
BRICS	Large middle-income countries (Brazil, Russia, India, China, South Africa)
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CDC	United States Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics & Policy
CHINET	China Antimicrobial Resistance Surveillance Study
CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem-resistant Enterobacteriaceae (type of bacteria)
CSF	Cerebrospinal fluid
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Program
DDDs	Defined daily doses
DUS	Drug-utilization studies
EAC	East African Community
EAPHLN	East Africa Public Health Laboratory Network
EAPHLNP	East Africa Public Health Laboratory Networking Project
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ECSA-HC	East, Central and Southern Africa Health Community
EIP	Emerging Infections Program
EQA	External quality assurance
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	Extended-spectrum beta-lactamase
ESPAUR	English Surveillance Programme for Antimicrobial Utilization and Resistance
ESR	New Zealand Institute of Environmental Science and Research
EU	European Union
EuSCAPE	European Survey on Carbapenemase-Producing Enterobacteriaceae
FAO	Food and Agricultural Organization of the United Nations

FAOSTAT	FAO Statistics
FDCs	Fixed-dose combinations
FINRES-VET	Finnish Veterinary AMR Monitoring and Consumption of Antimicrobial Agents
FoodNet	Foodborne Diseases Active Surveillance Network
GAP	Global Action Plan
GDP	Gross domestic product
GERM-VET	German National Veterinary Antibiotic Resistance Monitoring
GHSA	Global Health Security Agenda
GISP	Gonococcal Isolate Surveillance Program
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Hospital-acquired infection
HIC	High-income country
HIV	Human immunodeficiency virus
HIV/AIDS	Human immunodeficiency virus/acquired immune deficiency syndrome
ICT	Information, Communication, Technology
IEG	Independent Evaluation Group
IHR	International Health Regulations
IPC	Infection prevention and control
ITAVARM	Italian Veterinary Antimicrobial Resistance Monitoring
JANIS	Japan Nosocomial Infections Surveillance
JVARM	Japanese Veterinary Antimicrobial Resistance Monitoring System
KARMS	Korea Antimicrobial Resistance Surveillance
KONSAR	Korean Nationwide Surveillance of Antimicrobial Resistance
Ksh	Kenyan shilling
LICs	Low-income countries
LMIC	Low- or middle-income country
MDR	Multiple-drug resistance
MRSA	Methicillin-resistant Staphylococcus aureus
NAMRU-2 PP	United States Naval Medical Research Unit 2 Phnom Penh
NARMS	National Antimicrobial Resistance Monitoring System
NARS-Singapore	Singapore Network for Antimicrobial Resistance Surveillance
NDM-1	New Delhi Metallo-beta-lactamase 1
NETHMAP/MARAN	Consumption of Antimicrobial Agents and AMR among Medically Important Bacteria in the Netherlands/ Monitoring of AMR and Antibiotic Usage in Animals in the Netherlands
NHSN	National Health Care Safety Network
NLN	National Laboratory Network
NORM/NORMVET	Norwegian Surveillance System for Antimicrobial Drug Resistance
NPHL	National Public Health Laboratory
NRL	National Reference Laboratories
NSAR	Malaysia National Surveillance of Antimicrobial Resistance Program
NTSS	National Tuberculosis Surveillance System

OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
ONERBA	l'Observatoire National de l'Epidemiologie de la Resistance Bacterienne aux Antibiotiques
PCR	Polymerase chain reaction (a kind of laboratory test)
PCU	Population Correction Unit
PVS	Performance of Veterinary Services
QS	Quorum sensing
R&D	Research and development
ReLAVRA	Latin American Surveillance Network of Antimicrobial Resistance
Rif	Rifampicin
RSN	Resistance Surveillance Network
SDGs	Sustainable Development Goals
SEJ	Structured expert judgement
SLIPTA	Stepwise Laboratory Improvement Process Towards Accreditation
STAG	Strategic and Technical Advisory Group
SWEDRES/SVARM	Swedish Veterinary Antimicrobial Resistance Monitoring
TARGET	Treat Antibiotics Responsibly, Guidance, Education, Tools
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TB	Tuberculosis
TSAR	Taiwan Surveillance of Antimicrobial Resistance
UHC	Universal Health Coverage
UK	United Kingdom
UNTRL	Uganda National Tuberculosis Reference Laboratory
U.S.	United States
VINARES	Vietnam Resistance Project
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant Staphylococcus aureus
VSL	Value of a statistical life
WAHIS	World Animal Health Information System
WB	World Bank
WHO	World Health Organization
XDR	Extensively drug-resistant

All dollar amounts in this report are U.S. dollars, unless specified otherwise.

Glossary of Select Terms

Adverse drug events	When medical drugs, like antibiotics, have harmful effects; when someone has been harmed by a medication.
Antibiotic	Type of antimicrobial agent made from a mold or bacterium that kills or slows the growth of other bacteria. Examples include penicillin and streptomycin.
Antimicrobial agents	A general term for the drugs, chemicals, or other substances that either kill, inactivate, or slow the growth of microbes including bacteria, viruses, fungi and parasites.
Antimicrobial resistance	Antimicrobial resistance (AMR) is the ability of microbes to grow in the presence of substances specifically designed to kill them. AMR is the result of microbes changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents to cure or prevent infections they cause. AMR is a natural phenomenon, but human actions may promote avoidable emergence and spread of AMR. These actions include inappropriate use of antimicrobials in health care and in raising crops and animals, poor sanitary practices and conditions, inappropriate food handling (e.g., food not properly stored), disposal of wastes containing antimicrobials, and weak infection prevention and control practices in health care facilities.
Antimicrobials	Antimicrobials are drugs developed to treat infections.
Bacteria	Bacteria are microscopic single-celled organisms that thrive in diverse environments. They can live freely nearly anywhere, including in soil, water or plants, animals, and other organisms. Some bacteria help biological functions of their hosts (e.g., digestion), but others can be destructive, causing diseases.
Cross-resistance	Cross-resistance is the tolerance to a usually toxic substance as a result of exposure to a similarly acting substance. It is a phenomenon affecting e.g., pesticides and antibiotics. As an example rifabutin and rifampin cross-react in the treatment of tuberculosis.
Drug resistance	Drug resistance is the result of microbes changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents to cure or prevent infections.
Epidemiology	The study of the spread of disease, or disease patterns at the population level.
First-line antimicrobials	First-line drugs are generally inexpensive and widely consumed, and they were developed earlier than second-line drugs, so resistance to first-line drugs is generally higher than to newer drugs. Examples include amoxicillin, ampicillin, pivampicillin, trimethoprim/sulfamethoxazole, and doxycycline.
Fungi	Single-celled or multicellular organisms. Fungi can be opportunistic pathogens that cause infections in immunocompromised persons, such as cancer patients, transplant recipients, and persons with AIDS. Characteristic fungal diseases of this type include aspergillosis, candidiasis, and cryptococcosis. Some fungal pathogens can cause infections in healthy persons (such as histoplasmosis or coccidioidomycosis). Fungi are also used to develop antibiotics, antitoxins, and other drugs used to control various human diseases.
Infection	Entry and development or multiplication of an infectious agent (such as pathogenic bacteria or viruses) in the body of humans or animals. Some infections lead to disease.
Microbes	Organisms so small that a microscope is required to see them. Microbes are also called microorganisms.
Multidrug-resistance (MDR)	Property of a bacterial pathogen that is resistant to 2 or more antimicrobial agents.
Nosocomial	Referring to an infection acquired by a patient while in a hospital, or any other health care facility.

One Health	"One Health is a framework for enhanced collaboration in areas of common interests (intersections), with initial concentration on zoonotic diseases that will reduce risk, improve public health globally and support poverty alleviation and economic growth in developing countries. This concept involves a better way to deal with risks at the animal-human-environment interfaces." *—World Bank's operational definition, used since 2007*
Organism	Any living thing. Organisms include humans, animals, plants, bacteria, protozoa, and fungi.
Parasites	Any organism that lives in or on another organism without benefiting the host organism; commonly refers to protozoans and helminths.
Pathogens	Bacteria, viruses, parasites, or fungi that can cause disease.
Present value or present discounted value	Present value is the worth today of a future sum of money. The term is also used for discounting future sums by using a discount rate. A discount rate is like an interest rate. A specific percentage of a balance is added to the balance. Having $100 in an account that pays interest of 5% per year results in a balance in year 2 of $105. In year 3, the balance will be $110.25 (= 100*1.05*1.05). Discounting answers the question: How much is the $100 that is to be received in year 3 worth today if the discount rate is 5%? The present value is clearly less than $100—given the choice between $100 in year 3 and $100 now, most people will choose $100 now. If the discount rate is 5%, than the present value of $100 in year 3 is exactly $90.70 (= 100/(1.05*1.05). A balance of $90.70 in the account now will grow to $100 in year 3. The higher the discount rate, the smaller is the present value of future amounts. For instance, a low discount rate is used in some studies of the economic impact of climate change and corresponds to a greater concern with the well-being of future generations than a high discount rate. Use of a lower discount rate results in a higher present value of costs of climate change.
Second-line antimicrobials	Examples of such drugs include amoxicillin/clavulanic acid, macrolides, second-generation or third-generation cephalosporins, and quinolones.
Surveillance systems	The ongoing systematic collection, collation, and analysis of information related to public health (animal and human), and the timely dissemination of information so that action can be taken. The information is used, for example, in actions that prevent and control an infectious disease.
Virus	A strand of DNA or RNA in a protein coat that must get inside a living cell to grow and reproduce. Viruses cause many types of illness; for example, varicella virus causes chickenpox, and the human immunodeficiency virus (HIV) causes the acquired immune deficiency syndrome, or AIDS.

Executive Summary

This report examines the economic and development consequences of antimicrobial resistance (AMR)—the capacity that disease-causing microorganisms acquire to resist the drugs we've created to fight them. The report uses World Bank Group economic simulation tools to put a price tag on AMR's destructive impacts on the global economy from 2017 through 2050, if adequate measures aren't taken to contain the AMR threat.

The report highlights actions low- and middle-income countries and their development partners can take to counter AMR, and estimates the investment required. It shows that putting resources into AMR containment now is one of the highest-yield investments countries can make.

What Is AMR?

Antimicrobials are drugs that destroy disease-causing microbes, also called pathogens, such as certain bacteria, viruses, parasites, and fungi. The most familiar and important antimicrobials are antibiotics, which treat bacterial infections. Other antimicrobials combat viral and parasitic diseases, such as AIDS and malaria. Since their use began some 70 years ago, antimicrobials have saved hundreds of millions of lives.

AMR occurs when pathogens undergo adaptive evolutionary changes that enable them to withstand antimicrobials. People or animals who encounter resistant pathogens may then suffer infections that can't be treated. The pathogens survive, patients get sicker and may die, the cost of medical care rises, and disease continues to spread.

Every use of antimicrobials, even the most prudent, creates opportunities for AMR. However, rigorous management can limit the risks. In recent decades, though, overuse and misuse of antimicrobials have caused avoidable AMR emergence and spread. As a result, antimicrobial drugs are rapidly losing their effectiveness in both developing and developed countries. If this trend continues, humanity may face a reversal of the public-health gains of the past century, and the economic growth, development, and poverty reduction these gains enabled.

A Tragedy of the Commons

The loss of efficacy of antibiotics and other antimicrobials worldwide can be understood as a "tragedy of the commons." A tragedy of the commons occurs when people in a community squander a limited, shared resource, as each actor pursues her own short-term self interest by exploiting the resource for private benefit. No one wants the common resource to be exhausted. Yet the group's collective behavior leads to precisely this result. This concept has been applied, for example, to the collapse of fisheries due to overfishing. The overuse and misuse of antimicrobial drugs worldwide show a similar pattern.

Protecting a Global Public Good

As effective antimicrobial treatment is part of the global "commons," containment of AMR is a global public good. All countries can enjoy the benefits of successful AMR containment. Conversely, all countries will be harmed if AMR is not kept in check. The status of AMR containment as a global public good underscores the critical responsibility of public authorities, especially national governments, in protecting this good.

This responsibility is all the more crucial, because victory over AMR is never final, since pathogens constantly evolve, and they eventually develop resistance to any medication we discover. However, with wise policies and careful stewardship, the life-saving power of antimicrobials can be greatly extended. The inherent fragility of this public good makes it even more important to defend it well.

To date, action on AMR has been dangerously inadequate. Policy and financing choices by governments and development partners have resulted in weak public-health systems across broad regions of the world, enabling the undetected spread of pathogens, including drug-resistant strains.

A Threat to the Global Economy

What can motivate countries to focus on AMR and deploy the comprehensive response this threat demands? Often, economic interest provides an impetus to political action. In this report, we have used World Bank economic simulation tools to quantify the losses that AMR may inflict on the global economy between now and 2050.

Our simulations included two scenarios, corresponding to low AMR impacts and high AMR impacts. AMR impacts were modeled as shocks to labor supply and livestock productivity—a conservative approach that underestimates AMR's full economic effects.

In the optimistic case of low AMR impacts, the simulations found that, by 2050, annual global gross domestic product (GDP) would likely fall by 1.1 percent, relative to a base-case scenario with no AMR effects; the GDP shortfall would exceed $1 trillion annually after 2030. In the high AMR-impact scenario, the world will lose 3.8 percent of its annual GDP by 2050, with an annual shortfall of $3.4 trillion by 2030 (Figure ES1).

A Crisis That Won't Quit

During much of the period through 2050, the annual reduction in global GDP caused by AMR could be as large as the losses provoked by the 2008–2009 global financial crisis, at their most severe (Figure ES2). However, the cost impacts of AMR on GDP would be worse than those of the financial crisis in two respects. First, they would be felt during the entire simulation period (through 2050), not just for a couple of very bad years, as was the case in the acute phase of the recent financial crisis.

Poorer Countries Will Suffer Most

Moreover, with AMR, low-income countries would experience larger drops in economic growth than wealthy countries, so economic inequality between countries would increase. The differential impacts on GDP result from higher infectious disease prevalence and greater dependence on labor incomes in countries with lower per capita incomes.

Impacts on International Trade, Livestock Production, and Health Care Costs

International trade may be heavily affected if AMR spreads unchecked. By 2050, the volume of global real exports may fall below base-case values by 1.1 percent in the low-AMR scenario and by 3.8 percent in the high-AMR scenario. Output and trade in livestock and livestock products are especially vulnerable to AMR impacts. Livestock production in low-income countries would decline the most, with a possible 11 percent loss by 2050 in the high AMR-impact scenario.

FIGURE ES1. Substantial and Protracted Shortfalls in Global Economic Output

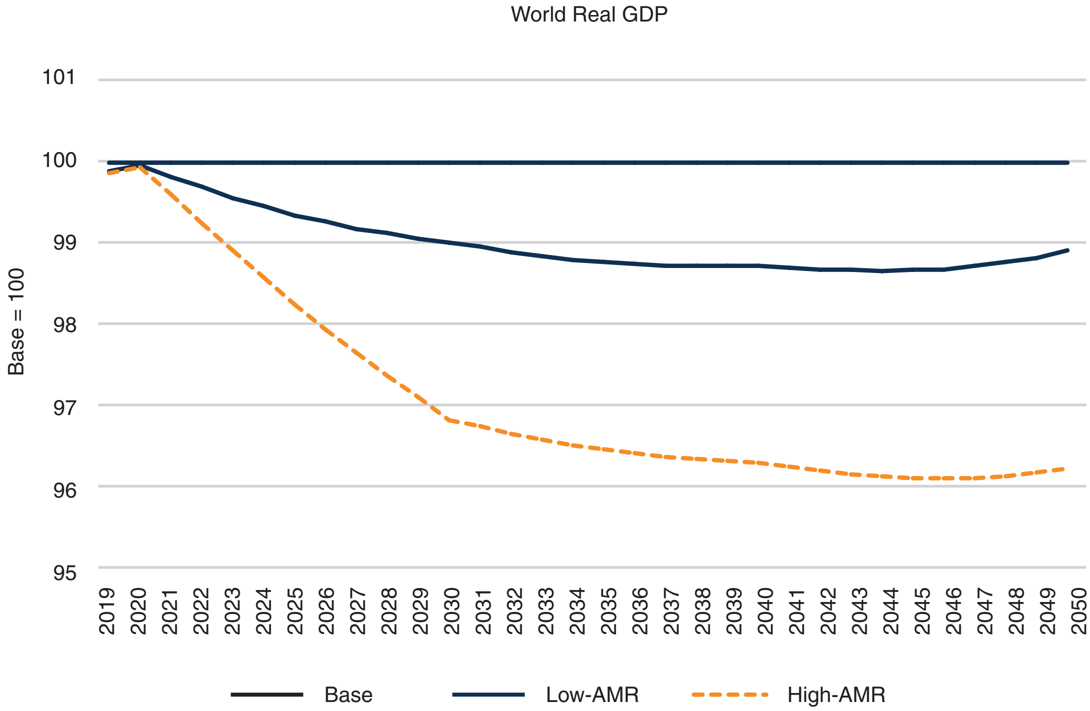
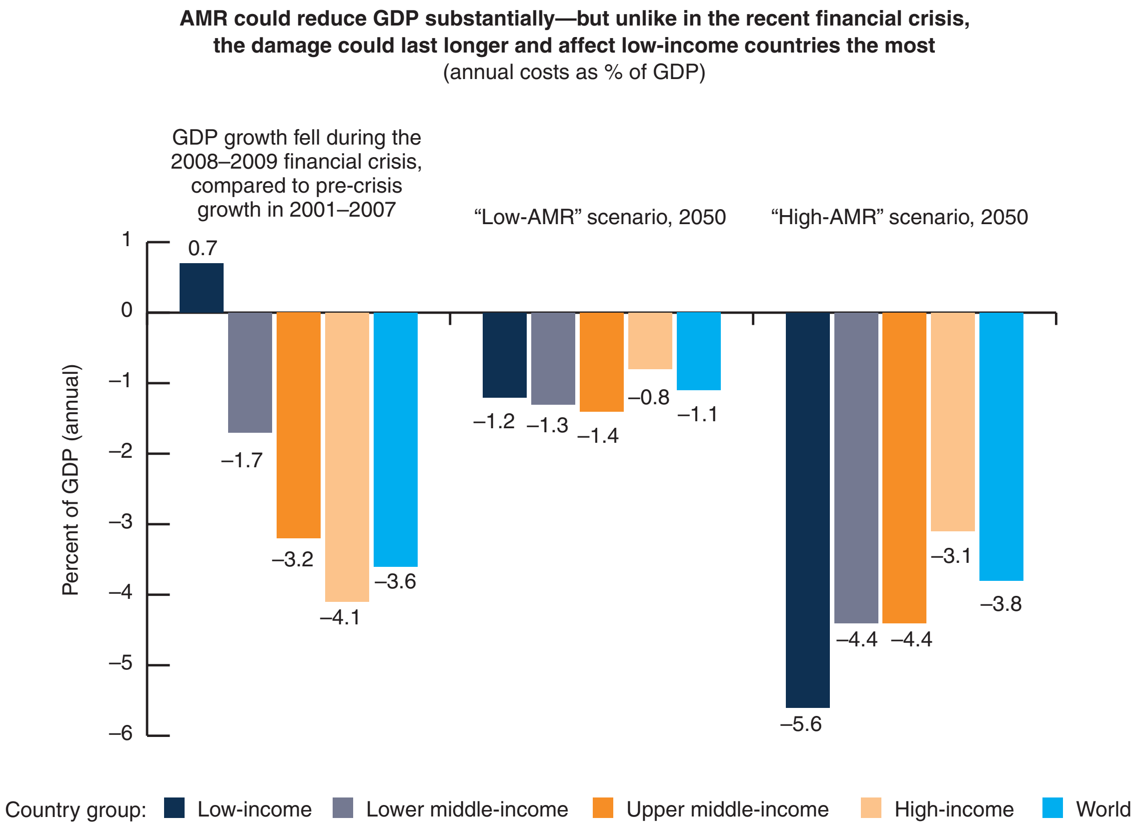


FIGURE ES2. Economic Costs of AMR May Be as Severe as During the Financial Crisis



Meanwhile, as AMR spreads, health care expenditures, both public and private, will increase in step with the rising disease burden; by 2050 the annual costs may exceed the base-case level by some 25 percent in low-income countries, 15 percent in middle-income countries, and 6 percent in high-income countries.

Derailing Global Development Goals

Without AMR containment, the Sustainable Development Goals for 2030—such as ending poverty, ending hunger, ensuring healthy lives, reducing inequality, and revitalizing global development partnerships—are less likely to be achieved.

The impacts of AMR on poverty are particularly concerning. In the high AMR-impact scenario, an additional 24 million people would be forced into extreme poverty by 2030. Most of the increase would occur in low-income countries. As a result, the World Bank Group goal of eliminating poverty by 2030 would be harder to reach.

High-Yield Investments

Policy makers may be concerned that the cost of tackling AMR will be excessive. On the contrary, our analysis shows that action on AMR constitutes one of the highest-yield development investments available to countries today.

The cost of AMR containment measures is estimated at $9 billion annually in low- and middle-income countries. About half of this amount is for investments in, and operation of, core veterinary and human public-health systems in 139 countries. The recommended investments in AMR containment are justified according to two key economic criteria.

The Net Present Value Test

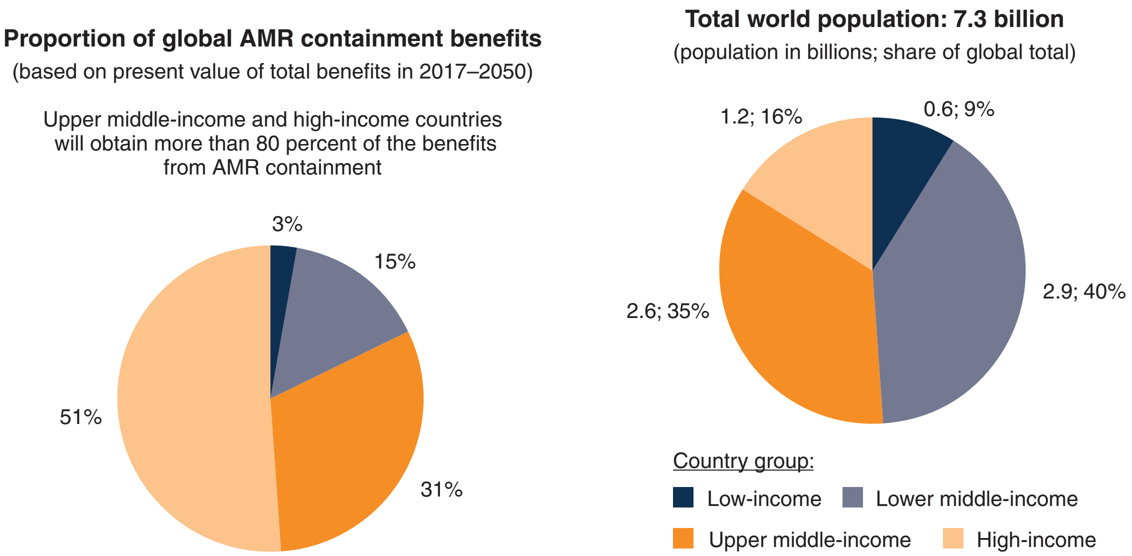
First, the test of net present value (NPV) is unambiguously satisfied. This is the case not only globally, but also separately for high-income countries and upper middle-income countries. Assuming that just 50 percent of AMR costs will be avoided by vigorous AMR containment efforts, the expected cumulative global benefits from AMR containment in 2017–2050 range between $10 trillion and $27 trillion, far greater than the investment costs of $0.2 trillion. The net present value is thus between $9.8 trillion and $26.8 trillion.

Different countries stand to benefit from AMR control in different ways. Low-income countries will see substantial economic payoffs, relative to the size of their economies. The largest absolute and per capita gains, however, will actually flow to upper middle-income and high-income countries. Assuming, very conservatively, that only 10 percent of the modeled costs were averted through AMR containment measures, high-income countries would still obtain benefits of $0.9 trillion and $2.7 trillion, in the low AMR-impact and high AMR-impact cases, respectively. This is four times and thirteen times more than the global investment cost of $0.2 trillion (Figure ES3).

Remarkable Returns

The second test of the investment case for AMR control considers the expected economic rate of return (ERR) on the $9 billion annual investment. Assuming that investments would be made for seven years before any benefits materialize, the ERR ranges from 31 percent annually (if only 10 percent of AMR costs can be mitigated) up to 88 percent annually (if 75 percent of AMR costs are avoided). The chance to obtain returns of this magnitude constitutes an exceptional investment opportunity for countries.

FIGURE ES3. High-Income and Upper Middle-Income Economies Stand to Benefit the Most from AMR Containment, Both in Absolute and per Capita Terms



A Bold Agenda: Integrated Public-Health Protection in All Countries

We have argued that aggressive action to tackle AMR is needed now. But what exactly must be done?

Before we discuss specific recommendations for action on AMR, we need to emphasize a general principle. AMR cannot be managed in isolation. Drug-resistant infectious diseases are a subset of the broader range of microbial threats to human and animal health and welfare. From a public-health and policy-making standpoint, drug-resistant infections have practical similarities to all infectious diseases with pandemic potential. The surveillance, diagnostic, and control capacities needed to deal with AMR are closely related to those required to control diseases like Ebola and Zika. Instead of viewing AMR as a separate issue isolated from other health challenges, it will be more effective and less costly over time to build a common core of permanent capabilities in all countries for managing the full range of infectious threats.

As AMR control is part of a wider agenda of infectious disease management, so the response to infectious diseases in turn depends on the robustness of countries' broader health systems. Competencies for the AMR fight can't be built independently of the health system's durable core capacities. Effective AMR action depends, for example, on reliable health information systems, rational procurement and management of drugs, and the presence of a trained and motivated health workforce.

Building core human and veterinary public-health and infectious disease surveillance capacities in all countries is the critical step in confronting the AMR threat. Where these capacities exist, AMR can be detected and contained. Where they don't, it can't. This is the fundamental fact.

When discussing AMR policy measures, we describe them as "AMR-specific" or "AMR-sensitive." AMR-specific actions are those whose primary purpose is combating AMR (though they may bring other benefits, too). An example is tightening legislation and enforcement on the sale of antimicrobials without a prescription. AMR-sensitive measures are those whose main purpose is not actually AMR-related, but which can be designed and implemented in such a way that they contribute indirectly to AMR containment. Expanding access to clean water and sanitation, thus reducing the incidence of infections, is an example. Both AMR-specific and AMR-sensitive measures are needed now to contain the spread of drug-resistant pathogens.

Options for Country Action

WHO's Global Action Plan on AMR (WHO 2015), developed in collaboration with the World Animal Health Organisation (OIE) and the United Nations Food and Agriculture Organization (FAO), defines five broad objectives for the AMR fight (Figure ES4). Building on the global plan, several recent landmark reports have provided additional guidance on national policies and implementation strategies to fight AMR. These publications include the final report from the U.K. Review on AMR (Review on Antimicrobial Resistance 2016) and global plans from OIE (2016) and FAO (2016). Together with the Global Action Plan, these sources have set forth a comprehensive high-level policy agenda for the AMR fight.

This also means that we don't need to "reinvent the wheel" here. Our recommendations concentrate on select areas where opportunities for important advances exist, and where World Bank knowledge, experience, and resources can add value to the country efforts we propose.

To implement the Global Action Plan and in particular to understand how it will be financed, it is useful to analyze country options through a sectoral lens. Accordingly, our recommendations for country AMR action are structured by sector, including: (a) health; (b) agriculture; and (c) water, sanitation, and hygiene.

Driving AMR Progress from the Health Sector

The health sector offers many entry points for AMR control. Our recommendations focus on three topics: (1) universal health coverage reforms as an enabling platform; (2) harnessing the International Health Regulations (IHRs) to accelerate AMR action; and (3) strengthening laboratory-based surveillance, including through regional networks.

1. **Universal health coverage (UHC) provides the best enabling framework to tackle AMR.** UHC models are diverse, but UHC efforts will generally strengthen AMR containment through the following mechanisms:

   - *Expanded coverage.* By definition, UHC designs lead to greater breadth and depth in the population coverage of health services. This includes services like vaccination, preventative care, and hygiene measures that lower the need for antimicrobials and thus slow the spread of AMR. Covering the whole population with vaccinations shows one potent way UHC will reduce the incidence of infections, advancing a key objective of the Global Action Plan on AMR.

   - *Better oversight and quality of care.* UHC models improve oversight in health care practice. Among other benefits, this helps ensure that antimicrobial use conforms to rational standards. UHC strategies promote rational, regulated access to antimicrobials for all patients under the guidance of trained health professionals. Thus, UHC provides a framework for simultaneously expanding the well-regulated use of antimicrobials where they have been lacking, and tackling the overuse and misuse that have accelerated AMR in other settings. UHC strengthens antibiotic stewardship in health facilities, reinforces the use of standard treatment protocols for infections, and can improve procurement, quality control, and other features of antimicrobial management—with the potential for major gains against AMR. These UHC features support another of the five Global Action Plan objectives: optimizing current antimicrobial use.

   - *Smarter, fairer financing.* The expansion of health systems towards UHC promises more efficient and equitable financing. This will help close existing access gaps for treatable infections. Pooled, prepayment financing also encourages rational purchasing and prescription, supporting the optimization of antimicrobial use and protecting the efficacy of current drugs.

FIGURE ES4. Five Objectives of the Global Action Plan on AMR, 2015–19

Strengthen Knowledge and Evidence Base	Reduce the Incidence of Infection	Optimize Use of Antimicrobials	Improve Awareness and Understanding of AMR
❊ Develop an AMR surveillance system for: • health care facilities and community • animal husbandry and agriculture • using at least one reference lab ❊ Share information internationally ❊ Collect and share data on antimicrobial use (human/animal/agriculture) ❊ Consider an AMR research agenda, including: • responsible use • infection prevention • development of novel agents	❊ Implement and strengthen hygiene and infection prevention programs • make it part of health care and veterinary training • develop and implement standards of practice ❊ Test and report susceptibility of hospital-acquired infections (HAI) ❊ Implement prevention best practices in animal health and agriculture ❊ Promote vaccination of food animals	❊ Implement a comprehensive action plan with: • antibiotics access only through qualified individuals • only quality, safe and efficacious drugs authorized • reimbursement, promotion and treatment guidelines • laboratory capacity to guide optimal use • evidence-based stewardship programs • elimination of financial incentives to prescribe • effective and enforceable regulation • reduction/phasing out of non-therapeutic antibiotic use in agriculture	❊ Public communication targeting human and animal health audiences as well as schools and public media ❊ Establish AMR as element of professional education ❊ Elevate AMR to priority agenda across government **Make Economic Case for Investment** ❊ Secure required financing for implementation ❊ Engage in international research collaboration—between developed and developing countries ❊ Public-private partnership ❊ New market models for investment and access

WHO Global Action Plan on Antimicrobial Resistance, adopted by the World Health Assembly in May 2015. See http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1.

- *Better information.* UHC generally enables improved data collection and management within the health system, at the population, facility, and individual provider levels. By strengthening data systems, UHC approaches may better equip them to support AMR surveillance, monitoring, and response. These features support the Global Action Plan (GAP) objective to strengthen AMR knowledge and the evidence base.
- *Improved stewardship and governance.* A robust UHC approach builds systems-governance and coordination capacities that are critical for the AMR fight. Moreover, under UHC models, regulatory capacities tend to be enhanced. Health facility accreditation provides an example. Requirements for improved antimicrobial stewardship can be built into accreditation processes for hospitals and clinics to bolster AMR control at the facility level. AMR training can also be incorporated into the pre-service and in-service education of health providers, advancing the Global Action Plan objective to improve awareness and understanding of AMR.

2. **Implementation of the International Health Regulations (IHR) can accelerate AMR action and focus global support.** Under the IHR, 196 countries have committed to work together to prevent, detect, report, and manage public health emergencies, such as infectious outbreaks. To meet their IHR implementation requirements, many countries are participating in systems-diagnostic and planning exercises, for example through the Joint External Evaluation (JEE) process, under the Global Health Security Agenda (GHSA). Systems-evaluation exercises provide opportunities for countries to assess their capacities and needs in areas like infectious-disease and AMR surveillance. Among other benefits, such efforts help lay foundations for the AMR Global Action Plan's five objectives, especially the first, strengthening knowledge and the AMR evidence base.

   In order for these exercises to achieve full impact, it is important that each country designate institutions and individuals who will be accountable for following up on the evaluation results. The designated actors will lead a process to translate assessment recommendations into methodical action to build national capacity for surveillance and response. Because each country's implementation of IHR commitments benefits all other countries by improving detection and response to transborder threats, the international community has an interest in adequately financing this global good.

3. **Countries at all levels of income can build laboratory capacities for AMR surveillance—and create synergistic regional laboratory networks.** Strengthening AMR surveillance capacities, including in low- and middle-income countries, is a cornerstone of AMR control, captured in the first objective of the Global Action Plan. The creation of a national AMR surveillance network is becoming technically feasible and affordable for an increasing number of countries. Kenya, for example, is in the process of launching its own national AMR surveillance network at an estimated annual cost of about $160,000. (This figure represents the specific added expense of AMR surveillance, beyond the ongoing costs of operating the country's clinical laboratory network.)

   A background study commissioned for this report examined the East Africa Public Health Laboratory Networking Project (EAPHLN), in which Kenya participates, along with Burundi, Rwanda, Tanzania, and Uganda. The study documented the benefits that can accrue when countries link their laboratory resources into a regional network structure. The EAPHLN has accelerated innovation and fostered new forms of learning and collaboration, including: (1) joint annual peer audits, in which countries assess each other's laboratories, and (2) cross-border disease surveillance, simulations, and investigations that have enabled swift regional responses to Ebola and Marburg outbreaks.

Agriculture: A Critical Frontier for AMR

The bulk of antimicrobial use in many countries occurs in the agriculture sector, particularly in livestock. Worldwide, in 2010, livestock consumed at least 63,200 tons of antibiotics and probably far more, exceeding total human consumption. The precise impacts of this heavy use of antimicrobials in animal production continue to spark debate, and data are scarce. However, recent research suggests that AMR is already common in agricultural systems in low- and middle-income countries.

1. **All countries can progressively reduce the use of antibiotics in animal production.** Systematic reduction and eventual elimination of antibiotic use for livestock growth promotion is critical for long-term AMR control. This goal has drawn increasing consensus among scientific experts and many political leaders. European Union countries have banned the use of antimicrobials as growth promoters since 2006.

   Countries' specific contexts must be taken into account in designing plans and establishing timelines. Countries that currently rely heavily on the use of antibiotic growth-promoters may require more time and support to adapt their production regimes. Some low-income countries may benefit from extensive technical support.

   Experts, including the U.K. Review on AMR, have recommended the use of national numerical targets to drive reductions in the use of antibiotics in agriculture. We support this approach. The use of time-bound, quantitative targets can be a powerful motivator.

   Solutions for the livestock sector should foster the adaptability of animal productions systems to reduced use of antimicrobials. Recommendations call for an integrated approach, with cycles of innovation and learning: First, developing policies, setting targets, and monitoring antimicrobial use in livestock production; then identifying gaps or problems in current production systems and methods to address them; and finally sharing knowledge on improved management.

   We can protect farmers as antimicrobial practices change. Small farmers may be especially vulnerable as changes to established production methods are introduced. Governments and development partners have a fundamental responsibility to accompany small farmers in adapting their modes of animal production, as we act to save a global public good.

   Policy action must also take account of global disparities in access to antimicrobials for livestock, mirroring those in human health. The same drugs that may be used excessively in livestock production in some parts of the world remain unavailable in others, where they could have legitimate applications and save lives and livelihoods.

2. **An urgent effort is needed to strengthen country surveillance systems for tracking the use of antimicrobials and the spread of AMR in animals.** A consistent finding from country case studies commissioned for this report was a deficiency in data needed to analyze antimicrobial use in livestock, in terms of epidemiology and economic impacts.

   Each country may commit to develop a system for collecting standard data on animal populations and animal production systems in its territory. Countries should be supported to build basic data collection systems to track both the use of antimicrobials and AMR in animal production. OIE's current effort to develop a worldwide system for data collection on antimicrobial use in animals merits strong support.

3. **New partnerships can spur innovation for AMR control across agriculture, the environmental sciences, and health.** Scientists and policy makers increasingly recognize that integrated strategies are needed to tackle the drivers of AMR simultaneously in livestock production, environmental management, and human health. Today, research on integrated strategies and new technologies to fight AMR is slowly gathering momentum. Yet the field remains under-resourced and fragmented.

   Evidence-based, consensus directions for priority research have yet to be defined. International coordination and stewardship of AMR knowledge production are urgently needed. In particular, there is a need to inform and incentivize the global innovation agenda to target the points of highest priority and greatest opportunity for the development of new AMR-management technologies. This would include not only new antibiotics, but also new vaccines (both animal and human), the rapid-diagnostics agenda, and policy innovation in areas like compensation or insurance mechanisms for farmers who cut antibiotic use. Targeted learning and innovation in a broad range of sectors, from pharmacology to development finance, must be nurtured simultaneously.

   How might this be done? We can point to promising precedents: innovative models of collaboration that have proven effective for other complex, multi-sectorial challenges. One example is CGIAR, a global consortium of agricultural research centers supported by an extensive network of partners, including the World Bank. For some 50 years, CGIAR has generated creative and practice-relevant research on food security, rural poverty reduction, and sustainable resource management. Today, to jumpstart new investment in AMR research and technological innovation, we can learn from CGIAR and other network models for knowledge production.

   A hybrid, networked research center might pursue learning and innovation simultaneously in agriculture, animal health, and human health. To our knowledge, no such hybrid research hub currently exists. However, its feasibility could be explored with existing CGIAR network centers, other research consortiums, countries, donors, and other stakeholders. Through such partnership models, countries will tap into networks of innovation to multiply the impact of their individual actions against AMR.

Water, Sanitation, and Hygiene: AMR-Sensitive Development Priorities

Historically, safe drinking water and sanitation facilities, along with basic hygiene practices such as hand washing with soap and water, were decisive in reducing the spread of infections, even before modern antimicrobials were invented. In the age of AMR, such infection-prevention strategies once again take on salience.

The Global Action Plan has incorporated this principle. Reducing the incidence of infections is one of the five objectives. Two complementary facets of the preventative agenda involve: (1) expanding access to water and sanitation; and (2) universalizing basic hygiene practices, particularly in health care facilities.

1. **Countries can harness the power of water and sanitation investments to check infections, fight AMR, and support economic growth.** Expanding access to sanitation and clean water is among the most powerful AMR-sensitive investments available. Improved access to clean water and sanitation delivers robust public health benefits in its own right. In addition, by preventing infections and reducing the need for antibiotics, these measures also reduce the pressures that drive antimicrobial resistance (Wellcome Trust 2016). The combined health impacts translate into remarkable gains in life expectancy, which imply productivity and economic gains for countries, as well. As leaders weigh the costs and benefits of development investments, it is important to incorporate public-health benefits, including AMR containment effects, in the expected gains from investing in water and sanitation.

2. **Hygiene in health facilities: simple tools, strong impacts.** The settings where water, sanitation, and hygiene practices can combine to powerfully impact AMR include health facilities. Infection prevention and control (IPC) strategies in health care settings are pillars of the AMR containment agenda, recognized in the infection-prevention objective of the Global Action Plan.

Basic hand hygiene (hand washing with soap and water or alcohol-based products) has repeatedly been cited as the single most important practice to reduce health care associated infections. Improved hand hygiene has been associated with a sustained decrease in the incidence of AMR infections in health care settings (Rainey and Weinger 2016). Today, in countries at all income levels, these basic tools are not being rigorously applied. While this is alarming, it also represents an opportunity for low-cost, high-yield action against AMR.

WHO, UNICEF, and partners have set out a global agenda for universal access to water, sanitation, and hygiene in health care facilities. By implementing the plan, governments, international organizations, donors, and civil society partners can achieve substantial gains against AMR (Rainey and Weinger 2016).

Country Leadership, Global Partnership

Today, political momentum for action on AMR is growing. At the United Nations General Assembly (UNGA) special session on AMR, in September 2016, 193 Member States pledged to "develop . . . multi-sectoral national action plans, programmes, and policy initiatives, in line with a One Health approach and the global action plan."

AMR containment will depend on country-led efforts implemented in countries. But effective AMR containment also demands coordinated action across national borders. Adequately resourced multilateral agencies can multiply the impact of country policies. Multilateral organizations mobilize international attention, facilitate cooperation and knowledge sharing, provide technical advice and standards, and catalyze multi-sectorial action. Successful AMR strategies will also engage private firms, research institutions, global and local civil society, and other partners.

What Will the World Bank Group Do?

The agenda for AMR action outlined in this report implies responsibilities for the World Bank Group.

Creating a Global Investment Framework for AMR Action

Thanks to the Global Action Plan and the efforts of many partners, substantial consensus exists on the types of policies and interventions needed to contain AMR. Moreover, we now have a reasonable idea of how much AMR containment will cost. The sums are modest by global investment standards, as we've seen, and the likely rewards exceptionally high. But the money still has to be put on the table.

The World Bank Group will work with countries and partners to develop an investment framework to deliver the objectives of the AMR Global Action Plan. The framework will include rigorous costing of priority AMR interventions at country, regional, and global levels. Costed plans for AMR will be integrated with broader country agendas for emergency preparedness, response, and resilience, which are gaining momentum through the WHO Monitoring and Evaluation Framework, the OIE Performance of Veterinary Services (PVS) pathway, and other mechanisms.

The AMR investment framework will be informed by the results of the International Working Group on Financing of Preparedness, whose research is currently in progress, and by experience with the Pandemic Emergency Financing Facility (PEF), created under World Bank leadership following the 2015 Ebola outbreak in Western Africa. The investment framework will emphasize integration of AMR activities and funding into finance mechanisms that will be sustainable over time.

In laying foundations for the global investment framework, World Bank experts will work at the country level with policy makers and technical colleagues to develop national AMR financing assessments, aligned with countries' AMR National Action Plans (NAPs). Country financing assessments will identify national priorities, needs, gaps, and best-value interventions. They will explore resource mobilization options, looking across sectors and including public and private sources.

The global AMR investment framework will then incorporate the results of country planning and costing exercises to develop a comprehensive instrument that can map and quantify needs worldwide and coordinate global investments in AMR action. The framework will be a decision tool for policy makers, planners, development finance institutions, donors, and other partners in the AMR effort, helping ensure that AMR finance flows to where it is most needed and achieves the greatest impact.

We consider the creation of a global AMR investment framework as a key step towards the realization of the Global Action Plan and as a logical follow-up to the September 2016 UNGA special session. The World Bank will deliver an initial version of the AMR investment framework by the time of the official AMR progress report to the UN General Assembly in September 2019.

An AMR Lens on Development Finance

The World Bank Group will review its own investment lending policies and instruments to support the AMR agenda across relevant sectors. We will also strengthen our institutional capacity on the ground in technical areas that can optimize our services to countries as they advance national AMR agendas.

Relevant sectors for World Bank Group investing include, but are not limited to, agriculture; water and sanitation; and urban development, in addition to the health, nutrition, and population sector itself. As the Bank Group weighs investment options in dialog with country leaders and partners, we will apply an AMR lens to identify those projects that hold promise for AMR-sensitive impacts. We will design projects to maximize these impacts.

The World Bank Group will also progressively incorporate AMR-related gains into the calculations used when assessing likely costs and benefits of projects competing for support. Over time, the systematic inclusion of an AMR perspective in investment conversations may evolve towards the creation of a formal screening instrument similar to the World Bank's mandatory Climate and Disaster Risk Screening tools.

Mobilizing Finance for AMR Innovation across Agriculture and Health

Investment in the AMR knowledge agenda must nurture new technologies in both animal and human health. It should also create connections and harness synergies between the two. To foster this kind of innovation, the World Bank will seek to engage existing multidisciplinary research networks, donors, and other partners around the idea of a combined animal and human health research center on AMR. Promising conversations have begun, and may advance to a detailed feasibility study. The effort may develop as a multifaceted collaboration, along the lines of the successful Coalition for Epidemic Preparedness Innovations (CEPI).

Bringing the Private Sector on Board

The private sector can contribute substantially to tackling AMR, and private-sector capacities and creativity in this area are only just beginning to be tapped. The World Bank Group's ability to engage national and global business actors is a strong comparative advantage.

The International Finance Corporation (IFC) is the arm of the Bank Group that invests in and advises private-sector companies. IFC is active in the animal protein sector through investment and advisory work. In engagement with its clients in animal production, IFC reviews operational practices and provides benchmarking for clients on good industry practices, including the use of veterinary services and antibiotics. IFC will seek to deepen this partnership by developing a more focused advisory offering as part of its animal protein advisory platform. Where government regulations evolve towards a more focused use of antibiotics, IFC will seek to partner with private producers and their associations to support the transition of the sector through management practices and investment.

