Discussion Draft

DRUG-RESISTANT INFECTIONS

A Threat to Our Economic Future

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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
ASP	Antibiotic stewardship program
ARSP	Philippines Antimicrobial Resistance Surveillance 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
CAIPARS	Canada Integrated Program on 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
ESAC-Net	European Surveillance of Antimicrobial Consumption 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
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 healthcare 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 either opportunistic pathogens (such as aspergillosis, candidiasis, and cryptococcosis) that cause infections in immunocompromised persons (such as cancer patients, transplant recipients, and persons with AIDS) or pathogens that 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 then 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), with a focus on the aspects that are most relevant to low- and middle-income countries and on the measures that these countries can take, together with the larger global community, to mitigate the economic and health costs of AMR. The report provides an overview of the fundamental reasons for the importance of AMR to policy-makers. It draws on evidence that supports minimizing and containing anthropogenic AMR as a priority objective, to set out the critical challenges in implementing measures to contain AMR. The report puts forward findings, options, and recommendations, while recognizing that many knowledge gaps remain.

The challenge of AMR containment is complex. To address it effectively, governance of veterinary and human public health will need to take account of interdependence of country actions, within a concerted global effort to reduce overuse and misuse of antimicrobial drugs in human and animal health and in other agricultural production. Development of new antimicrobial drugs is not addressed in this report because it is extensively treated elsewhere and because most low- and middle-income countries are not likely to have resources to fund research and development of new medicines. What is clear, however, is that if governance of the "global antimicrobial commons" does not improve, then any new drugs that may be developed will lose their effectiveness much too fast and the large investments in developing such drugs will be squandered. This report shows the extraordinarily high returns to AMR containment, which is the first-best option for ensuring adequate and equitable access to antimicrobials.

Based on what is known and the simulations of economic impacts prepared for this report, without AMR containment, the Sustainable Development Goals for 2030, such as ending poverty, ending hunger, ensuring healthy lives, reducing inequality, and revitalizing global partnerships are unlikely to be achieved. The recent G-20 Summit Communiqué succinctly underscored this point: "Antimicrobial resistance poses a serious threat to public health, growth, and global economic stability."[1]

Drug-resistant infections occur when pathogens change in ways that render antimicrobial drugs ineffective. As a result, the pathogens survive and continue to spread. When infections are treatable with antimicrobials, people can be cured and further spread within the population can be readily contained. This has saved hundreds of millions of lives since wide use of these "miracle drugs" started over 70 years ago. Loss of drug-effectiveness because of AMR is increasing in both developing and developed countries. If this trend continues unchecked, the world will confront a reality where many infectious diseases have "no cure and no vaccine." AMR containment would minimize the contribution of human actions to the emergence and spread of AMR. Without AMR containment, humanity may face a reversal of the massive public-health gains of the past century, and the economic growth, development, and poverty reduction that they enabled. Unchecked AMR may cause major economic damage at community, country, regional, and global levels. AMR impacts would be felt across all economic sectors.

This report provides insights into the extent and broad patterns of the economic impacts of AMR and their implications for poverty, should AMR continue to increase because of inadequate collective actions. Echoing other recent studies, this report underscores that the likely direct and indirect economic damage would be substantial. The annual costs could be as large as those of the global financial crisis that started in 2008.

The costly impacts of AMR on GDP would be worse in two respects, however: they would be felt during the entire simulation period (which extends to 2050) and inequality between countries would increase because low-income countries would experience the largest shortfalls in economic growth. Growth in middle-income countries, in turn, would decline less, but more than in high-income countries. The differential impacts on GDP result from higher infectious disease prevalence and

[1] G20 Hangzhou Leaders' Summit Communiqué, September 5, 2016, paragraph 46.

greater dependence on labor incomes in countries with lower per capita incomes. The immiserating pattern of the economic impacts of AMR directly undermines the prospect for attaining the Sustainable Development Goal for 2030 of reduced inequality.