IFC is also active in the private health care sector, mainly through the support of health service providers and companies that manufacture or distribute affordable pharmaceuticals or medical devices. IFC has developed a Quality Assessment Tool used to assess health service companies on various clinical governance and patient safety criteria. IFC plans to enhance this tool and, in the process, incorporate best practices for implementing policies, protocols, and training around antimicrobial drug use.

A clear opportunity for private-sector engagement in the AMR challenge is for pharmaceutical and biotech firms to pursue development of new antimicrobials and related technologies, such as rapid diagnostic tests that could inform antimicrobial prescribing decisions at the point of care. The complex topic of antimicrobial drug development is well analyzed elsewhere (Review on Antimicrobial Resistance 2015). Here, we note only that the World Bank Group and other development finance institutions might play a role in creating fresh incentives for pharmaceutical companies to engage in antimicrobial research. One approach is "delinking" company profits for any new antimicrobial product from the actual sales volumes, through a number of possible mechanisms. Country policy makers, in particular among the G77, have pressed for the implementation of delinking strategies.

Leveraging UHC Reforms to Reach AMR Objectives

In the World Bank's health sector practice, action on AMR containment will mesh with ongoing work programs on (1) health systems strengthening through UHC reforms, and (2) emergency preparedness and resilience.

Many countries are currently carrying forward ambitious UHC reforms with World Bank support, and more are poised to adopt UHC goals. As suggested above, countries' commitment to implement UHC provides multiple opportunities to reinforce AMR containment. The World Bank will work through its policy dialog and technical collaboration around UHC to support countries in leveraging health systems reforms to accelerate progress on AMR.

AMR and Resilient Health Systems: The Agendas Converge

Currently, the World Bank is financing improvements in core public-health functions in multiple countries, notably for disease surveillance and laboratory strengthening. These investments reflect a broad consensus on the need to strengthen global health security and reinforce preparedness.

We have emphasized that AMR is part of a wider spectrum of infectious threats that generate outbreaks with epidemic and pandemic potential. Thus, the AMR and health emergency preparedness agendas are intertwined. The consolidation of core human and animal public-health capacities; the creation of health systems resilient to emergencies; and the AMR fight reflect largely convergent and mutually reinforcing agendas. The World Bank will expand its action to help countries capitalize on these synergies.

Action Today—To Preserve Tomorrow

Many important aspects of the AMR threat lie beyond the scope of this report. Yet we hope our work can clarify implications of AMR that have been insufficiently understood, and help point the way toward viable solutions.

Those who will benefit most do not have a voice. Many of them have not yet been born. AMR is indeed a threat to our economic future, but above all to the future of our children. Bold action today can safeguard the health and prosperity of those who will come after us.

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Introduction

This report seeks to enhance understanding of the economic and development consequences of antimicrobial resistance (AMR) and to clarify the economic rationale for investing to contain AMR. The report aims to build on and add to the political momentum that informed the landmark September 2016 United Nations General Assembly declaration on AMR, signed by 193 countries (United Nations General Assembly 2016).

The present report reflects 15 months of work by the World Bank Group and its partners. By analyzing economic arguments for combating AMR, the report responds to a key recommendation of the World Health Organization (WHO) Global Action Plan on AMR (WHO 2015a), as well as to WHO's direct request to the World Bank to help make the case for AMR investments. This work harnesses the World Bank's comparative advantage as a global development financial institution, its economic research capabilities, and its multi-sectoral breadth.

At a moment of unprecedented political opportunity, quantifying the magnitude of the economic threat posed by AMR can help catalyze national and global action on the scale the AMR crisis demands. In the following pages, we use economic simulation tools to put a price tag on the losses that drug-resistant infections will inflict on the global economy by 2050. We detail the development and poverty implications of this economic damage, in particular for low-income countries, which will suffer the worst impacts from AMR.

The extensive economic losses foreseen in our economic simulations can be prevented or substantially reduced. We describe an agenda for action to put the brakes on AMR. Our recommendations align with the General Assembly political declaration, the WHO Global Action Plan, recent AMR strategies from the United Nations Food and Agriculture Organization (FAO) (2016) and the World Animal Health Organisation (OIE) (2016), and the contributions of other partners. Our aim is to identify measures that low- and middle-income countries, in particular, can consider in national action plans to tackle AMR. We show that, in many instances, these measures are likely to generate substantial co-benefits that will improve low- and middle-income countries' overall development prospects.

A number of major reports and studies on AMR have recently been published by other institutions: notably the remarkable research papers and final summary report issued by the U.K. Review on AMR, which addressed both economic and health aspects (Review on Antimicrobial Resistance 2016). Our analysis seeks to complement, rather than duplicate, these efforts. Many recent AMR publications—for example, key documents issued by the U.S. Centers for Disease Control and Prevention (CDC) (2013), the Center for Disease Dynamics, Economics & Policy (CDDEP) (2015), the Organisation for Economic Co-operation and Development (OECD) (2016a), and others—are largely focused on the health sector—predominantly human health. These reports are addressed mainly to public-health professionals and health sector policy makers. In contrast, while health-sector issues and opportunities are also prominent in our report, we hope a key audience for this publication will be policy makers, policy analysts, and development practitioners outside the health domain.

Further raising awareness of AMR outside the human health sector remains a critical pending task, despite some recent progress. Without the engagement of other sectors, the world will not succeed in containing AMR and reducing its substantial economic costs.

Today, when policy makers in ministries of finance, development, or commerce are aware of AMR, they still rarely consider the problem an urgent challenge, much less a key opportunity for strategic investment. Misinformation on AMR remains pervasive, inside non-health government agencies and among the wider public. The results of a 2015 WHO survey of 10,000 respondents are telling: three-quarters (76 percent) of persons surveyed thought that antibiotic resistance happens when the human body becomes resistant to antibiotics—in fact, it is bacteria that become resistant to drugs. Two-thirds (66 percent) said that individuals are not at risk of a drug-resistant infection if they personally take their antibiotics as prescribed—in fact, everyone is at risk of such an infection if they are exposed to drug-resistant pathogens (WHO 2015b).

Pervasive misinformation about the clinical aspects of drug-resistant infections is worrying. But failure to appreciate AMR's economic consequences may prove even more devastating in the long run. This is where we hope our report can make a difference.

This report is structured in five parts. Part I presents a brief overview of the AMR challenge. It argues that the present proliferation of drug-resistant infections can be understood as a "tragedy of the commons" and shows that the availability of effective antimicrobial drugs is a global public good. We draw lessons from this conceptual framing for how an appropriate global response to AMR can be organized. Part II then looks at the economic impacts of declining availability of effective antimicrobials due to AMR. Illustrative simulations to the year 2050 show possible AMR impacts on global economic output, incomes, health care costs, livestock trade, and poverty. While the simulations are not predictions (rather, a range of outcomes that are possible), they highlight potentially substantial impacts on incomes in countries at different income levels. Part III then discusses the measures and investments in AMR control that countries could make as part of their national action plans on AMR. We provide order-of-magnitude estimates of the impressive economic gains that are likely to be obtained from AMR containment—even if the effort is only partially successful. Links to the Sustainable Development Goals (SDGs) suggest some entry points for AMR action.

Part IV provides more in-depth information on a series of topics relevant to the choices countries face in creating national AMR action plans. The first half of this part summarizes the results of three background studies commissioned for this report. They address: (1) laboratory-based AMR surveillance and the power of regional laboratory networks; (2) the use of antimicrobials in human health; and (3) the use of antimicrobials in animals. Drawing on the background studies and other resources, the second half of the part presents policy options for countries working to tackle AMR. The WHO Global Action Plan guides our recommendations. However, where the Global Action Plan is high-level and comprehensive, this report drills down on a select number of policy topics in three key sectors: human health; agriculture (in particular livestock production); and water and sanitation.

Part V of the report then offers concluding messages and describes specific ways the World Bank Group will support countries and partners in the AMR fight.

This report does not aim to treat the economics of drug-resistant infections exhaustively, nor to address all related policy areas. For example, our discussion does not cover important topics like the weak pipeline of research and development (R&D) for new antimicrobial drugs, nor the feeble current incentives for development and use of vaccines and better diagnostic tests. Readers will find these subjects well analyzed in other settings (for example, Review on Antimicrobial Resistance 2015).

Part I.
Drug-Resistant Infections: A Primer on the AMR Challenge

A. What Is AMR?

Humans live in a permanent arms race with harmful microbes.[1] Most microbes either aid humans and animals or cause no great harm, but a limited number are pathogens, which cause disease and, too often, the premature death of their host. Evolution ensures a constantly shifting balance of power between microbes and humans.

Since the middle of the nineteenth century, humans have achieved unprecedented advances in their war on pathogens. This has mainly been due to three developments: improved public-health systems to promote measures such as hygiene, better sanitation, cleaner water, and disease surveillance and control; the development of vaccines to control the spread of viruses; and, for the last 70 years, the use of antibiotics to combat bacterial pathogens. These advances underpinned an enormous reduction in the incidence of infectious diseases during the twentieth century, raising hope for a complete victory over infectious threats.

Yet a final triumph over harmful microbes did not occur—and there is no scientific basis for expecting such a victory. In part, this is because of a painful paradox: antimicrobial drugs, our best weapons against pathogens, sow the seeds of their own permanent inactivation each time they are deployed. The science has been settled for more than a hundred years: any use of antimicrobial drugs can cause the emergence and spread of antimicrobial resistance (AMR), understood as certain pathogens' adaptive capacity to survive exposure to antimicrobial agents (Box 1).

Even the appropriate, prudent use of antibiotics and other antimicrobials to treat infections promotes AMR. However, in that case the risk is outweighed by the health benefits obtained. On the other hand, in recent decades, overuse and misuse of antimicrobials in human medicine, livestock, fisheries, and crop production have caused avoidable AMR emergence and spread.

Because public-health authorities in most countries have not monitored the level and trends of antimicrobial use, the exact extent of current antimicrobial mishandling is unknown. Initiatives from the World Organisation for Animal Health (OIE) and the World Health Organization (WHO) are under way to help improve the information base on the use of antimicrobials. It is essential to monitor consumption of antimicrobial drugs, because the value of this asset, and how long it will last, depend directly on the rate of use. Without better monitoring and stewardship, antibiotics and other antimicrobials risk going down in history as a textbook "tragedy of the commons."

B. A Tragedy of the Commons

A tragedy of the commons occurs when people in a community unduly diminish (or even exhaust) a limited, shared resource, despite the fact that disappearance of the resource is not in the community's long-term interests (Hardin 1968). This concept has been applied, for example, to environmental problems and to the collapse of fisheries due to overfishing. Individual fishermen, acting in their self-interest, all seek to catch as many fish as they can—till there are no fish left. This tragedy can be averted only if the community changes fishermen's incentives and limits individual rights to catch fish. Lowering the rate of depletion of the fishery lets the fish reproduce. Regulated access leads to benefits for the community as a whole that are higher and more sustainable than under a laissez-faire approach that allows each actor to pursue short-term private interest without constraint.

Antibiotics (and other antimicrobials) are well on their way to becoming an example of a tragedy of the commons—in this case, on a global scale. The looming post-antibiotic era will be costly for all countries, because antibiotics have brought such immense health and economic benefits. There are currently no effective substitutes for antibiotic drugs in the treatment of bacterial infections. Untreatable infections will cause excess illness and premature death, both in humans and in their livestock, with devastating effects on individuals, societies, and economies.

AMR has already diminished the effectiveness of drugs to treat infection, and this trend will continue. For some pathogen-drug pairs, drug effectiveness has unfortunately already vanished. Continuing uncontrolled emergence and spread of AMR will mean that drug effectiveness will also diminish for other pathogen-drug pairs. More and more infections will become harder, and eventually even impossible, to treat. Though the global community as a whole will be worse off than if antibiotics and other antimicrobials had been conserved and used rationally, the world is continuing to squander the cure. This is turning back major public-health gains

Box 1. The Basics about Bugs That Cause Disease

Microbes. Bacteria, viruses, protozoa, and fungi are types of microbes. Most are so tiny that millions fit into the eye of a needle. They are the oldest form of life on Earth. They evolve fast, thanks to a high reproduction rate: some bacteria double every 20 minutes. There are 2–3 billion microbe species. Microbes comprise over 60 percent of the Earth's living matter, which indicates their evolutionary prowess.

Pathogens. A small minority, some 1,415 microbe species, are pathogens that induce infectious disease patterns in their human, animal, and plant hosts. This is how pathogens spread and advance their own reproduction.

Antimicrobials. Humans developed antimicrobials to destroy disease-causing microbes, or pathogens. The best-known antimicrobials are antibiotics, which are designed to kill bacteria and thus treat bacterial infections. Other antimicrobials are antivirals, antifungals, and antiparasitics. Examples of antimicrobials include tetracycline, an antibiotic that is often used to treat common bacterial infections; oseltamivir, also known as Tamiflu, an antiviral that treats the flu; mefloquine, also known as Lariam, to treat malaria; and terbinafine, also known as Lamisil, an antifungal that treats athlete's foot.

Antimicrobial resistance (AMR) and superbugs. AMR occurs when microbes resist the effects of antimicrobials. When microbes are resistant, the drugs do not work to kill them. Bacteria and other microbes can get resistance by mutating or by "horizontal" transfer of resistance genes from already resistant microbes, even from very different species. Whenever microbes are exposed to antimicrobials (even for a short period), the selection pressure (evolution) inexorably results in the emergence of microbes that are resistant to the antimicrobials. These microbes and their AMR will then spread. Such microbes are sometimes called "superbugs" because of their resistance to treatment. Emergence and spread of AMR may take years, but resistance can also appear within days.

Impact on the host. An antimicrobial cannot stop the growth of microbes that have developed resistance to it. With the growth of pathogens unchecked because of AMR, the human, animal, or plant host can be harmed or even killed by the infection—the pathogens prevail. Pathogens can be resistant to several antimicrobials; a multidrug-resistant infection is harder to treat because fewer effective drugs are available. Treatment may even be impossible. The results are:

- People and animals can't be effectively treated.
- People and animals are ill longer and are at greater risk of dying.
- Others are at greater risk of infection—in hospitals and communities within the country, in the region, and in the world.
- Epidemics (in people) and epizootics (in animals) are prolonged and more costly.

Drug resistance has been rising rapidly for certain highly prevalent infectious diseases, including gonorrhea, malaria, and tuberculosis (TB). See Annex 2 for a list of examples of AMR threats.

Box 2. Indicators of Weak Governance of Antimicrobials

- Globally, WHO estimates that only 50 percent of antibiotics are used correctly.
- Of the 150 million prescriptions for antibiotics written by U.S. doctors every year, fully 50 million were not necessary, according to a study released in May 2016 by the U.S. Centers for Disease Control and Prevention (CDC).
- In many countries, antibiotics can be bought over-the-counter from pharmacies, grocery stores, and street vendors.
- Up to 60 percent of the antimicrobials used in Africa and Asia may be substandard; counterfeit drugs have infested markets in these and other regions.
- Public data on use of, and trade in, antimicrobials are lacking or poor, indicating weak governance of a high-value public asset. Estimates of global annual use in agriculture range considerably, from 63,000 tons to over 240,000 tons.

that have enabled broad-based economic growth and development for billions of people over the past century (Deaton 2013).

Incentives to Overuse and Misuse of Antimicrobials

Individual patients, farmers, fishermen, and others appear to have had more incentives to overuse and misuse antibiotics and other antimicrobials than to conserve them. The same is true for manufacturers, distributors, doctors, veterinarians, hospitals, and clinics. Expanding access to health care, which often includes antimicrobials, has been an objective of health programs in many low- and middle-income countries, using both domestic and donor funding. Universal access to quality health care promises gains for public health, but greater access to antimicrobials inevitably means heightened risks of AMR. On the other hand, wider availability of diagnostic services may help to restrain overuse and misuse of antimicrobial drugs. Access to diagnostics can promote appropriate use, especially where many patients self-medicate because the private-market supply of antimicrobials without a prescription is plentiful (Alsan *et al.* 2015).

Competition among pharmaceutical producers keeps prices of many common antibiotics and other antimicrobials low, which gives yet stronger incentives for overuse, both in livestock and other agricultural production, and in humans. The pharmaceutical industry can produce many antimicrobials at low cost, and there are no limits on production capacity, especially since most antimicrobials are long off-patent. The global supply of antimicrobials will not be a constraint on the level of use. Instead, the availability of drug effectiveness is the real constraint. It is this constraint that is becoming more and more severe as AMR increases. And it is resistance to antibiotics, including medicines for the treatment of devastating diseases like TB, that is most unsettling. The vanishing of effective antibiotics is the greatest and most urgent among the AMR risks.

Counterfeit and Poor-Quality Drugs

Use of counterfeit and substandard antimicrobials aggravates AMR and also harms patients directly. Substandard and counterfeit medicines seem to be widely available in many countries, though data are poor. WHO has estimated that some 10 percent of all the drugs worldwide may be counterfeits, with half of these factitious medications mimicking antimicrobials (WHO 1999, 2000). Public health in a country suffers when counterfeits penetrate its market, and this damage is even greater when the counterfeits promote AMR. There are also other cross-border costs, since organized crime, smuggling, tax evasion, and bribery are often linked to counterfeit drugs. Combatting the insidious traffic in counterfeit and substandard drugs would yield significant benefits, including less AMR, but would need to engage multiple sectors across countries.

Manufacturing of substandard and counterfeit drugs appears to be concentrated in India, followed by China and Thailand (United Nations Office on Drugs and Crime 2010). Overall, up to 60 percent of antimicrobials used in Africa and Asia may have low quality, often containing none, or too little, of the active ingredient. One study found that fraudulent information on drug quality was common (found in 59 percent of cases), while only 7 percent of sample medicines tested had the standard concentration of the active drug (WHO 1999, 2000). Widely used antibiotics, such as penicillins, amoxicillin, and tetracyclines, as well as antimalarials and antiretrovirals (used to treat AIDS), appear to be commonly counterfeited antimicrobials (Kelesidis and Falagas 2015).

The consequences of using substandard and counterfeit antimicrobials are serious. The individuals taking the drugs are harmed because they do not receive the intended treatment, which can result in protracted illness, complications, spread of disease to others, and death. In addition to harming the patient, use of counterfeits will promote AMR if the drugs contain a low level of the active antimicrobial ingredient; this is common in counterfeit drugs for both human and animal use. The drug is not strong enough to treat the infection, but it contains enough antimicrobial ingredients to contribute to AMR.

Drug-Resistant Infections Are Already Common Worldwide

AMR and the associated drug-resistant infections are unfortunately not hypothetical problems, but a real threat for all countries, both developing and developed. They impact increasing numbers of health care facilities and patients. “Hospital-based health care providers see them every day. We daily encounter infections resistant to first-line antibiotics, and we not infrequently encounter infections resistant to every antibiotic except colistin or tigecycline, two antibiotics that are highly undesirable because of excess toxicity and inadequate efficacy. We are also now seeing pan-resistant infections that are not treatable even with colistin or tigecycline” (Spellberg *et al.* 2016). This vignette is drawn from experience in U.S. hospitals, but the higher costs and worse health outcomes are already all too common in all countries. For instance, tests of 1,606 samples from inpatient and outpatient settings in an African country in 2014 indicate seriously diminished drug effectiveness: 80 percent of the pathogens were resistant to older antibiotics (such as ampicillin and tetracycline), 50 percent were resistant to “third-generation” antibiotics (cephalosporins and quinolones), and most were multidrug-resistant (CDDEP 2016).

A Human-Made Problem—with Human Solutions

AMR is driven by microbes’ natural evolutionary adaptation to their environment. However, the spread of AMR as we confront it today is mostly a human-made problem. Thus, we refer to “anthropogenic” AMR. Drug-resistant infections in humans and livestock have been hastened and aggravated by poor governance, irrational human practices, selfish behaviors, and low understanding. Public health authorities and governments more broadly have not handled the precious antimicrobial commons with a degree of care commensurate with the high social value and the fragility of this asset. Efforts to minimize emergence of AMR and avert its spread cannot be one-off or limited to a temporary action plan. Containment of AMR is a core public-sector function that needs to be sustained over decades if AMR containment is to be successful and achieved efficiently, at least cost.

Over Reliance on New Miracle Cures Is Unwise—and Immoral

When older drugs eventually fail, won’t they always be replaced by newer ones? The short answer is: “No.” New replacement drugs may be developed in some cases, but the prospects for such success have always been uncertain, and they have worsened in recent decades. The research and development (R&D) pipeline for new antimicrobial drugs has shrunk since the 1980s and is now nearly empty. R&D for antimicrobials is very costly and not as commercially attractive as for other drugs, especially those that are taken for long periods and can command high prices. The absence of market incentives to R&D for antimicrobials is an additional, and powerful, reason to conserve the effectiveness of existing drugs by minimizing misuse and overuse.

Improved governance of antimicrobial use will prevent the scarce common resource from being wasted—an objective that governments should have pursued since antibiotics were first marketed over 70 years ago. Sir Alexander Fleming, who won the Nobel Prize for discovering the first antibiotic (penicillin), warned in 1945: "The microbes are educated to resist penicillin . . . In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted."

C. AMR Containment: A Global Public Good

As effective antimicrobial treatment is part of the global commons, so containment of AMR is a global public good, which will prolong the availability of effective antimicrobials for all countries. Once this public good—AMR containment—is produced, it is impossible to exclude anyone from benefiting from it. All countries can enjoy the benefits of successful AMR containment. Conversely, all countries will be harmed if AMR is not controlled.

One difference between AMR containment and other major global public goods (such as slowing climate change, generating knowledge, and preventing pandemics) is that there is "rivalry" in the "use" of AMR containment benefits.[2] Once climate change is mitigated or a pandemic is prevented by early and effective control of the contagion at the source, all countries and their populations reap the benefits without diminishing the benefits that other countries can obtain. In contrast, use of antimicrobials in any one country exposes pathogens to selective pressure and thus contributes to reversing AMR containment. This will have negative impacts not only for that country, but also for all other countries. This distinctive trait requires that the global public good of AMR containment be managed with exceptional vigilance through international cooperation.

Protecting the global antimicrobial commons is made more challenging by the ease with which drug-resistant pathogens spread. Resistant microbes do not respect borders; they circulate through human travel and through trade in livestock (including poultry and fish) and livestock products. They can also spread through food products and in the environment, for instance in waterways and in migrations of wild birds and other wildlife. Unmonitored waste containing antimicrobials is generated by pharmaceutical manufacturers, hospitals, and livestock producers—all such waste can promote AMR in microbes in the environment. When drug-resistant pathogens infect people and animals, the pathogens and their AMR genes can continue to spread by human-to-human, animal-to-human, and animal-to-animal pathways; by means of vectors like mosquitoes and rats; and in the environment, including in water from aquaculture farms, sewage, and animal and other wastes from farms and slaughterhouses. In addition to these numerous routes, AMR can spread "horizontally," because drug-resistant microbes can transfer resistance genes to other microbes, including across microbe species.

Public-Sector Responsibility in Conserving Antimicrobial Effectiveness

Individual households and livestock producers are not able to prevent the spread of drug-resistant contagion on their own. Provision of this public good is the responsibility of public authorities: in particular, national governments and the multilateral institutions that national governments have created to facilitate cross-border collaboration.

A strong argument for government leadership on AMR concerns the impact on future generations. The threat of AMR transcends today's historical context and invokes the duty of the State to defend future generations who cannot speak for themselves. Throughout the coming decades, today's children will need access to drugs that work to treat life-threatening disease. However, if current practices continue, such drugs will not be available to them, because their parents' generation will have squandered drug effectiveness through reckless handling of antimicrobials. The free or weakly regulated market has resulted in a "first-come, first-served" allocation of the finite stock of antimicrobial effectiveness. There is misuse and excessive use today, at the expense of the generations to come (Tisdell 1982).

In reality, access to the scarce antimicrobial resource is not even being managed to maximize the welfare of today's human community. Many current users of antimicrobials actually do not obtain any benefits from them (because they are misusing the drugs) or benefit only to a small extent: for example, when some antimicrobials are used for growth promotion in livestock and when broad-spectrum antibiotics are prescribed unnecessarily for human patients.

An additional pragmatic argument for government responsibility on AMR will be discussed in Part II of this report. It concerns the magnitude of the economic stakes involved in controlling drug-resistant infections. As we will see, antimicrobial effectiveness is an asset with an approximate worth today between $20 trillion and $54 trillion (in constant 2007 dollars).[3] This asset is “too big to fail.” For government leaders, neglecting to protect a resource of this magnitude would be a staggering abdication of public trust.

D. AMR and Access to Treatment in Developing Countries

Even as there is overuse and misuse of antimicrobials, some poor populations still lack access to effective medicines. For example, one million children are estimated to die each year from untreated pneumonia and sepsis, which can be effectively managed with antibiotics (Laxminarayan *et al.* 2016). Weak health care systems, AMR, and the penetration of many countries’ antimicrobials markets by substandard and counterfeit drugs—these conditions all contribute to low access to effective antimicrobials. Relatively high prices of the more powerful, later-generation, antimicrobial drugs are also a factor. The development and marketing of these drugs occurred since the first-line, relatively inexpensive antimicrobials lost their effectiveness because of AMR. High drug prices then squeeze the finite health care budgets of governments, charities, and households, resulting in diminished access to treatment, especially for the poor and vulnerable. In addition to the effect on individual health outcomes, shrinking access to effective antimicrobials hinders progress toward universal health coverage (UHC), a pillar of the Sustainable Development Goals for 2030.[4] We will discuss the potential development impacts of AMR extensively in Part II. In Part IV, we will show how country action to promote UHC can simultaneously enable more effective AMR control.

Antimicrobial access constraints extend beyond the human health sector. The dire scarcity of basic veterinary services in most low-income countries is associated with lack of access to effective antibiotics to treat infections in livestock. This is a significant development challenge, because livestock are frequently the main economic asset for poor households, especially in low-income countries. Untreated disease in animals causes negative shocks to owners’ incomes and in some cases lasting damage to the welfare of poor households and communities. Counterfeit and substandard drugs are also a major factor in harming animal health and owners’ incomes.

This brings us to an idea that will be a recurrent motif throughout this report. Wealthy countries would be extremely unwise to regard inadequate treatment of infectious diseases in developing countries as “someone else’s problem.” All countries are at risk of importing infections. The risk is higher the greater the interconnectedness and volumes of trade and travel with other countries. Today, the volume and diversity of international trade and travel are dramatically higher than just twenty years ago, and global networks continue to expand. Each country thus benefits increasingly, if all other countries are equipped to effectively treat infectious diseases and adequately manage AMR threats.

E. Closing Governance Gaps

Surveillance Is Critical, but Systems Are Weak

When a drug-resistant disease starts spreading in an area where local public-health surveillance is weak, economic and health costs will escalate rapidly. If the disease is easily transmissible, the rate of escalation can be exponential. Multiple factors may facilitate this escalation, but the most important is the delay in detection.

Where AMR is present but undetected, humans and animals likely do not receive medical treatment that works against their drug-resistant infection. Uncured animals and patients may then spread the disease further, within hospitals or other health facilities and in the community at large. The weaker the local surveillance system, the less knowledge health authorities can gather about the spread of diseases. Critical information becomes available with a delay, if at all. Control measures are then less likely to succeed in containing the microbial threat, because they will confront a dramatically higher number of infected people or animals.

The risks of such outcomes can be significantly reduced by surveillance systems with the capacity to provide timely warning about microbial threats. Key components of a functioning surveillance system include:

- Laboratory capacity to detect and characterize resistant organisms through antimicrobial susceptibility testing (AST)
- Appropriate criteria and mechanisms for reporting
- Effective oversight by a reference laboratory.

Unfortunately, the policy and financing choices of governments and their development partners have resulted in inadequate infectious disease surveillance capacity across much of the globe. Early warning about AMR emergence is simply not possible with the existing public-health capacities in most countries, which means that those countries, as well as the rest of the world, will not learn in time about new AMR emergence and spread. The infectious disease surveillance "blind spots" extend across most of Africa and Asia, as well as parts of other regions.

Growing Threats

The overlap between surveillance "blind spots" and potential "hot spots" for drug-resistant disease emergence is a substantial concern. This menace is growing today, as the world confronts an expanding array of new, old, and re-emergent infections. Already, multiple-drug resistance (MDR) is spreading in several key pathogens. The infections caused by such pathogens have become diseases with no cure. For many of them, no vaccine is available, either. Such diseases join a growing list of infectious threats to which we can offer no effective medical response. These include virulent new strains of existing infections, as well as entirely new pathologies, most of which are zoonotic (of animal origin). Most are introduced into human populations through people's contact with livestock (including poultry). The novel and the drug-resistant pathogens spread unchecked from wherever they first appear, because we have no tools to stop them.

Because of AMR, even infectious diseases that were previously considered controlled may once again be poised to spread widely—even worldwide. When this occurs, there may be pandemics (in humans) and panzootics (in animals) of drug-resistant diseases. This could occur in successive waves as the drugs lose effectiveness in different drug-pathogen pairs. Waves of contagion from different sources could overlap, exacerbating health and economic impacts.

Coordination Is Key

To contain AMR successfully, all countries will need to act in a coordinated way. Prohibiting one kind of antimicrobial misuse in a country may not be effective unless all countries adopt a similar approach. Conversely, coordinated application of even basic measures could have a powerful effect. For example, consistent international labeling of antimicrobial medicines, agreed among all countries, would already reduce the scope for confusion and misuse among prescribers and patients. In the absence of international cooperation, drug-resistant pathogens will continue to emerge at the weakest links in the worldwide chain of antimicrobial use.

Of course, country strategies and implementation plans for action on AMR will not be entirely uniform. Timelines for the implementation of new regulations may need to differ across countries, and low-income countries may require assistance in building implementation capacity.

Collaboration remains critical in the AMR fight, because AMR containment can be diminished or even undone by "free riders." Any one country may tend to look to other countries to take the measures necessary to tackle AMR—and then benefit from the result without investing to contain AMR on its own territory. Such tactics would undermine the success of AMR containment, and all countries would eventually suffer the consequences.

Joining Forces to Strengthen Surveillance and Response

Fortunately, international organizations entrusted with the governance of global public goods already exist for human public health (WHO), for veterinary public health (OIE), and for food production (FAO). As we will see in subsequent parts, AMR containment will bring large benefits to all countries individually and to the global economy as a whole. This may provide incentives for sustained cooperation.

In this context, WHO, OIE, and partners are setting up a dedicated structure to facilitate AMR collaboration: the Global Antimicrobial Resistance Surveillance System (GLASS), which embeds AMR in the wider array of activities that comprise surveillance of microbial threats. GLASS promotes consistency of approaches (which is critical for maximizing the information value of surveillance data), quality assurance, and provision of data to inform global decision making (see Part IV). Ultimately, surveillance for AMR will be most reliable if the capacity of comprehensive surveillance systems is strengthened in all countries, for better performance in detecting and assessing the full range of threats to veterinary and human public health. Today, bold new initiatives such as the United Kingdom's Fleming Fund are bringing fresh resources and expertise to this global effort.

How International Coordination Can Lower Costs: The Example of Tuberculosis

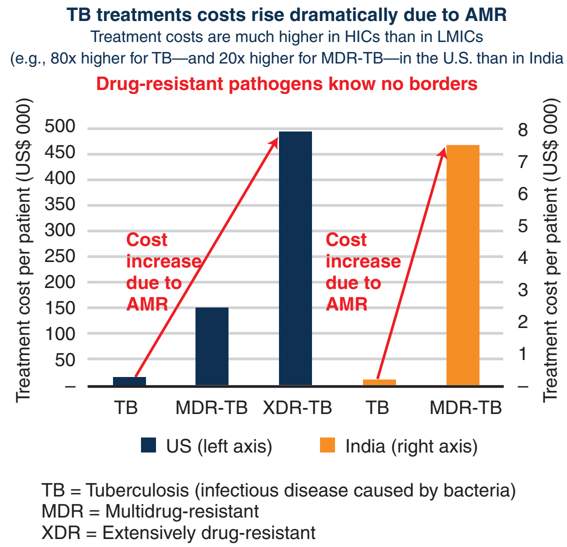
Infectious disease control has long been considered the quintessential global public good (International Task Force on Global Public Goods 2006; World Bank 2007). The risk of AMR further bolsters the economic case for effective and early control of infectious diseases at their source. As with preventing and fighting fires, reducing risks at their source is invariably more effective and more efficient than a reactive stance of waiting for a crisis to develop before responding.

In Parts II and III, we will analyze the economic case for AMR action in detail. For now, we focus on a specific aspect of the problem that again underscores the value of international cooperation. This example also shows that, when wealthy countries and low- or middle-income countries collaborate on AMR, economic benefits can accrue on both sides.

Our example concerns drug-resistant and emerging infectious diseases that are imported into high-income countries from countries currently unable to provide effective therapies for these conditions. Promoting treatment of infectious diseases in the countries of origin is an option that can be both more effective and more efficient than for wealthy countries to import cases and treat them in their own health systems.

The costs of some of the measures that will be required to contain AMR vary widely across countries. Figure 1 shows one example: the cost differentials in treating tuberculosis (TB), with and without AMR. TB is an infectious disease that can be treated with antimicrobials. Inadequate treatment of TB will not cure the patient, but it will promote AMR. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of TB have emerged.

FIGURE 1. AMR Makes TB Far Costlier to Treat



MDR TB and XDR TB infections are far more expensive to treat than drug-susceptible TB. Because of the higher costs and clinical factors, successful treatment of drug-resistant cases is also less likely than for drug-susceptible TB strains. Since uncured patients will pass the infection to more people, MDR TB and XDR TB will spread.

It is much more expensive to cure infectious diseases in high-income countries than in low- and middle-income countries, because the costs of medical personnel and supplies are much higher. Thus, it costs 80 times more to treat one TB patient in the United States than in India, as shown in Figure 1.

Such a large cost differential should inform the allocation of resources for control of TB globally. Reducing the prevalence of TB in low- and middle-income countries by treating all cases properly will, of course, improve health in those countries, but it will also reduce both AMR and the probability that drug-resistant TB will spread to other countries. For instance, in the United States, two-thirds of TB patients are foreign-born (with India among the top source countries). The number of TB patients treated in the United States and AMR risks would be lower if effective treatment had been provided to more patients in their countries of origin.

These considerations provide a powerful rationale for high-income countries and the international community as a whole to invest in the development of effective veterinary and human public-health systems—especially in the countries where these systems are currently weakest. The returns on investment in core public-health functions are especially high in these countries, and the economic benefits will flow to high-income countries, as well.

But how robust is this argument, really? Can it extend beyond the specific case of TB to a wider range of infections where drug-resistant variants may emerge? Few would deny, as a theoretical point, the desirability of international collaboration to tackle infectious health challenges, including AMR. In practice, however, are the economic stakes in fighting a potentially broad array of drug-resistant infections sufficient to justify the investments that will be required for large-scale, coordinated, global action?

The next part of this report explores the economic case for AMR containment in greater depth.

Endnotes

1. Part I of this report is based in part on Brahmbhatt and Jonas (2015).
2. Non-rivalrous consumption is commonly cited as a requirement for the good to be considered a “public” good. It refers to the property of the good’s being inexhaustible. National defense, clean air, and public health functions are commonly cited as public goods in countries. When consumption of the good is “non-rivalrous,” any one benefiting from the good does not reduce the benefits available to others. To benefit from AMR containment is to use the antimicrobials, but this promotes AMR to the detriment of all other users.
3. These estimates discount future benefits from antimicrobials at 3.5 percent annually. Much greater values of the antimicrobial commons result from using a lower discount rate. For instance the asset value is as high as $85 trillion, if future benefits are discounted at 1.4 percent annually; this lower rate was used in the 2007 report on climate change impacts by Sir Nicholas Stern. See Part II.
4. Sustainable Development Goal 3: “Ensure healthy lives and promote well-being for all at all ages.” This goal has 13 targets, including universal health coverage. See Annex 4 and compare: http://www.un.org/sustainabledevelopment/health/

Part II. Economic Impact of AMR

A. Rationale and Approach to the Simulations

In most countries, a host of competing issues place legitimate claims on scarce public funds. How much of their economic resources should countries be prepared to invest in tackling AMR?

The answer depends on the economic costs uncontrolled AMR will inflict. Logically, if the expected costs are high, then the world should be willing to spend more on AMR containment to preempt them. Part II of this report presents the results of economic simulations conducted by the World Bank to estimate the costs that AMR is likely to inflict on the global economy in coming decades, if effective action is not taken. The projection period ends in 2050, or well within the lifetimes of present-day children and young people. Impacts by the year 2030 were calculated as well, because of their relevance to the Sustainable Development Goals.

There are difficulties in estimating costs that will occur in the future, especially when these costs derive from the inherently uncertain pace of AMR emergence and spread. Weak surveillance yields sparse, low-quality information about AMR and pathogens. The impact simulations prepared for this report are thus necessarily based on assumptions, which the World Bank's Development Economics Group grounded in a review of recent simulations by other research groups, information on actual impacts of AMR to date, and expectations about its spread. With their strengths and limitations, we hope our simulations will contribute to a more complete understanding of the economic implications of AMR and stimulate further work.

Weak and missing data on the use of antimicrobials and on AMR trends, especially in low- and middle-income countries, are not reasons for ignoring AMR in analyses of countries' economic prospects. To do so implicitly assumes future AMR impacts in the country to be zero, meaning that disease outbreaks and pandemics will never occur. The results of the simulations of global impacts presented below may serve as an incentive to prepare country AMR cost simulations. Country policy makers and their development partners will probably make superior choices, especially on investments in the health sector, if assessments of major risks to economies and public health are routinely considered in the formulation of national budgets and economic development programs. The probability that future economic costs of AMR will be small enough to be ignored is miniscule. Such a scenario can safely be excluded from evidence-based policy making.

Economic Impacts Considered in the Simulations

The economic costs of AMR can be divided into several categories. For this report, we considered costs that are due to AMR impacts on the health of workers and costs that are due to AMR impacts on animal health. The report uses "high AMR" to mean "high AMR impact." Of note, health and economic impacts are not directly related to the amount of resistance *per se*. To illustrate: for a dangerous disease with high mortality, even a modest extent of AMR will have a large impact on population health. For a less lethal and less transmissible disease, however, even significant AMR would have a smaller impact on health. The impact on health depends on which pathogen-drug pair is affected by AMR.

Effective antimicrobials are a highly valuable public good that have brought enormous benefits to humanity. The erosion of this good will impose correspondingly high costs. When antimicrobials started to be used widely about 70 years ago, the rates of death from infection fell by some 80 percent. When drugs stop working because of AMR, the rates of death and illness could increase back to the levels of the pre-antimicrobial era. This would reduce economic output because of a lower effective labor supply. This reduction of gross domestic product (GDP), modeled as the consequence of "shocks" to the labor supply, is the standard approach to valuing the aggregate, macroeconomic impacts of morbidity and mortality. The value of the reduction in GDP from the baseline (a scenario without "shocks") is the strictly economic impact of these alterations in population health.

There would be additional reductions in human welfare in the scenarios described, but these are not included in the simulations for this report. Individuals and their families may experience a greater loss of welfare than those calculated in the simulations, as research into people's subjective valuation of morbidity and mortality suggests. There is empirical evidence that most people value their life more highly than the amount of their foregone wages due to premature death (Jamison *et al.* 2013), so a higher probability of premature death (which is a direct impact of AMR) reduces their welfare in line with their subjective valuation of life and not just as wages lost due to premature death.

A second reason that the simulations underestimate AMR impacts on human welfare is that some medical procedures require effective antimicrobials. AMR would render such procedures too risky to undertake and thus less available. There would be fewer (or no) simple and complex surgical procedures such as, for example, appendectomies, hip replacements, Caesarian deliveries, and removal of tumors, as well as less chemotherapy. Surgeons and others involved in the provision of these procedures would see their livelihoods diminished. The health and quality of life of patients would be worse, but the economic value of such impacts is not easily estimated and was not included in the simulations.

Our simulations also fail to capture a third reason that human welfare would worsen with the spread of AMR. This is the cost of resorting to inferior medical treatment methods. Older, less effective treatments may become the best available option if AMR is not contained. For instance, gonorrhea, which is a bacterial infection, is already becoming harder to treat because of AMR. One alternative to treatment with antibiotics could be the decidedly inferior and painful methods that were used to treat gonorrhea before antibiotics became available: "Mechanical interventions included genital instillation of large quantities of iodine solution instilled by urethral or vaginal catheters, or 'hot boxes' where a person's body was put in a box to 43°C to try to kill off the organism and not the host" (Kupferschmidt 2016).

Direct and Indirect Costs of Disease

The impacts of AMR on human health will be increased morbidity (illness) and mortality. These give rise to the direct and indirect costs of illness. The direct costs of illness are the resources used to treat, or cope with, disease, including costs of hospitalization and medication. When pathogens are drug resistant, such treatment will invariably be more costly and produce worse outcomes for patients and the community. Indirect costs of illness comprise the present and future costs to society from morbidity, disability, and premature death, in particular the loss of output caused by a reduced effective labor supply (due to lower productivity and deaths of workers).

In livestock production, the impact will also be increased morbidity and mortality; together these lead to lower productivity, lower supply of livestock products (both domestically and for exports), and increased prices for major sources of protein, including meat, fish, eggs, and milk. The modeling work carried out for this report ensures that impacts on prices, factors of production, and sector outputs are consistently modeled, across sectors, across countries, and over time. All sectors will be affected, because all sectors employ workers—the effective labor force and productivity of workers are key determinants of output in different sectors. More labor-intensive sectors would tend to have greater declines in output growth because of AMR than sectors where production is relatively capital-intensive.

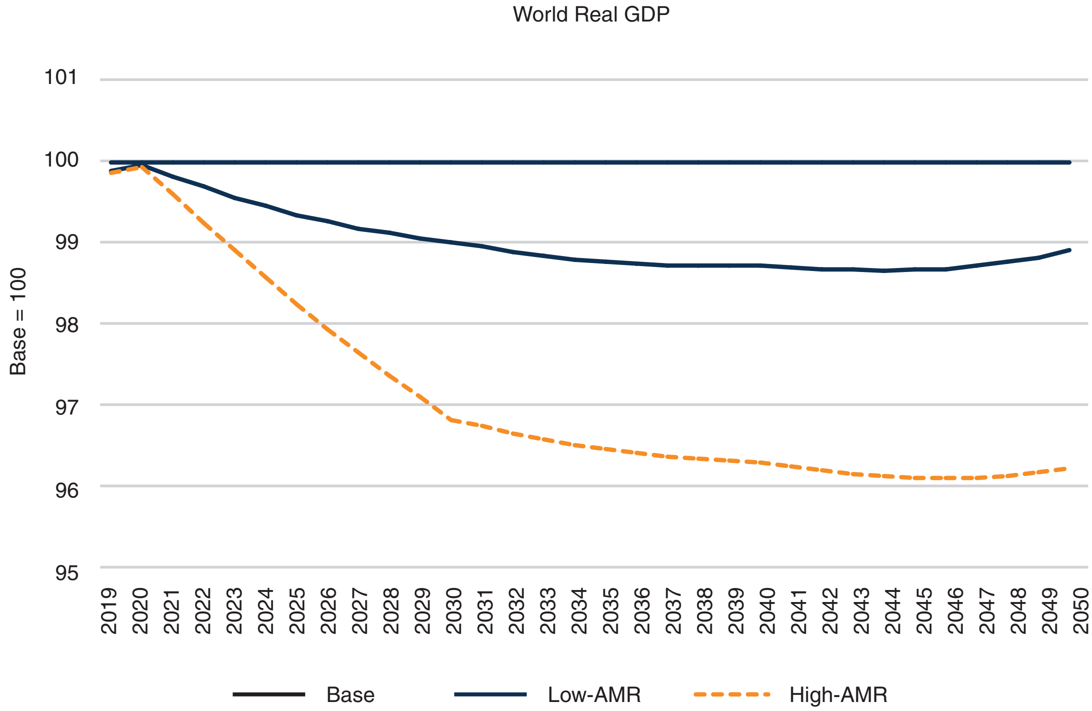
B. Impacts of AMR on the Global Economy

The results of the simulations of AMR impacts on global GDP in 2017–2050 are shown in Figure 2, under two scenarios. In the optimistic low-AMR scenario, global economic output is projected to be 1.0 percent lower by 2030 and 1.1 percent lower by 2050 than in the base case.[1] In the pessimistic high-AMR scenario, global economic output would be 3.2 percent lower in 2030 and then fall further, so that in 2050, the world would lose 3.8 percent of its GDP, relative to the base case (compare KPMG 2014; Review on Antimicrobial Resistance 2014; Taylor *et al.* 2014). In the low-AMR case, the costs, as measured by the reduction of GDP from the base case, will be a significant economic burden, while in the high-AMR scenario, the costs can be considered severe, especially since the costly impacts endure over time.

Given that the simulations for this report were done using a dynamic, multi-country, multi-sector, general equilibrium model with neoclassical growth features, economies do adjust to price signals caused by the AMR shocks. These adjustments lead to a reallocation of resources and to new investments (capital accumulation). These model characteristics explain the flattening of the output trajectories after 2040 in Figure 2; by this time much of the adjustment of the world economy to shifts in relative prices and reallocation among sectors would have occurred. Thereafter, growth factors coming from capital accumulation and labor growth start to prevail, resulting in an essentially constant shortfall relative to the base case during the decade to 2050.

Different assumptions about the timing and magnitudes of the AMR shocks would alter the shape of the lines in Figure 2. Additional, accelerated AMR

FIGURE 2. Substantial and Protracted Shortfalls in Global Economic Output



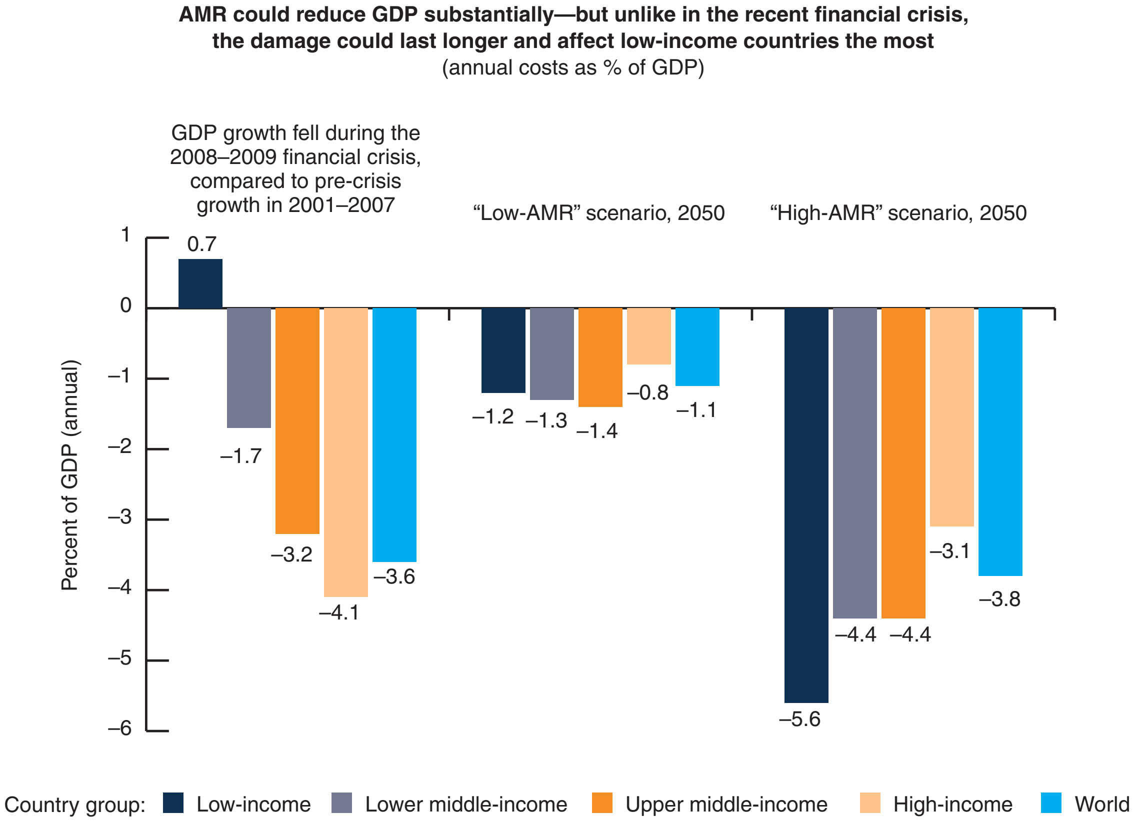
emergence and spread late in the projection period (after 2035, when adjustment to the initial shocks is nearly complete) would worsen the impacts, for example, but were not included in the modeling work. As noted, the scenarios prepared for this report are not predictions but illustrations of some of the plausible impact patterns that could materialize.

Further analysis of the results of the simulations shows that the costly impacts of AMR are not distributed equally among countries at different levels of per capita income. The negative impact in low-income countries is more pronounced than in high-income countries (Figure 3). The two main reasons for this difference are a higher incidence of infectious diseases and a higher dependence on labor incomes in low-income countries than in high-income countries. The larger impacts in low-income countries than in high-income countries might cancel decades of progress in global economic convergence.

How large are the potential economic impacts of AMR? To provide a point of reference, Figure 3 also shows indicators of the costly consequences of the major global financial crisis that started in 2008. Whereas global growth averaged 3.7 percent annually before the crisis, it dropped precipitously in 2008 and 2009, to an average of just 0.1 percent annually. The difference, a 3.6 percent reduction in global economic growth, is shown in Figure 3 and is a measure of the amount of economic output that was not produced during the crisis years. Growth in low-income countries remained relatively strong: it was in fact 0.7 percent higher in 2008–2009 than before the crisis. However, growth in high-income and upper middle-income countries plummeted, by 4.1 percent and 3.2 percent, respectively, compared to the pre-crisis period. The output losses from these shortfalls in growth in 2008–2009 were severe.

How do the simulated impacts of AMR compare to this recent major economic crisis? The annual economic damage from AMR during much of the projection period could be of the same order of magnitude as the impact during the major global financial crisis. In the high-AMR scenario, GDP in 2050 would be 3.8 percent lower than in the base scenario. For low-income countries, the impact is worse: their GDP would be more than 5 percent smaller than in the base case. Similarly substantial shortfalls in economic output would occur during the 20 preceding years (see Figure 3). Even in the optimistic low-AMR scenario, the simulated losses of world output exceed $1 trillion annually after 2030 and reach $2 trillion annually by 2050.[2] In the high-

FIGURE 3. Economic Costs of AMR May Be as Severe as During the Financial Crisis



AMR scenario, the absolute levels of losses are three times as high, reaching $3.4 trillion annually by 2030 and rising further to $6.1 trillion annually by 2050.

The global economic impact of AMR would differ from that of the financial crisis in two respects. First, AMR would be relatively more costly for low-income countries than for high-income countries; impacts on middle-income countries would be in between the two. The simulations point to a growing income gap between low-income and high-income countries. The impacts on middle-income economies would be substantial (in the high-AMR case) or moderate (in the low-AMR case). In both cases, growth of these economies would slow, delaying achievement of high-income status (especially in the high-AMR case).

The second difference is that there is little prospect for a "cyclical recovery." Development of new drugs and vaccines may take a decade or more (and may not succeed). Even if successful, such new products would take time to reach markets in low- and middle-income countries. The prolonged economic impacts would make AMR a more daunting challenge than the relatively short-lived financial crisis, from which the world economy started to recover in 2010 (though that recovery has been protracted). In contrast to cyclical economic downturns, AMR could cause persistent shortfalls in world economic output throughout the lifetimes of today's children and young people. These impacts would be largest in the poorest countries.

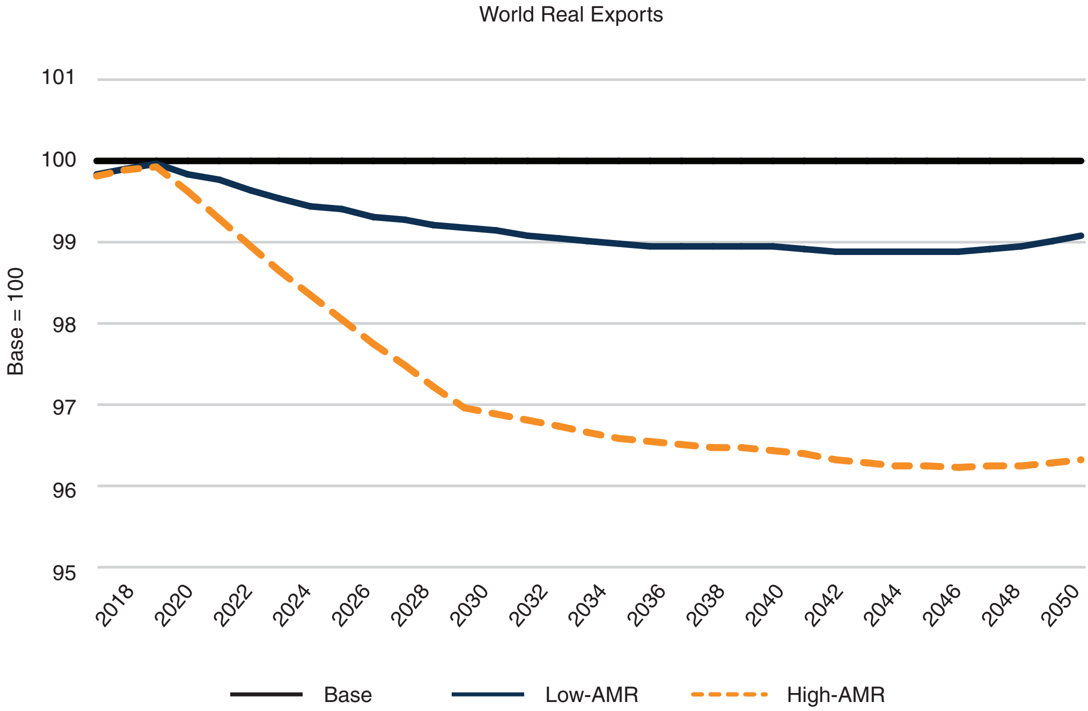
C. Impacts on Select Components of the World Economy

International Trade

Figure 4 shows the simulated impact of AMR on world trade (exports). By 2050, the volume of global real exports may be below base-case values by 1.1 percent in the low-AMR scenario and by 3.8 percent in the high-AMR scenario. The pattern of the impacts over time follows the pattern of impacts of AMR on GDP.

Trade in livestock and livestock products is vulnerable to AMR impact not only because untreatable disease

FIGURE 4. AMR Impact on World Trade



affects productivity, but also because a "fear factor" typically provokes trade disruptions (such as bans on imports) in response to disease outbreaks. While microbial threats are underestimated (and even ignored) in "peacetime," politicians, firms, and citizens exhibit strong, spontaneous avoidance behaviors during disease outbreaks. Such behaviors are often based on a substantial overestimation of risks. These reactions tend to sharply reduce and otherwise disrupt economic activity (Brahmbhatt and Dutta 2008). Predominantly based on fear, such responses are especially likely to accompany outbreaks of drug-resistant diseases, because there will be no cure available.

While trade in livestock is particularly sensitive to these forces, the effects do not materially affect our simulations of trade flows, because of the small share of aggregated livestock and livestock products in world exports. Instead, the effects of broad declines across all economic sectors dominate the simulation results for trade flows.

Livestock Production

The shocks to livestock production were modeled as both a decrease in productivity because of greater prevalence of untreatable disease and as reductions in exports due to restrictions imposed by trading partners. The "fear factor" would likely contribute to reductions in livestock production.

Livestock production is a small part of the global economy (about 2 percent of world GDP), so its reduced productivity has a minor influence on the overall simulation results. The sector is relatively more important in the economies and exports of low- and lower middle-income countries than in wealthier countries, however. In addition, the sector plays a substantial development role and makes a major contribution to nutrition, especially for children and women of reproductive age. AMR will worsen animal health, as well as undermine the welfare of the animals' owners and others in the sector, both by increasing the variability of incomes because of more frequent and severe infections, and by reducing income levels as an increased disease burden becomes the "new normal" (Figure 5).

Health Care Expenditures

Health care expenditures (both public and private) would increase in tandem with the rising disease burdens. The trends shown in Figure 6 are only two of a range of possible outcomes; they are not projections but simulations of two scenarios to illustrate the direction and order of magnitude of global AMR impacts. In the high-AMR scenario,

FIGURE 5. Decline in Livestock Production Could Be Substantial and Most Pronounced in Low-Income Countries

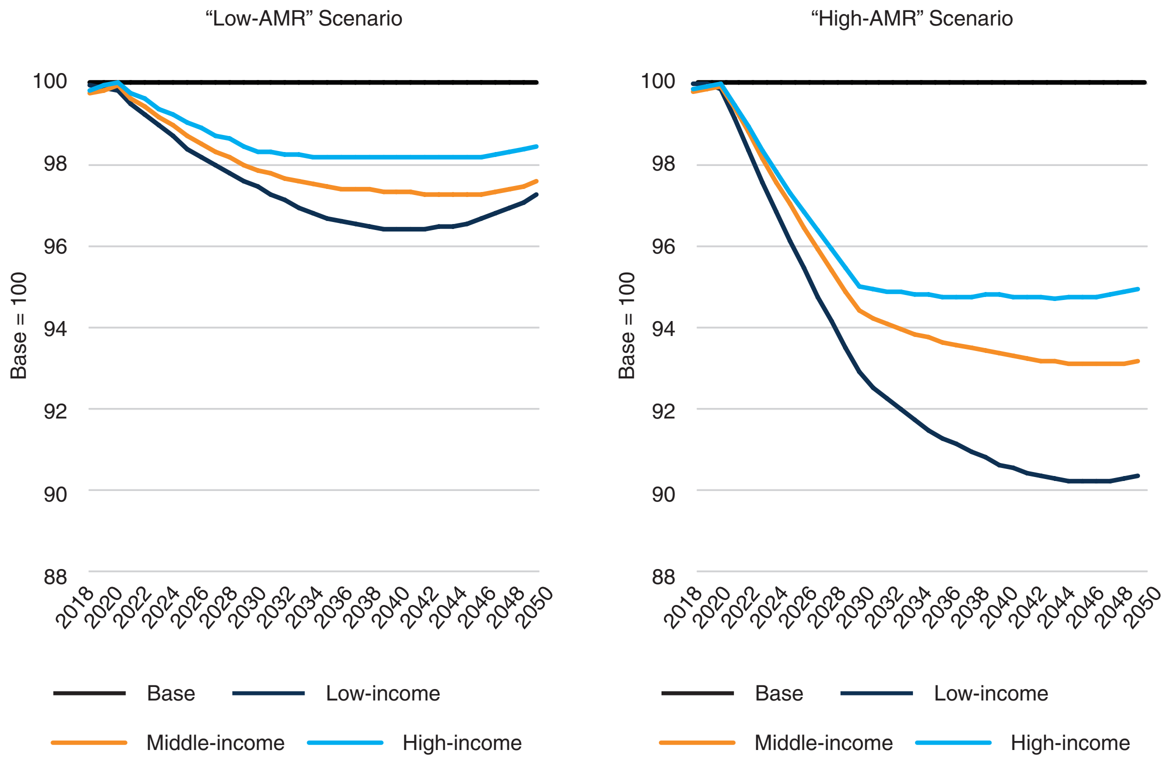
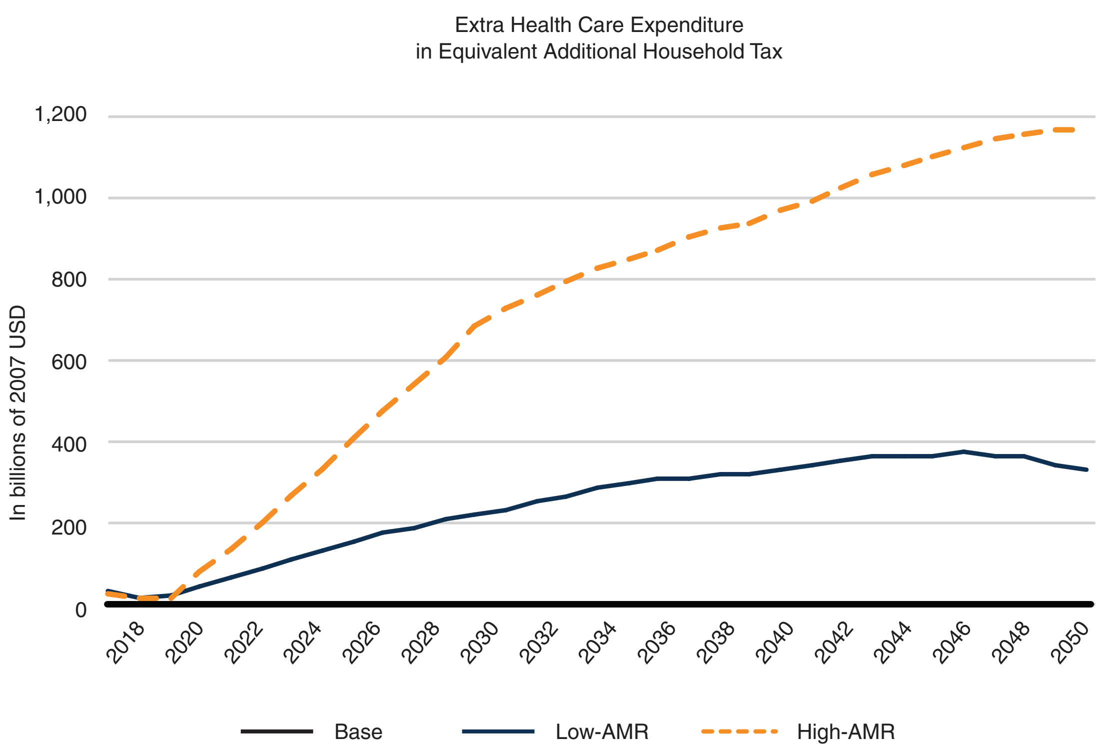


FIGURE 6. Health Care Costs Reach Nearly $1.2 Trillion in the "High-AMR" Case



health care expenditures in 2050 would be as much as 25 percent higher than the baseline values for low-income countries, 15 percent higher for middle-income countries, and 6 percent higher for high-income countries. Globally, annual expenditures in 2050 would be 8 percent higher than in the base case. The additional expenditures in 2050 would be $1.2 trillion annually in the high-AMR scenario. In the low-AMR scenario, the additional health care expenditure in 2050 would be $0.33 trillion annually.

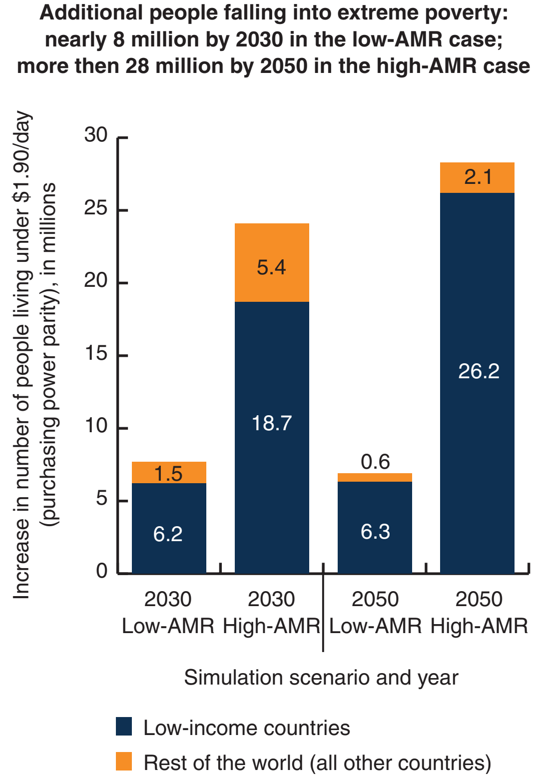
Since our economic modeling stipulates that these expenditures are not made unless they are financed, there would be a decline in consumption. This will mean a reduction in other aspects of population well-being, because resources that could have been devoted to reduce poverty or pursue other goals will have to be diverted to financing the extra costs of a larger health sector coping with a larger disease burden.

Similar simulations of health care costs under different AMR scenarios at national and subnational levels could prove useful in raising awareness of AMR risks in the health sector and among departments involved in managing public expenditures and revenues. In countries where the public sector finances a substantial part of health care costs, the required additional taxes may not be feasible to implement, or they would severely burden taxpayers, since people would have to reduce their consumption in order to pay the additional taxes.

D. Impacts on Poverty

The impact of AMR on economic growth will result in a pronounced increase in extreme poverty. The main reason is the disproportionate impact of AMR on the economies of low-income countries (Figure 3). These countries experienced substantial and protracted shortfalls in economic output in the simulations. Of the additional 28.3 million people living in extreme poverty in 2050 in the high-AMR scenario, the vast majority (26.2 million) would live in low-income countries (Figure 7). In the baseline scenario, the world is broadly on track to eliminate extreme poverty by 2030, moving toward the World Bank Group's target of less than 3 percent of people living in extreme poverty (i.e., on less than $1.90/day) worldwide. Because of AMR, however, the target would be harder to reach: there could be an additional 24.1 million extremely poor people by 2030 in the high-AMR scenario, of whom 18.7 million would be in low-income countries.

FIGURE 7. Most of the People Falling into Extreme Poverty Because of AMR Will Be in Low-Income Countries



Source: Simulation results and author's calculations.

E. The Economic Case for Tackling AMR: Focus on the Health Sector

The preceding discussion has shown that unchecked AMR is likely to inflict heavy losses on the global economy in the period 2017–2050. However, we have not yet suggested what can be done to avoid this highly undesirable outcome. Nor have we explicitly argued that the costs likely to be involved in AMR containment will be manageable for individual countries and the global community as a whole. While the costs of uncontrolled AMR will be vast, it does not necessarily follow that the costs of containing AMR will be much less so. These issues are the focus of Part III.

Here, it will be useful to anticipate the broad direction of subsequent arguments by looking specifically at the health sector.

Already by 2030, extra health care expenditures would rise to $0.22 trillion annually in the low-AMR scenario generated by our economic simulations. As we will see in Part III, this figure represents thirty times the amount that is likely to be needed in annual investments to contain AMR worldwide.

Thus, the amount of extra health care expenditures in just this one year would suffice to finance all the investments in containment of AMR that are required between now and 2050. Spending $9 billion annually on veterinary and human public-health systems and the other measures required to contain AMR (see Part III) is already a justified expenditure, even if we consider only the cost savings that would be generated for the human health sector—completely ignoring the benefits that other sectors would obtain.

Investing a cumulative $0.1 trillion in AMR containment at a steady pace between now and 2030 would lower health care expenditures in that single year by as much as $0.22 trillion if the low-AMR case is avoided, and by as much as $0.7 trillion if the high-AMR case is avoided. And there would be savings every year before and after 2030.

If the low-AMR case is avoided, the cumulative savings on extra health care costs over the full projection period of our simulations would be $4 trillion. If the high-AMR case is avoided, that figure would reach $11 trillion.[3] If the health sector were to receive all the savings from the avoided extra health care costs, and if the sector were also to pay all of the investment costs of AMR containment, the sector would still enjoy a cumulative total net gain ranging between $3.8 trillion and $10.8 trillion. These substantial resources could be invested in improved health care.

Are these scenarios too optimistic? It is possible that even strong AMR containment efforts may not be fully successful. Let us assume a very poor outcome for illustrative purposes: just 10 percent success for the containment efforts deployed. In this case, the health sector could still provide resources for the total costs of containment and come out ahead. The health sector's net gain ranges between $0.2 trillion and $0.9 trillion, thanks to avoiding 10 percent of the low-AMR and high-AMR cases, respectively.

The magnitude of the health sector's expected benefits from AMR containment could be considered in prioritizing health sector expenditures. Indeed,

it would be sufficient to avoid just 3 percent of AMR impacts on health care expenditure in the high-AMR case to justify spending the full amount required for AMR containment. From the health care sector's perspective, spending on AMR containment is an insurance proposition on attractive terms: the expected annual payout is a high multiple of the annual premium. Containment of AMR emerges as a highly productive use of public funds to provide an essential public service for the benefit of humanity, and especially today's children and young people.

Our calculations confirm the substantial economic gains that can be obtained through strategic investments in AMR control today. We can recall the commonsense firefighting analogy. Buying a fire alarm and extinguishing a fire early are always more efficient ways to reduce risks than waiting for fire to engulf the neighborhood before taking measures to control it. AMR impacts on health are already occurring, and the associated costs will continue to grow in the future, if the world does not act to contain AMR. Delayed responses will inevitably be more costly.

Endnotes

1. The base case is the standard World Bank long-term projection for the global economy and excludes AMR from the model.
2. All absolute amounts from the simulations for this report are in constant 2007 US$ terms.
3. Both figures for health care cost savings represent the present values of extra health care expenditures in the simulations, cumulative total in 2017–2050, and using a 3.5 percent discount rate. Use of a discount rate ensures that later amounts have less weight in the total than earlier amounts. For instance, in the high-AMR case, the extra expenditure is $1.2 trillion in 2050. Because 2050 lies in a relatively distant future, the present value is calculated as $0.35 trillion, which is the amount that is included in the $11 trillion total.

Part III. What Will It Take to Contain AMR?

Part II quantified the damage that drug-resistant infections can be expected to inflict on global economic performance in the coming decades, if countries and the international community fail to counter the threat. The remainder of this report explains how we can avoid these grim scenarios.

We will argue that there are good reasons to believe threatened AMR devastation can be mitigated. More, we'll make the case that putting resources into AMR control will yield large net economic payoffs for all countries—and that the biggest winners may be in unexpected places.

To get started, Part III maps the broad outlines of an AMR containment agenda and analyzes its costs and benefits. The outcome is a compelling investment case for aggressive AMR policies. Then, in Part IV, we'll drill down on a series of specific practical issues for AMR action in countries.

A. Expert Consensus on Measures to Contain AMR

Some threats to global well-being and prosperity leave experts profoundly divided on how to respond. This is not the case with AMR. Thanks to sustained research, consultation, and advocacy by WHO, FAO, OIE, and other partners, a consensus exists among leading experts on the broad directions countries can adopt to build effective national AMR strategies. This consensus is captured in the Global Action Plan on AMR, whose five objectives are summarized in Figure 8 (WHO 2015a).

A Bold Agenda: Integrated Public-Health Protection in All Countries

Where should country action start? While national contexts and priorities differ, one fundamental point is applicable everywhere. AMR cannot be managed in isolation. Drug-resistant infectious diseases are a subset of the broader range of microbial threats to human and animal health and welfare. From a public-health and policy-making standpoint, drug-resistant infections have practical similarities to all infectious diseases with pandemic potential. The surveillance, diagnostic, and control capacities needed to deal with AMR are closely related to those required to control infectious diseases like Ebola and Zika. Instead of viewing AMR as a separate issue isolated from other health challenges, it will be more effective and less costly over time to build a common core of permanent capabilities in all countries for managing the full range of infectious threats.

FIGURE 8. The Five Objectives of the WHO Global Action Plan on AMR, 2015–19

Strengthen Knowledge and Evidence Base	Reduce the Incidence of Infection	Optimize Use of Antimicrobials	Improve Awareness and Understanding of AMR	Make Economic Case for Investment
❊ Develop an AMR surveillance system for: • health care facilities and community • animal husbandry and agriculture • using at least one reference lab ❊ Share information internationally ❊ Collect and share data on antimicrobial use (human/animal/agriculture) ❊ Consider an AMR research agenda, including: • responsible use • infection prevention • development of novel agents	❊ Implement and strengthen hygiene and infection prevention programs • make it part of health care and veterinary training • develop and implement standards of practice ❊ Test and report susceptibility of hospital-acquired infections (HAI) ❊ Implement prevention best practices in animal health and agriculture ❊ Promote vaccination of food animals	❊ Implement a comprehensive action plan with: • antibiotic access only through qualified individuals • only quality, safe and efficacious drugs authorized • reimbursement, promotion and treatment guidelines • laboratory capacity to guide optimal use • evidence-based stewardship programs • elimination of financial incentives to prescribe • effective and enforceable regulation • reduction/phasing out of non-therapeutic antibiotic use in agriculture	❊ Public communication targeting human and animal health audiences as well as schools and public media ❊ Establish AMR as element of professional education ❊ Elevate AMR to priority agenda across government	❊ Secure required financing for implementation ❊ Engage in international research collaboration—between developed and developing countries ❊ Public-private partnership ❊ New market models for investment and access

As AMR control is part of a wider agenda of infectious disease management, so the response to infectious diseases in turn depends on the robustness of countries' broader health systems. Competencies for the AMR fight can't be built independently of the health system's core capacities. Thus, the fundamental priority in AMR containment is to invest in human and veterinary public-health systems.

The dependence of AMR action on underlying health-systems capacities means there are no simple, quick-fix solutions to the AMR challenge. But the systems connection also has an upside. Many policies that countries may be considering, or already implementing, to strengthen their health systems and core infrastructure can be crafted so as to yield benefits for the AMR fight. This underscores that AMR can and must be addressed in two complementary ways.

AMR-Specific and AMR-Sensitive Measures

Policies and actions that work to contain drug-resistant infections are described as "AMR-specific" or "AMR-sensitive."

AMR-specific actions are those whose main purpose is to reduce AMR. For example, a key AMR-specific action is establishing and enforcing regulations to ensure people can only obtain antimicrobial medicines with a valid prescription. AMR-specific measures also include antibiotic stewardship programs, which are an effective, low-cost method to change behaviors that drive excessive use of antimicrobial drugs in medical facilities.

AMR-sensitive measures are those whose primary purpose is not AMR control, but which can be designed and delivered in such a way that they contribute indirectly to combating AMR. Improving access to clean water and sanitation, thereby reducing the spread of infections, is an important example. Vaccination of humans and livestock likewise reduces the incidence of infections and is AMR-sensitive.

Both AMR-specific and AMR-sensitive measures are vital to prevent and contain drug-resistant infections.

Can the World Afford AMR Control?

Table 1 presents an overview of the costs of key measures for AMR containment. The estimated global total is $9 billion annually. About half is for building core veterinary and human public-health capacities in low- and middle-income countries. In addition to its critical importance for controlling AMR, the capacity-building agenda will reduce the risks of pandemic infections of all types, increase preparedness, and enhance numerous facets of public health. Strengthening systems capacities in countries will improve human and animal health, food safety, food security, livestock keepers' livelihoods, economic growth, and resilience.

A recent example of the dramatic difference core public-health functions can make was provided by the arrival of an Ebola patient in Lagos, Nigeria, in August 2014. The patient came from Liberia, where the Ebola epidemic was advancing rapidly. The disease could have spread in the large, densely populated city of Lagos, just as it had in Liberia, with catastrophic consequences. However, Nigeria's public-health service was prepared, the infection was detected and addressed promptly, and a disaster was averted. The savings from the control of Ebola in Nigeria, through swift action at the source, were enormous.

B. Two Threats to AMR Containment

Public-health action to monitor and contain AMR is technically challenging. However, the two most serious threats to successful AMR containment are not technical or scientific. They are political.

The first of these two risks is that policy makers' support will not be sustained over the time span of future decades, which is the appropriate duration of efforts to contain the emergence and spread of AMR. Building up functional veterinary and human public-health systems takes time and perseverance. It is a marathon, not a sprint.

The second risk relates to the deeply ingrained historical divisions between institutions, professions, and capacities for human and veterinary public health. Human and veterinary health systems need to work together seamlessly to reduce health risks at the animal-human-environment interfaces. However, in most countries at the present time, pathogens still appear to cross these interfaces with far more ease than highly educated professionals and public-health organizations. The fault line between human and animal health systems offers uninterrupted opportunities for the emergence and spread of AMR.

TABLE 1. Cost of Measures to Minimize and Contain AMR

Interventions and Services to Implement the Global Action Plan on AMR (2015)	Best Available Cost Estimates, US$ Billion per Year	Approximate Share of Total Cost
Capacities required in low- and middle-income countries to contribute to AMR containment and to benefit from it		
Veterinary and human public-health systems in 139 LMICs (investment in capacity, operations, maintenance)	3.4	89%
Active management of "antimicrobial commons" for effective, efficient, and equitable access		
As a priority, implement preventative measures to avoid the need for health care and so reduce suffering and costs. For example, minimize spread of disease in health facilities and resultant harm to patients through: infection prevention and control (IPC) programs in all publicly funded health facilities; improved waste disposal; raising awareness of AMR risks; and other measures.	1.3	
Make better use of existing antimicrobials to extend their effectiveness in treating diseases in humans and livestock. Exercise antimicrobial stewardship; strengthen oversight over quality, trade, distribution, and sales, both for human use and use in animals. Roll out existing and new diagnostics and vaccines both for humans and livestock (initial average proportion 30:70)	2.0	
Global and Regional Interventions (Interventions with global primary objective, implemented in countries and at global and regional levels)		
Active management of "antimicrobial commons" for effective, efficient, and equitable access		
(a) Technical support to countries, development of shared standards and interoperable systems, and assessments of system performance; (b) Promoting development of new antimicrobials	0.3	11%
Global Innovation Fund supporting basic and non-commercial research in drugs, diagnostics, vaccines, and other tools	0.4	
Global public awareness campaigns	0.1	
Total	**7.5**	
Contingency (cost increases, additional measures, and similar needs)—20% of total	1.5	
Financing required	**9.0**	

Sources: Estimates of costs of global/regional interventions and in-country costs of diagnostics, vaccines, and active management of antimicrobials are from the final report of the U.K. Review on AMR (Review on Antimicrobial Resistance 2016). Estimates of cost of public-health system capacities in low- and middle-income countries are from World Bank (2012); best available estimates.

Because of the importance of these two threats to effective, long-term AMR containment in countries, we will take time to examine each.

Support for Human and Veterinary Public-Health Systems: Changing the Paradigm

The frustration and powerlessness that many policy makers feel when confronted with the challenges of AMR containment are primarily a reminder that public-health systems have been neglected for decades. What can motivate countries to reverse that pattern of neglect, and how can they start to take action?

Underlying this report is the conviction that decision makers who appreciate the true magnitude of economic stakes in AMR control will be motivated to reconsider prior assumptions about financing public-health systems. As we have seen, AMR containment and reducing pandemic risk will generate extraordinarily high economic returns. The lowest estimate of benefits from complete AMR containment in our economic simulations was $20 trillion. To obtain this benefit, governments need to invest only $0.2 trillion—much of it in public-health systems strengthening. As governments consider domestic spending priorities and possible contributions to international cooperation, they have reason to prioritize the highly productive investments in AMR containment and related health security objectives.

In the past, a barrier to meaningful action on health systems strengthening was that it was hard for policy makers to know where to start—that is, what was actually broken in the system and where priority efforts should focus. Today, robust health systems diagnostic and performance analyses are changing that. Consistent use of systems performance measures can incentivize governments to protect public health and safeguard their economies through developing core public-health systems capacity. Equally important, performance measures can provide decision makers with clear information on where systems are weak and what is needed to fix them. Measurement of system performance is gaining traction today through WHO's Monitoring and Evaluation Framework, launched in connection with the Global Health Security Agenda (GHSA), as well as through the OIE Performance of Veterinary Services (PVS) pathway.

To sustain the focus on strengthening systems over time, such independent assessments of national veterinary and human public-health systems must become a permanent cornerstone of the global public-health agenda. AMR containment will be much more likely to succeed if WHO and OIE are supported to expand their systems-performance evaluations to more countries, so that more governments and development actors can use the evaluation results to guide investment decisions.

Mitigating Risks of Inadequate and Unpredictable Financing

Financing modalities for AMR containment must be aligned to the characteristics of the effort that is required: global, multi-sectoral, long-term, with a predictable and adequate capacity, and with appropriate sharing of financial burdens. In particular, these funding mechanisms should not be based on short-term, voluntary contributions.

A long-term effort to finance capacity building for core veterinary and human public-health functions is required in all countries, especially low-income countries. This recognition could prompt a review of the global financing institutions that currently operate in the sectors involved (animal health, human health, environment, disaster risk management) to identify which institutions could be mandated to take the lead in financing systems-strengthening projects as a priority. These investments are needed for AMR containment, but also for pandemic risk reduction, compliance with International Health Regulations (IHR) and OIE standards, and the achievement of other national health and economic objectives.

Pragmatic modifications of the existing criteria for allocating multilateral concessional funds might be one strategy to increase incentives for country governments to make these investments, and for development-finance partners to support them. An example of how such incentives might look comes from recent efforts to accelerate concessionary lending for regional development, for example through the International Development Association (IDA), the World Bank Group's fund for the poorest countries. Novel incentive arrangements have successfully encouraged countries to implement collaborative regional projects, and some experts have recommended adapting these mechanisms to incentivize AMR and health-systems investments (Glassman *et al.* 2016). Such innovations may help secure durable financing channels for health-systems strengthening.

Multiple Gains from One-Health Models

The second structural threat to AMR containment is the failure to bridge divisions between human and animal public health. Where One-Health perspectives are not operationalized, competition for resources between human and veterinary health systems is inevitable. In most low-income countries, veterinary services have been losing those battles, both for domestic financing and in donor envelopes. With One-Health approaches, the world can better succeed in containing AMR, because veterinary public-health capacities will be built up; it is these capacities that are currently weakest and that engender the greatest risks of AMR and infectious pandemics.

The divide between the medical and veterinary domains is a historical, human-made AMR hazard. Since human populations have much more exposure to livestock and other animals in low-income countries than in high-income countries, the risks from lack of collaboration are especially high where the populations can least afford to cope with them. In addition, infectious diseases that originate in animals (zoonoses) are the main group of pandemic-potential diseases, provoking global risks to health, economies, and societies. Adding AMR to the reasons why One-Health approaches are needed should provide a strong supplemental incentive to the human-health sector to advance One-Health collaboration.

In addition to improving disease prevention and control, One-Health models may generate cost savings, as human and veterinary public-health services can share some functions and tools. For example, the One-Health approach is generating large savings in operating costs (estimated at 26 percent annually) at Canada's national laboratory; such efficiencies, as well as greater effectiveness, could be obtained elsewhere (see Annex 3).

C. International Cooperation

Since AMR does not respect borders, international cooperation is necessary to tackle the problem. Moreover, as we've seen, the impacts of AMR will fall disproportionately on low- and middle-income countries, causing increased poverty and global economic inequality. This threat demands a concerted global response.

AMR Containment and the Global Development Agenda

If AMR is not contained, the prospects for achievement of the Sustainable Development Goals for 2030 will diminish. Achievement of a number of goals is particularly at risk (Figure 9), including ending poverty, ending hunger, promoting healthy

FIGURE 9. Synergies and Tensions with Global Development Goals for 2030

Risk That AMR Will Hinder Progress Toward Goal (Substantial / Moderate)	Goal	Impact of Progress Toward Goal on AMR Containment (Substantial / Potential *)
Substantial	1 End poverty in all its forms everywhere	
Substantial	2 End hunger, achieve food security and improved nutrition and promote sustainable agriculture	Substantial
Substantial	3 Ensure healthy lives and promote well-being for all at all ages	Potential *
Moderate	5 Achieve gender equality and empower all women and girls	
	6 Ensure availability and sustainable management of water and sanitation for all	Substantial
	7 Ensure access to affordable, reliable, sustainable and modern energy for all	Potential *
Substantial	8 Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all	
Moderate	10 Reduce inequality within and among countries	Substantial
	11 Make cities and human settlements inclusive, safe, resilient and sustainable	Potential *
	15 Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss	Substantial
	16 Promote peaceful and inclusive societies, provide access to justice for all and build effective, accountable and inclusive institutions at all levels	Potential *
Substantial	17 Strengthen the means of implementation and revitalize the global partnership for sustainable development	Potential *

* = With AMR-sensitive approaches

Source for the list of SDGs: *Transforming our world: the 2030 Agenda for Sustainable Development.* Resolution adopted by the General Assembly on 25 September 2015 (A/70/L.1).

lives and well-being, and achieving sustained economic growth. Additionally, if the international community does not mobilize the resources required to contain AMR and enable all countries to comply with the International Health Regulations (IHR), we will have failed to reach the key goal of revitalizing global development partnerships.

While unchecked emergence and spread of AMR will impair progress on the global development agenda, there are also a number of entry points for advancing AMR containment within the Sustainable Development Goals framework. Some of these opportunities are indicated on the right side of Figure 9. We've noted, for example, that water supply and sanitation measures are AMR-sensitive. They help reduce infectious disease risks, limiting the need to deploy antimicrobials and so reinforcing AMR containment. Thus, AMR control is an additional argument for devoting resources to the water and sanitation goal. We will explore this link and its policy implications further in Part IV.

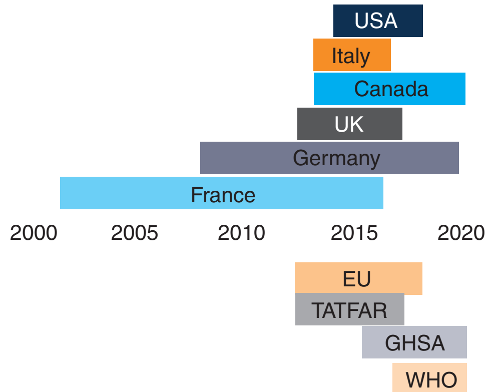
Another opportunity for synergy is in the pursuit of a revitalized global development partnership, which includes improving emergency and humanitarian responses. Such efforts can become AMR-sensitive if the balance of attention deliberately shifts to favor partnerships for prevention and preparedness. These examples are by no means exhaustive; there will be many additional opportunities in specific country contexts.

Organizing for International Collective Action

International cooperation depends on adequately funded international organizations. Existing multilateral agencies, including WHO, OIE, and FAO, have had to struggle with chronically insufficient funding. However, thanks to their continued efforts, there is growing cumulative experience in global collaboration to contain AMR. Such collaboration has progressed over nearly 20 years. A resolution adopted by the World Health Assembly in 1998 already urged countries to contain the use of antimicrobials and improve relevant legislation. Early WHO guidelines for containment of AMR were issued in 2001.

In Europe, the European Commission issued a comprehensive AMR action plan in 2011; subsequent activities in human health have emphasized surveillance systems, research, recommendations, and guidelines, as well as collaboration within and

FIGURE 10. National and International Plans to Tackle AMR: Year of Implementation and Duration



Source: Cecchini et al. (2015), p. 29.

beyond the European Union (EU).[1] The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) has engaged both Europe and the United States, while the Global Health Security Agenda (GHSA), launched in January 2014, now extends to more than 60 countries. These international initiatives and a number of country plans (which also have international components) are currently ongoing through 2017 (Figure 10).

This discussion reminds us that promising vehicles for cross-border collaboration on AMR have been established. However, delivery of needed actions on the ground has been uneven. International plans to contain AMR have foreseen measures for low- and middle-income countries, but financing and implementation capacities have not been sufficiently considered. These concerns were also neglected following adoption of the revised International Health Regulations (IHR) in 2005, with the result that, in a large number of countries, the public-health capacities that are needed for both IHR compliance and AMR containment have not yet been built. Even as we work to generate fresh momentum for coordinated global action on AMR, we must be clear that collective action can once again founder in the absence of strong international institutions and realistic arrangements to support progress in countries with limited resources.

Distribution of AMR Containment Benefits

Improved public-health governance and AMR containment can be seen as a single, joint challenge. Both can advance if at least three things happen: risk awareness, international leadership, and adequate, stable financing that shares cost burdens fairly.

Clarifying the distribution of economic benefits from AMR containment may help motivate high- and middle-income countries to increase their participation in the needed long-term financing efforts.

As shown in Part II, economic impacts from AMR (measured by percentage shortfalls of GDP relative to the base case) largely depend on the prevalence of infectious diseases and the labor intensity of production in a given country; both are generally higher in low-income countries than high-income countries. Thus, low-income countries will suffer the largest proportional shortfalls in GDP because of AMR impacts. However, absolute economic losses will be much higher in high-income countries, where workers affected by higher mortality and morbidity have much higher productivity and wages than workers in low-income countries.