The simulations were done for two illustrative scenarios, corresponding to low AMR impacts and high AMR impacts, using the World Bank's main model of the global economy. The economic costs were calculated as reductions of output from the base-case standard projection. In the optimistic case with low AMR impacts (modelled as shocks to the labor supply and to livestock productivity), global GDP fell short by 1.1 percent annually by 2050; the shortfall exceeded $1 trillion annually after 2030. In the high AMR impact scenario, global GDP fell short by 3.8 percent annually by 2050, and the shortfall reached $3.4 trillion annually by 2030. In both scenarios, the absolute amounts of annual losses would double by 2050.

The goal of eliminating poverty by 2030 would be harder to reach: the additional number of people living in poverty would be 8 million in the optimistic (low AMR impact) scenario. This number would rise to 24 million in the high AMR impact scenario. Most of the increase in the number of extremely poor people would occur in low-income countries.

Impacts on health care costs and livestock production were simulated as well. Health care expenditures, both public and private, would increase in tandem with the rising disease burden; by 2050 the annual costs would 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. Output and trade in livestock and livestock products are especially vulnerable to AMR impacts not only because of reduced productivity due to disease, but also because of international trade disruptions in the wake of disease outbreaks. Whether import restrictions are imposed on the basis of risk analysis or are due to the "fear factor," output in the sector is reduced further, compounding the disease impacts. The simulations show that by 2050 the decline in global livestock production could range between 2.6 percent and 7.5 percent. Livestock production in low-income countries would decline the most, with as much as an 11 percent loss in the high AMR impact scenario.

The resilient, multifaceted, and permanent nature of the microbial threat has important implications for how the battle against AMR should be fought. Instead of viewing AMR as a distinct issue isolated from other health challenges, it will be more effective and less costly over time to build a common core of permanent capabilities. All countries need such capacities, which, together with complementary regional and global capacities, can be applied against a wide range of microbial threats, including AMR. Drug-resistant diseases are very much like infectious diseases with pandemic potential: because there is "no cure," their spread can be hard to control. The surveillance, diagnostic, and control capacity to deal with the first group of diseases is the same capacity that is required to control of diseases in the second group.

The additional costs of introducing AMR into an existing surveillance system for animal health or human health do need to be funded. The special study on laboratory-based surveillance in this report suggests that this amount is modest relative to the investments already made to establish the system. It is also small relative to the benefits for patients (who will be less likely to receive the wrong treatment) and for public health in the country. In all low-income and in many middle-income countries, however, surveillance and the other core veterinary and human public-health systems are weak. Investing in this capacity is a pre-condition for AMR surveillance, as well as for measures that countries can take to contribute to AMR containment.

A number of other actions are set forth in the WHO Global Action Plan on AMR. Responsibility for implementation of national action plans on AMR will rest with countries and be led by them. There is scope for adapting existing programs to be "AMR-sensitive." Initiatives to pursue the target for universal health coverage warrant particular attention. The stakes are higher than ever: access to health care is to expand rapidly, with prospects for higher misuse and overuse of antibiotics and other antimicrobials. Measures to improve regulation and monitoring of antimicrobial drug distribution and use and prioritizing antibiotic stewardship programs can contribute to AMR containment, as well as

improve the quality of care. Vigorous attention to infection prevention and control in hospitals and other health care facilities will have quality of care and other co-benefits.

More broadly, synergies between AMR containment and the pursuit of a number of the Sustainable Development Goals suggest entry points for actions that complement the "AMR-critical" and "AMR-specific" measures. For instance, achievement of the water, sanitation, and safe, resilient and sustainable urban development goals would clearly help in AMR containment through prevention of infections and thus reduced demand for treatment with antimicrobials. Since more than half of the world's population is now urban, there is a need for municipal public-health programs to become "AMR sensitive."