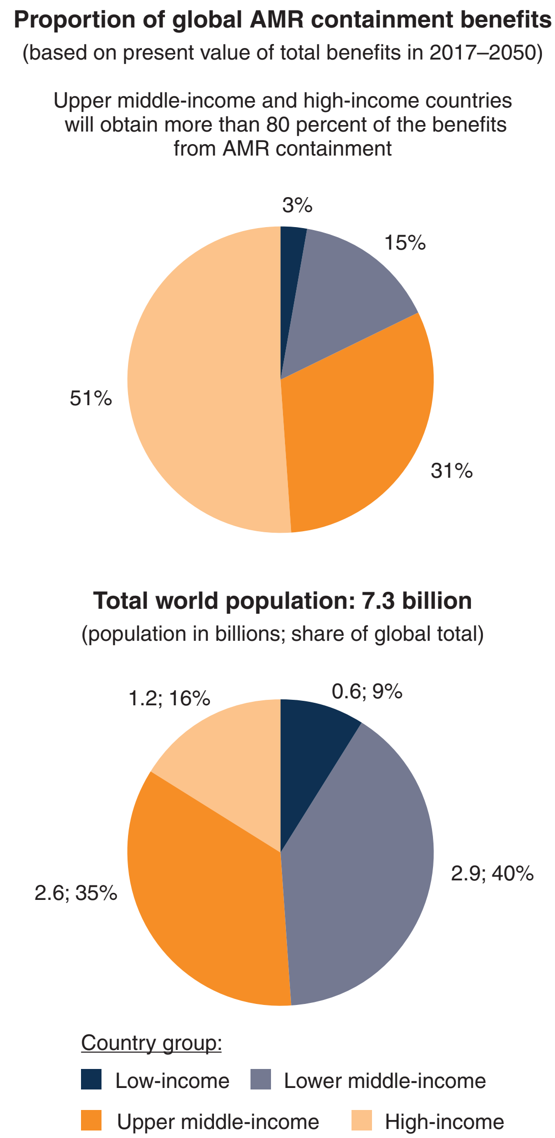
We clearly can't prescribe what shares different countries should bear in the investments needed to contain AMR. What we can do, however, is to underscore the magnitude of benefits expected from AMR containment and clarify the distribution of these benefits across countries. These results can inform deliberations on financing arrangements for AMR action.

If we use a discount rate of 3.5 percent and assume that containment efforts will succeed in reducing the economic costs of AMR by 50 percent, we find that high-income countries, with a population of 1.2 billion people, would obtain benefits ranging between $4 trillion and $14 trillion in the low-AMR and high-AMR scenarios, respectively. Even efforts that are only 10 percent successful would bring immense benefits to high-income countries: $0.9 trillion in the low-AMR scenario and $2.7 trillion in the high-AMR scenario.

For upper middle-income countries, which have a total population of 2.6 billion people, reducing AMR costs by half brings benefits of $3 trillion in the low-AMR scenario and $8 trillion in the high-AMR scenario. If AMR containment were only 10 percent successful, the benefits would be $0.6 trillion and $1.6 trillion, respectively.

Together, high-income and upper middle-income countries would obtain about 80 percent of the total global economic benefits from AMR containment (Figure 11). The expected benefits of even partial AMR containment are clearly far more than the total

FIGURE 11. High-Income and Upper Middle-Income Economies Stand to Benefit the Most from AMR Containment, Both in Absolute and per Capita Terms



cost of the measures that need to be implemented between now and 2050. Recall that the estimate of these costs is $9 billion annually. The present value of the cumulative cost of the measures during the simulation period is $0.2 trillion.

Importantly, the measures to be deployed have been developed by global experts and are based on settled science. They have been tested, and their effectiveness is known in most cases. Thus, we can be relatively confident that adequate investment in these measures and the underlying delivery systems will indeed yield economic rewards on the order our simulations describe. Nonetheless, should the control actions that experts have foreseen prove inadequate at first, and AMR continue to increase even as they are implemented, the magnitude of the expected benefits from AMR containment still offers a wide financial margin to develop and deploy additional measures.

In other words, the likely rewards of AMR containment are so great that countries could spend considerably more than is called for in our models and still come out well ahead. However, without spending $9 billion annually, no AMR containment will occur. High- and upper middle-income countries can then expect to suffer cumulative losses ranging from some $15 trillion (if the low-AMR scenario materializes) to $44 trillion (in the high-AMR scenario). Even a partial success in reducing these costs will require the world's leading countries and relevant financial institutions to make robust arrangements for investing $0.2 trillion in AMR containment over the coming 30 years.

The public-health capacities that would be developed to contain AMR have very large expected co-benefits. Global co-benefits include reduction of pandemic risk thanks to compliance with IHR and improved preparedness. The expected value of pandemic impact on the world economy has been estimated to be $60 billion annually (National Academy of Medicine 2016). By itself, this risk is so large that it also justifies substantial investments in strengthening veterinary and human public-health systems in low- and middle-income countries. In addition, however, there will be large national and regional co-benefits that will come from preventing and controlling disease outbreaks and from improving the quality of health care, thanks to better information on pathogens.

D. Economic Justification of Investments in AMR Containment

We have already begun to explore the impressive economic gains that countries and the international community are likely to derive from systematic, coordinated, global action on AMR. Now is the time to review these arguments, clarify key points, and summarize the investment case for tackling AMR as a national, regional, and global policy priority.

The bottom line is that investing in AMR containment is an exceptionally productive use of resources. For modest investments, accompanied by mandates for international organizations and sustained political support from world leaders, an enormous benefit can be had. Importantly, moreover, our estimate of this benefit is not derived subjectively, as in studies on valuation of life. Instead, our reckoning is based on economic impact simulations that use pure market valuations.

The economic payoff from containment will of course depend on what proportion of anticipated costs will be averted. The costs of AMR were calculated in the simulations as occurring every year between now and 2050, with trajectories of economic impacts as shown in the graphs in Part II. The undiscounted value of cumulative costs of AMR in the World Bank simulations is $120 trillion (in constant 2007 dollars) in the high-AMR scenario and $40 trillion in the low-AMR scenario. However, because the values arise in the coming 34 years, they must be discounted. Discounting of future costs is needed because people care less about getting a given benefit in 2040 than about getting it tomorrow. The higher the discount rate, the lower is the value today of amounts in the future. For example, the milestone report on the economic impacts of climate change by Sir Nicholas Stern (2007) used a discount rate of 1.4 percent. Table 2 reports the main outcomes of our AMR simulations, using the 1.4 percent discount rate as well as results with more conventional discount rates of 3.5 percent and 5.5 percent.

The results in Table 2 assume that 50 percent of the costs of AMR impacts can be averted. Success in reducing the costs of AMR will be possible only if action plans with measures reflecting expert consensus are implemented in all countries, by capable public-health authorities, and adjusted as needed based on performance and evidence. All this will cost money. Will these investments prove worthwhile, given competing uses for the resources?

Even when discounted, the values of the net benefits of AMR containment that reduces costs by 50 percent range from very large in the low-AMR scenario with a high discount rate ($5.8 trillion, discounted at 5.5 percent), to extremely large in the high-AMR scenario with a moderate discount ($26.8 trillion, discounted at 3.5 percent), to enormous ($42.2 trillion) in the high-AMR scenario when the 1.4 percent annual discount rate is adopted. By the test of positive net present value, the investments are unambiguously justified and should be financed as a priority.

There are, of course, uncertainties, including on the extent and pace of future AMR emergence and

TABLE 2. Cumulative Costs of AMR, Benefits of Containment, and Costs of Measures Cumulative to 2050, Present Discounted Values

Under Alternative Social Discount Rates, in $ Trillion (2007 Constant Dollars)				
	Social Discount Rate (Annual)			
	0%	1.4%	3.5%	5.5%
1. Costs (results of simulations)				
Low AMR-impact scenario	40	30	20	13
High AMR-impact scenario	120	85	54	36
2. Benefits if 50% of costs averted				
Low AMR-impact scenario	20	15	10	6
High AMR-impact scenario	60	42	27	18
3. Costs AMR action plan (Table 1)	0.3	0.3	0.2	0.2
4. Net benefits (2.–3.)				
Low AMR-impact scenario	19.7	14.7	9.8	5.8
High AMR-impact scenario	59.7	42.2	26.8	17.9

Source: Simulation results and authors' calculations, and Table 1.

spread, which pathogen-drug pairs may be affected (this is important for the impact on health), and, finally, how much containment may be possible. To examine whether the investment of $9 billion per year in AMR containment is worthwhile, sensitivity analysis was carried out on the expected rate of return (Table 3).

The assumptions were that no benefits from AMR containment would occur for the first seven years, while investment in containment would start in year 1 and continue to be made until 2050. The benefits of containment would thus occur only starting in year 8. Even under this conservative assumption (which reduces the rate of return considerably), the expected returns on investments in AMR containment are very high. For the most pessimistic outcome from containment efforts, where only 10 percent of the costs of AMR are avoided, the expected annual rate of return is 31 percent in the low-AMR scenario and 47 percent in the high-AMR scenario.

TABLE 3. Sensitivity of Expected Rate of Return to AMR Containment Success (Assuming $9 Billion Annual Investment in AMR Containment)

	Expected Annual Rate of Return
Low AMR-Impact Scenario	
10% containment achieved	31%
25% containment achieved	45%
50% containment achieved	58%
75% containment achieved	66%
High AMR-Impact Scenario	
10% containment achieved	47%
Reach low-AMR scenario	84%
75% containment achieved	88%

Source: Simulation results and authors' calculations.

All other combinations show even higher expected annual rates of return, up to 88 percent in the high-AMR scenario with containment of 75 percent. This analysis confirms that AMR containment is a "hard-to-resist" investment opportunity for the global community. Investment opportunities with such high expected economic returns are extremely rare in the public sector. The results of the analysis of net present values and expected rates of return are a compelling reason to reallocate resources away from less-productive investments toward the highly productive investments in containment of AMR.

E. Turning Evidence into Action

This part has described high-level priorities for action on AMR and clarified the investment case for AMR containment. We've presented strong arguments for countries at all levels of income to invest in the human and veterinary public-health systems that are the engines of the AMR fight. Wealthy countries have sound economic reasons to support these efforts in countries whose domestic resources are limited.

The measures we've discussed face implementation challenges. Knowledge gaps persist on how best to translate widely accepted policy principles into country-level results. In the next part, we'll summarize the findings from three special field studies commissioned for this report, whose purpose was to help bridge that knowledge gap. Drawing on the results of these studies and other research, we'll analyze specific pathways for country action to contain AMR.

Endnotes

1. EU agencies engaged in AMR collaboration have included the European Centre for Disease Prevention and Control (ECDC), the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), and the European Antimicrobial Resistance Surveillance Network. European actors have built AMR collaborations with non-European partner countries, including China and Russia.

Part IV. Directions for Country Action

The early parts of this report provided background on the crisis of drug-resistant infections and presented the investment case for an aggressive global response. Economic modeling exercises indicated the magnitude of losses that unchecked AMR will inflict on the global economy from 2017 to 2050. Over against these threatened losses, we calculated the approximate level of investment required for global AMR containment. Comparing costs and benefits confirmed that controlling AMR, even partially, will yield exceptional economic rewards. Bold action on AMR is justified on purely economic grounds, independent of the ethical and humanitarian arguments that are often in the forefront when the topic is discussed. Ethical perspectives are essential, but for many policy makers they may fail to clarify how AMR is different from other concerns that compete for attention and funds.

Our earlier discussion also sketched the broad outlines of containment strategies that countries may elect to implement, in line with the Global Action Plan on AMR. In this part, we will focus on three specific domains of country AMR strategies. While individual countries' approaches to tackling AMR will differ in many respects, all effective strategies will involve these three features: (a) laboratory-based AMR surveillance; (b) measures to improve the use of antimicrobial drugs in human health care; and (c) measures to rationalize the use of antimicrobials and contain AMR in livestock production.

Our discussion of these topics is based on three original research studies commissioned for this report. Each study aimed to: summarize the state of knowledge in its assigned field; identify key data gaps; report and analyze the results of original case studies in selected countries and/or regions; and offer evidence-based recommendations that technical experts and policy makers may consider in formulating and implementing national AMR plans.

The complete final reports for all three commissioned studies are included as annexes in this report (Annexes 8, 9, 10). Readers with special interest in the respective technical areas are encouraged to consult these annexes. Each represents a substantive contribution to its field. In this part, we briefly summarize the main findings and recommendations from the three special studies. At the end of the part, drawing on our special studies and other recent research, we present selected recommendations for countries committed to moving forward on AMR control. We focus our discussion of policy options in specific areas where the World Bank can add value to the sound recommendations provided by other recent reports.

Our studies are by no means a comprehensive treatment of the topics of AMR surveillance, use of antimicrobials in human health care, and use of antimicrobials in animals. Many important issues fall outside the scope of our field studies and of this part.[1] With their recognized limitations, we believe these original studies nonetheless contribute to a practical knowledge base countries can use to advance swiftly in AMR control.

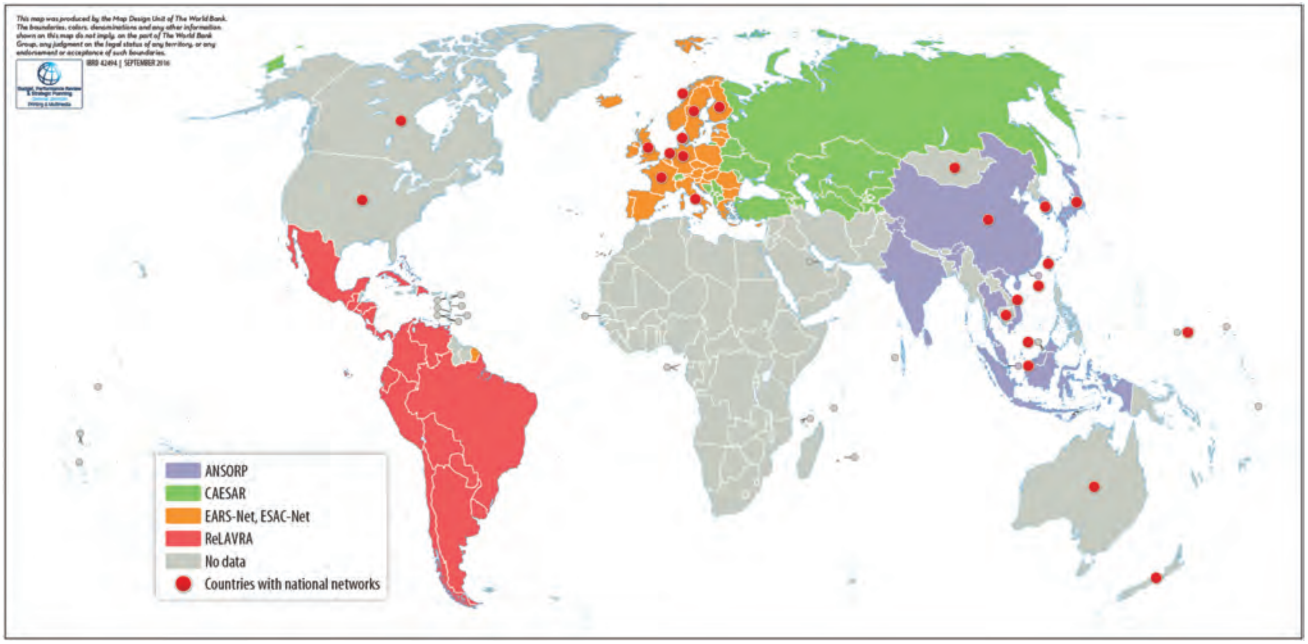
A. Laboratory-Based AMR Surveillance

We now turn to the first of our specific topics. Earlier parts of this report argued that AMR surveillance is an indispensable component of the response to a rising tide of antibiotic resistance worldwide. WHO recommends surveillance as part of every national AMR action plan. Here, we will discuss the status of AMR surveillance globally, the expected benefits and costs of AMR surveillance, the components of surveillance networks, and the main findings from a capacity assessment of laboratories supported under the World Bank-funded East Africa Public Health Laboratory Networking Project (EAPHLN). The assessment sought to document these laboratories' readiness to participate in national and, ultimately, regional AMR surveillance.[2]

Status of Global AMR Surveillance

In some regions, strong networks exist to track AMR among a broad set of pathogens, but there are major gaps in coverage (Figure 12). Currently, Europe and the Americas have the best surveillance coverage and Sub-Saharan Africa and South and Southeast Asia the least developed. Creating comprehensive, effective surveillance systems is more challenging in low- and middle-income countries due to weak laboratory and communications infrastructure; lack of trained laboratory and clinical personnel; and higher prevalence of counterfeit and substandard antibiotics and diagnostics (Dar *et al.* 2016; Opintan *et al.* 2015).

FIGURE 12. Global AMR Surveillance Networks



Benefits and Costs of AMR Surveillance

The broad benefits of AMR surveillance include improved availability of data and information on levels and patterns of resistance, and the opportunity to introduce evidence-based policies and interventions, which in turn contribute to reduced disease burden, lower treatment costs, and reduced mortality.

The cost of AMR surveillance *per se* will be a relatively modest add-on to existing laboratory costs, when built on an established national network of well-functioning clinical laboratories. The routine testing carried out by each laboratory forms the raw surveillance data. Apart from some additional quality control testing, no further laboratory analyses are required to support an AMR surveillance network. Supplemental costs are largely for information technology, data analysis capacity, personnel time and training, and software. Epidemiologic and general public-health expertise is also needed to interpret the data for public-policy use.

Currently, Kenya is in the process of constructing a national AMR surveillance network. Kenyan colleagues have provided the draft implementation plan and associated cost estimates as a reference for this report. Their network will initially include the National Public Health Laboratory (NPHL) and eight county or satellite laboratories.

Annex 5 outlines the incremental costs—beyond the laboratories' general operating budgets—to start and operate an AMR surveillance network in Kenya. Expenses include additional personnel to analyze data and consult on surveillance; training and strategic planning related to data collection and management; and equipment and supplies. The Kenyan team estimates that roughly $2.0 million are required to perform antimicrobial susceptibility testing at the NPHL and satellite laboratories, with the bulk representing running costs (see Annex 6). The $2.0 million are not part of AMR surveillance spending *per se,* since they fund the routine activities that the laboratories must conduct anyway, regardless of whether they engage in AMR surveillance work.

Based on current expenses in Kenya, establishing and running an AMR surveillance network with eight county or satellite laboratories will cost about $160,000 annually. Researchers believe that most low- and middle-income countries aiming to set up national AMR surveillance networks would initially plan for a size of operations similar to the proposed Kenya network.

Components of an AMR Surveillance Network

In general terms, how does a national AMR surveillance network actually operate, and what components does it need to include?

A laboratory-based AMR surveillance network is a partnership between clinicians, microbiology laboratories, and a central organizing body. Clinicians working in hospitals and other health facilities collect and send samples to clinical laboratories. In the laboratory, technicians culture the specimens, identify bacterial isolates, and test isolates for antimicrobial susceptibility. Antimicrobial susceptibility testing (AST) results are then transmitted back to clinicians, who use them in developing informed treatment plans for individual patients. Simultaneously, these same test results and the patient demographic information form the basis of laboratory-based AMR surveillance (Blomberg *et al.* 2004).

Surveillance data from laboratories can be aggregated for analysis on the local, national, and regional levels to identify resistance levels and trends. Data from multiple surveillance networks can also be combined to facilitate research, visualization, and mapping of global trends in resistance.

Critical components of laboratory-based AMR surveillance networks include capacity and proficiency for antibiotic susceptibility testing in the laboratories; infrastructure; instrumentation; availability of consumables; quality control measures; and the availability and skill level of personnel. In addition to the components of the network itself, countries need to have the capacity to actually use data generated by the laboratories for effective surveillance and response. This involves functions such as data management with specific software packages (including equipment and training), as well as centralized data analysis.

East Africa Public Health Laboratory Networking Project

The East Africa Public Health Laboratory Networking Project (EAPHLN) offers an example of a regional laboratory network that may soon be able to support AMR surveillance capabilities. The EAPHLN project was launched to tackle the historical neglect of public-health laboratories in the region. The $128.66 million project, approved by the World Bank in May 2010 with a recent extension to 2020, is establishing a network of efficient, high quality, accessible public-health laboratories in the East African Community (EAC) member states (Burundi, Kenya, Rwanda, Tanzania, and Uganda). The project is: (a) strengthening diagnostic and surveillance capacity; (b) expanding training and capacity building; and (c) supporting operational research.

The EAPHLN project has supported 32 laboratories in the participating countries in both capital cities and cross-border areas to become centers of excellence and increase access to laboratory services for poor and vulnerable populations (Figure 13). To date, the project's main achievements include:

- *State-of-the-art laboratories:* Renovated/constructed public-health laboratories; rolled out molecular technologies, including for diagnosis

FIGURE 13. Location of Satellite Laboratories

of drug-resistant tuberculosis, resulting in more rapid and accurate results.

- *Regional specialization:* Supported Uganda National Tuberculosis Reference Laboratory to be certified internationally and qualify as a WHO Supranational Reference Laboratory, signing agreements with 20 countries to provide specialized services.
- *Skilled human resources:* Trained over 10,000 health personnel in both short- and long-term courses; provided mentorship; recruited qualified personnel; and established an e-learning platform.
- *Technical and managerial innovations:* Introduced (a) joint annual peer audits, whereby countries assess each other's laboratories; (b) performance-based financing, whereby facilities receive incentive payments based on progress towards accreditation; and (c) cross-border disease surveillance, simulations, and investigations that have enabled swift responses to Ebola and Marburg outbreaks.
- *Operational research studies:* Conducted multi-country studies, including a study on drug resistance patterns to newly prescribed antibiotics to deal with key bacterial enteric pathogens, which found high levels of drug resistance at project-supported facilities.

Building on these initial achievements, and a strong track record of collaboration, stakeholders in East Africa have come together to explore the feasibility of using the project-supported facilities to introduce laboratory-based surveillance of antimicrobial resistance.

Findings from the EAPHLN Network Case Study and Capacity Assessment

A case study and capacity assessment of the EAPHLN were recently conducted by the Center for Disease Dynamics, Economics & Policy. The learning from this exercise will be useful to EAPHLN countries themselves, as they continue to work towards establishing functional laboratory-based AMR surveillance systems, and for other low- and middle-income countries that want to develop their own AMR surveillance capacities. Here, we have briefly summarized some of the study's main descriptive and analytic results.

Kenya, an EAPHLN country, is in the process of establishing its own national AMR surveillance system. Such systems are increasingly within the technical and financial reach of low- and middle-income countries. Kenya is sharing full documentation on its experience, so that other countries can learn from the process.

While Kenya's efforts are encouraging for all countries, it is clear that the creation of a laboratory-based AMR surveillance system faces substantial technical challenges in every setting, and particularly where capacities and resources have historically been limited. The study reports that one of the major stumbling blocks to AMR surveillance in the EAPHLN network countries concerns the specific issue of microbiology laboratory capacity. In these countries' laboratories, bacteriology capacity lags behind other services, a pattern likely repeated in other low- and middle-income settings.

Three key factors appear to contribute to the weakness in microbiology capacity within EAPHLN. The first is a lack of demand for microbiology-driven services from frontline clinicians, related to the length of time needed to get results (at least two days); lack of trust in results; and lack of laboratory capacity for blood cultures, which are needed for many of the most serious, life-threatening infections in the clinical setting.

The second factor concerns weak supply chains and frequent stock-outs, which constitute a major roadblock to routine antimicrobial susceptibility testing. Stock-outs disproportionately affect bacterial culture and antimicrobial susceptibility testing, which require that all essential components be immediately available when testing is needed.

A third key challenge is some administrators' failure to recognize that microbiology requires dedicated, trained personnel, leading some facilities and/or ministries of health to rotate staff too frequently.

Addressing these obstacles will be imperative, as EAPHLN countries move forward to implement national and regional laboratory-based AMR surveillance. The specific policy and implementation recommendations derived from EAPHLN case study findings are incorporated in the list of recommendations for country action at the end of this part.

B. Antimicrobial Use in Human Health Care and AMR

We now take up a second issue of central importance for countries planning practical action on AMR. This concerns the use of antimicrobial medications in human health care. This is the topic of the second major background study commissioned for this report.[3]

To generate new evidence on this issue, our researchers conducted a literature review and five field studies. The case studies were carried out in six low- and middle-income countries (Botswana, Croatia, Georgia, Ghana, Nicaragua, and Peru) from November 2015 to April 2016. The aim in each case was to identify factors in the health system that may contribute to AMR, along with possible interventions to promote more prudent use of antimicrobial agents.

Here, we briefly summarize the results of the five case studies. Action recommendations based on the findings are reflected at the end of this part.

Case Study 1—Antibiotic Market Offer

The first study reviewed the antimicrobials authorized by the ministry of health or equivalent agency in the participating countries to analyze drug approval, offers, and marketing processes. Objectives included documenting the presence of antimicrobials that do not have proven superiority over already marketed products—sometimes referred to as "me-too drugs." The market presence of such drugs tends to raise the cost of medicines and increase providers' and patients' exposure to promotional messaging that may spur irrational behavior and ultimately contribute to AMR. Researchers were also concerned to assess the market prevalence of fixed-dose combinations medications (FDCs) containing an antimicrobial agent. These drugs often create confusion among prescribers and patients and increase the risk of involuntary exposure to antimicrobials.

The study found significant differences in the six countries regarding the type and number of available antimicrobials. For example, Peru and Botswana have almost twice as many different antimicrobials on the market as Georgia, Nicaragua, or Croatia. The variability is explained in part by the high number of bio-equivalent drugs offered as different brand name drugs containing the same active ingredient (Figure 14), and also by the multiplicity of "me-too" or redundant medicines.

The proportion of brand names per individual antimicrobial varied significantly among countries, being lower in Croatia (3:1) and higher in Peru (7:1). A plethora of products with the same active ingredient causes confusion among prescribers and users, complicates therapeutic decision making, and gives more scope to misleading pharmaceutical promotion. There can be little clinical justification for having 27 products containing ceftriaxone in Georgia or 23 containing levofloxacin in Peru.

Case Study 2—Antibiotic Consumption in the Public Health System

The second study reviewed expenditure data in the public health system to analyze prescription and consumption processes at the national level.

The most-consumed antimicrobials differ among countries. In Botswana, Ghana, and Nicaragua, four to six different antimicrobials represented 90 percent of the total consumed units, while in Peru and

FIGURE 14. Top Five Active Ingredients According to Number of Brand Names

Country	1st (n)	2nd (n)	3rd (n)	4th (n)	5th (n)
Botswana	Amoxicillin (18)	Metronidazole (17)	Erythromycin (16)	Gentamycin (11)	Ciprofloxacin (11)
Croatia	Cefuroxime (14)	Azithromycin (10)	Ciprofloxacin (9)	Moxifloxacin (9)	Metronidazole (8)
Georgia	Ceftriaxone (27)	Azithromycin (27)	Chloramphenicol (15)	Amoxicillin (13)	Amikacin (10)
Ghana	Ciprofloxacin (38)	Cefuroxime (31)	Ceftriaxone (26)	Azithromycin (23)	Metronidazole (22)
Nicaragua	Ciprofloxacin (33)	Azithromycin (18)	Metronidazole (16)	Amoxicillin (14)	Clarithromycin (13)
Peru	Ciprofloxacin (69)	Azithromycin (43)	Amoxicillin (32)	Clarithromycin (28)	Levofloxacin (23)

Georgia, the same share of total consumed units was divided across 15 and 19 different antimicrobials, respectively. This finding suggests that in the first set of countries the public prescription of antimicrobials may be more tightly controlled (either by restricted drug lists or better adherence to drug guidelines).

Significantly, the list of the most-consumed antimicrobials in each country was dominated by antimicrobials that are sold under multiple different brand names.

Case Study 3—Antimicrobial Availability without Prescription

Researchers aimed to document dispensation and advice provided to self-referred patients by pharmacists in the six countries. To explore this issue, in each country, a young woman simulating lower urinary-tract infection symptoms visited 20–50 pharmacies.

The study is key, because pharmacists are the first point of contact with the health care system in many countries, and their dispensing practices for self-referred patients often determine how antimicrobials are actually used. In many low- and middle-income countries, pharmacists are the de facto prescribers of most drugs.

In more than 60 percent of pharmacy visits by the study's simulated patient, antimicrobials were dispensed without a prescription derived from appropriate clinical diagnosis. This pattern was highly prevalent in five out of six countries, with Croatia as a notable exception (only one dispensation in 20 visits). (See Figure 15.)

In more than 90 percent of the visits, the simulated self-referred patient was not clinically evaluated: for example, the pharmacist did not ask the patient about drug allergies. Such negligence can place patients at severe risk of developing drug-related complications.

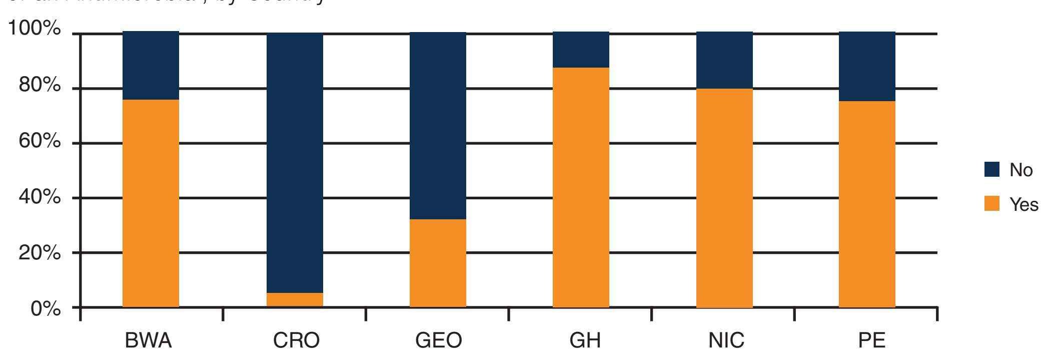
The pattern of antimicrobial recommendations by pharmacists in the different countries reflected the prevailing pharmaceutical market offer in each country. For example, irrational fixed-dose combinations with phenazopyridine were common in Peru and Nicaragua. Also, a relationship was observed between some "redundant" products and high sales (for example, cefuroxime with 31 brand names in Ghana accounted for 25 percent of sales).

Case Study 4—Hospital-Acquired Infections (HAIs)

Researchers reviewed medical records or information provided by health care professionals on patients with HAIs to analyze adherence to guidelines, compliance with prophylactic measures, prescription, and health care quality-assurance processes.

Health personnel identified a number of factors that appeared to contribute to HAIs. These included structural deficiencies, such as lack of safe water and basic sanitation systems, and operational problems, such as overcrowded wards, lack of cleaning supplies and protective equipment, or poor hand hygiene. Adherence to Infection Prevention and Control (IPC) protocols was partial overall, and sometimes poor. These findings underscore the need to address both structural factors and health care processes in efforts to reduce the spread of HAIs and resistant microorganisms.

FIGURE 15. Distribution of "Simulated Self-Referred Patient" Visits That Ended with Dispensation of an Antimicrobial, by Country



Case Study 5—Multidrug-Resistant Tuberculosis

To analyze factors influencing patients' compliance with treatment regimens, a review of the medical records of MDR-TB patients was conducted in one or more hospitals in each country. "Non-adherence to treatment" was frequently noted in these patients' records. Specific causes of withdrawal from treatment varied. For example, in Botswana, patients' inability to tolerate the prescribed medicines reportedly contributed to abandoning therapy in three out of ten cases. Findings from Peru also highlighted nonmedical drivers of noncompliance. Some patients quit therapy because they lived far from treatment facilities and could not afford the out-of-pocket transportation costs.

Countries Can Win the Battle

By providing new country-level data on antimicrobial use in human health, our study has underscored the complexities involved in attempting to contain AMR. However, some countries have already begun to confront antimicrobial-stewardship challenges systematically, with impressive results.

The responsibility for promoting rational use of antimicrobials clearly includes policy makers, pharmaceutical companies, health system administrators, and health care providers. But responsibility for protecting the efficacy of these crucial agents must also be shared by patients themselves and the wider public. A society-wide effort is required.

In countries where such an inclusive effort has been undertaken, remarkable gains have been achieved. A recent study of the experience in the Netherlands (Sheldon 2016) has confirmed that it is possible to reduce AMR to low levels across a national population. According to the study, success is determined by many of the factors we have discussed in this report: for example, coordination between the health and agricultural sectors, working together under a One-Health approach. Authorities have also deliberately worked to change the medical culture and public perceptions around antimicrobials. As a result, the study finds, Dutch primary care doctors are consistently parsimonious in prescribing antimicrobials, and Dutch patients do not routinely demand them, reflecting a shared culture of "cautious prescribing" built up over time. Part of creating this culture has been general practitioners' acceptance of strict professional guidance. Indications for use, type, and dosage of antimicrobials are issued by the College of General Practitioners (NHG), and these guidelines are increasingly followed. The Dutch experience also reflects a deliberate policy and operational decision to prioritize AMR control through sustained action on hospital infections.

The effective application of this array of measures has helped the Netherlands achieve one of the lowest levels of AMR in the world. A comprehensive national effort to reduce antimicrobial mis- and overuse and contain AMR can succeed.

C. Antimicrobial Use in Animals and AMR

We have just noted once again the importance for AMR containment of close collaboration between human and veterinary health systems. Without progress in tracking and controlling drug-resistant infection sources in animal populations, efforts to contain AMR in human communities cannot achieve lasting success. This section summarizes the results of a study commissioned for this report to document the use of antimicrobials in livestock and explore relevant policy strategies to combat AMR.[4]

The study included a literature review, country case studies, and a regional case study. Here, drawing on those inputs, we briefly outline the current state of knowledge on antimicrobial use in livestock. Then we analyze the mechanisms by which antimicrobial use in animal production systems may engender AMR in animals and humans. Finally, we review current strategies to reduce antimicrobial use in livestock and discuss the obstacles these efforts face. Specific policy options for low- and middle-income countries are presented in the final section of this part.

Use of Antimicrobials in Animal Production: Background

Antimicrobials are used to treat clinical and subclinical infectious diseases in animals. In some livestock production systems, they are also used to prevent diseases, either because of an increased risk of exposure (metaphylactic treatment) or as part of routine health management. In addition to these therapeutic uses, antimicrobials may be used as animal growth promoters, based on continuous delivery of subtherapeutic doses.

Estimates of total global antibiotic consumption in livestock vary widely, from around 63,000 to over 240,000 metric tons per year. With growing human populations and increasing demands for food, the quantities of antimicrobials used in livestock production are expected to rise steadily. Global consumption of antibiotics in agriculture is expected to increase by 67 percent from 2010 to 2030. Consumption in five major emerging economies—Brazil, China, India, Russia, and South Africa—could grow by 99 percent in the same period.

A number of medically important antibiotics are administered to animals in agriculture via feed or water. Out of the 27 different antimicrobial classes used as growth promoters in livestock, only nine classes are exclusively used in animals. Even some second-line antibiotics for humans are being used in animals.

Concerns in Low- and Middle-Income Countries

In most low- and middle-income countries, veterinary antimicrobials, including antibiotics, are sold over the counter without veterinary prescription. There are essentially no controls on the use of these agents. Most data sources do not specify whether antibiotics are used for growth promotion rather than treatment or prevention of diseases. As a result, it is difficult to track antimicrobial use, not only as regards quantities and classes, but also the species in which the drugs are used and the specific purposes of use.

Several studies suggest that AMR is already common in agricultural systems in low- and middle-income countries.

AMR Transmission Pathways

Resistant bacteria and genetic material conferring resistance in bacteria can be transmitted from animals to humans in multiple ways. Mainly this transfer occurs through the food chain, from close or direct contact with animals, and through the environment. Whether all three routes of transmission are equally important remains unclear. To date, public-health measures have tended to focus on the food system to ensure that food consumers are protected.

Transmission pathways other than food may be significant, however. A proportion of antibiotics used in food animals are excreted unmetabolized and enter sewage systems and water sources. Animal waste may contain resistant bacteria, and could also contain antibiotics that may foster the emergence of AMR in microbes living outside animals' bodies—including bacteria that may pose a greater risk to humans.

Measures to Reduce Antimicrobial Usage and Find Alternatives

Some countries have already banned the use of antibiotics for growth promotion. Banning this use in livestock has generally resulted in a substantial decrease in antibiotic resistance. Some countries have also enacted policies to limit the therapeutic use of antibiotics in livestock, with subsequent impact on AMR incidence.

Some argue that the sudden withdrawal of antibiotics as growth promoters in lower middle-income countries would have major negative consequences. However, European countries were able to impose a ban on the use of growth promoters without excessive, long-term negative impact on productivity, profitability, animal health, or welfare.

One response to AMR in animal production systems may be the development of new, alternative treatments that might partially replace antimicrobials. An overview of the current state of research in this area is included in Annex 10. At present, however, there is still a considerable efficacy gap between antibiotics and any proposed new alternatives (Cheng *et al.* 2014). We found no studies that assess the cost-effectiveness of such alternative interventions.

Knowledge Gaps Revealed by Country Case Studies

Our country case studies were conducted in four countries, ranging in per capita GDP from approximately $700 to $14,500 ($1700 to $22,000 PPP).

The main finding of the country case studies was a serious deficiency in data required to undertake economic analysis of antimicrobial use, AMR impacts, and the costs and benefits of alternative approaches. In all countries, obtaining data on antimicrobial manufacture, import/export, and usage was difficult. It was also problematic to achieve standardization and comparability among data that were available.

Country surveillance systems for AMR were poorly developed. There was no surveillance activity at all in the lowest-income country. It was striking that even countries that collect some AMR data in animal production settings were not willing to share the information, due perhaps to the concern that disclosure of worrisome AMR data might compromise export opportunities.

Given the extreme paucity of data now available, countries should be supported to establish the building blocks for future analyses as a matter of urgency. The most basic requirement would be standardized data collection on the use of antimicrobials and AMR. In this light, OIE's current effort to progressively develop a worldwide system for data collection on antimicrobial use in animals merits the strongest support.

Conclusions

Our research on antimicrobial use in livestock yields the following conclusions:

- **Improved estimates of the use of antimicrobials in animals are needed.** This could be delivered by the OIE data collection system in the future, and must be combined with an appropriate description of livestock production systems at country levels. These data are critical for AMR containment, which can only be undertaken with confidence if the estimates are adequate. This could be achieved by collaborative efforts to improve the World Animal Health Information System (WAHIS) at OIE and FAO Statistics (FAOSTAT) at FAO.
- **Major knowledge gaps must be addressed.** There are major difficulties in low- and middle-income countries in monitoring antimicrobial use and residues and in implementing AMR surveillance. A robust knowledge base would also encompass multi-method data and analysis on institutional environments and stakeholder behavior.
- **Economic arguments can demonstrate the benefits of strengthening human and veterinary public-health systems.** There is a critical need to reinforce these systems, and to do so will require the engagement of governments, private companies, and individuals involved in livestock production. All these actors are likely to be sensitive to economic arguments. Clarifying the economic case may help change attitudes and behaviors around the use of antimicrobials among key stakeholders.

D. Recommendations for Country Action

While global development institutions, NGOs, private firms, and other partners will have important roles in containing AMR, countries will lead the fight, and their engagement will determine its success. We now summarize the key recommendations for country AMR action that emerge from our special studies and related analyses.

The Global Action Plan on AMR, developed by WHO in collaboration with OIE and FAO, has established a durable, comprehensive framework for policy making and program implementation in the AMR fight (WHO 2015a). Our recommendations reflect the Global Action Plan's conceptual structure and key objectives.

Building on the Global Action Plan, several recent landmark reports have provided additional expert guidance on national policies and implementation approaches to tackle AMR. These publications include ambitious global strategies from OIE (2016) and FAO (2016), along with the background studies and final report from the U.K. Review on AMR, among others (Review on Antimicrobial Resistance 2016).[5] These documents have presented action agendas spanning multiple dimensions of the AMR fight.

These contributions make it unnecessary for us to "reinvent the wheel" here. For readers seeking a complete inventory of relevant policy domains and strategies, we suggest directly consulting these excellent sources. Here, we will concentrate on selected issues, where the World Bank's expertise enables us to present ideas that may advance and clarify options for country action, beyond what has already been exhaustively discussed elsewhere.

To implement the Global Action Plan and in particular to understand how it will be financed, it is useful to analyze policy options through a sectoral lens. Critical to effective implementation will be mobilizing AMR finance in a way that recognizes and draws on existing resources in different development sectors to support and expand AMR-sensitive interventions. Accordingly, our recommendations for country AMR action are structured by sector, including: (a) health; (b) agriculture; and (c) water, sanitation, and hygiene.

Driving AMR Progress from the Health Sector

The health sector offers numerous entry points for AMR control policies. Our recommendations focus on four select topics: (1) universal health coverage reforms as an enabling platform; (2) harnessing the International Health Regulations to accelerate AMR action; (3) strengthening laboratory-based surveillance, including through regional networks; and (4) the promise of the Global Antimicrobial Surveillance System (GLASS).

1. Universal health coverage (UHC) provides the best enabling framework to tackle AMR. Today, a large number of countries are undertaking UHC reforms, and UHC occupies a prominent place in the Sustainable Development Goals. The UHC agenda offers a launching platform to accelerate AMR action through multiple AMR-sensitive and some AMR-specific measures. UHC models are diverse, but UHC efforts will generally strengthen AMR containment through the following mechanisms:

- *Expanded coverage.* By definition, UHC designs lead to greater breadth and depth in the population coverage of health services. This includes services like vaccination, preventative care, and hygiene measures that lower the need for antimicrobials and thus slow the spread of AMR. Covering the whole population with vaccinations shows one potent way UHC will reduce the incidence of infections, advancing a key objective of the Global Action Plan on AMR.
- *Better oversight and quality of care.* UHC models improve oversight in care practice. Among other benefits, this helps ensure that antimicrobial use conforms to rational standards. UHC strengthens antibiotic stewardship in health facilities, reinforces the use of standard treatment protocols for infections, and can improve procurement, quality control, and other features of antimicrobial management—with the potential for major gains against AMR. These UHC features support another of the five Global Action Plan objectives: optimizing current antimicrobial use. With UHC, opportunities exist for substantial improvements in the control of major global diseases exacerbated by AMR, including HIV/AIDS, TB, and malaria.
- *Smarter, fairer financing.* The expansion of health systems towards UHC promises more efficient and equitable financing. This will help close existing access gaps for treatable infections. It will also promote better systems for the appropriate production, purchase, and prescription of antimicrobials. Pooled, prepayment financing encourages rational purchasing and prescription, supporting the optimization of antimicrobial use and protecting the efficacy of current drugs.
- *Better information.* UHC generally enables improved data collection and management within the health system: at the population, facility, and individual provider levels. By strengthening data systems, UHC approaches may better equip them to support AMR surveillance, monitoring, and response. By giving all people access to the health system, UHC also helps health authorities build a more comprehensive knowledge base on health patterns and trends across the population, which can inform efforts against AMR. All these features support the Global Action Plan objective to strengthen AMR knowledge and the evidence base.
- *Improved stewardship and governance.* A robust UHC approach builds systems-governance and coordination capacities that are critical for the AMR fight. Under a UHC model, governments can make better informed, more deliberate decisions about health investments, including in areas such as vaccination and infection prevention and control (IPC), that have direct implications for antimicrobial use levels and AMR. Moreover, under UHC models, regulatory capacities tend to be enhanced. Health facility accreditation provides just one example. Requirements for improved antimicrobial stewardship can be built into accreditation processes for hospitals and other care delivery sites to bolster AMR control at the facility level. AMR training can be incorporated into the preservice and in-service education of health providers, advancing the Global Action Plan objective to improve awareness and understanding of AMR.

With UHC, countries can strengthen AMR containment and expand access to needed antimicrobial treatments at the same time. Leaders from G77 nations and other countries, along with civil society voices, have argued that concerns about AMR must not be allowed to further obstruct poor and vulnerable populations' access to lifesaving medicines.

AMR containment is compatible with expanded access to appropriate antibiotics and other antimicrobial therapies for populations that have historically been excluded. UHC strategies promote rational, regulated access to antimicrobials for all patients under the guidance of trained health professionals. Thus, UHC provides a framework for simultaneously expanding the well-regulated use of antimicrobials where they have been lacking, and tackling the overuse and misuse that have accelerated AMR in other settings.

2. **Implementation of the International Health Regulations (IHR) can accelerate AMR action and focus global support.** Under the IHR, 196 countries have committed to work together to prevent, detect, report, and manage public health emergencies, such as infectious outbreaks. To meet their IHR implementation requirements, many countries are participating in systems-diagnostic and planning exercises, for example through the WHO Joint External Evaluation (JEE) process, under the Global Health Security Agenda (GHSA). International collaboration on the IHR acknowledges countries' profound interdependence in the face of infectious threats and other health emergencies that transcend borders, including AMR.

Systems evaluation exercises provide opportunities for countries to assess their capacities and needs in areas like infectious-disease and AMR surveillance. Through self-assessment and evaluation by external experts, countries diagnose system shortfalls and develop plans for strengthening capacity. Among other benefits, such efforts help lay foundations for the AMR Global Action Plan's five objectives, especially the first, strengthening knowledge and the AMR evidence base.

In order for these exercises to achieve full impact, it is important that each country designate institutions and individuals who will be accountable for following up on the evaluation results. The designated actors will define and lead a process to translate recommendations from the assessment into methodical action to build national surveillance and response capacity. Global partners, including the Tripartite agencies and the World Bank, will work with countries to design technically and politically realistic follow-up processes with clear lines of responsibility.

Because each country's implementation of IHR commitments benefits all other countries by improving detection and response to transborder threats, the international community has an interest in adequately financing this global good. Wealthy countries' stake in the success of the IHR may be leveraged to bolster financing for country capacity building and AMR action in settings where systems are weak.

3. **Countries at all levels of income can build laboratory capacities for AMR surveillance—and create synergistic regional laboratory networks.** Strengthening AMR surveillance capacities, including in low- and middle-income countries, is a cornerstone of AMR control, captured in the first objective of the Global Action Plan. Countries can accelerate the development of their domestic laboratory-based AMR surveillance capacities by participating in regional laboratory networks.

Our study of regional laboratory collaboration in East Africa suggests that the creation of a national AMR surveillance network is becoming technically feasible and affordable for an increasing number of low- and middle-income countries. Kenya, a member of the EAPHLN consortium, expects to operate its national AMR surveillance network at an added annual cost of approximately $160,000. (These are new costs for AMR-related activities, beyond the basic expenses involved in providing clinical laboratory services for patient care.) Many countries will want to consider such an investment in health security for their people.

The East Africa study also showed the benefits that can accrue when countries link their laboratory resources into a regional network structure. Numerous synergies may emerge, even or perhaps especially when countries create a regional collaborative structure early in the development of their national laboratory systems.

In the case of the EAPHLN network, evaluators found that the regional structure has promoted and disseminated innovations in service delivery, facilitated knowledge sharing among participating countries, and helped foster an evidence-based approach. Each member country takes the lead in a specific thematic area and provides regional leadership, generating knowledge and then disseminating experiences and lessons to partners. As described above, the network has promoted specific scientific and management innovations, including: (a) joint annual peer audits, in which countries assess each other's laboratories; (b) performance based financing, whereby facilities receive incentive payments based on progress against formal, internationally recognized accreditation standards; and (c) cross-border disease surveillance, simulations, and investigations that have fostered regional public-health collaboration and enabled an effective response to recent infectious outbreaks in the region.

The EAPHLN experiences suggest that early participation in a regional structure can accelerate the development of each country's laboratory capacities and lay the groundwork for future cross-border cooperation in AMR surveillance.

Questions persist about how to finance regional surveillance in the long run. The value of regional disease surveillance networks is indisputable. However, countries and partners are still seeking optimal financing models that would engage, for example, reliable national co-financing of these regional structures.

4. The Global Antimicrobial Surveillance System (GLASS) holds transformative potential. If regional laboratory networks are powerful, global knowledge sharing and collaboration may be even more so. WHO's leadership in launching the GLASS is a key advance in the global AMR fight. As countries develop national surveillance systems, many will seek participation in the GLASS in order to benefit maximally from added WHO support for AMR surveillance efforts.

Meanwhile, it is critical that member governments and donors support WHO's efforts in creating and managing the network, along with OIE's related work to build a global database on the use of antimicrobials in animals.

Options for Specific Actions

Our commissioned study on antimicrobial management in human health has generated additional specific recommendations for country action in major functional areas of the health system.

Health information and knowledge sharing: A systematic effort to collect data and generate evidence on antimicrobial use practices is required at the country level, to inform strategic action. Countries can harness a number of proven tools. For example, drug-utilization studies (DUS) can help identify failures in any link of the therapeutic chain. Designing and implementing DUS with the participation of frontline health professionals can identify antimicrobial management problems and contextually appropriate solutions in local settings.

At a higher level, countries may also consider the creation of national, regional, and/or global observatories of grey literature and local studies. These resources would fill a crucial knowledge gap. They would increase understanding of real-world practice in antimicrobial use and facilitate the design of pragmatic interventions.

Information, educational, and communications campaigns addressed to both health services personnel and the general population are another key strategy to improve understanding of the AMR challenge and rationalize antimicrobial use. Such campaigns should incorporate behavioral and social aspects.

Finally, countries should look to accelerate their transition to electronic recording of antimicrobial consumption data, and to electronic medical records. In addition to their other benefits, these tools will facilitate action on AMR.

Governance, regulation, enforcement: A range of regulatory and governance strategies are available to countries to counter AMR. For example, a separate legal and regulatory framework and payment/reimbursement modalities could be considered to promote appropriate use of antimicrobials. Such special arrangements already exist in the pharmaceutical sector for opioids. Whether or not this approach is favored, some countries may want to develop new legislation and regulations or revise and update existing rules governing antimicrobial distribution and use. This could include developing enforcement capacity to limit or eliminate perverse financial incentives that prompt individual providers and institutions to use antimicrobials indiscriminately.

Countries may act to strengthen political oversight of the antimicrobial market offer and dispensing practices. Two areas where priority adoption of oversight measures is likely to yield immediate benefits are: (a) limiting the market offer of fixed-dose combinations and (b) setting limits on the marketing of a single antimicrobial agent under multiple brand names. Progress in these two areas will help prevent confusion among providers, patients, and payers; improve therapeutic options and health outcomes; and reduce AMR.

Harm reduction from nonprescription sales of antimicrobials is another priority area for action. In almost all of the countries studied by our researchers, it was easy for simulated patients to obtain antimicrobials in pharmacies without a prescription. Training pharmacists on the risks of inappropriate dispensation while strictly enforcing regulations—including through fines and legal consequences—may help limit harm caused by the inappropriate sale and use of antimicrobials.

On this point, our recommendations rejoin those of the U.K. Review on AMR, which urged the adoption in all countries of robust regulations to prevent the over-the-counter sale of antibiotics and other antimicrobials. The U.K. authors rightly stress that such policies need to be locally tailored to recognize instances where over-the-counter sales may be some people's only means of accessing antimicrobials. Where this is the case, strengthening the formal health system to promote proper, clinician-led access is the long-term answer (Review on Antimicrobial Resistance 2016). Once again, we see the utility of framing AMR action at the country level in terms of UHC.

Proven optimization strategies: High-level political leadership can help generalize the application in hospitals and other health facilities of tools that we know work to get the best mileage out of existing antimicrobials, while protecting reserve medications for second-line use.

Antimicrobial Stewardship Programs (ASPs) have proven efficacy in controlling AMR by improving how antimicrobials are used in daily practice. These programs are especially effective in cutting down the unnecessary use of broad-spectrum antimicrobials in health care facilities—a powerful driver of resistance. The adoption of ASPs should be vigorously promoted, including in nonhospital health facilities.

Agriculture: A Critical Frontier for AMR

The bulk of antimicrobial use in many countries occurs in the agriculture sector, particularly in livestock. Worldwide, in 2010, livestock consumed at least 63,200 tons of antibiotics and probably far more, substantially exceeding total human consumption. Overuse and misuse of antimicrobials in animal production systems are major global drivers of AMR. Accordingly, the livestock sector, particularly in low- and middle-income countries, is a key battleground for AMR containment.

1. All countries can progressively reduce the use of antibiotics in animal production. Systematic reduction and eventual elimination of antibiotic use for livestock growth promotion is critical for long-term AMR control. This is a challenging goal, but it has drawn increasing consensus among scientific experts and many political leaders. At a 2016 AMR policy summit convened by the Wellcome Trust, for example, policy makers and scientists from 30 countries agreed that antibiotic use for growth promotion should be phased out worldwide, as has already been achieved in a number of countries (Wellcome Trust 2016). European Union countries have banned the use of antimicrobials as growth promoters since 2006.

Countries' specific contexts and constraints must be taken into account in designing plans and establishing timelines. Countries that currently rely heavily on the use of antibiotic growth-promoters may require more time and support to adapt their production regimes. Some low-income countries may benefit from extensive technical support.

Experts including the authors of the U.K. Review on AMR have recommended the use of national numerical targets to drive reductions in the excess use of antibiotics in agriculture. The U.K. Review authors propose 10-year targets, formulated in terms of total agricultural antibiotic use. They argue that, with the support of a global body of experts, most countries might be able to set targets as soon as 2018. Targets and milestones would be defined consistent with countries' economic and technical capacities. Interim milestones would be set to encourage progress on the way to the 10-year goal. U.K. Review researchers have explored how governments might use regulation, taxation, and subsidies for alternatives to lower antibiotic use. Many governments may choose to combine all three (Review on Antimicrobial Resistance 2016).

We support this approach. The use of time-bound, quantitative targets can be a powerful motivator. The World Bank Group is prepared to work with the full range of stakeholders who will be engaged in defining targets and setting strategies to reach them, including: country governments; the Tripartite agencies; farmers and private industry; civil society organizations; and donors.

Solutions for the livestock sector should foster the adaptability of animal productions systems to reduced use of antimicrobials. Recommendations call for an integrated approach, with cycles of innovation and learning: first, developing policies, setting targets, and monitoring antimicrobial use in livestock production; then identifying gaps or problems in current production systems and methods to address them; and finally sharing knowledge on improved management techniques.

We can protect farmers as antimicrobial practices change. Small farmers may be especially vulnerable as changes to established production methods are introduced. Governments and development partners have a fundamental responsibility to accompany small farmers in adapting their modes of animal production. Small farmers' livelihoods can be preserved, as we act to protect a global public good.

Policy action must also take account of global disparities in access to antimicrobials in the livestock sector, mirroring those in human health. The same drugs that may be used excessively in livestock production in some parts of the world remain unavailable in others, where they could have legitimate applications and save lives and livelihoods. This creates a dual problem of how to eliminate overuse and misuse of antimicrobials while providing responsible access to those who desperately need them, especially in low-income countries.

2. An urgent effort is needed to strengthen country surveillance systems for tracking the use of antimicrobials and the spread of AMR in animals. A consistent finding from country case studies commissioned for this report was a deficiency in data needed to analyze antimicrobial use in livestock, in terms of epidemiology and economic impacts.

Each country may commit to develop a system for collecting standard data on animal populations and animal production systems in its territory. Without the information such a system can provide, tracking progress on national targets for antibiotic use in agriculture, for example, will be virtually impossible. Countries should be supported to build basic data collection systems to track both the use of antimicrobials and AMR in animal production. Countries may also work to develop systems for monitoring antimicrobial residues in food originating from farmed terrestrial and aquatic animals. OIE's current effort to develop a worldwide system for data collection on antimicrobial use in animals merits strong support.

3. New partnerships can spur innovation against AMR across agriculture, the environmental sciences, and health. Scientists and policy makers increasingly recognize that unified strategies are needed to tackle the drivers of AMR simultaneously in livestock production, environmental management, and human health. But once we've acknowledged the problem, what do we do next? The proliferation of resistant pathogens is outpacing our knowledge and in particular our capacity to invent and disseminate solutions.

Research on new technologies to fight AMR is slowly gathering momentum. Yet the field remains under-resourced and fragmented. Clear, evidence-based, consensus directions for priority research have yet to be defined. International coordination and stewardship of AMR knowledge production are urgently needed. In particular, there is a need to inform and incentivize the global innovation agenda to target the points of highest priority and greatest opportunity for the development of new AMR-management technologies. This would include not only the discovery of new antibiotics, but also new vaccines (both animal and human), the new rapid-diagnostics agenda, and policy innovation in areas like compensation or insurance mechanisms for farmers who cut antibiotic use. Targeted learning and innovation in a broad range of sectors, from pharmacology to development finance, must be nurtured simultaneously.

How might this be done? We can point to promising precedents: innovative models of collaboration that have proven effective for other complex, multi-sectorial challenges. Some of these may be adapted to accelerate learning and action on AMR.

One example is CGIAR, a global consortium of agricultural research centers supported by an extensive network of partners, including the World Bank. For some 50 years, CGIAR has generated creative and practice-relevant research on food security, rural poverty reduction, and sustainable resource management. Today, to jumpstart new investment in AMR research and technological innovation, we can learn from CGIAR and other network models. We can picture the emergence of a networked research center that would be a novel hybrid—pursuing learning and innovation simultaneously in agriculture, animal health, and human health. To our knowledge, no such hybrid research hub currently exists. However, its feasibility could be explored with existing CGIAR network centers, other research consortiums, countries, donors, and other stakeholders. Through such partnership models, countries will tap into networks of innovation to multiply the impact of their individual actions against AMR.

Options for Specific Actions

Within the broad directions just sketched out, our background study has generated a series of specific options on antimicrobial use in livestock that countries may consider.

Health information and knowledge sharing. We've noted that each country has an interest in developing a standard data collection system to monitor animal populations and livestock production in its territory. Ultimately, many countries will move toward the creation of sample collection, testing, and data capture systems for national risk-based AMR surveillance in animal production.

Governance, regulation, enforcement. The legislative and regulatory sphere offers important levers for country action on antimicrobial use in livestock. Policy analysts may be tasked to examine existing legislation and implementation of public and private standards relating to antimicrobials, to identify weaknesses in the institutional environment. Legislators can then act to strengthen standards along the antimicrobial supply chain concerning registration, manufacture, distribution, sales, and use of these agents, particularly in agricultural contexts. Countries may also act to reinforce legislation and implementation applying to animal feed, in particular medicated feed.

Optimization strategies. A number of important options are on the table for countries to move towards optimizing antimicrobial use in livestock in the medium and long term. Some of these strategies will involve international cooperation in research, including implementation science.

For example, national governments and their technical agencies may undertake applied research to improve rapid diagnostic methods for veterinary diseases, which would reduce the use of antimicrobials by establishing the sensitivity of infectious agents to antimicrobials before treatment starts. Countries with the appropriate research capacities may also work to develop veterinary vaccines and vaccination strategies that will ultimately reduce reliance on antimicrobials.

In addition to bench science studies, countries may pursue implementation science research to solve the practical challenges of moving new vaccines and other technologies from the laboratory to actual use in livestock production settings. Tackling implementation challenges will involve overcoming multiple logistical, economic, technological, and systems-management obstacles, particularly in resource-constrained settings. As it comes on line, the hybrid human health-animal health research center on AMR described above may play a supportive role.

Countries may also choose to invest in strengthening veterinary education and the role of veterinary professional standards in governing antimicrobial use. Countries may use resources like the OIE Performance of Veterinary Services (PVS) pathway to identify gaps and training needs, and create strategies to fill them.

Water, Sanitation, and Hygiene: AMR-Sensitive Development Priorities

The most efficient way to deal with drug-resistant infections is to prevent them from happening in the first place. Historically, safe drinking water and sanitation facilities, along with basic hygiene practices such as hand washing with soap and water, were decisive in reducing the spread of infections, even before modern antimicrobials were invented. These tools and practices brought dramatic improvements in the health and productivity of human populations. In the age of AMR, such infection-prevention strategies once again take on salience.

The Global Action Plan has incorporated this principle. Reducing the incidence of infections is one of the five objectives. Two complementary facets of the preventative agenda involve: (1) expanding access to water and sanitation; and (2) universalizing basic hygiene practices, particularly in health care facilities.

1. **Countries can harness the power of water and sanitation investments to check infections, fight AMR, and support economic growth.** Expanding access to sanitation and clean water is among the most powerful AMR-sensitive investments available. Improved access to clean water and sanitation delivers robust public health benefits in its own right. In addition, by preventing infections and reducing the need for antibiotics, these measures also reduce the pressures that drive antimicrobial resistance (Wellcome Trust 2016). The combined health impacts translate into remarkable gains in life expectancy, which imply productivity and economic gains for countries, as well. As leaders weigh the costs and benefits of development investments, it is important to incorporate public health benefits, including AMR containment effects, in the expected gains from investing in water and sanitation.

2. **Hygiene in health facilities: simple tools, strong impacts.** The settings where water, sanitation, and hygiene practices can combine to powerfully impact AMR include health facilities. Infection prevention and control (IPC) strategies in health care settings are pillars of the AMR

containment agenda, recognized in the infection-prevention objective of the Global Action Plan. While infection prevention can be technologically sophisticated, its most important ingredients are simple, beginning with hand washing.

Hand hygiene (hand washing with soap and water or alcohol-based products) has been repeatedly cited as the single most important practice to reduce health care-associated infections. Improved hand hygiene practices have been associated with a sustained decrease in the incidence of AMR infections in health care settings (Rainey and Weinger 2016). This is an area in which relatively simple actions can bring powerful results against AMR.

Today, in many settings, and in countries at all income levels, these basic tools are not being rigorously applied. Field studies for this report confirm previous research in finding inconsistent and often poor observance of hand hygiene and other basic IPC practices in health facilities in many countries. While this is alarming, it also represents an opportunity for low-cost, high-yield action against AMR.

One of the best ways to prevent a return to the pre-antibiotic era is to practice hygiene in health facilities as if that return had already happened. WHO and UNICEF, working with their partners, have set out a global agenda for universal access to water, sanitation, and hygiene in health care facilities. Leadership and commitment from governments, international organizations, donors, and civil society can turn the plan into changes in practice and gains against AMR (Rainey and Weinger 2016).

This part has looked at three domains that will be central to country-led action on AMR: surveillance systems, the use of antimicrobials in the human health sector, and the use of antimicrobials in livestock. In each area, we have summarized key learning from a background study commissioned for this report. Drawing on our special studies and other sources, we have put forward selected recommendations for country action on AMR.

Our next and last part will review the major findings of this report and discuss how the World Bank Group will support countries in the AMR fight.

Endnotes

1. The special study on laboratory-based surveillance, for example, sought to analyze how to introduce AMR surveillance into an existing regional public-health laboratory network that is still being developed and includes five countries. Extending the analysis to include veterinary public-health laboratories was considered, but could not be accomplished in the time and with the resources available. Likewise, our investigation of antimicrobial use in human health care is limited to the pressing problem of misuse and overuse of antibiotics and does not consider other categories of antimicrobials. Finally, our field research on antimicrobial use in livestock did not deal with other agricultural subsectors, such as crops, that also use antimicrobials, nor did the investigators consider companion animals, which have been implicated as sources of drug-resistant infections in some settings.
2. For a detailed discussion and relevant references, see the full summary report, Annex 8.
3. The full summary report on this study is presented in Annex 9.
4. The full summary report is presented in Annex 10.
5. Some experts have set out to show in detail how successful AMR-control practices developed in high-income countries can be adapted by low- and middle-income countries. See for example: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G7/Best-Practices-Broschuere_G7.pdf

Part V. Conclusions

We conclude this report by reviewing our key arguments and highlighting actions the World Bank Group will take to support countries in the AMR fight.

A. The Costs of Inaction

This report has attempted to shift the conversation on drug-resistant infections from health impacts on patients and populations to the threat that AMR poses to economies. Our main aim has been to put a price tag on the damage AMR may inflict on global economic output in the coming decades.

World Bank economic simulations suggest that failure to contain AMR could result in substantial losses to the global economy between now and 2050. In an optimistic scenario of comparatively low impacts, unchecked AMR will likely reduce annual global GDP by 1.1 percent by 2050. In the case of high AMR impacts, by 2050, drug-resistant infections may cut annual global GDP by 3.8 percent.

Thus, the reductions in annual global GDP due to AMR may be comparable to the losses caused by the 2008–09 financial crisis. Except that, instead of resolving after a couple of hard years, the economic damage inflicted by unchecked AMR would continue for decades, with low-income countries suffering the worst effects.

B. The Rewards of Leadership

The threat AMR poses to the global economy and to global shared prosperity also means, however, that timely investment in AMR control can bring extraordinary rewards. Putting funds into AMR control is likely to be among the highest-yield investments that countries and partners can make today. Assuming that 50 percent of AMR costs can be avoided by robust containment efforts from 2017 to 2050, AMR investments of just $0.2 trillion will bring cumulative global benefits between $10 trillion and $27 trillion during this period. Rates of return on AMR control investments through 2050 may range from 31 percent annually (if only 10 percent of AMR costs can be mitigated) to as much as 88 percent annually (if 75 percent of AMR costs are avoided).

Middle-income and high-income countries will derive the largest economic rewards, in absolute and per-capita terms, from successful AMR containment. To obtain these gains, wealthier nations will need to support other countries' AMR efforts, in addition to strengthening surveillance and response systems within their own borders. All countries will need to mobilize political will and invest resources.

C. Action at Country Level

The Global Action Plan on AMR, developed by WHO in collaboration with FAO and OIE, provides a comprehensive high-level framework for tackling the AMR threat. Taking the Global Action Plan as a guiding framework, this report has aimed to deepen knowledge on select topics that can help countries set policy priorities on AMR.

As a foundational point, we have emphasized that AMR cannot be managed in isolation. Drug-resistant infectious diseases are one part of a broad range of microbial threats to human and animal health. The most efficient and cost-effective answer to AMR is to build a core of permanent infectious-disease surveillance and management capabilities in all countries, integrated within functioning human and veterinary health systems. The bulk of AMR expenditures called for in this report are directed to that purpose.

We have proposed specific policy recommendations for countries in health, agriculture, and the water and sanitation sector. In health, we have argued that universal health coverage (UHC) models provide a comprehensive enabling platform for action against AMR. By implementing UHC reforms, countries will accelerate gains against AMR through multiple channels, generally including better health information, more effective prevention of infections, and more robust antimicrobial stewardship. Countries' efforts to implement the International Health Regulations (IHR) on public health emergency preparedness also provide an opportunity to accelerate AMR action and harness financing and technical support for AMR progress.

In agriculture, all countries can take steps to progressively reduce antimicrobial use in livestock production. Limiting the use of antibiotics as growth promoters is the first step. To guide progress and document results, countries need robust monitoring systems that can track the use of antimicrobials and the spread of AMR in the livestock sector. Wealthy countries and development partners have an interest in supporting low- and middle-income countries to build such surveillance capacities.

Country action in the water, sanitation, and hygiene sector will contribute to the Global Action Plan objective of reducing infections—thus lowering antimicrobial demand and slowing AMR. Governments weighing spending options in cost-benefit terms should incorporate public-health benefits, including AMR containment, in the expected rewards from investment in water and sanitation.

Partnerships Build Power

Managing the AMR threat will require engagement from multiple sectors and stakeholders, under national government leadership. The strongest strategies will involve the business sector, civil society organizations, multilateral agencies, private philanthropies, and research institutions. For example, partnerships among government, development partners, researchers, and farmers' groups will be needed to protect the livelihoods of livestock producers in low- and middle-income countries, as farmers cut antibiotic use and transition to more sustainable production models.

Support from Multilateral Organizations

AMR control demands coordinated action across national borders. Country efforts can be strengthened by capable and adequately resourced multilateral agencies. Multilateral organizations mobilize international attention, facilitate knowledge sharing, provide technical advice and standards, and catalyze action across sectors. International agencies can sustain political leadership and support long-term capacity development during the inevitable periods when national policy makers turn to other issues, and AMR containment risks losing ground.

The One Health Tripartite agencies—WHO, OIE, and FAO—have provided this leadership continuity over decades. Today's growing global awareness and momentum for action on AMR are substantially the fruit of their efforts. These agencies must be mandated and resourced to pursue their AMR leadership. Other multilateral agencies will also contribute to the AMR fight. The multilateral development banks, for example, have financing, convening power, and technical capacity to support country AMR efforts.

D. What Will the World Bank Group Do?

The agenda for AMR action outlined in this report implies responsibilities for the World Bank Group. Our task is to support countries and partners in implementing the Global Action Plan on AMR and the AMR agenda adopted by the United Nations General Assembly in September 2016. The World Bank Group will support the One Health Tripartite's global leadership on AMR containment and related health security agendas. The World Bank Group will also take specific actions to support country progress on AMR.

Creating a Global Investment Framework for AMR Action

Thanks to the Global Action Plan and the efforts of many partners, substantial consensus exists on the types of policies and interventions needed to fight AMR. Moreover, work by others and research for this report provide a reasonable idea of how much AMR containment will cost. The sums are modest by global investment standards and the likely rewards exceptionally high. But the money still has to be put on the table.

The World Bank Group will work with countries and partners to develop an investment framework to deliver the objectives of the Global Action Plan on AMR. The framework will include rigorous costing of priority AMR interventions at country, regional, and global levels. Costed plans for AMR will be integrated with broader country agendas for emergency preparedness, response, and resilience, which are gaining momentum today through the WHO Monitoring and Evaluation Framework, the OIE Performance of Veterinary Services (PVS) pathway, and other mechanisms.

The AMR investment framework will be informed by the results of the International Working Group on Financing of Preparedness, whose research is currently in progress, and by experience with the Pandemic Emergency Financing Facility (PEF), created under World Bank leadership following the 2015 Ebola outbreak in Western Africa. In keeping with the principle that AMR is not an isolated phenomenon that can be addressed with one-off measures, the investment framework will emphasize integration of AMR activities and funding into broader health and development finance mechanisms that will be sustainable over time.

In laying foundations for the global investment framework, World Bank experts will work at country level with policy makers and technical colleagues to develop national AMR financing assessments, aligned with countries' AMR National Action Plans (NAPs). Country financing assessments will identify national priorities, needs, gaps, and best-value interventions. Country assessments will explore resource mobilization options, looking across sectors and including public and private sources. Teams preparing the studies will analyze the best uses of donor assistance and plan how to sustain financing into the future.

The global AMR investment framework will then incorporate the results of country planning and costing exercises to develop a comprehensive instrument that can map and quantify needs worldwide and coordinate global investments in AMR action. The framework will be a decision tool for policy makers, planners, development finance institutions, donors, and other partners in the AMR effort, helping ensure that AMR finance flows to where it is most needed and achieves the greatest impact.

We consider the creation of a global AMR investment framework as a key step towards the realization of the Global Action Plan and as a logical follow-up to the September 2016 UNGA special session. The World Bank will deliver an initial version of the AMR investment framework by the time of the official AMR progress report to the General Assembly in September 2019.

One way for countries to rapidly boost the impact of their infection-control and AMR investments is to participate in a formal systems-diagnostic exercise like WHO's Joint External Evaluations (JEE) or the OIE PVS pathway. These evaluations show promise to yield substantial gains in systems performance—if countries act on the findings. Multilateral organizations and bilateral health and development agencies like WHO, OIE, and the U.S. CDC are supporting countries in the technical phase of the evaluations. The World Bank will reinforce its work with countries to ensure that costed plans are developed to fill the needs that evaluation teams detect, and that appropriate financing sources are identified to turn plans into action.

An AMR Lens on Development Finance

The World Bank Group will review its own investment lending policies and instruments to support the AMR agenda across relevant sectors. We will also strengthen our institutional capacity on the ground in technical areas that can optimize our services to countries as they advance national AMR agendas.

We've seen some of the technical sectors that can contribute to the AMR fight through AMR-specific and AMR-sensitive interventions. Relevant sectors for World Bank Group investing include, but are not limited to, agriculture; water and sanitation; and urban development; in addition to the health, nutrition, and population sector itself. As the Bank Group weighs investment options in dialog with country leaders and partners, we will apply an AMR lens to identify those projects that hold promise for AMR-sensitive impacts. We will design projects to maximize these impacts.

The World Bank Group will also progressively incorporate AMR-related gains into the calculations used when assessing likely costs and benefits of projects competing for support. Over time, the systematic inclusion of an AMR perspective in investment conversations with countries may evolve towards the creation of a formal screening instrument similar to the World Bank's existing mandatory Climate and Disaster Risk Screening tools. Along with its other utilities, an AMR screening tool would help identify regional and global spillover benefits.

Mobilizing Finance for AMR Innovation across Agriculture and Health

Investment in the AMR knowledge agenda must nurture new technologies in both animal and human health. It should also create connections and harness synergies between the two. To foster this kind of innovation, the World Bank will seek to engage existing multidisciplinary research networks, donors, and other partners around the idea of a combined animal and human health research center on AMR. Promising conversations have begun, and may shortly advance to a detailed feasibility study. The effort may develop as a multifaceted collaboration, along the lines of the successful Coalition for Epidemic Preparedness Innovations (CEPI).

Bringing the Private Sector on Board

The private sector can contribute substantially to tackling AMR, and private-sector capacities and creativity in this area are only just beginning to be tapped. The World Bank Group's ability to engage national and global business actors is a strong comparative advantage.

The International Finance Corporation (IFC) is the arm of the Bank Group that invests in and advises private-sector companies. IFC is active in the animal protein sector through investment and advisory work. In engagement with its clients in animal production, IFC reviews operational practices and provides benchmarking for clients on good industry practices, including the use of veterinary services and antibiotics. IFC will seek to deepen this partnership by developing a more focused advisory offering as part of its animal protein advisory platform. Where government regulations evolve towards a more focused use of antibiotics, IFC will seek to partner with private producers and their associations to support the transition of the sector through management practices and investment.

IFC is also active in the private health care sector, mainly through the support of health service providers and companies that manufacture or distribute affordable pharmaceuticals or medical devices. IFC has developed a Quality Assessment Tool used to assess health service companies on various clinical governance and patient safety criteria. IFC plans to enhance this tool and, in the process, incorporate best practices for implementing policies, protocols, and training around antimicrobial drug use.

A clear opportunity for private-sector engagement in the AMR challenge is for pharmaceutical and biotech firms to pursue development of new antimicrobials and related technologies, such as rapid diagnostic tests that could inform antimicrobial prescription decisions at the point of care. The complex topic of antimicrobial drug development is well analyzed elsewhere. Here, we note only that the World Bank Group and other development finance institutions might play a role in creating fresh incentives for pharmaceutical companies to engage in antimicrobial research. One approach is "delinking" company profits for any new antimicrobial product from the actual sales volumes, through a number of possible mechanisms. Country policy makers, in particular among the G77, have pressed for the implementation of delinking strategies.

Leveraging UHC Reforms to Reach AMR Objectives

In the World Bank's health sector practice, action on AMR containment will mesh with ongoing work programs on (1) health systems strengthening through UHC reforms, and (2) emergency preparedness and resilience.

Many countries are currently carrying forward ambitious UHC reforms with World Bank support, and more are poised to adopt UHC goals. As suggested above, countries' commitment to implement UHC provides multiple opportunities to reinforce AMR containment. The World Bank will work through its policy dialog and technical collaboration around UHC to support countries in leveraging health systems reforms to accelerate progress against AMR. Mechanisms include: universal vaccination coverage to reduce the demand for antimicrobials; improved antibiotic stewardship in hospitals and other health care settings; strengthened IPC practices in health facilities; more rigorous "gating" to ensure that people obtain antimicrobials only with a prescription and take them under the guidance of a qualified health professional; and better health information.

AMR and Resilient Health Systems: The Agendas Converge

The World Bank's large work program of studies and policy dialogue with countries on health systems financing has been under way for over two decades. In the past, this work has not systematically included costing of investments in core public-health functions or analyses of their relative priority. Currently, however, the World Bank is financing improvements of core public-health functions in multiple countries, notably for disease surveillance and laboratory strengthening. Such investments were also part of the Bank's contribution to the emergency response to recent avian and pandemic flu threats. These promising investments mark a new direction—spurred by a wide consensus on the need to strengthen global health security and reinforce collective preparedness.

AMR is part of a wider spectrum of infectious threats that generate outbreaks with epidemic and pandemic potential. Thus, the AMR and health emergency preparedness agendas are deeply intertwined. Multiple opportunities for synergy exist between the AMR agenda as set out in the Global Action Plan and the World Bank's expanding work with countries and partner organizations on emergency preparedness, response, and resilience.

As the World Bank develops and transforms its health systems work to encompass greater emphasis on emergency preparedness and systems resilience, in answer to country demand, the Bank is helping countries build stronger capacities for public-health functions, such as infectious disease and outbreak surveillance. This in turn nurtures many of the same capacities needed to detect, track, and manage AMR. The consolidation of core human and animal public-health capacities; the creation of health systems resilient to emergencies; and the AMR fight reflect largely convergent and mutually reinforcing agendas. The World Bank will act to help countries capitalize on these potential synergies.

Action Today—To Preserve Tomorrow

Because the benefits of AMR containment are distributed among all individuals and all countries, as well as across present and future generations, leadership by the world's public authorities—international organizations and above all national governments—is indispensable to overcome inertia, free-rider behaviors, and the other governance shortcomings that threaten public goods. The World Bank Group will contribute to the collective effort. Countries will make AMR containment real.

Those who will benefit most do not have a voice. Many of them have not yet been born. We, however, have the knowledge, the means, and the opportunity to act in their interest. AMR is indeed a threat to our economic future, but above all to the future of our children. Bold action today can safeguard the health and prosperity of those who will come after us.

Annex 1. September 2016 Political Declaration of the United Nations General Assembly on Antimicrobial Resistance, and Statements to the General Assembly by the WHO and OIE Directors-General

Political Declaration of the UN General Assembly on Antimicrobial Resistance

We, Heads of State and Government and representatives of States and Governments, meeting at United Nations Headquarters in New York on 21 September 2016, in accordance with General Assembly resolution 70/183, in which the Assembly decided to hold a high-level meeting in 2016 on antimicrobial resistance:

1. Reaffirm that the blueprint for tackling antimicrobial resistance is the World Health Organization global action plan on antimicrobial resistance and its five overarching strategic objectives developed by the World Health Organization in collaboration with, and subsequently adopted by, the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health;
2. Also reaffirm that the 2030 Agenda for Sustainable Development offers a framework to ensure healthy lives, and recall commitments to fight malaria, HIV/AIDS, tuberculosis, hepatitis, the Ebola virus disease and other communicable diseases and epidemics, including by addressing growing antimicrobial resistance and neglected diseases affecting developing countries in particular, while reiterating that antimicrobial resistance challenges the sustainability and effectiveness of the public health response to these and other diseases as well as gains in health and development and the attainment of the 2030 Agenda;
3. Acknowledge that the resistance of bacterial, viral, parasitic and fungal microorganisms to antimicrobial medicines that were previously effective for treatment of infections is mainly due to: the inappropriate use of antimicrobial medicines in the public health, animal, food, agriculture and aquaculture sectors; lack of access to health services, including to diagnostics and laboratory capacity; and antimicrobial residues into soil, crops and water: within the broader context of antimicrobial resistance, resistance to antibiotics, which are not like other medicines, including medicines for the treatment of tuberculosis, is the greatest and most urgent global risk, requiring increased attention and coherence at the international, national and regional levels;
4. Also acknowledge that, due to antimicrobial resistance, many achievements of the twentieth century are being gravely challenged, in particular: the reduction in illness and death from infectious diseases achieved through social and economic development; access to health services and to quality, safe, efficacious and affordable medicines; hygiene, safe water and sanitation; disease prevention in community and health-care settings, including immunization; nutrition and healthy food; improvements in human and veterinary medicine; and the introduction of new antimicrobial and other medicines;
5. Recognize that the above achievements are now gravely challenged by antimicrobial resistance, including: the development of resilient health systems and progress towards the goal of universal health coverage; treatment options for HIV and sexually transmitted infections, tuberculosis and malaria, as well as other infections acquired in community and health care settings; gains in infection prevention and control in community and health care settings; advances in agriculture and animal husbandry that help to ensure that the quality of food is preserved; and prevention and treatment options for infectious diseases in veterinary medicine;
6. Also recognize that, due to antimicrobial resistance, there will be fewer options for the protection of people most vulnerable to serious life-threatening infections, especially women giving birth, newborns, patients with certain chronic diseases or those undergoing chemotherapy or surgery;
7. Note with concern that the fulfilment of the right to the enjoyment of the highest attainable standard of physical and mental health, as well as access for millions of people to health services and to quality, safe, efficacious and affordable antimicrobial medicines, food, clean water and a healthy environment, remain a distant goal, especially in developing countries;
8. Also note with concern that while the current lack of access to health services and access to antimicrobial medicines in developing countries contributes to more deaths than antimicrobial resistance, without an effective One Health approach and other multi-sectoral cooperation and actions, antimicrobial resistance is projected to cause millions of deaths worldwide, with massive social, economic and global public health repercussions;

9. Recognize that the keys to tackling antimicrobial resistance are: the prevention and control of infections in humans and animals, including immunization, monitoring and surveillance of antimicrobial resistance; sanitation, safe and clean water and healthy environments; investing in strong health systems capable of providing universal health coverage; promoting access to existing and new quality safe, efficacious and affordable antimicrobial medicines based, where available, on diagnostic tests; sustained research and development for new antimicrobial and alternative medicines; rapid diagnostic tests, vaccines and other important technologies, interventions and therapies; promoting affordable and accessible health care; and resolving the lack of investment in research and development, including through the provision of incentives to innovate and improve public health outcomes, particularly in the field of antibiotics;

10. Also recognize that the overarching principle for addressing antimicrobial resistance is the promotion and protection of human health within the framework of a One Health approach, emphasize that this requires coherent, comprehensive and integrated multi-sectoral action, as human, animal and environmental health are interconnected, and in this regard:

    a. Recognize further that effective antimicrobial medicines and their prudent use represent a global public benefit and, for addressing antimicrobial resistance, it is essential to allow people to have access to efficient and resilient health systems; as well as to quality, safe, efficacious and affordable antimicrobial medicines and other technologies, when they are needed; and healthy food and environments;

    b. Underline that basic and applied innovative research and development, including in areas such as microbiology, epidemiology, traditional and herbal medicine and social and behavioural sciences, as appropriate, are needed in order to better understand antimicrobial resistance and to support research and development on quality, safe, efficacious and affordable antimicrobial medicines, especially new antibiotics and alternative therapies, vaccines and diagnostics;

    c. Underline also that all research and development efforts should be needs-driven, evidence-based and guided by the principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility: in this regard, we acknowledge the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development, and welcome innovation and research and development models that deliver effective solutions to the challenges presented by antimicrobial resistance, including those promoting investment in research and development; all relevant stakeholders, including Governments, industry, nongovernmental organizations and academics, should continue to explore ways to support innovation models that address the unique set of challenges presented by antimicrobial resistance, including the importance of the appropriate and rational use of antimicrobial medicines, while promoting access to affordable medicines;

    d. Underline further that affordability and access to existing and new antimicrobial medicines, vaccines and diagnostics should be a global priority and should take into account the needs of all countries, in line with the World Health Organization global strategy and plan of action on public health, innovation and intellectual property, and taking into consideration its internationally agreed follow-up processes;

    e. Improve surveillance and monitoring of antimicrobial resistance and the use of antimicrobials to inform policies and work with stakeholders from industry, agriculture and aquaculture, local authorities and hospitals to reduce antimicrobial residues in soil, crops and water;

    f. Enhance capacity-building, technology transfer on mutually agreed terms and technical assistance and cooperation for controlling and preventing antimicrobial resistance, as well as international cooperation and funding to support the development and implementation of national action plans, including surveillance and monitoring, the strengthening of health systems and research and regulatory capacity, without jeopardizing, in particular in the case of low- and middle-income countries, health or posing barriers for access to care;

g. Acknowledge that increasing awareness and knowledge on antimicrobial resistance and all of its implications requires the sharing of good practices and findings, collaboration with the media and national and multi-sectoral actors and the provision of sufficient financing for these activities across sectors;

11. Recognize that national conditions and priorities should be taken into account at all levels, and that relevant sectors of government should be engaged in the development and implementation of multi-sectoral national action plans, policies, regulations and regional initiatives, taking into account the national context, legislation and jurisdictional responsibilities;

12. We therefore commit to work at national, regional and global levels to:

   a. Develop, in line with World Health Assembly resolution 68.7 multi-sectoral national action plans, programmes and policy initiatives, in line with a One Health approach and the global action plan on antimicrobial resistance, including its five overarching strategic objectives, with a view to implementing national measures for strengthening appropriate antibiotic use in humans and animals: to support the implementation of such plans, national and international collaboration is needed to assess resource needs and to provide sustained technical and financial investment in shared research, laboratories and regulatory capacities, as well as professional education and training, with a view to safeguarding human health, animal health and welfare and the environment;

   b. Mobilize adequate, predictable and sustained funding and human and financial resources and investment through national, bilateral and multilateral channels to support the development and implementation of national action plans, research and development on existing and new antimicrobial medicines, diagnostics, vaccines and other technologies and to strengthen related infrastructure, including through engagement with multilateral development banks and traditional and voluntary innovative financing and investment mechanisms, based on priorities and local needs set by governments, and ensuring public return on investment;

   c. Take steps to ensure that national action plans include the development and strengthening, as appropriate, of effective surveillance, monitoring and regulatory frameworks on the preservation, use and sale of antimicrobial medicines for humans and animals that are enforced according to national contexts and consistent with international commitments;

   d. Initiate, increase and sustain awareness and knowledge-raising activities on antimicrobial resistance in order to engage and encourage behavioural change in different audiences; promote evidence-based prevention, infection control and sanitation programmes; the optimal use of antimicrobial medicines in humans and animals and appropriate prescriptions by health professionals; the active engagement of patients, consumers and the general public, as well as professionals, in human and animal health; and professional education, training and certification among health, veterinary and agricultural practitioners; and consider, as appropriate, innovative approaches to increase consumer awareness, giving attention to local conditions and needs;

   e. Support a multi-sectoral One Health approach to address antimicrobial resistance, including through public health-driven capacity-building activities and innovative public-private partnerships and incentives and funding initiatives, together with relevant stakeholders in civil society, industry, small- and medium-sized enterprises, research institutes and academia, to promote access to quality, safe, efficacious and affordable new medicines and vaccines, especially antibiotics, as well as alternative therapies and medicines to treatment with antimicrobials, and other combined therapies, vaccines and diagnostic tests;

13. Call upon the World Health Organization, together with the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health, to finalize a global development and stewardship framework, as requested by the World Health Assembly in its resolution 68.7, to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and to promote affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries and in line with the global action plan on antimicrobial resistance;
14. Call upon the World Health Organization, in collaboration with the Food and Agriculture Organization of the United Nations, the World Organization for Animal Health, regional and multilateral development banks, including the World Bank, relevant United Nations agencies and other intergovernmental organizations, as well as civil society and relevant multi-sectoral stakeholders, as appropriate, to support the development and implementation of national action plans and antimicrobial resistance activities at the national, regional and global levels;
15. Request the Secretary-General to establish, in consultation with the World Health Organization, the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health, an ad hoc interagency coordination group, co-chaired by the Executive Office of the Secretary-General and the World Health Organization, drawing, where necessary, on expertise from relevant stakeholders, to provide practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance, and also request the Secretary-General to submit a report for consideration by Member States by the seventy-third session of the General Assembly on the implementation of the present declaration and on further developments and recommendations emanating from the ad hoc interagency group, including on options to improve coordination, taking into account the global action plan on antimicrobial resistance.

Statements to the High-Level Meeting of the UN General Assembly by the WHO and OIE Directors-General, 21 September 2016

Address by Dr. Margaret Chan, Director-General of the World Health Organization:

Excellencies, distinguished delegates, colleagues in public health, ladies and gentlemen, antimicrobial resistance is a global crisis—a slow-motion tsunami. The situation is bad, and getting worse.

Last month, an increase in the number of drug-resistant pathogens forced WHO to revise its treatment guidelines for chlamydia, syphilis, and gonorrhoea. On current trends, a common disease like gonorrhoea may become untreatable. Doctors facing patients will have to say, “Sorry, there is nothing I can do for you.”

The crisis can be succinctly summarized. The misuse of antimicrobials, including their underuse and overuse, is causing these fragile medicines to fail. The emergence of bacterial resistance is outpacing the world’s capacity for antibiotic discovery. Over the past half century, only two new classes of antibiotics reached the market.

With few replacement products in the pipeline, the world is heading towards a post-antibiotic era in which common infections, especially those caused by gram-negative bacteria, will once again kill.

Superbugs, resistant to nearly all currently available medicines, already haunt hospitals and intensive care units in every region of the world. Nearly all of us know someone who underwent a routine operation only to die from a hospital-acquired infection.

Last year, the World Health Assembly approved a global action plan for combatting antimicrobial resistance. What we must see now is the action.

The pharmaceutical industry is reluctant to invest in costly antibacterial discovery. The return on investment is poor, as antibiotics are taken for a short time, cure their target disease, and can fail after a brief market life.

Incentives must be found to re-create the prolific era of antibiotic discovery that took place from 1940 to 1960. Consumers have to stop demanding antibiotics when they have a viral infection, like a cold or the flu. Doctors have to stop prescribing them.

The medical profession needs better diagnostic tests, so that antibiotics are prescribed only on the basis of a firm diagnosis. More vaccines are needed to prevent infections in the first place.

The food industry needs to reduce its massive use of antibiotics, at subtherapeutic doses, as growth promoters. Specific antibiotics, listed by WHO as critically important for human medicine, should not be used in animal husbandry or agriculture.

Consumers should make antibiotic-free meat their preferred choice.

All of these actions are urgently needed.

The World Health Organization welcomes this high-level meeting. A global crisis of this magnitude demands attention at the highest political level.

Thank you for recognizing the importance of this issue.

Address by Dr. Monique Éloit, Director-General of the World Organisation for Animal Health (OIE):

Your Excellencies, Ministers, Dear Delegates,
Dear Colleagues from International Organisations,
Honourable participants,

Superbugs. If someone had told me, when I was a young vet student, that one day, I would be standing in front of you talking about bugs as the major health threat of the century, I would not have believed it.