Implementation of AMR containment measures in low-income and many middle-income countries will not occur in the absence of adequate and predictable long-term financing; the costs for "AMR critical" and "AMR-specific" measures are estimated at $9 billion annually in low- and middle-income countries. About half of this amount is for investments in, and operations of core veterinary and human public health systems in 139 low-and middle-income countries. To ensure improved performance of these systems, independent assessment should be carried out regularly, such as those in the Performance of Veterinary Services pathway of the OIE and joint external evaluations in the Global Health Security Agenda. Systematic focus on performance of core public health functions will advance containment of AMR. Assuming these investments in core public-health systems are made with such a focus on performance, the report finds that the investment of the total estimated amount for AMR containment is justified from the following perspectives.

First, the test of net present value 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. The expected benefits are far greater than the investment costs of $0.2 trillion (this is the present value of annual spending of $9 billion in 2017–2050). The net present value is thus between $9.8 trillion and $26.8 trillion. This is an enormous amount, but it will certainly not materialize if the investments of $0.2 trillion are not made.

The benefits from AMR containment differ among countries. Assuming that only 10 percent of the costs were averted through AMR containment measures, high-income countries would 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. If we succeed in AMR containment such that there will be a 50 percent reduction of AMR costs, the high- and upper middle-income countries can together expect to obtain a benefit between $7 trillion to $22 trillion (under the low and high AMR impact scenarios, respectively).

The second test of the investment case examined the expected economic rate of return on the $9 billion annual investment. Assuming that investments would be made for 7 years before any benefits materialize, the expected returns on investments are exceptionally high. They range from 31 percent annually (if only 10 percent of AMR costs can be mitigated) to 58 percent (if half of AMR costs are mitigated), and further to 88 percent (if 75 percent of AMR costs are mitigated).

The report concludes that AMR containment is a hard-to-resist investment opportunity. Based on our analysis, there is an overwhelming rationale for reallocating resources from public investments with lower returns, toward AMR containment and the veterinary and human public-health systems that are "AMR critical." Some development-financing institutions, including the multilateral development banks, normally consider that more productive investments should be financed first, as a priority before less productive investments.[2]

In addition to an analysis of the case for investing in AMR containment, the report delves into three specific policy areas that may be relevant to the country action plans on AMR. These are: developing

[2] For example, see Article 1 of the Articles of Agreement of the International Bank for Reconstruction and Development.

robust laboratory-based surveillance of AMR; tackling complex behavior and governance issues related to antimicrobial use in human health care; and examining the options for reducing misuse of antimicrobials in livestock. Each of the special studies reviews what is known and the major knowledge gaps, and offers recommendations with a view to contributing to the implementation options for country action plans on AMR.

This approach has led the following main conclusions:

- There is an urgent need to invest in disease surveillance as part of building strong veterinary and human public-health systems in low- and middle-income countries. The additional cost of AMR surveillance is small, provided that the underlying systems and surveillance programs are established, and their performance is regularly assessed.
- Increased global cooperation is essential as AMR containment is a global public good. It will require coordinated efforts to monitor, regulate, and reduce the use of antibiotics and other antimicrobials. It will also require efficient arrangements for adequate and predictable financing of capacities for AMR containment in low- and middle-income countries. The G-20 Summit and the UN General Assembly High Level Meeting on AMR in September 2016 are important for galvanizing action, which must be sustained. Resourcing WHO, OIE, and FAO (the One Health tripartite) adequately would improve the expected results of this necessary long-term effort.
- The links with veterinary public health have not been adequately addressed to date. It has a substantial interface with human health, especially in low-income countries. The lack of veterinary capacity in many low-income countries presents a substantial (and rising) risk to global economic and health security and causes a large ongoing human health burden in those countries. Continuing dismissive attitudes and low support to One Health approaches will reduce the effectiveness of other efforts.
- More attention is required to incentives for reducing the need for antimicrobials in the livestock sector (including aquaculture), while recognizing that the scope for implementing measures in the coming decade may be limited in most countries by the absence of information. Assessments of impacts on the livelihoods of farmers in developing countries will be essential before international organizations advocate for policy changes that would affect these farmers.
- AMR is not a separate issue; it is a systemic issue and needs to be treated as such.