But here we are. Talking about bugs becoming resistant to our most precious medicines, antimicrobials.

Here we are, facing the hard reality: if we do not act now, protecting not only human health but also animal health and welfare, food safety and food security, this might become tremendously difficult.

However, this situation is not yet inevitable.

- We all know how prudent use and good practices could decrease the risk of antimicrobial resistance development.
- We all know that alternatives exist and are only waiting to be developed.
- Here in this room, we all know that research on new molecules needs to be boosted through private and public collaboration.

But how can we turn this into action in the field?

With solutions adapted to national specificities, sectors and activities? Without endangering human and animal health sectors and economic activities?

In short: How can we drive sustainable change into our practices?

In Animal health, the World Organisation for Animal Health has been working on this topic for a long time.

- We have developed international Standards aimed at defining responsible and prudent use of antimicrobials to control animal diseases under veterinary supervision.
- We have built a list of antimicrobial agents of veterinary importance.
- We have defined adequate legislation to control their production, circulation and distribution.

And to help you implement these Standards at your national level, the OIE has developed a process for evaluation and performance improvement of veterinary services named the "PVS Pathway."

Tools also exist as far as "One Health" is concerned, with the adoption of the WHO Global Action Plan on Antimicrobial resistance, in which both OIE and FAO are closely collaborating, and which directly leads us here, to this High-level meeting.

But these tools, standards, recommendations and action plans, internationally built by you as UN or OIE Member Countries, can only be useful if they are reflected and implemented at the national level, and if they are the basis on which we create the necessary sustainable change in the way we use antibiotics.

To allow this sustainable change at the national level, we—WHO, FAO and OIE—need your strong and long-term political commitment in order to:

- build tailor-made national action plans based on a systemic inter-sectorial and coordinated approach favoring cohesion and collaboration;
- invest in the long-term sustainability of health systems, including the strengthening of veterinary services;

- and last but not least, we need to gain support of stakeholders and populations, by raising awareness through education and communication.

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In conclusion,

- Much work has already been accomplished, but a great deal remains to be implemented in order to see tangible results.
- By endorsing the outcome document of this High Level meeting, I hope that you will show your strong commitment to continue in these efforts and command actions required to fight against antimicrobial resistance.
- We all share responsibility for the development of Antimicrobial Resistance. Consequently, if we successfully tackle this threat, we will share victory.

I thank you all for your attention.

Annex 2. Top 18 Drug-Resistant Threats to the United States

(Published by U.S. Centers for Disease Control and Prevention in 2013)

Urgent Threats

Clostridium difficile (C. difficile) causes life-threatening diarrhea. These infections mostly occur in people who have had both recent medical care and antibiotics. Often, *C. difficile* infections are in hospitalized or recently hospitalized patients. A 2015 CDC study found that *C. difficile* caused almost half a million infections among patients in the United States in a single year. An estimated 15,000 deaths are directly attributable to *C. difficile* infections, making it a substantial cause of infectious disease deaths. Over 5 years, up to $3.8 million of medical costs are due to *C. difficile* resistance.

Carbapenem-resistant Enterobacteriaceae (CRE) bacteria cause untreatable and hard-to-treat infections; they are on the rise in patients in medical facilities. CRE have become resistant to all, or nearly all, of the antibiotics we have today. Almost half of hospital patients who get bloodstream infections from CRE bacteria die from the infection.

Neisseria gonorrhoeae causes gonorrhea, a sexually transmitted disease. The bacteria is already resistant to many drugs. More than 800,000 infections occur in the United States annually, many go undetected and untreated, and more than 1 in 4 are resistant to at least one antibiotic. Left untreated, gonorrhea can cause serious problems, particularly for women, including chronic pelvic pain, life-threatening ectopic pregnancy, and even infertility. Infection also increases the risk of contracting and transmitting HIV. Growing resistance to azithromycin, the currently recommended drug, suggests that it may be next in the long line of drugs to which the bacteria have become resistant—a list that includes penicillin, tetracycline, and fluoroquinolones. Early signs of resistance to cephalosporins, the class of antibiotics that includes ceftriaxone, are also being monitored.

Serious Threats

Multidrug-resistant Acinetobacter

Drug-resistant Campylobacter

Fluconazole-resistant Candida (a fungus)

Extended spectrum b-lactamase producing Enterobacteriaceae (ESBLs)

Vancomycin-resistant Enterococcus (VRE)

Multidrug-resistant Pseudomonas aeruginosa

Drug-resistant Non-typhoidal Salmonella

Drug-resistant Salmonella Typhi

Drug-resistant Shigella

Methicillin-resistant Staphylococcus aureus (MRSA)

Drug-resistant Streptococcus pneumoniae

Drug-resistant tuberculosis

Concerning Threats

Vancomycin-resistant Staphylococcus aureus (VRSA)

Erythromycin-resistant Group A Streptococcus

Clindamycin-resistant Group B Streptococcus

Annex 3. Potential Savings from Using One Health Approaches

SAVINGS IN DELIVERY OF PUBLIC HEALTH FUNCTIONS Background Analysis for Estimates of Costs of Veterinary and Human Public Health Systems in 60 Low-Income and 79 Middle-Income Countries (139 Countries)

Task	Investment/ Recurrent Cost	Savings %	Specific Areas of Savings in Peacetime and Emergency Operations
Surveillance	Investment	10–30%	Joint transport and communication systems, as shown in campaigns to control avian flu and other zoonoses
Surveillance	Recurrent	20–40%	Shared front-line staff, as already has been demonstrated in many countries with para-veterinary systems
Bio-security	Investment	5–20%	Shared border control and abattoir and market inspection in buildings and equipment, as already done in several countries; sharing also possible with plant sanitary service
Bio-security	Recurrent	10–30%	Shared border control and market inspection, with clear agreement on responsibilities. Sharing also possible with plant sanitary service
Diagnostics	Investment	5–25%	Joint facilities and equipment, as already done in a number of countries
Diagnostics	Recurrent	15–30%	Shared support staff, as already done in a number of countries and recommended in other countries
Control (vaccinations, hygiene, and rapid response)	Investment	5–15%	Shared quarantine of infected areas, as successfully done in campaigns to control highly pathogenic avian influenza
Control (vaccinations, hygiene, and rapid response)	Recurrent	10–30%	Shared staff and hygiene and awareness programs
Additional costs	Training	5–10%	Of total budget
Research		5–10%	Of total budget
Assumptions endorsed by expert panel as “reasonable first estimates.”			

Canada’s National Microbiology Laboratory. A detailed analysis of *Canada’s National Microbiology Laboratory* found savings of 26% annually in the One Health facility in Winnipeg, which provides both animal and human public health services. Adoption of such One Health approaches is rare, however, suggesting that advocacy is needed to overcome the cemented sectoral and professional silos. The outcome in Canada is a substantial and ongoing saving of taxpayers’ resources. Moreover, such facilities are also more effective, with faster and more accurate diagnoses. In LMICs, a disproportionately high amount of financing has flowed to human health systems (relative to veterinary public health systems), which has inadvertently encouraged development of silos and reduced prospects for highly desirable collaboration (since collaboration requires some capacity in both sectors).

Source: World Bank (2012). *People, Pathogens and Our Planet. The Economics of One Health.*

Annex 4. Targets for Sustainable Development Goal #3

Ensure Healthy Lives and Promote Well-being for All at All Ages

SDG #3. Ensure Healthy Lives and Promote Well-being for All at All Ages

	Targets	Global?
1	reduce the global **maternal mortality** ratio to less than 70 per 100,000 live births	No
2	end preventable deaths of **newborns and children under five**	No
3	end the **epidemics of AIDS, tuberculosis, malaria, and neglected tropical** diseases and combat hepatitis, water-borne diseases, and other communicable diseases	**Yes**
4	reduce by one-third premature mortality from **non-communicable diseases (NCDs) and promote mental health** and well-being	No
5	strengthen prevention and treatment of substance abuse, incl. narcotic **drug abuse and harmful use of alcohol**	No
6	halve global deaths and injuries from **road traffic accidents**	No
7	ensure universal access to sexual and **reproductive health care** services	No
8	achieve **universal health coverage (UHC), including financial risk protection, access to quality essential health care,** and access to safe, effective, quality, and affordable essential medicines and vaccines for all	No
9	substantially reduce the number of deaths and illnesses from **hazardous chemicals and air, water, and soil pollution and contamination**	**Partially**
10	implement Framework **Convention on Tobacco Control** in all countries as appropriate	**Partially**
11	**support research and development of vaccines and medicines that primarily affect developing countries;** provide access to affordable essential medicines and vaccines	**Partially**
12	increase substantially **health financing and health workforce** in developing countries, esp. in LDCs and SIDS	No
13	**strengthen the capacity of all countries, particularly developing countries, for early warning, risk reduction, and management of national and global health risks**	**Yes**

Global public goods share two qualities. First, their benefits are non-excludable so that once a good is available, everyone in the world can enjoy it. Second, consumption of global public goods is non-rivalrous because consumption by one person does not reduce the availability to others, across nations.

Annex 5. Example of a Budget for AMR Surveillance

ANNUAL BUDGET FOR AMR SURVEILLANCE IN KENYA AT THE NATIONAL PUBLIC HEALTH LABORATORY AND EIGHT SATELLITE LABORATORIES

Item*	Total Needed	Unit Cost (Ksh)	Total Cost (Ksh)
NPHL Personnel (Salary and Benefits)			
Principal investigator/project manager (full-time)**	1	120,000	120,000
Clinical consultant (hourly)	108	8,000	864,000
Data analyst (per session)	5	200,000	1,000,000
Data manager (full-time)	1	600,000	600,000
Subtotal			2,584,000
Training and strategic planning			
Strategic planning session	1	2,000,000	2,000,000
Training for NPHL microbiologists	1	50,000	5,0000
Training for satellite laboratory microbiologists	8	90,000	720,000
Sensitization of hospital sites	96	80,000	7,680,000
Subtotal			10,450,000
Equipment			
Printer/scanner	8	25,000	200,000
Desktop computer	24	100,000	2,400,000
Subtotal			2,600,000
Services			
Internet access***	0	0	0
Subtotal			0
Office Supplies			
Printer toners	16	15,000	240,000
Printing paper (carton)	40	3,000	120,000
Printing	1	100,000	100,000
Subtotal			460,000
TOTAL (Ksh)			16,094,000
TOTAL (USD)			159,347

**See* Appendix C for item descriptions.
***A* principal investigator was already present in Kenya and thus not included in their national surveillance budget, but would otherwise be an essential budget item.
****Internet* access is currently available in most EAPHLN laboratories, but would be an additional cost if needed.

Annex 6. Example of a Laboratory-Improvement Budget to Perform Antibiotic Susceptibility Testing (AST)

ANNUAL BUDGET FOR THE KENYA NATIONAL PUBLIC HEALTH LABORATORY AND EIGHT SATELLITE LABORATORIES

Item	Total	Unit Cost (Ksh)	Total Cost (Ksh)
NPHL Personnel (salary and benefits)			
Laboratory supervisor (1)	0	0	0
Laboratory technicians (16)	0	0	0
ICT staff (3)	0	0	0
Data manager/statistician (1)	1	50,000	50,000
Procurement officer (1)	0	0	0
Subtotal			50,000
Satellite Laboratory Personnel			0
Laboratory microbiology technicians (2 per lab; 45,000 Ksh/mo.)	2	45,000	90,000
Additional hospital staff (nurses, technicians; 10,000 Ksh/mo.)	64	120,000	7,680,000
Subtotal			7,770,000
Equipment Autoclave (2 per lab)	0	0	0
Water distiller (1 per lab)	0	0	0
Refrigerators/freezers (2 per lab)	0	0	0
Incubators (2 per lab)	0	0	0
Slide dryer (1 per lab)	8	40,000	320,000
Carbon dioxide gas cylinder (2 per lab)	16	20,000	320,000
Temperature data loggers (2 per lab)	16	2,500,000	40,000,000
Cool boxes (4 per hospital, 20 per lab)	288	2,500	720,000
Thermometers (8 per lab)	64	5,000	320,000
Ultra low freezers (3 for NPHL)	1	2,500,000	2,500,000
Bacticinerator (3 per lab)	24	400	9,600
Freezer management system and barcoding licensing (1 per lab)	8	300,000	2,400,000
Freezer management system and barcoding installation (1 per lab)	8	300,000	2,400,000
Subtotal			48,989,600
Services Courier (G4S)			
External quality assurance for NPHL	3	200,000	600,000
External quality assurance for satellite laboratories	1	2,000,000	2,000,000
Subtotal			2,600,000
Equipment Service VITEK	8	400,000	3,200,000
BACTEC	1	50,000	50,000
PCR machine	2	100,000	200,000
Other basic equipment, including biosafety cabinets	8	300,000	2,400,000
Subtotal			5,850,000

Item	Total	Unit Cost (Ksh)	Total Cost (Ksh)
Reagents API-10 (pack of 20 strips)	80	8,000	640,000
API-20E (pack of 20 strips)	80	8,000	640,000
API-20NE (pack of 20 strips)	80	8,000	640,000
MacConkey agar (bottle of 500g)	5	10,000	50,000
MacConkey agar with sorbitol (bottle of 500g)	5	10,000	50,000
Mueller Hinton agar (bottle of 500g)	5	10,000	50,000
Nutrient agar (bottle of 500g)	5	10,000	50,000
Sheep blood, defibrinated (bottle of 500g)	60	1,000	60,000
Triple sugar iron agar (TSI) (bottle of 500g)	5	10,000	50,000
Tryptone soya agar (TSA) (bottle of 500g)	5	10,000	50,000
Urea agar base (Christensen's agar base) (bottle of 500g)	5	10,000	50,000
Urea solution, sterile 40% (5mL)	50	10,000	500,000
Xylose lysine desoxycholate agar (XLD) (bottle of 500g)	5	10,000	50,000
Colombia blood agar base (bottle of 500g)	5	10,000	50,000
Cary blair medium (bottle of 500g)	5	10,000	50,000
Amies transport medium (pack of 50 packs)	80	8,000	640,000
Subtotal			3,620,000
Antibiotics Ampicillin, 10µg (5 cartridges per lab)	40	2,500	100,000
Cefotaxime, 30µg (5 cartridges per lab)	40	2,500	100,000
Ciprofloxacin, 5µg (5 cartridges per lab)	40	2,500	100,000
Erythromycin, 15µg (5 cartridges per lab)	40	2,500	100,000
Gentamicin, 10µg (5 cartridges per lab)	40	2,500	100,000
Tobramycin, 10µg (5 cartridges per lab)	40	2,500	100,000
Azithromycin (5 cartridges per lab)	40	2,500	100,000
Clindamycin (5 cartridges per lab)	40	2,500	100,000
Penicillin, 10 units (5 cartridges per lab)	40	2,500	100,000
Cefuroxime, 30µg (5 cartridges per lab)	40	2,500	100,000
Tetracycline, 30µg (5 cartridges per lab)	40	2,500	100,000
Rifampin, 5µg (5 cartridges per lab)	40	2,500	100,000
Norfloxacin, 10µg (5 cartridges per lab)	40	2,500	100,000
Nitrofurantoin, 300µg (5 cartridges per lab)	40	2,500	100,000
Sulfamethoxazole/trimethoprim (5 cartridges per lab)	40	2,500	100,000
Ertapenem (5 cartridges per lab)	40	2,500	100,000
Colistin (5 cartridges per lab)	40	2,500	100,000
Tigecycline (5 cartridges per lab)	40	2,500	100,000
Cefoxitin (5 cartridges per lab)	40	2,500	100,000
Mac Farland standard (2 per lab)	16	5,000	80,000
Sodium chloride (NaCl) (2 per site)	16	7,000	112,000
Glycerol (2 per site)	16	8,000	128,000
Gram stain kits large (12 kits per lab)	96	2,000	192,000
Subtotal			2,412,000

(*continued*)

Item	Total	Unit Cost (Ksh)	Total Cost (Ksh)
VITEK Reagents Saline 0.45% (20 per lab)	160	7,500	1,200,000
VITEK 2 GN bacilli identification (21341) (200 per lab)	1,600	15,400	24,640,000
VITEK 2 GP cocci identification (21342) (200 per lab)	1,600	15,400	24,640,000
VITEK 2 AST GN (200 per lab)	1,600	15,400	24,640,000
VITEK 2 BCL GP bacilli identification (21345) (200 per lab)	1,600	15,400	24,640,000
VITEK 2 AST GP (200 per lab)	1,600	15,400	24,640,000
Subtotal			124,400,000
Consumables Blue pipette tips, non-sterile, 100–1000µl (5 packs per lab)	40	1,000	40,000
Yellow pipette tips, non sterile, 1–200µl (5 packs per lab)	40	800	32,000
BACTEC blood culture bottles (100 per lab)	800	1,000	800,000
Petri dishes, 100 x 15mm polysterene (10 cartons per lab)	80	9,000	720,000
Test tubes, beakers, flasks (1 set per lab)	8	80,000	640,000
Cryo vials (20 packs for NHPL)	20	3,000	60,000
Cryovial boxes (50 per lab)	400	1,000	400,000
Aluminium plate holders (10 per lab)	80	8,000	640,000
Graduated wire loops with handle (2 per lab)	16	3,000	48,000
Graduated wire loop replacements (20 per lab)	160	1,000	160,000
Inoculating loops and needles, disposable (100 packs per lab)	8,000	100	800,000
Petri dishes, 9cm (10 box per lab)	80	7,000	560,000
Urine collection containers, sterile (2000 per lab)	16,000	25	400,000
Slides (10 boxes per lab)	80	70	5,600
Slide boxes (20 per lab)	1,600	1,000	1,600,000
Polysterene tubes, 75mm (1 carton per lab)	8	12,000	96,000
Subtotal			7,001,600
Safety and Waste Management supplies Lab coats (2 per person, 15 people/lab)	240	1,000	240,000
Gloves (1 box/day/lab)	2,920	100	292,000
Biohazard autoclave bags, polyethylene (pack of 100;10 per lab)	80	1,000	80,000
Hand wash liquid soap (4 per lab)	32	500	16,000
Ethanol (5L bottle, 12 per lab)	96	3,000	288,000
Paper towels (1 carton per lab)	8	4,000	32,000
Bleach (1 bottle per lab)	40	1,000	40,000
Subtotal			988,000
Office Supplies Permanent markers (2 packs per lab)	16	2,000	32,000
Stationery (paper punches, staplers, staples, scissors, etc.)	8	10,000	80,000
Pens (2 packs per lab)	16	500	8,000
Pencils (2 packs per lab)	16	600	9,600
Folders (10 per lab)	80	400	32,000
CLSI guidelines for AST (500 USD)	1	50,500	50,500
Subtotal			212,100
TOTAL (Ksh)			203,893,300
TOTAL (USD)			2,018,746

Annex 7. National, Regional, and International Antimicrobial Resistance Surveillance Networks

Country or Region	Programs
European Union	European Antimicrobial Resistance Surveillance System (EARS-Net) European Antimicrobial Consumption Network (ESAC-Net)
Latin America	Latin American Surveillance Network of Antimicrobial Resistance (ReLAVRA)
Asia	Asian Network for Surveillance of Resistant Pathogens (ANSORP)
Central Asia and Eastern Europe	Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR)
Global	Global Antimicrobial Resistance Surveillance System (GLASS)
Australia	Australian Group on Antimicrobial Resistance (AGAR)
Cambodia	United States Naval Medical Research Unit 2 Phnom Penh (NAMRU-2 PP)
Canada	Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) Canadian Nosocomial Infection Surveillance Program (CNISP) Both CIPARS and CNISP fall under the Canadian Antimicrobial Resistance Surveillance System (CARSS)
China	China Antimicrobial Resistance Surveillance Study (CHINET)
China, Hong Kong	Hong Kong Antibiotic Stewardship Program (ASP)
Denmark	Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP)
Federated States of Micronesia	Federated States of Micronesia Surveillance Network
Finland	Finnish Veterinary Antimicrobial Resistance Monitoring and Consumption of Antimicrobial Agents (FINRES-VET)
France	l'Observatoire National de l'Epidemiologie de la Resistance Bacterienne aux Antibiotiques (ONERBA)
Germany	German National Veterinary Antibiotic Resistance Monitoring (GERM-VET)
Italy	Italian Veterinary Antimicrobial Resistance Monitoring (ITAVARM)
Japan	Japan Nosocomial Infections Surveillance (JANIS) Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)
Malaysia	National Surveillance of Antimicrobial Resistance Program (NSAR)
Mongolia	National Laboratory Network
Netherlands	Consumption of Antimicrobial Agents and Antimicrobial Resistance among Medically Important Bacteria in the Netherlands/ Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands (NETHMAP/MARAN)
New Zealand	New Zealand Institute of Environmental Science and Research (ESR) Antibiotic Reference Laboratory
Norway	Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM/NORM-VET)
Philippines	Antimicrobial Resistance Surveillance Program (ARSP)
Republic of Korea	Korea Antimicrobial Resistance Surveillance Program (KARMS) Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR)
Singapore	The Network for Antimicrobial Resistance Surveillance (NARS-Singapore)
Sweden	Swedish Veterinary Antimicrobial Resistance Monitoring (SWEDRES/SVARM)
Taiwan	Taiwan Surveillance of Antimicrobial Resistance (TSAR)
United Kingdom	English Surveillance Programme for Antimicrobial Utilization and Resistance
United States	National Antimicrobial Resistance Monitoring System (NARMS) Emerging Infections Program (EIP) National Health Care Safety Network (NHSN) Gonococcal Isolate Surveillance Program (GISP) National Tuberculosis Surveillance System (NTSS)
Vietnam	Viet Nam Resistance Project (VINARES)

Annex 8. Laboratory-Based Surveillance of AMR: Summary Report

AMR surveillance is an indispensable component of the response to a rising tide of antibiotic resistance worldwide. WHO recommends surveillance as part of every national AMR action plan. National-level surveillance systems are critical for guiding local and national policy, while regional systems can enhance the value of the data, depicting larger patterns and trends.

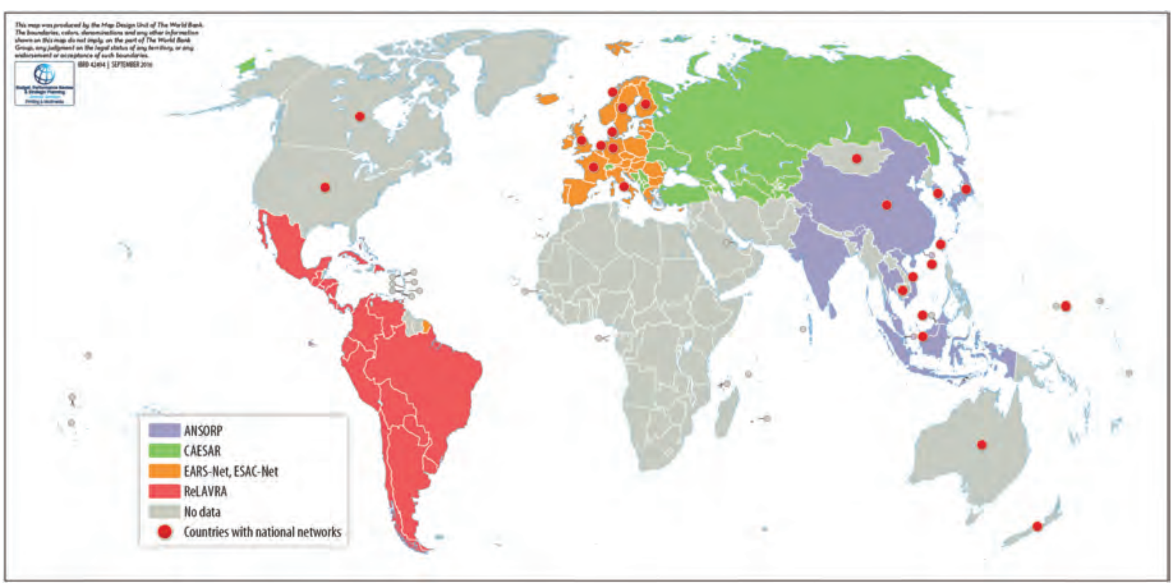
In the following pages, we will discuss the status of AMR surveillance globally, the expected benefits and costs of AMR surveillance, the importance of surveillance networks, and the main findings from a capacity assessment of laboratories supported under the World Bank-funded East Africa Public Health Laboratory Networking Project (EAPHLNP). The assessment sought to document these laboratories' readiness to participate in national and, ultimately, regional AMR surveillance. The report ends with a set of recommendations that are relevant to countries in East Africa and other low- and middle-income countries facing similar challenges.

A. Status of Global AMR Surveillance

WHO defines public-health surveillance as the systematic collection, analysis, interpretation, and dissemination of public-health data. In 2014, WHO surveyed its member states about their AMR surveillance efforts. Results indicated that AMR among some specific pathogens—such as those that cause tuberculosis, malaria, and gonorrhea—have been tracked to some extent for many years. In some regions, strong networks existed to track AMR among a broad set of pathogens, but there were major gaps in coverage (Figure A8.1). Europe and the Americas had the best surveillance coverage and Sub-Saharan Africa and South and Southeast Asia the least developed. Creating comprehensive, effective surveillance systems is more challenging in low- and middle-income countries due to weak laboratory and communications infrastructure; lack of trained laboratory and clinical personnel; and higher prevalence of counterfeit and substandard antibiotics and diagnostics (Dar *et al.* 2016; Opintan *et al.* 2015). A six-month surveillance program through 24 laboratories in Ghana recently demonstrated the feasibility of establishing surveillance in this lower middle-income country, producing evidence of higher than expected resistance rates (Opintan *et al.* 2015) (Box 3).

In addition to tracking AMR, it is important to understand the patterns and trends in antimicrobial use. Per capita use is generally highest in high-income countries, but is increasing most rapidly in low- and middle-income countries (Van Boeckel *et al.* 2014). However, few data have been gathered to indicate the precise extent of antibiotic resistance in low- and middle-income countries or to quantify the related health and health care costs (Laxminarayan *et al.* 2013). Low- and middle-income countries typically have weaker public-health systems, fewer resources, and higher burdens of infectious disease. In these countries, antimicrobial resistance is

FIGURE A8.1. Global AMR Surveillance Networks



Box 3. Pilot Program for an AMR Surveillance Network in Ghana

In Ghana, data on antimicrobial resistance are scarce, and no continuous surveillance network exists. In 2014, a six-month pilot program established a laboratory-based national surveillance network to generate baseline resistance data and evaluate current capacity.

The study included a three-day workshop where scientists from 24 laboratories were trained to identify bacterial isolates and perform antimicrobial susceptibility testing (AST). During the study period, scientists from each laboratory recorded test results and sent data sheets and isolates to a central location each week. A research assistant at the central laboratory then performed quality control and other tests, and entered data into WHONET (WHO-supported database software for management and analysis of microbiology data with a special focus on antimicrobial susceptibility test results).

Over the six-month period, 1606 isolates from 18 laboratories serving both inpatient and outpatient settings were submitted. Susceptibility testing showed that existing antimicrobials are not as effective as previously thought. Eighty percent of isolates were resistant to older antibiotics such as ampicillin, tetracycline, chloramphenicol, and trimethoprim/sulfamethoxazole. In addition, more than 50 percent of isolates were resistant to third-generation cephalosporins and quinolones.

These results highlighted the need for continued surveillance of antimicrobial resistance in Ghana and corresponding changes in treatment guidelines. The study also highlighted the need for capacity building. Twenty-five percent of participating laboratories—including two of three participating public-health reference laboratories—did not submit samples due to poor microbiology facilities, managerial problems, and lack of samples from clinicians. Furthermore, none of the participating laboratories had the capacity for anaerobic cultures, which are standard for resistance surveillance in high-income countries.

common in community-acquired infections such as pneumonia, diarrheal disease, tuberculosis, malaria, and sexually transmitted diseases (Gelband *et al.* 2015). In addition, resistance makes it more difficult to treat patients with HIV/AIDS, which has a high prevalence in many low- and middle-income countries (Gelband *et al.* 2015).

B. Benefits and Costs of AMR Surveillance

Benefits of AMR Surveillance

The broad benefits of AMR surveillance are improved availability of data and information on levels and patterns of resistance, and introduction of evidence-based policies and interventions, which in turn contribute to reduced disease burden, lower treatment costs, and reduced mortality. Table 4 presents the multiple benefits of an effective AMR surveillance system and cites country-specific examples illustrating the value of AMR surveillance data.

Estimating the Cost of Implementing AMR Surveillance—The Example of Kenya

The cost of AMR surveillance should be a relatively modest add-on to existing laboratory costs, when built on well functioning laboratories that produce reliable results. The routine testing carried out by the laboratory forms the raw surveillance data. Apart from some additional quality control testing, no additional laboratory analyses are required to support a surveillance network. Additional costs are largely for information technology, data analysis capacity, personnel time and training, and software. Epidemiologic and general public-health expertise is also needed to interpret the data for public policy use.

Kenya, one of the EAPHLN Project participating countries, is in the process of constructing a national AMR surveillance network. Kenyan colleagues have provided the draft implementation plan and associated cost estimates as a reference for this report. Their network will initially include the National Public Health Laboratory (NPHL) and eight county or satellite laboratories, including the five supported under the World Bank-funded project.

Annex 4 outlines the incremental costs—beyond the laboratories' general operating budgets—to start and operate an AMR surveillance network in Kenya. Expenses include additional personnel to manage and analyze data and consult on surveillance; training and strategic planning related to data collection and management; and additional equipment and supplies. In addition, the Kenyan team estimates that roughly $2.0 million are required to perform antimicrobial susceptibility testing at the NPHL and eight satellite laboratories with the bulk representing running costs (Annex 5).

Based on current expenses in Kenya, establishing and running an AMR surveillance network with eight county or satellite laboratories will cost about $160,000 annually. Some costs scale to the size of the network (for example, personnel and hardware at satellite sites) and some would increase in larger steps, depending upon how many laboratories would be supported centrally by core surveillance staff. We could find no data to establish the breakpoints at which increases would be needed. However, we believe that most low- and middle-income countries would initially plan for a size similar to the proposed Kenya network. Estimates for other countries can be made by applying appropriate national unit costs to the volume of goods and services required.

Estimating the Economic and Health Benefits of AMR Surveillance

The economic benefits of AMR surveillance networks, as detailed above, are multifaceted and challenging to measure and quantify. Some benefits, such as increased knowledge of trends in antimicrobial resistance and improved data quality, are not routinely quantified. As many of the other benefits of surveillance aim to reduce the prevalence of antimicrobial resistance, the economic benefits can be estimated by assessing the impact of reduced disease burden. Reductions in antimicrobial resistance will reduce deaths from resistant infections, health care costs for treating those infections, and productivity losses. Even if changes are observed, attributing all or some of the changes to a surveillance system is difficult if not impossible, underscoring the complexities and challenges of quantifying the benefits. In fact, even if no changes are seen, the system may be keeping the rates from rising. This is not to suggest that AMR surveillance is not effective, and in fact, all indications suggest that it is.

TABLE 4. Specific Examples of Benefits of AMR Surveillance

Benefits	Actions Taken
Monitor trends and increase knowledge of antimicrobial resistance trends	❊ *Ghana*: 80% of isolates resistant to ampicillin, tetracycline, chloramphenicol, and trimethoprim/sulfamethoxazole ❊ *South Africa*: Emerging fluoroquinolone resistance in *Salmonella* Typhi and increasing ciprofloxacin resistance in non-typhoidal *Salmonella*, 2011 ❊ *United Kingdom*: Increase in ciprofloxacin-resistant *E. coli*, 1993–2007
Establish and evaluate targets for AMR reduction	❊ *France*, *South Korea*, and *Turkey*: Set reduction targets ❊ *United Kingdom*: Set target of 50% reduction of MRSA, 2004–2008; 56% reduction achieved
Guide epidemiologic studies; modeling; and set priorities for research and data collection	❊ *United Kingdom*: Increase in MRSA in 1990s attributed to 2 emerging strains; led to further study on related risk factors ❊ *United States*: 500 deaths per year attributed to multidrug-resistant *Acinetobacter* spp.
Develop evidence-based public health policy	❊ *Denmark*: Increased CRE in poultry and hogs contributed to growth promoter ban, 1990s; "yellow card" system implemented to force high users to reduce antibiotic use ❊ *India*: Discovery of NDM-1 led to creation of a high-level AMR committee in the Ministry of Health ❊ *South Africa*: Hospital VRE outbreaks in 2012 led to a national AMR strategy framework and early warning and notification system ❊ *United Kingdom*: Increased carbapenem resistance in *E. coli* and *Klebsiella* spp. included in national action plan ❊ *United States*: Cephalosporin resistance in *Salmonella* led to restrictions on use in food animals
Design and evaluate public-health interventions	❊ *India*: High resistance rates led to implementation of laboratory-based AMR surveillance ❊ *Latin America*: High carbapenem resistance led to establishment of AMR surveillance programs in Brazil, Argentina, and Colombia ❊ *United Kingdom*: Created the TARGET tool for antimicrobial use in primary care; developed 5-year national action plan for AMR; created national alert system to inform clinicians about emerging types of resistance
Update treatment guidelines	❊ *United Kingdom*: Vancomycin added to treatment guidelines for staphylococcal endocarditis due to methicillin resistance; treatment guidelines for gonorrhea updated to address ciprofloxacin resistance
Create public-health engagement campaigns and support training for professionals	❊ *Europe*: EARS-Net provides capacity building for laboratory technicians in participating facilities ❊ *South Africa*: National AMR strategy established web-based and in-person AMR training for clinicians ❊ *United States*: FoodNet epidemiologists train local public-health officers to conduct outbreak investigations
Influence industry practices	❊ *Canada*: Link between multidrug-resistant *Salmonella* in humans and ceftiofur use in poultry led to voluntary ban on ceftiofur in Quebec chicken industry ❊ *Denmark*: ESBL in *E. coli* led to voluntary withdrawal of cephalosporin and new management practices for disease control in the hog industry ❊ *Japan*: Cephalosporin resistant *E. coli* in broilers led to voluntary withdrawal of ceftiofur in Japanese hatcheries
Improve data quality	❊ *Europe*: Regular data reporting for EARS-Net improved data quality and reporting and facilitated development of a standardized definition of resistance

Box 4. Structured Expert Judgment

One method to estimate the counterfactual scenario—that is, what would have happened if no surveillance system had been in place—is through structured expert judgment (SEJ). A recent Center for Disease Dynamics, Economics & Policy (CDDEP) study used this method to examine return on investment of an environmental health tracking program in the United States (Colson *et al.* 2015). SEJ could be used as one input into determining the value of AMR surveillance. In the case of AMR surveillance, a group of experts would be asked to predict the burden of resistance—through resistance rates or mortality—for specific antimicrobial organism combinations without the surveillance network. Experts then provide a range of percentile values to represent an uncertainty distribution for their prediction. Each expert's predictions are weighted according to their responses to similar questions for which the answers are known. Predictions from the group of experts are then combined and compared to observed surveillance data to estimate the change in resistance that could be attributed to the surveillance network.

The most likely chain of events through which AMR surveillance can lead to health benefits is as follows:

- ***High and/or increasing rates of resistance to first-line antibiotics by specific pathogens are confirmed*** (or susceptibility to cheaper antimicrobials is identified) and made known to policy makers.
- ***Policy makers revise treatment guidelines,*** changing first-line recommendations to highly effective (that is, low-resistance) antibiotics.
- ***Guidelines are disseminated and clinical practice changes.***
- ***Deaths are reduced*** by an amount equal to the excess caused by antibiotic-resistant infections (from epidemiologic studies).
- ***Treatment costs are reduced*** by an amount corresponding to the decrease in the proportion of resistant infections from hospital-based studies or the decrease in antibiotic costs, if cheaper antibiotics are found effective or effective treatments are instituted promptly to avoid treatment failure.

Taking the five-step chain described above as the main route for achieving benefit, the rates at which these steps occur and the extent of change that eventually ensues cannot be measured easily under the best of conditions. However, some estimates can be made for each step. Various elements of cost can also be estimated. To estimate the benefits of surveillance, it is necessary to predict how much resistance rates would have changed in the absence of surveillance, a complicated task that has not been satisfactorily carried out anywhere, to the best of our knowledge. Box 4 describes the structured expert judgment (SEJ) approach for quantifying this counterfactual scenario. Once the change in resistance rates attributable to surveillance is identified, other methods can be used to estimate the health and economic benefits of this change. Various techniques are used to value lives lost, which include both direct and indirect costs.[1]

Aside from increasing mortality, antimicrobial resistance also increases the cost of treating disease. The cost of illness method can be used to estimate the direct and indirect costs of health care and lost productivity due to antimicrobial resistance. This method requires estimates of the total cost of treating resistant infections from previous studies. In order to reflect treatment costs in East Africa or other low- and middle-income countries, estimates of the direct costs of treatment can be adjusted by health expenditure per capita and estimates of indirect costs can be adjusted by GDP per capita, adjusted for purchasing-power parity (Springmann *et al.* 2016).[2]

FIGURE A8.2. Theoretical Framework for a Cost-Benefit Analysis of Antimicrobial Resistance

Benefits → Increased resistance information to clinicians and patients + Increased knowledge of resistance in the surveillance network area + Reduced disease burden of resistance through mitigation activities triggered by surveillance data

Costs → Cost of implementing the antimicrobial resistance surveillance network + Cost of sharing resistance data from the network with the public health community + Cost of implementing mitigation activities triggered by surveillance data

Cost-Effectiveness Analysis of AMR Surveillance

Cost-effectiveness is a tool often used to guide public-health decisions in countries at all resource levels (Boyce *et al.* 2015). The public-health and economic benefit of AMR surveillance derives from the actions triggered by the information gathered, so the cost of these actions must be taken into account when assessing the value of surveillance networks. A cost effectiveness analysis of the surveillance network would have to account for the cost of implementing the network, as outlined in Annex 4; the cost of sharing surveillance data with the regional and global public-health communities; and the cost of further actions triggered by surveillance data (Babo *et al.* 2015). Further actions could include public-health interventions or educational campaigns, targets for reduction in use, or changes in treatment guidelines or industry practices (Figure A8.2).

C. AMR Surveillance Networks

While most AMR surveillance networks are in high-income countries, some low- and middle-income countries have established or are participating in AMR surveillance networks (Annex 6). A laboratory-based AMR surveillance network is a partnership between clinicians, microbiology laboratories, and a central organizing body. Clinicians collect and send samples to clinical laboratories (Blomberg *et al.* 2004). If possible, these samples are annotated with patient information such as age, gender, specimen type, date, and geographic location. In the laboratory, technicians culture the specimens, identify bacterial isolates, and test isolates for antimicrobial susceptibility (Blomberg *et al.* 2004).

Antimicrobial susceptibility testing (AST) results are used by clinicians to aid in developing informed patient treatment plans. These same results and the patient demographic information form the basis of laboratory-based AMR surveillance.

Surveillance data from laboratories can be aggregated for analysis on the local, national, and regional levels to identify resistance levels and trends. Data from multiple surveillance networks can also be combined to facilitate research, visualization, and mapping of global trends in resistance. For example, CDDEP's Resistance Map online tool summarizes national and subnational antimicrobial use and resistance and is the largest such repository in existence (ResistanceMap 2016). Users can create maps and charts of antibiotic resistance to specific combinations of pathogens and antibiotics.

Critical components of laboratory-based AMR surveillance networks include capacity and proficiency for antibiotic susceptibility testing of the laboratories, infrastructure, instrumentation, availability of consumables, quality control measures, availability and skill level of personnel, and capacities needed to use data generated by the laboratories for surveillance, including:

- Standardization of procedures and terminology, above what is needed for clinical testing
- Computerization of data using specific software packages (including equipment and training)
- Centralized data collection (at national and regional levels) and analysis.

The next section looks at the situation on the ground with respect to laboratory capacity and antimicrobial susceptibility testing practices at a group of public-health laboratories participating in the World Bank-funded East Africa Public Health Laboratory Networking Project.

D. East Africa Public Health Laboratory Networking Project

The East Africa Public Health Laboratory Networking Project tackles the historical neglect of public-health laboratories. The $128.66 million project, approved by the World Bank in May 2010 with a recent extension to 2020, is establishing a network of efficient, high quality, accessible public-health laboratories in the East African Community member states (Burundi, Kenya, Rwanda, Tanzania, and Uganda). The project is: (a) strengthening diagnostic and surveillance capacity; (b) expanding training and capacity building; and (c) supporting operational research. The operation also promotes innovations in service delivery, facilitates knowledge sharing among participating countries, and fosters an evidence-based approach. Each country takes the lead in a specific thematic area and provides regional leadership, generating knowledge and sharing experiences and lessons. The East, Central, and Southern Africa Health Community (ECSA-HC) facilitates knowledge sharing at the regional level, in collaboration with the East African Community.

The project has been supporting 32 laboratories in the participating countries in both capital cities and cross-border areas to become centers of excellence and increase access to laboratory services for poor and vulnerable populations (Figure A8.3). The laboratories are expected to provide specialized services to communities in these regions that are otherwise available only in the national reference facilities. The main achievements include:

- *State-of-the-art laboratories*: Renovated/constructed public-health laboratories; rolled out molecular technologies, including GeneXpert for diagnosis of drug-resistant tuberculosis, resulting in more rapid and accurate results.
- *Progress towards accreditation*: Attained substantial quality improvements in the Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA), with 90 percent of the project-supported facilities attaining at least two stars, in comparison to 20 percent at baseline, and 60 percent reaching at least three stars.[3]
- *Regional specialization*: Supported Uganda National Tuberculosis Reference Laboratory (UNTRL) to be certified internationally and qualify to serve as a WHO Supranational Reference Laboratory, signing agreements with 20 countries to provide specialized services.
- *Strengthened human resources*: Trained over 10,000 health personnel in both short- and long-term courses; provided mentorship; recruited qualified personnel; and established an e-learning platform.
- *Supported innovations,* such as: (a) *joint annual peer audits,* whereby countries assessed each other's laboratories; (b) *performance-based financing,* whereby facilities received incentive payments based on progress towards accreditation; and (c) *cross-border disease surveillance, simulations, and investigations*

FIGURE A8.3. Location of Satellite Laboratories

that have enabled swift responses to Ebola and Marburg outbreaks.

- *Operational research studies*: Conducted multi-country studies, including a study on drug resistance patterns to newly prescribed antibiotics to deal with key bacterial enteric pathogens, which found high levels of drug resistance at project-supported facilities.

Building on these initial investments, and a strong track record of collaboration, stakeholders in East Africa came together to explore the feasibility of using the project-supported facilities to introduce laboratory-based surveillance of antimicrobial resistance.

The case study included four key activities:

- *Carrying out a capacity assessment* of 30 facilities in the five countries, which was led by the East, Central, and Southern Africa Health Community (East, Central and Southern Africa Health Community 2016).
- *Organizing a two-day consultative workshop*, where scientists and policy makers from East Africa discussed the findings of the capacity assessment in collaboration with regional and global experts (including participants from WHO, CDC, CDDEP) (CDDEP *et al.* 2016).
- *Producing a short film* to improve awareness of the importance of AMR surveillance.
- *Commissioning a technical report*, produced by the Center for Disease Dynamics, Economics & Policy, that summarizes the status of global AMR surveillance, provides a discussion of expected benefits and costs of investing in AMR surveillance, presents the main findings from the capacity assessment, and includes a detailed set of recommendations (CDDEP 2016).

The study found that while substantial funds have been invested in upgrading laboratories, the bacteriology capacity lags behind other services. Most laboratories perform relatively few microbiology cultures and ASTs. The specific findings with respect to laboratory capacity and antimicrobial susceptibility testing practices are summarized in Box 5.

E. Major Findings and Recommendations

This section summarizes the major findings from the case study, and synthesizes the key recommendations for the five countries in East Africa and other low- and middle-income countries that may face similar challenges.

Surveillance

Laboratory-based AMR surveillance is the second consumer of antibiotic susceptibility test results, after the patient and treating clinician.

- The added value of surveillance is not free, but comes at a relatively low cost, assuming well functioning laboratories that produce reliable results, which are needed for the primary, patient-level use. Additional costs are largely for information technology, data analysis capacity, personnel time and training, and software at the facility and national levels. Beyond that, epidemiologic and general public-health expertise is essential for interpreting the data for public policy use. Kenya is in the process of establishing a national AMR surveillance system, with an estimated annual budget of about $160,000.

***AMR surveillance creates value at the facility, national, and global levels. Aggregated at each level, these include*:**

- *Facility level*: information to guide antimicrobial treatment when laboratory results are analyzed regularly and communicated to clinical staff; early detection of outbreaks of particular AMR strains and hospital-acquired infections generally.
- *National level*: information to update standard treatment guidelines and track trends in AMR, including geographic variations.
- *Global level*: promote understanding of AMR in each country compared to global patterns; helps complete the global picture.