The report first frames the global problems and then moves to specific topics that are likely to be relevant to implementation of action plans on AMR in countries. If AMR efforts are to be successful, then low- and middle-income countries must buy into the solutions. AMR containment will depend 90 percent (or more) on promoting country-led efforts implemented in countries. The topics for the special studies in this report and the approach of focusing on practical aspects were chosen with the aim of supporting countries as they embark on actions to contain AMR. The special studies also indicate where policy research is needed.

The expected economic impacts of AMR and of major disease outbreaks and pandemics can be usefully included in routine country-economic projections, to inform ministries of finance, development, agriculture, health, and others about the impacts of inaction. To date, awareness of the existence of these threats is confined primarily to the health sector, although the impacts will be far more costly in other sectors.

This is not the definitive work on the subjects, but rather a means to contribute to framing the challenges and making the case for solutions. We hope the report will be useful as a stepping stone for advancing decisions and actions on AMR containment.

Introduction

This report, the result of twelve months of work by the World Bank and its partners, seeks to enhance understanding of the economic and development consequences of antimicrobial resistance (AMR), building on the World Bank's comparative advantage as a global development-financing institution, its multisectoral character, and its economic research capabilities. It seeks to complement, rather than duplicate, the extensive and thorough analytical work by the UK Review on AMR, which addressed both economic and health aspects in a series of reports that were issued between December 2014 and May 2016. To this end, it aims to provide an appreciation of the economics of the human and animal health dimensions of the AMR challenge. What are the development and poverty implications of rising drug-resistant infections in humans, livestock, and fisheries? Analyses of select options for action by low- and middle-income countries to control AMR are presented. The aim is not to treat the economics of drug-resistant infections exhaustively, nor to address all related policy areas. For example, this report does not cover important topics like the weak pipeline of research and development (R&D) for new antimicrobial drugs and the low incentives for the development and use of vaccines and better diagnostic tests. It draws on the World Health Organization's (WHO) Global Action Plan on AMR,[3] to frame analysis of measures that low- and middle-income countries can consider in their action plans to control AMR and, in some cases, generate co-benefits that improve low- and middle-income countries' development prospects more broadly. An important objective of the analysis was to present the economic rationale for investments in containment of AMR, because this responds directly to a key recommendation in the WHO Global Action Plan as well as to a WHO's request to the World Bank to help make the case for such investments.

Major recent reports on AMR by other institutions—by the Organization for Economic Cooperation and Development (OECD), U.S. Centers for Disease Control and Prevention (CDC), WHO, Food and Agriculture Organization (FAO), the Center for Disease Dynamics, Economics and Policy (CDDEP) and others—have had a single-sector focus, predominantly on human public health. These reports were addressed mainly to public health professionals and health sector policy makers. We hope a key audience for the present report are development practitioners and policy analysts outside the health sector. The AMR phenomenon and its implications are not well-known beyond the specialized microbiology, epidemiology, and public health domains. Raising awareness of AMR outside the human health sector is critical for a simple reason: without engagement of other sectors, the world will not succeed in containing AMR and reducing its substantial economic costs. Even when policy makers in ministries of finance, development, or commerce are aware of AMR, they rarely consider the problem; if they do so, they may not have access to adequate information. The results of a WHO survey of 10,000 respondents in 2015 were telling: three quarters (76%) 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%) 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.

The report is structured in seven parts. Part I presents a brief overview of AMR, how the present challenge can be understood as a "tragedy of the commons," and how availability of effective antimicrobial drugs is a global public good. 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 impacts on incomes, health care costs, livestock trade, and poverty. While the simulations are not predictions (rather, a range of outcomes that are possible), they highlight impacts on incomes and poverty in countries at different income levels. Part III then discusses the measures and investments in AMR control countries could make effectively and efficiently as part of their action plans on AMR. While each country should have an action plan on AMR, its specific scope and implementation need to respond to the conditions and opportunities in the country. Links to the Sustainable Development Goals (SDGs) suggest some entry points for AMR action.