Box 5. Main Findings from the Laboratory Capacity Assessments

Laboratory Capacity:

- *Infrastructure and capacity:* All laboratories are performing below capacity in microbiology, though a sufficient number of stool, urinary, cerebrospinal fluid, and other specimens are cultured to form the basis for robust surveillance. However, the laboratories process few or no blood cultures that capture data from severe and invasive systemic bacterial infections, and which are critical for a surveillance network in Africa.
- *Equipment:* In contrast to some other resource-poor settings, equipment is not presently the capacity-limiting feature of these laboratories. All are equipped to perform susceptibility testing by disc diffusion and some have functional VITEK machines, which can be used for both bacterial identification and susceptibility testing and are easy to quality assure.
- *Reagents and supplies:* Many of the laboratories suffer from stock-outs that can shut down selected laboratories services and cause temporal biases in surveillance results. Many lack adequate control organisms for culture, identification, and susceptibility testing quality assurance. There are also reports of stock-outs, meaning that bacterial culture and susceptibility testing might be available only intermittently or are only periodically quality assured (Gelband *et al.* 2015).
- *Staffing capacity and training:* All but three of the laboratories have at least one staff member holding a bachelor's degree or higher, which bodes well for increasing the activities and responsibilities. However, qualified clinical pathologists are in short supply. Additional training is needed in bacteriology and AMR.

Antimicrobial Susceptibility Testing (AST) Practices:

- *Culture media preparation and specimen processing:* Most of the laboratories use brands of media that are certified for diagnostic testing. About half of the facilities listed animal blood procurement as a key barrier. A reliable and quality-assured supply of sheep or horse blood is essential to improve bacterial isolation and identification.
- *Bacterial identification:* Most laboratories identify bacterial isolates biochemically, which is standard for diagnostic laboratories. However, most do not have automated systems that are easier to use and quality assure.
- *Blood culture:* The vast majority of cultures processed are for urinary tract and enteric infections, primarily at sites in Uganda. While physicians value blood cultures, which provide lifesaving information for difficult cases, these services are challenging to set up and maintain. Only four laboratories can currently perform blood cultures, but with ongoing training, select district laboratories will have similar capacity. Automated blood culture is only available in Kenya.
- *Susceptibility testing:* All laboratories use disc diffusion methods that work well for routine testing and surveillance in resource-constrained settings. All laboratories use Clinical Laboratory Standards Institute (CLSI) standards, but some need to acquire documentation. Data capture, analysis, and dissemination are not carried out systematically. There is also insufficient communication between clinicians and laboratories in terms of data sharing.
- *Quality Assurance:* Four of the five national reference laboratories are enrolled in external quality assurance schemes. About 65 percent of the satellite laboratories have trouble in procuring proficiency testing.

***Countries should develop national AMR surveillance systems and contribute to regional and global surveillance initiatives*:**

- All countries should develop AMR surveillance plans that confirm country commitment and define the structure, scope, and process of establishing national AMR surveillance networks.
- Enrollment of all countries in the Global Antimicrobial Surveillance System (GLASS) should be facilitated in order to benefit maximally from added WHO support for AMR surveillance.
- Adequate investments need to be made in information technology and systems, laboratory equipment and reagents, and continual staff training.

Microbiology Laboratory Capacity

Bacteriology capacity lags behind in contrast to other services, a pattern that is likely similar to that found at other laboratories in the region, and possibly in other low- and middle-income countries, due to three key factors:

- *Lack of demand from clinicians*, related to length of time to get results (at least two days); lack of trust in results; and lack of laboratory capacity for blood cultures, which are needed for many of the most serious, life-threatening infections.
- *Weak supply chains and frequent stock-outs* are a major roadblock to routine antimicrobial susceptibility testing; stock-outs disproportionately affect bacterial culture and antimicrobial susceptibility testing that require that all essential components be available when testing is needed.
- *Lack of recognition that microbiology requires dedicated trained personnel,* leading some facilities and/or ministries of health to rotate staff frequently.

At the national and facility level, a focus should be placed on:

- *Emphasizing services that clinicians value most strongly* (for example, blood and cerebrospinal fluid cultures).
- *Preventing stock-outs* by consolidating and prioritizing inventories for infectious disease management, to ensure optimal use of antimicrobials, conserve expensive reserve drugs, and work toward the global goal of containing AMR.
- *Addressing human resources constraints* by: appointing/recruiting clinical microbiologists and/or relying on visiting consultants; ensuring that laboratory scientists are fully trained for all specialized tasks; conducting joint training for clinical and laboratory staff to strengthen core competencies and improve understanding of AMR; and minimizing staff turnover.
- *Establishing antibiotic stewardship programs* to address low demand for microbiology services, while routinely sharing AMR surveillance reports.
- *Maintaining the highest standards and practices* by: (a) relying on proficiency testing from WHO or other reliable sources to assess antimicrobial testing for surveillance; (b) using National Reference Laboratories (NRL) to facilitate the provision of standard microorganisms for internal quality control of media, which is critical for validating the accuracy and reliability of laboratory test results for patient management and surveillance; (c) adopting and maintaining up-to-date standards for susceptibility testing; and (d) sourcing animal blood or preparing blood agar plates centrally or regionally in order to reliably culture and sensitivity test certain pathogens from clinical specimens.
- *Enrolling laboratories in the Stepwise Laboratory Improvement Process towards Accreditation,* as it builds quality awareness, improves performance, builds confidence among clients, provides some external assurance for laboratories, and boosts professionalism, skills, and morale among laboratory staff.

Endnotes

1. The value of a statistical life (VSL) represents the amount that a society is willing to pay to prevent one death. Estimates of this value vary widely; however, a global meta-analysis conducted by the Organisation for Economic Co-operation and Development (OECD) in 2012 provides VSL estimates for use in policy analysis based on a compilation of stated-preference studies. The OECD estimates that the VSL in member countries is US$1.5 to 2.5 million (Lindhjem *et al.* 2012). The VSL for countries in East Africa can be estimated by adjusting this OECD-specific estimate by the country's GDP per capita, adjusted for purchasing power parity (Lindhjem *et al.* 2012). The VSL is then multiplied by the number of deaths avoided to estimate the value of reduced mortality.
2. For example, a 2006 study (Cosgrove 2006) provides estimates of the cost of treating methicillin-resistant *S. aureus* (MRSA), VRE, and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae,* compared to non-resistant strains, in the United States. A 2012 study (Neidell *et al.* 2012) compared the cost of health care through hospital charges and length of stay for resistant and susceptible infections in New York hospitals.
3. SLIPTA is a WHO system to measure and evaluate the progress of laboratories toward international accreditation and identify areas for improvement. Facilities are awarded a rating of up to five stars based on an on-site audit of laboratory operating procedures, practices, and performance.

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Annex 9. Antimicrobial Use in Human Health Care and AMR: Summary Report

Misuse of antimicrobials in humans is prevalent in both low- and high-income countries. Observers routinely find, for example, serious overuse of antibiotics for viral upper respiratory tract infections—but underuse of appropriate antibiotics for pneumonia; and serious overuse of antibiotics in acute cases of diarrhea—but underuse of oral rehydration solution (Kathleen 2011).

Multiple studies[1] have found that the causes contributing to the spread of AMR in countries include numerous factors related to the production, distribution, and use of antimicrobial agents in human health care. Among these factors are: excessive numbers of antimicrobials in the pharmaceutical market, aggressive pharmaceutical promotion, economic incentives whereby prescribers gain income from dispensing or selling the medicines they prescribe, over-prescription or irrational prescription in primary health care facilities and hospitals, poor adherence to infection prevention and control protocols in health facilities, and treatment interruption by patients. In sum, many features of antimicrobial use in human health care contribute powerfully to AMR. Improving antimicrobial stewardship in the human health system is thus a key objective for all countries pursuing AMR containment. This report provides tools that can help countries advance towards that objective.

Rather than generalizing widely from the specific country experiences reported in our case studies, this report aims above all to demonstrate methods that countries can use to diagnose the functioning of their own antimicrobial use chain and identify measures that would improve antimicrobial stewardship in their specific contexts. Our concluding action recommendations are geared toward this goal.

To complement the findings from a literature review conducted for this report (Figueras *et al.* 2016), case studies in six low- and middle-income countries (Botswana, Croatia, Georgia, Ghana, Nicaragua, and Peru) were prepared from November 2015 to April 2016 to provide a cross-country "snapshot" of factors in the health system that may contribute to AMR. In comprehensively examining the antimicrobial use chain, the objective was to identify the weak links and factors that may contribute to misuse or overuse of antimicrobial drugs, along with possible interventions to promote more prudent use of these agents. Figure A9.1 describes the therapeutic chain processes reviewed and sources of data collected for generating country comparisons. The case studies carried out focused on bacteria, antibacterials, and resistance to antibacterials. The terms "antibiotic" and the more general term "antimicrobial" are used interchangeably in this report.

A. Purpose, Rationale, and Findings of the Case Studies

Case Study 1—Antibiotic Market Offer

Purpose: Review the list of antimicrobials authorized by the Ministry of Health or equivalent agency in the participating countries to analyze drug approval, offers, and marketing processes.

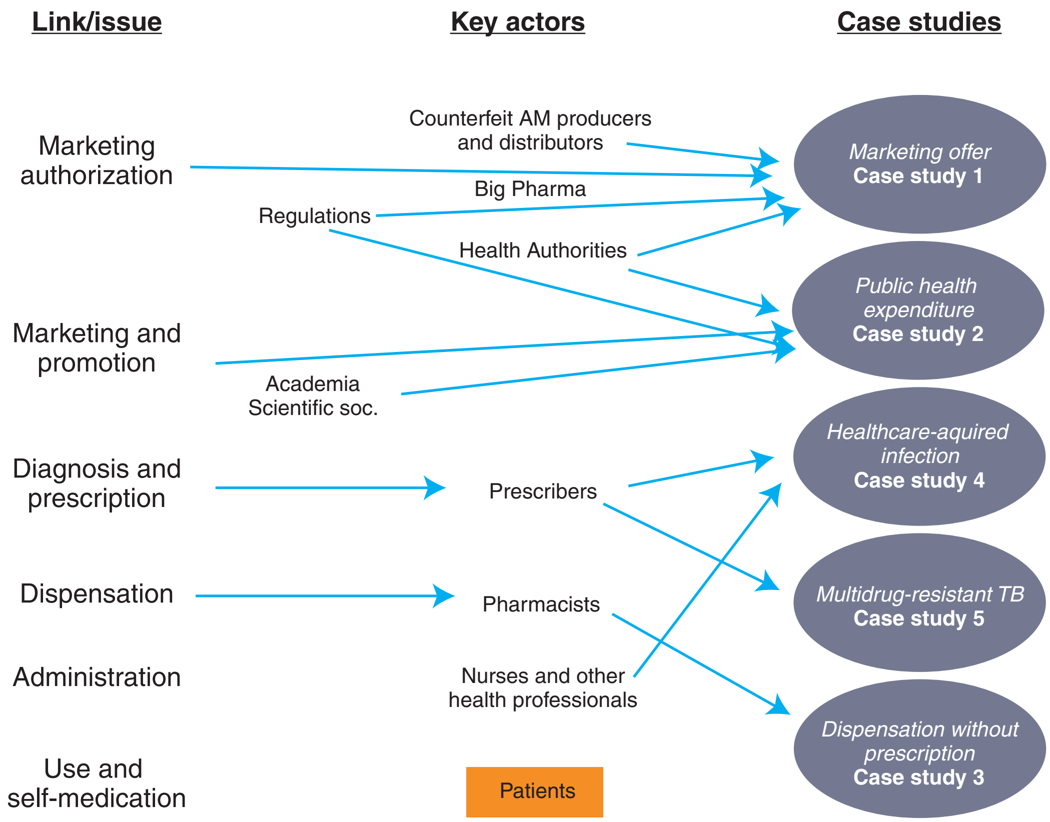
Rationale: A reasonable antimicrobial offer in the pharmaceutical market could improve the selection of appropriate antimicrobials and how these drugs are prescribed and used. Two specific considerations were:

- The introduction of antimicrobials that do not have proven superiority over already marketed products—sometimes referred to as "me-too drugs"—increases the cost of medicines and the unnecessary exposure to promotional activities that contribute to AMR.
- Some fixed-dose combinations (FDCs)[2] which include an antimicrobial in their formulation do not offer any clear advantage to the use of the components separately. Additionally, they increase the risk of involuntary exposure to antimicrobials because prescribers or users are not aware that the product contains an antimicrobial.

Findings:

- There were significant differences in the six countries regarding the type and number of available antimicrobials (Figure A9.2). Peru and Botswana have almost twice as many different antimicrobials as Georgia, Nicaragua, or Croatia.
- The variability is explained in part by the high number of bio-equivalent drugs offered as different brand-name drugs containing the same active ingredient (Figure A9.3), and also by the multiplicity of "me-too" or redundant medicines.
- The proportion of FDCs, relative to single brand-name products, ranged from less than 20 percent (Croatia and Peru) to almost 30 percent (Ghana).

FIGURE A9.1. A Basic "Antimicrobial Use Chain"



- The proportion of brand names per individual antimicrobial also varied significantly among countries, being lower in Croatia (3:1) and higher in Peru (7:1). Such a plethora of products with the same ingredients causes confusion among prescribers and users, complicates antimicrobial selection and therapeutic decision making, and increases pharmaceutical promotional pressure (useful for the manufacturer, but not beneficial and indeed often counterproductive for prescribers and users). The "ideal minimum" of brand names to ensure clinically adequate coverage and maintain prices should be encouraged.
- Some antimicrobials found in the different countries are not sold in the United States and in European Union countries (for example, sultamicilin, netilmicin, prulifloxacin, or nifuroxazide), and some have been withdrawn from the market due to their toxicity (for example, fusafungine). This demonstrates the lack of harmonization in regulatory schemes—where such schemes exist.

Case Study 2—Antibiotic Consumption in the Public Health System

Purpose: Review expenditure data in the public health system to analyze prescription and consumption processes at the national level.

Rationale: Consumption data analyses are useful to identify potential misuse of antimicrobials in the health system. The combination of market offers and consumption data is helpful to identify appropriate antimicrobial use.

Findings:

- Data on consumption of antimicrobials expressed in units were available in the participant countries, although the data were not always comparable. Harmonizing information about antimicrobial consumption in terms of defined daily doses (DDDs) helps analyze cross-country consumption patterns.
- Consumption in the system tended to be higher, in per capita terms, in countries with higher per capita GDP, although the relationship was not

FIGURE A9.2. Single-Compound Antibacterial Products

Country	Active Ingredients*	Brand Names (Products)	Brand Names/Active Ingredient	Presentations**
Botswana	76	304	4.0	613
Croatia	59	168	2.9	306
Georgia	53	238	4.5	388
Ghana	44	271	6.3	399
Nicaragua	55	274	5.0	396
Peru	77	513	6.7	1,226

**Individual* antibacterials; **Different strengths and packages.

→ Peru and Botswana have about twice as many antimicrobial drugs on the market as Georgia, Nicaragua, or Croatia. These are "me-too" or redundant medicines.

→ The average number of different marketed brand names per single antibacterial is almost 2.5 times greater in Peru and Ghana than in Croatia.

→ What is the added value of having an average of six different brand names containing the same antimicrobial agent? Besides confusing the prescriber and user, this may contribute to increased pressure on firms to sell more antimicrobials than their competitors, in order to preserve and/or expand market share.

FIGURE A9.3. Top Five Active Ingredients According to Number of Brand Names

Country	1st (n)	2nd (n)	3rd (n)	4th (n)	5th (n)
Botswana	Amoxicillin (18)	Metronidazole (17)	Erythromycin (16)	Gentamycin (11)	Ciprofloxacin (11)
Croatia	Cefuroxime (14)	Azothromycin (10)	Ciprofloxacin (9)	Moxifloxacin (9)	Metronidazole (8)
Georgia	Ceftriaxone (27)	Azithromycin (27)	Chloramphenicol (15)	Amoxicillin (13)	Amikacin (10)
Ghana	Ciprofloxacin (38)	Cefuroxime (31)	Ceftriaxone (26)	Azithromycin (23)	Metronidazole (22)
Nicaragua	Ciprofloxacin (33)	Azithromycin (18)	Metronidazole (16)	Amoxicillin (14)	Clarithromycin (13)
Peru	Ciprofloxacin (69)	Azithromycin (43)	Amoxicillin (32)	Clarithromycin (28)	Levofloxacin (23)

→ Levofloxacin, clarithromycin, and azithromycin are broad-spectrum, second-choice, expensive antimicrobials.

→ There is no clinical or therapeutic justification for having 27 products containing ceftriaxone in Georgia, 23 containing levofloxacin in Peru, or 13 containing clarithromycin in Nicaragua.

→ A redundant market offer increases the risk of irrational or inappropriate use of antimicrobials.

statistically significant. The lowest consumption was in Ghana (2015 per capita GDP $1,381) and the highest in Botswana (2015 per capita GDP $6,360) and Croatia (2015 per capita GDP $11,535). Consumption data for private health services providers and self-medication were not available.

- The most consumed antimicrobials differ among countries. In Botswana, Ghana, and Nicaragua, four to six different antimicrobials represented 90 percent of the total consumed units, while in Peru and Georgia, the same share of total consumed units was divided across 15 and 19 different antimicrobials, respectively. This finding suggests that in the first set of countries the public prescription of antimicrobials may be more tightly controlled (either by restricted drug lists or better adherence to drug guidelines). A comprehensive consumption analysis including public and private sectors would help further assess country patterns.

- The list of the most consumed antimicrobials, in units, in each country was dominated by antimicrobials that are sold under different brand names (Figure A9.4). The specific rankings differed to some extent among countries. The observed difference probably does not reflect different disease profiles, because some of these antimicrobials are second-line or broad-spectrum. The high use of some antimicrobials suggests irrational prescription and use. (For example, among the most prescribed antimicrobials are azithromycin, imipenem-cilastatin, dicloxacillin, or cefuroxime).
- Examples of potential inappropriate use of antimicrobials that could not be detected by careful analyses of macro prescription and expenditure data are nonetheless provided by observed practices in some of the study countries. In Croatia, for example, the second antimicrobial in expenditure was azithromycin (AZM), which has unique pharmacokinetic and pharmacodynamic characteristics that give it unusual clinical properties for an antibiotic.

Azithromycin is used to treat or prevent a range of common bacterial infections, including upper and lower respiratory tract infections and certain sexually transmitted diseases. Azithromycin has become one of the top 15 most prescribed drugs and best-selling antibiotics. However, a growing body of evidence derived from post-marketing surveillance, including analysis over an eight-year period by the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), links azithromycin to sudden cardiac death risk (Giudicessi and Ackerman 2013). Researchers have also noted additional risks associated with widespread use of azithromycin,

FIGURE A9.4. Top Five Antimicrobials Consumed

(Units/1,000 Population;
Except in Georgia, Where Data Are in Defined Daily Doses/1,000 Population)

Shows broad-spectrum antimicrobial or antimicrobial used in case of resistance

Shows a relationship between most-consumed antimicrobials and antimicrobials with most marketed brand names for that active ingredient

	SWA	PER	HRV	GHA	GEO	NIC
amoxicillin	**134**	**2,215**	268	278		**4,607**
amoxicillin + clavulanic			976		1,353	
azitromycin			**565**		**1,357**	
cefalexin		371				
ceftriaxone	90				**4,130**	
cefuroxime			**344**			
ciprofloxacin		**646**	**309**	**132**	1,300	**1,292**
clindamycin					872	
cloxacillin	91					
co-trimoxazole				182		
dicloxacillin		1,046				
doxycycline				38		1,326
isoniazide		1,092				
metronidazole	**129**			**330**		**899**
nitrofurantoine						2,687
penicillin	160					

→ In all participant countries, a relationship is observed whereby antimicrobials marketed under a larger number of brand names exhibit higher consumption.

as the drug is a serious pollutant in the water environment. Accordingly, experts have recommended that azithromycin be used only in situations where well conducted clinical studies have demonstrated an indisputable superiority over standard treatment or placebo (Cohen and Grimpel 2013; Gros *et al.* 2010).

- Imipenem + cilastatin (second in Peru) and meropenem (third in Peru and fifth in Croatia) are examples of expensive antimicrobials that should be treated as reserve drugs. Although meropenem is an expensive product, 79 units/1,000 inhabitants were prescribed in Croatia during the study period, while in Peru, 44 units/1,000 inhabitants were sold in the same period. In the case of the fixed-dose combination of imipenem + cilastatin, 30 units/1,000 inhabitants were prescribed in Peru. While this figure appears relatively low, it is important to note that this agent was the second most expensive antimicrobial in Peru, according to our study findings. Beyond the high cost, there is the problem of potential irrational use of such restricted antimicrobials. Depending on their availability, these drugs tend to be used as empirical treatments.
- Although it is difficult to compare the participant countries, the macro data of the antimicrobial consumption profile in Nicaragua appear more aligned with principles of rational prescribing. The only antimicrobial consumed that attracts attention is dicloxacillin, third in the expenditure ranking of this country, with a prescription rate of 593 units/1,000 inhabitants. Dicloxacillin is an example of the beta-lactam antimicrobials useful in bacteria resistant to penicillinase; for this reason, it is strongly recommended to use it only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.
- These country examples highlight the need to closely survey potential problems that can be identified from macro consumption data, but that should be monitored locally, in order to design the most appropriate interventions.

Case Study 3—Antimicrobial Availability Without Prescription

Purpose: Document dispensation and advice provided to self-referred patients after a young woman simulating lower urinary tract infection symptoms visited 20–50 pharmacies.

Rationale: Pharmacists are often the first point of contact with the health care system in many countries, and their dispensing practices for self-referred patients contribute to rational or irrational use of antimicrobials. Indeed, in many low- and middle-income countries, pharmacists are the *de facto* prescribers of the drugs that are sold and consumed by patients.

Findings:

- In more than 60 percent of pharmacy visits by the case study's simulated "self-referred patient" (156 out of 246 visits), antimicrobials were dispensed without a prescription derived from appropriate clinical diagnosis. This practice in five of the six countries studied reflects limited or absent enforcement of health regulations that prevent dispensing of antimicrobials without prescription. Croatia was an exception (only one dispensation in 20 visits). See Figure A9.5.
- In more than 90 percent of the visits, the simulated self-referred patient was not clinically evaluated: for example, the pharmacist did

FIGURE A9.5. Distribution of "Simulated Self-Referred Patient" Visits That Ended with Dispensation of an Antimicrobial, by Country

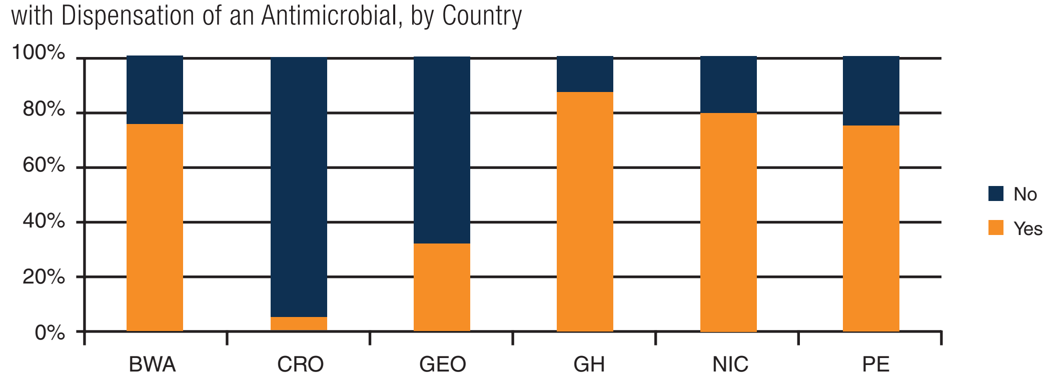


TABLE 5. Antimicrobials Dispensed without Prescription

In orange, products with more brand names or irrational fixed-dose combinations, by country

Country	Specific Antimicrobials Dispensed (number of pharmacies dispensing the antimicrobial)
Botswana	norfloxacin (11), amoxicillin + clavulanic acid (7), ciprofloxacin (7), metronidazole (2), nalidixic acid (1), nitrofurantoin (1)
Croatia	amoxicillin + clavulanic acid (1)
Georgia	ciprofloxacin (11), doxyciclin (2), norfloxacin (1), amoxicillin (1), furacillin (1)
Ghana	amoxicillin + clavulanic acid (10), cefuroxime (7), ciprofloxacin (5), cefuroxine + tinidazole (4), cefixime (1), fluconazole (1)
Nicaragua	nalidixic acid + phenazopyridine (9), nitrofurantoin (7), ciprofloxacin (4), cefixime (2), nitrofurantoin + phenazopyridine + ciprofloxacin, cefadroxil, furazolidin, gentamycin, levofloxacin, ofloxacin
Peru	norfloxacin + phenazopyridine (16), ciprofloxacin + phenazopyridine (14), ciprofloxacin (7), nitrofurantoin (2), levofloxacin (2), amoxicillin + clavulanic acid (1)

Source: Case study 3, data from 156 pharmacies that agreed to sell antimicrobial without prescription in the six study countries.

not ask the patient about drug allergies. Such negligence can place patients at severe risk of developing drug-related complications, including drug ineffectiveness, adverse drug effects, overdosage, underdosage, and multiple-drug interactions.

- The pattern of antimicrobial recommendations by pharmacists in the different countries reflected the prevailing pharmaceutical market offer in each country (Table 5). For example, irrational fixed-dose combinations with phenazopyridine were common in Peru and Nicaragua. Also, a relationship was observed between some “redundant” products and high dispensation (for example, cefuroxime with 31 brand names in Ghana accounted for 25 percent of dispensations).
- Advice to visit a physician was provided in 48 out of the 90 simulated cases in which no antimicrobial was dispensed (53 percent of cases); the remaining 47 percent of pharmacist interactions with “fake” self-referred patients ended without treatment and without advice to visit a physician for follow-up consultation.

Case Study 4—Hospital-Acquired Infections (HAIs)

Purpose: Review medical records or information provided by health care providers on patients with HAIs in one or more hospitals to analyze adherence to guidelines, compliance with prophylactic measures, prescription, and health care quality assurance processes.

Rationale: HAIs are a growing global problem, not only in terms of associated morbidity, mortality, and increased health care costs, but because of the growing recognition that most HAIs can be prevented (Lobdell *et al.* 2012).

- Some HAIs are avoidable if health professionals involved in hospital care follow the necessary prophylactic measures and infection prevention control norms.
- The problem of HAIs is greatly aggravated by the increasing presence of resistant and multi-resistant microorganisms and inappropriate antimicrobial use.
- Reducing HAIs requires a multifaceted, holistic response, because the problem involves multiple actors and processes in the therapeutic chain.

Findings:

- Health personnel in selected hospitals in the study countries recorded a number of factors that appeared to contribute to observed onset of HAIs. These included structural deficiencies, such as lack of safe water and basic sanitation systems, and operational problems, such as overcrowded wards, lack of cleaning supplies and protective equipment, or poor hand hygiene practices. These findings underscore the need to address both structural factors and health care processes in efforts to reduce the spread of resistant microorganisms that cause HAIs.
- Adherence to Infection Prevention and Control (IPC) protocols was partial overall, and sometimes

poor. Rigorous compliance with IPC protocols is a necessary and highly effective means to prevent infection in health care facilities.

- Access to patients' information and data quality were poor. Researchers frequently noted incomplete and improperly recorded information, or found hospitals requiring fees to provide data from medical records, despite Ethical Committee guidance.
- Urgency sometimes dictates empirical treatment based on the experience and judgment of health care personnel. For example, a dangerous infection with an unknown organism may be treated with a broad-spectrum antibiotic while the results of bacterial culture and other tests are awaited. In some of these cases, reserve antimicrobials are prescribed, although the microbe might be sensitive to a "less strong" antimicrobial. For example, in Croatia, all 24 analyzed cases received an antimicrobial appropriate to the causal bacteria, but in one-third of patients, the causal organism was ultimately determined to be sensitive to common antimicrobials. Knowing the resistance patterns in the microorganisms associated with an HAI is important to improve the precision of empirical treatments and avoid an unnecessary switch of antimicrobials later in the treatment course. Reserve antimicrobials should be prescribed only when need has been demonstrated.
- HAIs tend to complicate the recovery of hospitalized patients. For example, in seven out of nine analyzed cases in Georgia, recovery time varied between 45 and 120 days. Four of nine patients died as a result of HAI complications.

Case Study 5—Multidrug-Resistant Tuberculosis

Purpose: To analyze treatment compliance, a review of the medical records of MDR-TB patients in one or more hospitals was conducted, after health professionals helped identify MDR-TB cases.

Rationale: Multidrug-resistant tuberculosis is a growing global public-health problem. Data from WHO show that, in 2012, there were 450,000 new cases of MDR-TB, and that extensively drug-resistant tuberculosis (XDR-TB) has been identified in 92 countries.

- Failures along the therapeutic chain for MDR-TB increase the risk of AMR. MDR-TB exhibits multiple aspects of AMR. Moreover, problems in treating TB can indicate a country's or institution's readiness (or otherwise) to deal with AMR.
- Observation of a number of cases in the study countries served to identify relevant issues at the level of the individual patient, the end user of antimicrobials. Adherence to treatment is especially difficult for diseases that, once controlled, can be asymptomatic.

Findings:

- Multidrug-resistant tuberculosis is a growing problem. MDR-TB and XDR-TB depend on genetic modifications of the causal TB microorganisms (*M. tuberculosis*). To control the spread of disease, it is important to understand the mechanisms that contribute to the appearance of MDR.
- Possible causes of AMR in particular patients were inferred from their treatment history. "Non-adherence to treatment" was a frequent comment in the medical reports of patients with MDR-TB.
- Specific causes of withdrawal from treatment for MDR-TB (and other diseases) vary and are important to identify, understand, and address.
- For example, in Botswana, the appearance of MDR-TB was attributed to patients' non-adherence to treatment in four of ten cases. Inability to tolerate the prescribed medicines was reported to have contributed to patients' withdrawal from treatment in three out of ten cases.
- Eight MDR-TB patients were identified in two Ghanaian hospitals. For all patients, there was complete information regarding onset dates, initial treatment, and changes in the treatment regime. This allowed researchers to understand the temporal sequence between the initial TB diagnosis and the MDR-TB diagnosis. All patients had at least one relapse, but three out of eight patients had four, three, and two relapses, respectively. Moreover, five of the patients had failed to come for treatment; they were without treatment for 50, 26, 25, 20, and 14 days, respectively. Lack of adherence to treatment increases risk of MDR-TB or XDR-TB. Personal, family, cultural, religious, and financial factors may explain the lack of adherence to treatment.
- Findings from Peru show the diversity of causes contributing to poor treatment adherence or

withdrawal from treatment. Nonmedical causes for poor adherence included transportation problems linked to financial constraints. Some patients reportedly interrupted or abandoned therapy because they lived far from treatment facilities, and out-of-pocket transportation costs were unsustainable for patients and families. More strictly medical causes of non-adherence included: the length of the treatment course; difficulties in treating comorbidities; adverse reactions to some medications; and patients' decisions to seek alternative or traditional treatments.

- Another observation in Peru was the number of family members living together who had MDR-TB. Up to 23 patients had one or more relatives diagnosed with TB, including 16 with MDR-TB.

B. Recommendations

Overuse and misuse of antimicrobials contribute significantly to AMR. On the basis of the literature review and case study findings, some targeted or system-oriented approaches were identified to improve rational prescribing and a more prudent use of antimicrobials. They are outlined here.

From Surveillance to "Surveillance + Action"

To address the imbalance of information in the health system and counteract the pharmaceutical industry's often indiscriminate promotion of products to prescribers and dispensers, a systematic effort to collect data and generate evidence on antimicrobial use practices is required. Promising tools and approaches include:

- *Drug-utilization studies (DUS).* These can help identify failures in any link of the therapeutic chain. Designing and developing DUS with the active participation of the involved health professionals could help identify problems and contextually appropriate solutions within particular settings.
- *Knowledge management.* Local information regarding the use and misuse of medicines is not published in indexed medical journals and remains as "grey" medical literature. Easy access to this source of knowledge would help policy makers identify appropriate context-specific interventions to include in countries' AMR action plans. To this end, consideration should be given to the establishment of global, regional, or national observatories of grey literature and local studies. This would increase understanding of real-world practice in antimicrobial use and facilitate the design of pragmatic interventions.
- *Better use of information and communications technologies (ICT).* To improve knowledge of antimicrobial consumption and related expenditures, and to detect problems of antimicrobial overuse or inappropriate use, efforts should be made to promote the transition to electronic recording of consumption data, and to electronic medical records. This would require the definition of minimum common information to be included in such systems to facilitate analyses and comparisons. Training in the use of ICT tools would be needed for health professionals, including health governance authorities. Such training could encompass electronic database research, analysis of results obtained from databases, and awareness of biases that may arise due to the characteristics of such information.

  Use of electronic records has the potential to help identify patterns related to antimicrobial misuse by health personnel, health care facilities, and among patients. Electronic records might also guide the adoption of corrective measures. Similarly, there may be opportunities to capitalize on "big data" research by aggregating data sets to generate new knowledge for policy making and program development. ICT tools could be harnessed to track antimicrobials after their market introduction to determine their safety and efficacy, and any emergence of adverse effects.
- *Antimicrobial Stewardship Programs (ASPs)* have proven efficacy in controlling AMR by improving how antimicrobials are used and in reducing the use of broad-spectrum antimicrobials in health care facilities. ASPs have a bigger impact if they combine different methods and approaches and are adapted to local culture and peculiarities of antimicrobial use. The adoption of these programs should be promoted, and health professionals should be trained appropriately, including those working in nonhospital health facilities. Antimicrobial stewardship is critical for improving patient outcomes, reducing adverse events, decreasing health care costs, and preventing spread of AMR.

Various definitions and models of ASPs exist. According to the U.S. CDC, core elements of hospital ASPs may include:

- ***Leadership commitment:*** Dedicating necessary human, financial, and information technology resources.
- ***Accountability:*** Appointing a single leader responsible for program outcomes and accountable to an executive-level or quality-focused hospital committee. Experience with successful programs shows that a physician or pharmacist leader is effective.
- ***Drug expertise:*** Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- ***Action:*** Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (antibiotic "time-out").
- ***Tracking:*** Monitoring antibiotic use and resistance; process measures (for example, adherence to facility-specific guidelines, time to initiation or de-escalation); and impact on patients (for example, antibiotic-related adverse effects or emergence of *Clostridium difficile* infections).
- ***Reporting:*** Regular reporting of information related to these condition to doctors, nurses, and relevant staff.
- ***Education:*** Clinicians can be educated about disease state management, resistance, and optimal prescribing. Training can also encompass adoption, adaptation, promotion, and adherence monitoring for treatment protocols and guidelines. Training on prudent use of antimicrobials and clear information about common diseases that should not be routinely or preventively treated with antimicrobials is a paramount concern.
- ***Incentives:*** The adoption and implementation of the above measures could be promoted by positive financial incentives, while removing perverse incentives for prescribers. Measures could include changes in how health care providers are reimbursed, and prohibiting antimicrobial sales by prescribers to remove the financial incentive for overprescribing (U.S. CDC 2014).

Prevention of Antimicrobial Misuse at All Levels

- *Governance arrangements*. AMR is aggravated by antimicrobial misuse. This problem is made worse by the absence of effective legislation and regulations that influence prescribing through restrictions and requirements, including pharmaceutical registration, limited medicine lists, prescribing restrictions, and dispensing restrictions. Given the special nature of antimicrobials, a separate legal and regulatory framework and payment/reimbursement modalities could be adopted to promote appropriate use of these drugs. Such special arrangements already exist in the pharmaceutical sector for opioids.
- *Legislation and regulations*. Countries may strengthen their capacity to control AMR by developing new legislation and regulations or revising existing ones. This could include developing enforcement capacity to control and/or remove any financial incentives to individual providers and institutions to use antimicrobials indiscriminately. Deliberate managerial strategies can strengthen the capacity of national authorities to institute and enforce legal measures in the health system for promoting and ensuring rational antimicrobial use. The deployment of such strategies merits priority attention from governments. Adequate oversight of both supply and demand in the antimicrobial market also requires effective coordination with non-health sector entities (for example, in trade and customs, finance, veterinary, and specialized international agencies).
- *Oversight of offer and prescribing*. The spread of AMR, simultaneous lack of access to effective antimicrobials in many poor communities, and evidence of rampant misuse of these drugs in the health system reinforce the need for political commitment to strengthen oversight of antimicrobial market offer and dispensing practices.

  Two areas where priority adoption of oversight measures is likely to yield immediate benefits are limitations on the market offer of fixed-dose combinations and reduction in the number of "uniquely-named" products. Progress in these two areas will help prevent confusion among providers, patients, and payers, and improve therapeutic options and health outcomes.

The formulation, adoption, and adaptation of clinical guidelines advising against using or unnecessarily prescribing antibiotics for common problems should also be reinforced with dedicated training, supervision, and monitoring and evaluation of prescription patterns in health facilities, pharmacies, and among individual doctors. Measures toward effectively combating counterfeit/substandard antimicrobials and increasing compliance with "by prescription only" labeling are also critical actions to be pursued.

- *Harm reduction from nonprescription sales* of antimicrobials is another priority area for action. Obtaining antimicrobials in pharmacies without a prescription was a common practice in the studied countries. Widespread training to explain the risks of inappropriate dispensation, strict enforcement of norms and regulations, accompanied by fines and legal consequences may help prevent harm caused by inappropriate use of antimicrobials. Croatia is the only country among the six studied that can serve as an example of good practice.

- *Decreasing the risk of hospital-acquired infections* is very important, both because of the vulnerability of immunocompromised hospital patients and because of the high risk of AMR emergence and spread in health care facilities. By spreading disease in settings where patients come for healing, HAIs fundamentally undermine the mission of hospitals and other health facilities. Unfortunately, hospitals and health facilities are also the places where multidrug-resistant diseases are most likely to emerge.

  Many structural and care-process factors involved in the prevention of HAIs need to be addressed, including: availability of safe water and basic sanitation services in health care facilities; medical waste management systems and provision of related training to health personnel; unbroken availability of cleaning supplies; deployment of infection prevention and control measures; and adherence to clinical guidelines and recommendations for the proper use of antimicrobials and reserve drugs.

- *Non-adherence to treatment regimens* is another factor to control since the emergence of numerous cases of drug-resistant pathogens can be traced to this source. Treatment compliance is important for infectious diseases generally, but it is vital in severe conditions such as TB, as our literature review and country cases studies confirmed.

- *Information, educational, and communications campaigns* that incorporate behavioral and social aspects and address both health services personnel and the general public are also essential. This effort should include the provision of accurate, evidence-based information grounded in actual clinical practice and not only on data from clinical trials.

  Authorities may launch national and local campaigns to raise public awareness of the need to avoid demanding and unnecessarily using antibiotics for common conditions. Children and adolescents, in particular, should be the focus of well-designed and innovative campaigns to promote the appropriate use of medicines in general and antimicrobials in particular. While doctors should not overprescribe antimicrobials, it is also important that patients not indiscriminately demand them, under the influence of manipulative drug advertising. The country case studies found many examples of such supplier-induced antimicrobial use.

Countries Can Win the Battle

By providing frontline data on antimicrobial use in human health in six countries, our discussion has underscored the multiple complexities involved in attempting to contain AMR. Moreover, our analysis has not yet touched the question of antimicrobial management in veterinary health. Thus, the overall picture emerging from our discussion may appear discouraging. However, as we conclude this report, we want to emphasize that some countries have already begun to confront antimicrobial stewardship challenges systematically, with impressive results. Progress is possible. It's already happening.

Clearly, to reduce growing AMR risks, antimicrobials must no longer be considered as "just another drug." These are unique products that have the potential, if well handled, to save vast numbers of lives and significantly improve population health. However, unlike most other medicines, antimicrobial agents can lose their efficacy for whole human populations with disconcerting speed, if their use is poorly managed. Promotion of the prudent use of medicines in general and antimicrobials in particular should be at the core of efforts to prevent AMR in health systems. Programs and interventions to ensure rational use of antimicrobials should be seen as an integral part of continuous quality-assurance processes for improving the delivery of safe, effective health and medical care services for all.

The responsibility for promoting rational use of antimicrobials clearly includes policy makers, pharmaceutical companies, health system administrators, and health services providers. But this is just the beginning. Responsibility for protecting the efficacy of these crucial agents must also be shared by patients themselves, and the wider public. What is required is a society-wide effort, based on scientific evidence, to act in all settings where antimicrobials are used.

In countries where such a society-wide effort has been undertaken, remarkable gains have been achieved. A recent study of the experience in the Netherlands has confirmed that it is possible to reduce AMR to low levels across a national population (Sheldon 2016). To do so requires active promotion and effective coordination between the health and agricultural sectors, working together under a One Health approach. But success also demands implementing policy and operational measures in the health system to create a different medical culture. For example, in the Netherlands, antibiotics are supplied only on prescription at the primary care level, which serves an effective gatekeeper function in the health system. The study documents that Dutch doctors do not overprescribe antimicrobials, and Dutch patients do not routinely demand them, reflecting a culture of "cautious prescribing" built up over time.

Part of creating this culture has been general practitioners' acceptance of strict professional guidance. Indications for use, type, and dosage of antimicrobials are issued by the College of General Practitioners (NHG), and these guidelines are increasingly followed. A 6 percent decrease in daily doses of antibiotics dispensed by pharmacies was recorded between 2011 and 2014 alone.

The Dutch experience also reflects a deliberate policy and operational decision to prioritize control of AMR through sustained work on hospital infections. This effort has been coordinated through the national Prevention Working Group, while prudent antimicrobial use has also been promoted through a Working Group on Antibiotic Policy. The effective application of these measures has helped the Netherlands achieve one of the lowest levels of AMR in the world.

The Netherlands program demonstrates that a comprehensive national effort to reduce antimicrobial mis- and overuse and contain AMR can succeed.

Endnotes

1. To assess the state of knowledge about AMR in the health system, a PubMed literature search was undertaken for this report using "antibiotic," "utilization," and "resistance" as keywords. The search covering the 2013–2015 period retrieved 981 references, which were reviewed and summarized. References were retrieved, organized and analyzed by Ishani Premaratne (WB) and Paul Pérez (FICF). Albert Figueras, with input from Patricio V. Marquez, prepared a summary note "Antimicrobial Use and Resistance: Initial Observations from Reviewed Literature," March 8, 2016, used for this report.
2. A combination drug is a fixed-dose combination (FDC) that includes two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in fixed doses (Collier 2012).

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Annex 10. Antimicrobial Use in Animals and AMR

Issues and Options for Low- and Middle-Income Countries: Summary Report

Without progress in tracking and controlling drug-resistant infection sources in animal populations, efforts to contain AMR in human communities cannot achieve lasting success. This report seeks to clarify what we know and don't about antimicrobial use and AMR in livestock today, with a view to informing policy makers' decisions on how best to engage the livestock production sector in country efforts on AMR.

The discussion draws on sources including a literature review, country case studies, and a regional case study. We first summarize what is currently known about the use of antimicrobials in animal production systems, the reasons producers use these drugs, and the limited available data on usage trends over time. Next, we analyze the mechanisms by which antimicrobial use in animal production systems may engender AMR in animals and humans. The report then reviews current strategies to reduce antimicrobial use in livestock and the obstacles these efforts face. The closing pages describe specific actions countries can take to limit antimicrobial use in livestock and contain the AMR threat in animal production. The options proposed align with the WHO Global Action Plan, the FAO Action Plan, and the OIE strategy on AMR.

Background and Research Questions

Antimicrobial use in livestock[1] is an important component of health management as defined by the OIE Terrestrial Code (Box 6). Antimicrobials are used to treat clinical and subclinical infectious diseases in animals. In some production systems, they are also used to prevent diseases, either because of an increased risk of exposure (metaphylactic treatment) or as part of routine health management. In addition to these therapeutic uses, antimicrobials may also be used as animal growth promoters, based on continuous delivery of sub-therapeutic doses.

Overall, the use of antimicrobials currently translates into more stable and, in some cases, higher incomes for farmers. Antimicrobials benefit consumers, as well, by enabling greater animal-source food production, leading to more accessibly priced livestock products. However, the use of antimicrobials also creates evolutionary pressures that allow the selection and spread of resistant microorganisms. Excessive and inappropriate use of antimicrobials accelerates the emergence of resistance (see Box 1). Increasing emergence and spread of AMR will affect the capacity to treat animal infectious diseases. Ultimately, this will undermine current livestock production practices and create uncertainties in food production systems.