Unlike Parts I–III, which cover global topics at an aggregate level, Parts IV–VI delve into three select topics, which were chosen because of their likely pertinence to LMIC's country action plans on AMR in low- and middle-income countries and because of the expected high impacts from measures in these areas. The special analyses carried out for this report were: laboratory-based surveillance, use of antimicrobials in humans, and use of antimicrobials in animals. In each of these areas, the report

[3] 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.

suggests ways to identify policy gaps, how particular measures could be chosen in low- and middle-income countries, and how low- and middle-income countries could approach implementation of the measures. The recommendations of the special studies can be adapted to specific country conditions and are intended to help improve consideration of policy choices, rather than to be prescriptive. In general, focusing on measures with large co-benefits across sectors could help make sustained implementation of public health system strengthening more likely than if programs are narrowly concerned with control of AMR. Part VII offers concluding messages.

The World Bank's Development Economics Group is planning to issue a working paper with further technical details on the global modeling simulations of the costs of AMR.

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.[4] Most microbes either aid humans and animals or cause no great harm, but a limited number are pathogens, which cause disease and, too often, 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 diseases.

Yet a victory over harmful microbes did not occur–and there still is no scientific basis for expecting a lasting victory. Notably, weak governance of public health has permitted what appears to be substantial and widespread overuse and misuse of antibiotics and other antimicrobials in human medicine, in livestock, and in fisheries. 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). But while appropriate use of antibiotics and other antimicrobials also promotes AMR, this risk is far outweighed by the health benefits from effective treatment of the infection. Treatment of infections is the intended purpose and an appropriate use of the drugs.

Overuse and misuse of antimicrobials have caused avoidable AMR emergence and spread, however.[5] Public health authorities in most countries have not performed the basic function of monitoring the level and trends of antimicrobial use so the extent of overuse and misuse is unknown. OIE and WHO initiatives are underway to help improve the information basis on the use of antimicrobials, which is important because antimicrobial effectiveness is a finite resource and a valuable asset for the world. 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 monitoring and strong governance that minimizes overuse and misuse, antibiotics and other antimicrobials are a classic example of a "tragedy of the commons."

B. A Tragedy of the Commons

A tragedy of the commons occurs when people in a community ultimately 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.[6] This concept has been applied, for example, to environmental problems and to 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 incentives of the fishermen 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 of allowing market forces to prevail as everyone freely pursues their self-interest.

One way to constrain frivolous, excess consumption of antimicrobials is to ensure appropriate market signals; raising the price by introducing a tax would change incentives and reduce effective demand from those least willing to pay the higher price. The rationale is similar to that for a carbon tax: when users pay for the impact that their use has on others, the outcome tends to be more efficient and more equitable than unfettered access at low prices. Instead, regulatory approaches can also achieve reductions of misuse and overuse, but implementation of such measures (as well as of new taxes) would require capacities that many countries do not have (see Part VI). Still, the taxation

[4] This section is based on "*International Cooperative Responses to Pandemic Threats: A Critical Analysis,*" by Milan Brahmbhatt and Olga Jonas, Brown Journal of World Affairs, Spring/Summer 2015.

[5] Indicators of the high and rising use of antimicrobials are concerning. Use in humans is reported to have increased between 2000 and 2010 by 30 percent. Estimates of use in agriculture suggest that it could be about as large as use in humans. But use in agriculture is (very probably) rising rapidly in tandem with fast-growing demand for meat, especially in middle-income countries.

[6] G. Hardin, *The Tragedy of the Commons,* Science, vol. 162, no. 3859, pp. 1243–1248, 1968. See also E. Ostrom, R. Gardner, and J. Walker, *Rules, Games, & Common-Pool Resources,* University of Michigan Press, Ann Arbor, Michigan, USA, 1994.

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 most well-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 are tetracycline, an antibiotic that is often used to treat common bacterial infections; oseltamivir, also known as Tamiflu, an antiviral that treats the flu; 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 (sometimes even just for a few days), the selection pressure (evolution) inexorably results in the emergence 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 a few days or years.

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).

Box 2. Indicators of Weak Governance of Antimicrobials

- Globally, WHO estimates that only 50% 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% 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.

option could be explored further, especially where substantial overuse and misuse are suspected.

Antibiotics (and other antimicrobials) are well on their way to become an example of a costly tragedy of the commons—in this case, on a global basis. The looming post-antibiotic era would be costly to all countries because antibiotics have brought such immense health and economic benefits; so far there are no effective substitutes for treating bacterial infections.[7] While the fishermen may find other employment and other foodstuffs can substitute for fish, untreatable infections will cause excess illness and premature death, both in humans and in their livestock. AMR has 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 diminish also 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 setting back major public health gains that have enabled broad-based economic growth and development for billions of people over the past century.[8]

Incentives to Overuse and Misuse Antimicrobials

In fact, individual patients, farmers, fishermen and others appear to have had more incentives to overuse and misuse antibiotics and other antimicrobials than to conserve and reduce their use. The same is true for manufacturers, distributors, doctors, veterinarians, hospitals, and clinics. Expanding access to health care treatment, which often includes antimicrobials, has been an objective of health programs in many low- and middle-income countries, using both domestic and donor funding. While conservation of antimicrobials has received less attention than expansion of access, expanded access to diagnostic services is very important in reducing overuse and misuse of the 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

[7] Preventing infections is the best approach, but it remains grossly underused. Even with optimal prevention, some infections may occur, however.

[8] Deaton, Angus. 2013. *The Great Escape: Health, Wealth, and the Origins of Inequality.* Princeton: Princeton University Press.

plentiful.[9] The overuse and misuse of the drugs hasten the emergence and spread of AMR, which renders the drugs less effective in treating infections, and eventually they become useless.

Competition among pharmaceuticals 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 pharmaceuticals 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 tuberculosis, that is most unsettling. The vanishing of effective antibiotics is the greatest and most urgent among the AMR risks; it will affect all countries.

Tackling a Man-Made Problem

Though it is a natural phenomenon, AMR is mostly a man-made problem. Drug-resistant infections in humans and livestock have been hastened and aggravated by poor governance, irrational human practices, selfish behaviors, low understanding, and absence of education. 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 therefore cannot be one-off or limited to a temporary priority action plan. Containment of AMR is clearly 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. That pathogens will continue to evolve also means that any new antimicrobial "miracle cures" that are developed will not last. New antimicrobial drugs will lose effectiveness faster if governance of human and veterinary public health remains weak and allows continuing overuse and misuse of the drugs.

Drug-Resistant Infections 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 have been impacting greater 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."[10] 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 much 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.[11]

Over-Reliance on New Miracle Cures Is Unwise—and Immoral

When older drugs eventually fail, will they not be always 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 R&D pipeline for new drugs has shrunk since the 1980s and is nearly empty. R&D is very costly and not as commercially attractive as 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

[9] One study found that expansion of access to health care thanks to elimination of user fees for diagnoses and other services was associated with lower AMR. See Marcella Alsan, Lena Schoemaker, Karen Eggleston, Nagamani Kammili, Prasanthi Kolli, Jay Bhattacharya, *Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis,* Lancet Infectious Diseases 2015; 15: 1203–10, July 9, 2015. http://dx.doi.org/10.1016.

[10] Brad Spellberg, Gail R. Hansen, Avinash Kar, Carmen D. Cordova, Lance B. Price, and James R. Johnson. Antibiotic Resistance in Humans and Animals, National Academy of Medicine Discussion Paper, June 2016.