Livestock species and animal production systems vary by regions, countries, and areas within countries. The roles of the veterinary profession and government veterinary services in antimicrobial distribution, use, regulation, and enforcement also vary.[2] Surveillance, monitoring, and regulatory infrastructure to address antimicrobial use in animals creates costs for countries. However, such infrastructure can also generate significant benefits by regulating the use of antimicrobials, limiting overuse and misuse, and reducing AMR risk.

The research summarized in this annex has focused on the following four issues:

1. The costs of antimicrobial use in livestock, in terms of financial costs at the farm level and the costs of registration, manufacture, and distribution by the pharmaceutical industry;

Box 6. Animal Health Management

Animal health management is "a system designed to optimise the physical and behavioural health and welfare of animals. It includes the prevention, treatment and control of diseases and conditions affecting the individual animal and herd, including the recording of illness, injuries, mortalities, and medical treatments where appropriate."

Source: OIE

2. Benefits from the use of antimicrobials in livestock, in terms of animal health and food production;
3. The impact of AMR on productivity and production costs in livestock, with the collection of data, where possible, on any linkages to human and environmental health;
4. The costs that would be involved in controlling antimicrobial use in animals so as to minimize AMR: including the costs associated with monitoring use, authorization, regulation, and enforcement, and the cost of implementing alternative approaches to livestock production and animal-health management that may be indicated to limit AMR.

A. Literature Review and Gaps in Knowledge

There have been a number of extensive reviews of antimicrobial use in livestock and animals with regard to the emergence and spread of AMR (Grace 2015; Landers *et al.* 2012; Rushton *et al.* 2014; Van Boeckel *et al.* 2015). Of note, much of the literature is focused exclusively on antibiotics, since these are the medicines about which there is currently most concern regarding the impact of resistance on human health. The term "antimicrobial" is often used to mean only antibiotics, rather than including anthelmintics, antifungals, antivirals, antiseptics, and disinfectants. Similarly, AMR in this context often refers specifically to drug-resistant bacteria.

A review commissioned by the OECD, supported by a global estimate of antimicrobial use (Van Boeckel *et al.* 2015), indicates that much is known about the biology of resistance mechanisms. However, the epidemiology of AMR in livestock and its impact on human and animal health have not been studied in detail. Little concrete information has been generated on this topic, beyond the observation of an association between the use of antimicrobials in animals and an increase in the levels of resistance found in those animal production systems (Bisdorff *et al.* 2012; van Cleef *et al.* 2015). Of note, most reviews to date have relied on antimicrobial usage data from a limited number of countries, with estimates of usage in other parts of the world based on modeling of livestock populations and extrapolation of usage from countries with data. There are concerns about how these estimates have been made and a suggestion that future estimates be based on more systematic, comprehensive data collection.

B. Use and Role of Antimicrobials in Animal Production

A number of authors have attempted to compare the overall amount of antibiotic used in humans versus in animals worldwide. One global study concluded that quantitatively, by weight of active ingredient, more antimicrobials are now used in food production than in humans. This relationship varies by region and country, however.

In livestock, antimicrobials are not only used for therapeutic purposes (to treat and prevent infectious diseases); they are also used for nontherapeutic purposes. Not long after antibiotics were first used in human medicine, in the 1950s, it was discovered that they had the effect of promoting more rapid growth when given to farm animals at low doses, helping the animals reach full market weight more quickly. Subtherapeutic quantities of some antibiotics (for example, procaine, penicillin, and tetracycline), delivered to animals in feed, can enhance the feed-to-weight ratio for poultry, swine, and beef cattle.

The purpose of using antimicrobials in animal production systems is not only to contribute to animal health and welfare, but also indirectly to contribute to human welfare by improving food security, food safety, and producer livelihoods. As it potentially increases producers' earnings through greater livestock productivity, the use of antibiotics in livestock also indirectly contributes to poverty alleviation.

Quantifying the Use of Antimicrobials Globally

There is wide variation in estimates of the total annual global antibiotic consumption in livestock, ranging from around 63,000 to over 240,000 metric tons. With growing human populations and increasing demands for food, the quantities of antimicrobials used in livestock production are expected to rise steadily as well. It is suggested that the global consumption of antibiotics in agriculture will increase by 67 percent from 2010 to 2030, and that consumption of antibiotics in the five major emerging national economies, Brazil, China, India, Russia, and South Africa, could increase by 99 percent in the same period.

It is, however, difficult to obtain exact figures on the use of antimicrobials. Causes include weak capacity among veterinary services to collect data at the country level. It is especially difficult to obtain figures in low- and middle-income countries, where the majority of livestock animals are kept on smallholdings and where antimicrobials are often sold without prescription. In these countries, official controls on the manufacture, importation, distribution, sale, and use of antimicrobials tend to be weak.

In addition, as discussed earlier in this report, there is growing concern over parallel markets, based on the production, distribution, and use of illegal, counterfeit, or suboptimal drugs. The share of such markets in some regions could be substantial.

C. Emergence and Impact of AMR in Livestock

A number of medically important antibiotics are also administered to animals in agriculture via feed or water. Out of the 27 different antimicrobial classes used as growth promoters in livestock, only nine classes are exclusively used in animals. Even some second-line antibiotics for humans are being used in animals, with no replacements for these agents in human use as yet in view.

Very little information is available about the impacts of AMR on the productivity of livestock production systems. The lack of data or data aggregation means that the health and economic costs related to AMR are also difficult to estimate. It is known that the consequences of AMR in both high-income countries and low- and middle-income countries would include failure to successfully treat infections, leading to more prolonged illness, production losses, death, and negative consequences for livelihoods and food security. Among other consequences, if medicines used to prevent and cure diseases no longer work, then animals would be less productive and potentially die prematurely.

As discussed in detail in Part II, AMR could also impact trade in livestock and livestock products. Food consumers may be increasingly concerned about contamination risks from imported products, while producers may worry about importing animals which might carry resistant microorganisms, for example livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA). In such scenarios, the economic impacts of AMR will likely be greatest in low- and middle-income countries, with the poorest regions of the world disproportionally affected.

Antimicrobial Use in Livestock and AMR in Low- and Middle-Income Countries

Effective livestock health management requires knowledge of current antibiotic use in local animal production systems, the purposes of such use, and the factors influencing livestock owners' decisions to deploy antibiotics or refrain from doing so. This information is also crucial for effective antibiotic stewardship.

However, as noted, in most low- and middle-income countries, veterinary antimicrobials including antibiotics are sold over-the-counter without veterinary prescription. These agents are essentially available without restriction. Most sources of information do not specify whether antibiotics are used for growth promotion rather than treatment or prevention of diseases. As a result, it is difficult to track antimicrobial use, not only as regards quantities and classes, but also the species in which these drugs are used and the specific purposes of use.

What appears certain is that the current increase in demand for animal-source food is fueling an increase in antimicrobial use. This increase in demand reflects rising populations in developing countries, alongside increasing wealth, urbanization, and changing dietary preferences. These factors are driving a change in dietary practices, in which consumption of eggs, milk, meat, and farmed fish is increasing much more rapidly than the consumption of staples or pulses.

This in turn is spurring changes in how animals are farmed. Poultry, pig, and fish production is increasing fastest, and ever more animals are kept in high input/high output intensive systems. In some instances, this development has been based on genetically improved breeds or lines, some of them poorly adapted to local conditions, either from the point of view of basic physiology and animal performance, or from the standpoint of health and susceptibility to infectious diseases. Rising animal numbers and changes in farming systems, against a background of endemic and epidemic diseases, are expected to increase the use of antibiotics in low- and middle-income countries' animal production systems—with a corresponding rise in the risk of AMR.

Indeed, several studies suggest that AMR is already common in agricultural systems in low- and middle-income countries. Resistance primarily appears to concern first-line antibiotics. However, there is a high level of uncertainty on the available figures, either because of the methodology used to produce them, or because of the partial representativity of the underlying studies.

Transmission Pathways for AMR

Any use of antimicrobials (in human, animal, plant, or environment) creates evolutionary pressures that can generate AMR. Resistant bacteria and genetic material conferring resistance in bacteria can then be transmitted from animals to humans in multiple ways. Mainly this transfer occurs through the food chain, from close or direct contact with animals, and through the environment. Whether all three routes of transmission are equally important remains unclear. To date, public-health measures have tended to focus primarily on the food system to ensure that food consumers are not affected.

Transmission pathways other than food may be significant, however. A proportion of antibiotics used in food animals are excreted unmetabolized and enter sewage systems and water sources. Animal waste may contain resistant bacteria, and could also contain antibiotics that could then foster the emergence of AMR beyond those in an animal's gut—including bacteria that may pose a greater risk to humans. Manure from farm animals is often used on crops as fertilizer. This has been shown to create resistance in soil organisms. Such mechanisms need further specific exploration to document precise transmission pathways and environmental impacts.

The OIE Terrestrial and Aquatic Codes provide guidance on how to assess AMR risk arising from the use of antimicrobials in animals.[3] The antimicrobial compounds used and how they were used, microbial co-selection, fitness and persistence mechanisms, host lifestyle, and food treatment conditions are among factors that influence the antibiotic resistance cycle.

Significance of Antimicrobial Residues

The administration of antimicrobials to farm animals, both therapeutically and for growth promotion, may result in antimicrobial residues in tissues, milk, or eggs. These residues are usually present in very small amounts and most of them do not create public-health problems, as long as their toxicological significance is below a predetermined threshold. However, if present in high concentrations, the residues can have important public-health and economic implications, such as: allergic reactions, selection of resistant pathogenic and nonpathogenic bacteria, toxicity, and carcinogenicity of certain food products.

The most important cause for the occurrence of antimicrobial residues in animal tissues is insufficient time for the drug to be eliminated from the body of the animal before slaughter or harvesting of food, such that the persisting residue exceeds the maximum residue limit. Maximum residue limits for residues of veterinary drugs are the maximum concentrations of residues legally permitted in or on a food, as determined by the internationally recognized standards of the Codex Alimentarius Commission. It is important that veterinarians, producers, and farmers respect the prescribed withdrawal times prior to slaughter or harvesting of food products. This minimizes the risk of AMR emerging through consumption of animal-source food products.

D. Measures to Reduce Antimicrobial Usage and Find Alternatives

Some countries have already banned the use of antibiotics for growth promotion. Banning this use in livestock has generally resulted in a substantial decrease in antibiotic resistance. Other countries have also engaged in voluntary re-labeling of antibiotics to reduce their use as growth promoters and help tackle at source the problem of AMR arising in livestock. Some countries have also put in place policies for drastic reductions of therapeutic uses, with subsequent impact on the incidence of AMR.

Given poor or nonexistent monitoring of the use of antimicrobials in livestock and the associated impacts on production, public health, and environmental health, it can be a challenge to generate the interest among decision makers that is required to bring about positive change. This applies particularly to lower middle-income countries. An incentive for the creation of national monitoring systems could be that the economic impact of an eventual global ban on antimicrobial use for growth promotion would be more severe in lower-income countries because of less optimized production systems. A further incentive to raise awareness and encourage the fight against AMR might be to compare benefits from antimicrobial use in animals against both their financial cost and the risks of antimicrobial resistance. This approach can make the problem less abstract and encourage livestock producers to change the way they use antimicrobial medicines. In developing countries, where the burden of infectious diseases remains high, successful interventions have been based on either educating farmers or training veterinary auxiliaries, who in turn explain to farmers the potentially negative consequences of using antimicrobials.

Some argue that, given production systems' lack of resilience, the sudden withdrawal of antibiotics as growth promoters in lower middle-income countries would have major negative consequences. However, European countries were able to impose a ban on the use of growth promoters without excessive, long-term negative impacts on productivity, profitability, animal health, or welfare. The feed industry developed alternative approaches to growth promotion, and good practices were adopted to ensure healthy herds and flocks. This level of resilience to growth-promoter or prophylactic use bans may not exist among farmers in developing countries, where such a ban could lead to the use of (poor-quality) antimicrobials obtained on the black market—exacerbating the problem—or to a considerable increase in disease, with consequent losses due to livestock mortality and morbidity. Of note, the ban on antimicrobials for growth promotion in the European Union in 2006 resulted in an initial increase of disinfectants and therapeutic use of antibiotics in animals, probably due to an increased incidence of infectious diseases.

One response to AMR applicable to animal production systems may be the development of new, alternative treatments that might partially replace antimicrobials. Several alternatives that could substitute for antibiotics in targeting bacterial infections have been proposed, including: antibacterial vaccines, immunomodulatory agents, bacteriophages and their lysins, antimicrobial peptides, pro-, pre-, and synbiotics, plant extracts, inhibitors for bacterial quorum sensing, biofilm and virulence, and feed enzymes.

There is still a considerable gap between antibiotics and these proposed alternatives, in terms of effectiveness in disease prevention and growth promotion (Cheng *et al.* 2014). Currently, only a small number of bacterial diseases can be prevented and controlled by the use of vaccines, although antiviral vaccines can help to maintain general health and reduce antibiotic use to treat secondary infections, or viral infections having similar clinical manifestations. Other approaches including immunomodulators and feed enzymes mainly preserve the health of animals, but do not directly kill or inhibit bacteria. Bacteriophages are currently only used in food, and their safety is still questionable. The composition of plant extracts and probiotics is complex and the quality in terms of stability is poor, resulting in varying effects and safety risks.

Inhibitors targeting quorum sensing (QS) and virulence of bacteria are still in research with no approved products, and most inhibitors are also toxic to eukaryotic cells. Biofilm inhibitors show good results only when used in combination with antibiotics. Although antimicrobial peptides (AMPs) can treat bacterial infections, the high cost and narrow antibacterial spectrum restrict their use, and they can still induce bacterial resistance. Meanwhile, proteinaceous compounds, for example, feed enzymes and AMPs that have been put on the market, as well as bacteriophage lysins, QS quenching enzymes and enzymatic biofilm inhibitors under development, are naturally unstable and easily degraded in the digestive tract.

No information could be found on the actual costs of these alternative therapies. The economic impacts of such alternative interventions will vary across producers, depending on location, farm size, contracting arrangements, production variables, management, and existing health and sanitation processes. Again, the economic effects of a complete ban of antimicrobials will be more strongly felt in countries where animal management and hygiene practices are suboptimal. There is little economic research on preventive strategies such as enhanced farm biosecurity and better animal hygiene. No studies were found that assess cost-effectiveness of these different interventions.

A set of alternatives to the use of antimicrobial agents in pig production were ranked by an expert knowledge elicitation process (Postma *et al.* 2015a). The ranking was based on perceived effectiveness, feasibility, and return on investment. The top five measures in terms of perceived effectiveness were: improved internal biosecurity, improved external biosecurity, improved climate/environmental conditions, high health/specific pathogen free/

disease eradication, and improved water quality. The top five measures in terms of perceived feasibility were: increased vaccination, increased use of anti-inflammatory products, improved water quality, feed quality/optimization and use of zinc/metals. The top five measures in terms of perceived return of investment were: improved internal biosecurity, zinc/metals, diagnostics/action plan, feed quality/optimization, and climate/environmental improvements. This study showed that with rather simple and inexpensive measures, pig investments could be increased. Improvements in biosecurity seemed to rank high in almost all cases, with higher biosecurity resulting in healthier animals. The findings of this study highlighted the benefits of an improved internal and external biosecurity status at the farm. These results appear relevant to efforts to keep animals healthy while reducing need for antimicrobials. No study of a similar kind in lower middle-income countries was identified, but it can be assumed that findings would be similar.

E. Summary of What We Know and Major Knowledge Gaps

Prudent and responsible use of antibiotics and continuous development of alternatives to antibiotics are needed to ensure the long-term, sustainable development of animal production systems. Key results from our survey of the relevant literature can be summarized as follows:

- The use of antimicrobials in animal production systems covers therapeutic and nontherapeutic purposes, including growth promotion.
- Antimicrobials are an important component of animal health management, and the impact of AMR goes far beyond public health.
- There is a general lack of data on the use of antimicrobials in animal production systems, particularly in low- and middle-income countries.
- There is a link between the use of antimicrobials in animals and the emergence of AMR in humans; the pathways for transmission of AMR are not limited to the food chain, and are poorly documented.
- While it is difficult to quantify the use of antimicrobials in animal production systems, it is projected that this use will increase significantly in some parts of the world.
- Lack of understanding of the drivers and needs for the use of antimicrobials in animal production systems remains a strong obstacle to positive change.
- There is no or limited information on the cost of alternatives to antimicrobials.
- Performance of national veterinary public-health systems and resilience of animal production systems will be key factors in successfully reducing reliance on antimicrobials.

In light of this stocktaking of knowledge on AMR in livestock production, our research has proceeded to examine the nature and characteristics of antimicrobial use in livestock in order to illustrate the magnitude of the potential AMR problem in low- and middle-income countries. Our research has used four sources of information:

- **Country case studies**—An assessment of the level of antimicrobial use in the livestock sector was made for Morocco, Chile, Thailand, and Uganda.[4] The costs and benefits of antimicrobial usage were estimated, and weaknesses in the systems of manufacture, marketing authorization, distribution, storage, prescription, and end-use of antimicrobials identified. The study looked for trade-offs between the benefits of use and the associated costs, including emergence of AMR. The importance of the institutional environment was also considered.
- **OIE global survey**—The OIE conducted a survey of its member countries in late 2015, as a part of the OIE's program to develop a system for data collection on antimicrobial (specifically antibiotic) use in animals at a global level. Our analysis primarily used the survey data from lower middle-income countries.
- **Regional case study**—The use of antimicrobials should be related to the animal population it is intended for. Data should be presented per population correction unit, which requires that the livestock sector be properly described and data made available. Our study included a regional case for description and presentation of animal production systems. The region chosen was South America.
- **Other sources of information**—Our study has also included other sources of information identified in the course of the literature review.

Key Considerations for Each of the Studies

Country Case Studies

- The country case studies were conducted in four countries, ranging in per capita GDP from approximately $700 to $14,500 (PPP $1700 to $22,000) (World Bank, 2015 data).
- The main finding of the case studies was a serious deficiency in data required to undertake economic analysis of antimicrobial use, the impact of AMR, and the costs and benefits of alternative approaches. In all countries, obtaining data on antimicrobial manufacture, import/export, and usage across species was difficult. It was also problematic to achieve any sort of standardization or comparability between data that were available. Areas of divergence included: the time period to which the different datasets pertained (both within country and between countries), whether data related to all antimicrobials or only antibiotics, how the weight of active ingredient had been calculated, and whether all animal species were included or only terrestrial species. Most of the AMR information in the case study countries comes from research studies, but is not comparable or consistent in methodology and not linked to the use of antimicrobials.
- In all cases, the use of antibiotics as growth promoters was either banned or in the process of being banned, and in the latter cases it was not possible to distinguish the quantity used for prophylactic purposes versus growth promotion purposes.
- In all countries, it was possible to establish the size of the livestock sectors at a national level and to characterize the production systems, although the way data were presented nationally varied between countries. Farm level information was, however, almost completely absent, and data on the output of livestock products each year were inconsistent, with different data sources sometimes contradicting each other.
- All countries had in place some structures and institutions of government and industry for controlling the manufacture, import, distribution, sale, and use of animal medicines, including antimicrobials. All countries had facilities for laboratory testing to isolate bacteria and test antibiotic sensitivity. However, the robustness and effectiveness of these structures and institutions varied greatly.
- In the case of the lowest-income country, there were clear capacity issues, particularly in the control over end-usage of antibiotics and in surveillance for AMR. Residue monitoring was also lacking, and was more likely to be developed where export markets were more significant. Whilst it is recognized that residue monitoring does not relate to antimicrobial use overall, if such monitoring is linked to market access for products, then it provides pressure for more nuanced and informed use of veterinary medicines, including antimicrobials. The latter point indicates that it is possible to manage antimicrobial use at the latter stages of production, and to be truly effective this needs to be linked to markets that have a mechanism to convey this need across the food animal system to the producers. This is more likely to apply in countries with export markets, which drive standards.
- Systems for collecting data on antimicrobial sales and use in animals need to be improved in most cases. This accords with the findings of the OIE surveys of 2012 and 2015, though some progress has been observed. Countries have made efforts to improve, with one-off exercises to allow completion of the OIE 2015 survey and, in one case, a significant program planned to establish ongoing monitoring systems. Country surveillance systems for AMR were found to be poorly developed. In all countries, there had been studies of AMR in bacteria from animals, but passive surveillance was not observed in the lower middle-income countries studied, while active surveillance programs were only just being implemented and were largely export driven. There was no surveillance activity in the lowest income country.
- The lowest income country in the group was the only country where no significant national changes were yet ongoing, though there were detailed studies being run by universities, as well as one supported by WHO. This country study also reported the least control over the dispensing of antibiotics for animal use, and the lowest level of surveillance for AMR, and this coincided with much less intensive systems of livestock production. Where export markets exist for animal products, much greater efforts and investment are being made to establish control systems. There is a noticeable increase in activity in this area very recently.

- Data on pricing were not available in most cases, and in no case was the government involved in setting or controlling prices of veterinary medicines. There appear to be no specific fiscal policies with regards to the use of antimicrobials in the livestock sector. Although some data were available on the overall value of the pharmaceutical sector, farm-level medicine costs which would be necessary to evaluate alternatives to antibiotic use were only available in the high-income countries studied and were presented mainly as total animal health costs, rather than being disaggregated to allow specific understanding of antimicrobial costs.
- A major question raised by the case studies concerns the relative importance, in terms of risk related to AMR, of uncontrolled usage in extensive systems versus the higher levels of usage in intensive systems even in the presence of greater control. The data available through the case studies would not allow any assessment of whether uncontrolled usage of antibiotics in extensive systems poses a threat in terms of AMR development, or the extent of the threat presented by the use of antibiotics in intensive systems supplying export markets. In order to inform the prioritization of future investments, it would be helpful to analyze whether countries with extensive systems and weak control over antimicrobial use have reason to worry in terms of AMR emergence, or whether control efforts are best focused on exporting countries where any mismanagement of antibiotics could have much wider impacts globally.
- The case studies provide a stark illustration of the deficiencies in data that currently exist in both lower middle-income countries and high-income countries (though these were more acute in the lower middle-income countries studied), as well as the sensitivities that surround such data. It was not possible in any of the case country studies to undertake detailed economic analysis of antimicrobial use and the impacts of AMR, or to assess the economics of alternatives to the use of antimicrobials. In many cases, there was a genuine lack of capacity to collect and analyze these data nationally. In other cases, it was evident the countries were not willing to share data, due perhaps to the comparatively high profile of the AMR debate and the potential sensitivities of countries' trading partners.
- It is clear that the building blocks for future analyses need to be put in place as a matter of urgency, along with policy initiatives which give countries confidence to take a transparent approach. The most basic requirements for future analysis would be standardized data collection on the use of antimicrobials and AMR. As mentioned earlier, OIE is developing a system for data collection that will be refined and enhanced over time. Absolute quantity data need to be matched by data on the animal populations, levels of production, and production systems to which this usage relates, in order to develop a robust and standardized denominator. Work to establish a global denominator is under way at the OIE. Publication of guidelines and frameworks, based on intergovernmental standards adopted by OIE member countries, could assist countries in setting up harmonized systems and methodology for data collection on the use of antimicrobials, AMR, population, and production.

OIE Survey

- OIE conducted a survey of its member states in late 2015 with a response rate of 131 countries out of 180. Nearly three-quarters of low- and middle-income countries provided information. However, there are regional variations.
- Of those low- and middle-income countries that reported data on the use of antimicrobials, approximately one-half provided qualitative data and a further half the basic level of information around quantitative data. Only four out of 74 low- and middle-income countries provided fully detailed data on the use of antimicrobials under the highest-level reporting option (which had been mainly used by EU countries, for example).
- Eighty percent of reporting low- and middle-income countries stated that their official system authorized the use of antimicrobials for growth promotion in 2015. The main antimicrobial classes used for growth promotion are: aminoglycosides, amphenicols, cephalosporins (all generations), fluoroquinolones, glycophospholipids, lincosamides, macrolides, nitrofurans, penicillins, polypeptides, quinoxalines, streptogramins, sulfonamides (including trimethoprim), and tetracyclines. This list is based on a very low level of responses and should be treated with caution.

- At this stage of the OIE program of data collection on the use of antimicrobials in animals, there is insufficient data available on the quantities of antimicrobials used to perform an analysis at the global level.

Regional Case Study—South America

- The key consideration from the South American case study is the need to improve livestock information systems in countries and make the information obtained intelligible and widely available.
- The benefit of such systems is the provision of timely data for politicians and decision makers whose role is to support and facilitate the sustainable growth of their countries' livestock sectors. In turn, such growth will benefit livestock producers, owners of livestock processing industries, consumers, and the stability of economies that are heavily reliant on the livestock sector.
- Detailed analysis of livestock populations needs to be matched by detailed data on the use of antimicrobials in these populations, in order to assess impact.
- To date this has not been done for most countries.
- It would be recommendable to update the estimates of livestock population and production data for South America and provide a similar estimate for Africa and Asia. To estimate demand, this information would need to be combined with likely antimicrobial use by species, system, and product. The supply data could be provided by information on antimicrobial manufacture and the balance of imports and exports. This process will probably highlight where gaps exist and raise questions on how these will be filled in future interventions. By asking questions about livestock, production systems, and antimicrobial use, this research will ultimately promote critical thinking on how best to harness antimicrobials in livestock while protecting the drugs' efficacy and safeguarding animal and human health.

Other Sources of Information

- A previous study (Van Boeckal *et al.* 2015) calculated antimicrobials per population correction unit (PCU), using a Bayesian logistic regression model, and incorporating data from 32 countries that have monitoring systems for antimicrobial use. Researchers estimated that cattle, chickens, and pigs would use 45, 148 and 172 mg/PCU, respectively. These three species account for 88 percent of the world's terrestrial meat production and produce a majority of the milk and eggs consumed by humans. These three species also represent 80 percent of the domesticated terrestrial animal biomass and are the species that tend to be kept in intensive and semi-intensive systems where antimicrobials are used for growth promotion, prophylaxis, metaphylactic and therapeutic treatments.
- Of interest in the calculations of antimicrobial use is a specific estimate from a country in Asia regarding small-scale poultry fattening operations. The total amount of antimicrobial used for relatively long-lived birds was between 52–276 mg per kilogram of live chicken production; a high proportion of this amount stemmed from antimicrobials placed in the feed (Carrique-Mas *et al.* 2013).
- The 2015 analysis suggests that the benefits from the use of antimicrobials for growth promotion have become less pronounced since they were first introduced in the 1950s (Van Boeckal *et al.* 2015).
- The analysis also concludes that the use of these growth promoters could be stopped with little or no impact on productivity or other economic effects. However, the analysis makes little or no reference to how the hygiene and production systems found in low- and middle-income countries differ, compared to the systems where growth promotion effects have been calculated. The authors of this work have also not necessarily compared like with like, as the pigs and poultry and their feed and water systems pre- and post-2000 are not comparable. The researchers' arguments on the potential to eliminate antimicrobials for growth promotion and perhaps for prophylaxis across low- and middle-income countries need more careful thought, if protection is to be provided for smallholder farmers, small-scale traders, and of course the urban and rural consumers in these countries, the majority of whom are poor.
- Promising targets for early action to scale back antimicrobial use in animals might include the large, well-organized multinational companies whose activities span both high-income contexts and low- and middle-income settings. These corporations have the resources and technical capacities to rapidly bring production systems

to a standard where reliance on antimicrobials can be reduced. A high proportion of pig and poultry farmers currently working in such systems were ignorant of whether they were using antimicrobials or not (Sneeringer *et al.* 2015). In this context, reducing the use of antimicrobials for growth promotion would likely bring only minor changes in production and productivity. This would suggest, as has been demonstrated in Europe, that current levels of antimicrobial use in livestock are well beyond a technical optimum and almost certainly beyond an economic optimum, if there is stability in prices and health status.

Potential Interventions and Their Impacts

- The paucity of data and information on the use of antimicrobials in terms of quantity, class, and species-specific use in the large majority of countries indicates that the basis for making an estimate of total use and the impact of use is lacking, and any such estimates have so far been guesswork.
- More particularly, it is impossible to estimate the financial costs of farm-level use. The necessary data are likewise unavailable to estimate overall benefits in terms of additional livestock production, which might lead to: (1) producer surplus, due to an improvement in productivity; and (2) consumer surplus, due to a greater supply at a lower price.
- The only conclusive cost that can be dismissed at this moment is the research and development costs of the most commonly available antimicrobials, since all are now of such age that patent periods have passed.
- This leads to a further problem: If the current antimicrobial use cannot be described with accuracy, how can the interventions be described and evaluated to change antimicrobial usage, either in terms of reducing or simply optimizing use? Therefore the actions themselves are difficult to prescribe and their impacts in terms of costs, livelihoods and risks even further from the piece. In an attempt to indicate what is possible, Table 6 presents a descriptive assessment of the interventions that could be carried out at the country level.

F. Conclusions and Recommendations

Overuse and misuse of antimicrobials in animal production systems can be a source of emergence and spread of AMR. This also signifies, however, that the livestock sectors in low- and middle-income countries could contribute to the effective and sustained containment of AMR.

Research commissioned for this report set out to examine the nature and characteristics of antimicrobial use in animals, in order to help to illustrate the magnitude of the AMR problem in low- and middle-income countries and prepare a comprehensive set of evidence-based recommendations. The research yields the following conclusions and recommendations:

- **Improved estimates of the use of antimicrobials in animals are needed.** This could be delivered by the OIE data collection system in the future, and must be combined with an appropriate description of the livestock production systems at country levels. These data are critical for AMR containment, which can only be undertaken with confidence if the estimates are adequate. This could be achieved by the collaborative efforts to improve the World Animal Health Information System (WAHIS) at OIE and FAO Statistics (FAOSTAT) at FAO. Both international organizations participate in the Tripartite and have networks and opportunities to inform technical services that are responsible for data collection and analysis in member countries.
- **Major knowledge gaps must still be addressed.** This includes knowledge on specific interventions and individual countries. An adequate knowledge base would encompass understanding of institutional environments, human behavior, and communication. There are also major difficulties in low- and middle-income countries in monitoring the use of antimicrobials and their residues and in implementing AMR surveillance.
- **Economic arguments can demonstrate the benefits of strengthening human and veterinary public-health systems.** There

TABLE 6. Proposed List of Potential Country-Level Actions to Contain AMR in Livestock
Estimated Costs, General Impact, Impact on Livelihoods, and Levels of Risk (Authors' Assessment)

Action	Cost	Impact	Livelihood	Risks
Monitoring Antimicrobial Manufacture	Data collection, database development and maintenance, data analysis and report writing, feedback	No initial impact Would allow analysis of productivity change	Short-term low Mid-term low to medium	No risks
Monitoring Antimicrobial Distribution, Including Importation	Data collection, database development and maintenance, data analysis and report writing, feedback	Knowledge and increased control of the distribution chain Would allow evaluation of management options analysis of productivity change	Short-term low Mid-term low to medium	No risks
Monitoring Antimicrobial Sales and Use	Data collection, database development and maintenance, data analysis and report writing, feedback	Raise awareness amongst prescribers and livestock owners Information on human behavior, and the institutional environment Refinement of policy making	Low impact	Could be risks for the businesses that depend on antimicrobial sales
Monitoring Residues	Laboratory equipment and training, reagents and maintenance, database development, analysis and report writing, feedback	Potentially an immediate impact of raising awareness across the farming system	Low impact	Could be risks to farmers with little access to information
Surveillance of AMR	Laboratory equipment and training, reagents and maintenance, study design and data collection, database development, analysis and report writing, feedback	Raising awareness Needs to be linked to policy and private standard change that is informed by evidence on the links between AMU and the management of AMR Interest for treatment guidance	Medium to high impact	Risks of creating food scares
Removal of Antimicrobial Growth Promoters	Potentially low production, Potentially lower farm level productivity, investments in farm infrastructure (?), investments in farm-level water quality (?), investments in feed mills (?), extension and farm-level support	Predicted in developed countries to have little impact on food supply and farm incomes Yet unknown if these assumptions are transferable to other less well supported setting with different levels of management Will require investments and training across the input and farm-level parts of the livestock sector It may improve productivity	Low to medium impact	Potential risk of reducing livestock product food supply
Reduction and/or Change of Antimicrobials for Prophylaxis	Greater risks of disease, lower production and productivity in general, potentially risks to humans with zoonoses, farm level training on management practices, reduction in practices that cause animal stress	Lowers costs of antimicrobials Lower AMR risks Greater disease risk Potential reduction in productivity with impacts on food supply	Introduces additional risks to incomes	Low to medium
Reduction and/or Change in Therapeutic Use of Antimicrobials	Greater risks of disease, lower production and productivity in general, potentially risks to humans with zoonoses, farm level training on management practices, reduction in practices that cause animal stress, may undermine entire farm management practices, need for research to support change	Lowers costs of antimicrobials Lower AMR risks Greater disease risk Potential reduction in productivity with impacts on food supply May greatly increase zoonotic disease risks	Introduces additional risks to incomes	Low to medium
Improved Data and Information on Livestock Sector Trends	Data collection, database development, analysis and report writing, information sharing	Medium- to long-term impact to allow the assessment of productivity change Improved estimates of the denominator used for AMU Refinement of vaccination strategies These changes can be linked to AMU and AMR changes to guide public policy and private standards and practices	Low to medium	Minimal to low risk

is a critical need to reinforce these systems, and to do so will require the engagement of governments, private companies, and individuals involved in livestock production. All these actors are likely to be sensitive to economic arguments. Clarifying the economic case may help change attitudes and behaviors around the use of antimicrobials among key stakeholders.

Options for Action at Country Level

In addition to the broad conclusions just sketched out, our research suggests specific policy recommendations, addressed primarily to low- and middle-income countries. These recommendations fall under three headings: (1) mitigation options to reduce antimicrobial use in animals; (2) strategies to help production systems adapt to reduced antimicrobial use; and (3) optimization options to promote responsible and prudent use, given that the use of antimicrobials in livestock production will continue, even if at lower levels.

1. ***Mitigation options to reduce the use of antimicrobials***

❊ **Monitoring and surveillance at the national level**

- Design and implement data collection and capture systems to **generate national data on the use of antimicrobials, including uses in animals**. Data can be gathered at multiple levels of the antimicrobial production, supply, and distribution chain.
- Develop a system to **collect standard data on animal populations, production, and production systems**. This is required to enable standardized calculations of antimicrobial use in livestock for each country, using internationally accepted units of measure, such as milligrams of antimicrobials per kilogram of animal mass.
- Develop systems to **monitor antimicrobial residues** in food originating from farmed terrestrial and aquatic animals.
- Design and implement sample collection, testing, and data-capture systems for risk-based **national surveillance of AMR in animal production systems**.
- Couple monitoring and surveillance with adequate **capacity to assess risks** related to any detected emergence of AMR.

❊ **National targets for the reduction of antimicrobial use**

- **Establish national targets** for substantial reductions in the use of antimicrobials in livestock, prioritizing reductions in nontherapeutic usages.
- Establish intersectoral collaboration to **jointly report national data** on the use of antimicrobials, residue monitoring, and AMR.
- **Produce annual reports** on progress against national AMR targets to be submitted to the Tripartite.

❊ **National standards on antimicrobials, residues, and AMR**

- **Analyze legislation and implementation** of public and private standards at the country level, to identify weaknesses in the institutional environment.
- **Strengthen public and private standards** along the antimicrobial supply chain for registration, manufacture, distribution, sales, and use of antimicrobials.
- **Strengthen implementation of legislation and standards** applying to the manufacture and distribution of animal feed, in particular medicated feed.
- **Establish enforcement systems** that will be activated when inappropriate use of antimicrobials, use of suboptimal or counterfeit antimicrobials, or residues are detected; investigate how enforcement can be strengthened in resource-constrained environments to target areas of highest risk.

2. ***Adaptation of animal production systems to reduced use of antimicrobials***

❊ **Resilient animal production systems**

- **Identify animal production systems that are heavily reliant on antimicrobials** and critical points in animal life cycles where antimicrobial use is highest and where interventions would have greatest impact in reducing antimicrobial use.

- **Engage large private-sector actors**, for example animal feed companies, to develop and test alternatives to antimicrobial use. For example, feed companies could be incentivized to explore alternative approaches to growth promotion. This might include development of innovative techniques and rations to maintain animals' gut health, immune systems, and respiratory health.
- Undertake applied **research on alternatives to the use of antimicrobials** under field conditions, for example, through systems redesign that would reduce the need for antimicrobials. Measures to test might include improved livestock housing, genetic selection, vaccination strategies, dietary adjustments, improved hygiene procedures, and staff training.
- Undertake research to **identify where current levels of antimicrobial use may unnecessarily increase production costs**, to the detriment of producers and consumers.
- **Communicate recommended interventions** clearly to decision makers.
- Manage any changes in livestock production practices so as to **reduce disease without compromising food supply or animal health and welfare**. For instance, developing insurance against livestock diseases for farmers who do not use antibiotics is impossible in the current state of veterinary services.

❊ **Behavioral and cultural aspects**

- **Undertake social science research** to understand how people manage livestock health at the farm level, including **how and why they use antimicrobials**. Apply knowledge of actors' motivations and decision-making processes to analyze how their behavior could be influenced to reduce reliance on antimicrobials.
- Raise awareness and **educate professionals and livestock owners** to better understand how antibiotics function and the potential adverse consequences of inappropriate use (including negative impacts on their own health); provide education on potential alternatives to antimicrobials.

3. ***Optimization options towards responsible and prudent use of antimicrobials***

❊ **Rationalization of antimicrobial use**

- Undertake applied research to **improve rapid diagnostic methods**, which would reduce the use of antimicrobials by establishing the sensitivity of infectious agents to antimicrobials before treatment is begun.
- Investigate the **relative AMR risk** of poorly controlled use of antimicrobials in **extensive systems** versus the higher levels of use in better controlled **intensive systems** which have much larger markets and therefore exposure potential.
- Develop appropriate **vaccines and vaccination strategies** to reduce the use of antimicrobials in livestock.

❊ **Education, training, and communication at national and global levels**

- **Educate professionals and livestock owners** on the importance of veterinary oversight, the need for responsible and prudent use of antibiotics, and the value of adhering to prescriptions, including dose rates and withholding periods.
- **Develop advocacy messages** on the importance of AMR that will convey evidence-based guidance on potential individual actions; for example, such messages could highlight the financial feasibility of alternatives to antimicrobial use through improved animal husbandry and infection prevention in livestock production systems.
- **Strengthen veterinary education** and the role of veterinary professional standards in governing antimicrobial use—the extent to which prescribing is required and the veterinarian is involved in treatment decisions (when to treat, dose, duration).
- Use OIE Performance of Veterinary Services (PVS) pathway to **identify gaps and training needs** in low- and middle-income countries, to direct and prioritize currently available funding, and to **help low- and middle-income countries attract additional funding**.

Endnotes

1. This term includes poultry and farmed aquatic species. This report does not address companion or sporting animals. This report does not address usage of antimicrobials in agriculture other than livestock.
2. Defined by OIE as "the governmental and nongovernmental organisations that implement animal health and welfare measures and other standards and recommendations in the Terrestrial Code and the OIE Aquatic Animal Health Code in the territory. The Veterinary Services are under the overall control and direction of the Veterinary Authority. Private sector organisations, veterinarians, veterinary paraprofessionals or aquatic animal health professionals are normally accredited or approved by the Veterinary Authority to deliver the delegated functions."
3. See "Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals" (Chapter 6.10 of the Terrestrial code).
4. The selection of countries aimed for geographic representativeness and attempted to include at least one lower-income country; the selection was highly constrained by data availability (data availability even in these four countries was disappointing), budget, and short time available for the study. Similar work would be warranted in additional countries.

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World Bank List of Economies (July 2016)

Low-Income	Lower Middle-Income	Upper Middle-Income	High-Income
Afghanistan	Armenia	Albania	Andorra
Benin	Bangladesh	Algeria	Antigua and Barbuda
Burkina Faso	Bhutan	American Samoa	Aruba
Burundi	Bolivia	Angola	Australia
Central African Republic	Cabo Verde	Azerbaijan	Austria
Chad	Cambodia	Belarus	Bahamas, The
Comoros	Cameroon	Belize	Bahrain
Congo, Dem. Rep.	Congo, Rep.	Bosnia and Herzegovina	Barbados
Eritrea	Côte d'Ivoire	Botswana	Belgium
Ethiopia	Djibouti	Brazil	Bermuda
Gambia, The	Egypt, Arab Rep.	Bulgaria	British Virgin Islands
Guinea	El Salvador	China	Brunei Darussalam
Guinea-Bissau	Ghana	Colombia	Canada
Haiti	Guatemala	Costa Rica	Cayman Islands
Korea, Dem. People's Rep.	Honduras	Cuba	Channel Islands
Liberia	India	Dominica	Chile
Madagascar	Indonesia	Dominican Republic	Croatia
Malawi	Kenya	Ecuador	Curacao
Mali	Kiribati	Equatorial Guinea	Cyprus
Mozambique	Kosovo	Fiji	Czech Republic
Nepal	Kyrgyz Republic	Gabon	Denmark
Niger	Lao PDR	Georgia	Estonia
Rwanda	Lesotho	Grenada	Faroe Islands
Senegal	Mauritania	Guyana	Finland
Sierra Leone	Micronesia, Fed. Sts.	Iran, Islamic Rep.	France
Somalia	Moldova	Iraq	French Polynesia
South Sudan	Mongolia	Jamaica	Germany
Tanzania	Morocco	Jordan	Gibraltar
Togo	Myanmar	Kazakhstan	Greece
Uganda	Nicaragua	Lebanon	Greenland
Zimbabwe	Nigeria	Libya	Guam
	Pakistan	Macedonia, FYR	Hong Kong SAR, China
	Papua	Malaysia	Hungary
	New Guinea	Maldives	Iceland
	Philippines	Marshall Islands	Ireland
	Samoa	Mauritius	Isle of Man
	Sao Tome and Principe	Mexico	Israel
	Solomon Islands	Montenegro	Italy
	Sri Lanka	Namibia	Japan
	Sudan	Palau	Korea, Rep.
	Swaziland	Panama	Kuwait
	Syrian Arab Republic	Paraguay	Latvia
	Tajikistan	Peru	Liechtenstein
	Timor-Leste	Romania	Lithuania
	Tonga	Russian Federation	Luxembourg
	Tunisia	Serbia	Macao SAR, China
	Ukraine	South Africa	Malta
	Uzbekistan	St. Lucia	Monaco
	Vanuatu	St. Vincent and the Grenadines	Nauru
	Vietnam	Suriname	Netherlands
	West Bank and Gaza	Thailand	New Caledonia
	Yemen, Rep.	Turkey	New Zealand
	Zambia	Turkmenistan	Northern Mariana Islands
		Tuvalu	Norway
		Venezuela, RB	Oman
			Poland

(*continued*)

Low-Income	Lower Middle-Income	Upper Middle-Income	High-Income
			Portugal Puerto Rico Qatar San Marino Saudi Arabia Seychelles Singapore Sint Maarten (Dutch part) Slovak Republic Slovenia Spain St. Kitts and Nevis St. Martin (French part) Sweden Switzerland Taiwan, China Trinidad and Tobago Turks and Caicos Islands United Arab Emirates United Kingdom United States Uruguay Virgin Islands (U.S.)

Argentina, which was classified as a high-income economy in 2015, is temporarily unclassified pending the expected release of revised national accounts statistics.

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Today, in countries at all income levels, people are dying from infections that used to be curable.

Antimicrobial medicines, including the antibiotics that treat bacterial infections, have been mainstays of health care for 70 years. These medications have saved hundreds of millions of lives and substantially accelerated economic growth. Now, they are losing their power, as disease-causing microbes relentlessly mutate to elude them, health systems fail to manage drugs wisely, and research on new antimicrobials remains stalled.

Harmful microorganisms' acquired capacity to withstand the drugs designed to kill them is called antimicrobial resistance (AMR). While AMR has long preoccupied the health sector, this report expands the conversation from medicine and public health to economics. The report uses World Bank Group economic simulation tools to put a price tag on AMR's destructive impacts on the global economy from 2017 through 2050. It shows that, unchecked, drug-resistant infections will severely reduce global economic output and hobble development progress in the decades ahead.

But these destructive effects can be avoided. The report highlights actions low- and middle-income countries and their development partners can take to counter AMR, and estimates the investment required.

Analyzing costs and benefits under multiple outcome scenarios, the report shows that putting resources into AMR containment now is one of the highest-yield investments countries can make. By investing in the fight against drug resistance, low-, middle-, and high-income countries will all reap exceptional economic rewards.

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