[11] CDDEP (2016). *East Africa Public Health Laboratory Networking Project: Strengthening the Role of Laboratories in Tracking Antimicrobial Drug Resistance in East Africa.*

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

Drug-resistant pathogens do not respect borders; they spread through travel of humans and trade in livestock (including poultry and fish) and other livestock products. They can spread through food products and in the environment, for instance in waterways and in migrations of wild birds and other wildlife. Unmonitored quantities of waste that contain antimicrobials are generated by pharmaceuticals 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 many pathways, such as human-to-human, animal-to-human, and animal-to-animal, by the 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. Slowing the rate at which AMR emerges and spreads is possible and brings substantial benefits (Part II).

Containment of AMR is a global public good, which will prolong the availability of effectiveness of 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 contained.

One difference between AMR containment and other major global public goods (such as preventing climate change, generating knowledge, and preventing pandemics) is that there is "rivalry" in the "use" of AMR containment benefits.[12] 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.

Indispensable Public Sector Role in Conserving Antimicrobial Effectiveness

Using antimicrobials rationally benefits patients, farmers, communities, regions, and other countries because the infection is controlled and a further spread of pathogens is thwarted. The benefit to the patient or the farmer is a private good, but the benefits that arise from prevention of spread of contagion are a public good. Individual households and livestock producers are not able to prevent a spread of drug-resistant contagion on their own; provision of this public good is, indeed, a core public function, both within countries (a national public good) and among countries (a global public good).

The case for strong governance of the world's antimicrobial commons is overwhelming. As is shown in Part II, antimicrobial effectiveness is an asset with an approximate worth today that is between $20 trillion and $54 trillion (in constant 2007 dollars).[13] This asset is too big to fail even in narrow economic terms. It is also fundamentally critical to public health. Not only are we letting this asset dissipate rapidly, but access to the scarce antimicrobial resource is not managed to maximize

[12] 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 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.

[13] These estimates discount future benefits from antimicrobials at 3.5% 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% annually; this lower rate was used in the 2007 report on climate change impacts by Sir Nicholas Stern. A summary of these results from the simulation of AMR economic impacts is in Table 1 on page 34.

the overall welfare of the human community and to reduce the negative externalities—that is, the costs imposed on others (according to Sir Fleming, such behavior is immoral, as noted above). Unfortunately, many current users do not obtain any benefits (because they are misusing antimicrobials) 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), while they impose costs on future users. Today's children will need access to drugs that work during the coming decades to treat life-threatening disease, but such drugs will not be available to them because their parents' generation will have squandered drug-effectiveness through overuse and misuse of antimicrobials. Consumers and farmers need to know and understand the consequences of their use of antimicrobials and the benefits that refraining from use will bring to society. Awareness of the risks is a necessary first step toward risk management.

"Because drug-resistant bacteria spread from person to person, your use of antibiotics affects the ability of every other person to use the same antibiotics. Your use of an antibiotic affects our ability to use them. Our use affects your grandchildren's future ability to use them."[14] Because of these strong externalities that reach communities across the world and future generations, unregulated access gives rise to inefficiency and inequities. 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 today's children and the next generation.[15]

Use of counterfeit and substandard antimicrobials aggravates AMR as well as harms patients directly. Substandard and counterfeit medicines seem to be widely available in many countries, but data are poor. The WHO has estimated that some 10 percent of all the drugs worldwide may be counterfeits, and half of these concern antimicrobial drugs, predominantly generics. 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 "global public bad" of counterfeit and substandard drugs would need to engage multiple sectors across countries, and it would yield significant benefits, including less AMR. Manufacturing of substandard and counterfeit drugs appears to be concentrated in India, followed by China and Thailand.[16] Overall, up to 60 percent of antimicrobials used in Africa and Asia may have low quality, often having none, or too little, of the active ingredient. Moreover, fraudulent information on drug quality was common (found in 59 percent of cases studied), and only 7 percent of cases had the standard concentration of the active drug.[17] Widely used antibiotics, such as penicillins, amoxicilin, and tetracyclines; as well as antimalarials and antiretrovirals (used to treat AIDS) appear to be commonly counterfeited antimicrobials.[18]

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.[19]

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[14] Brad Spellberg et al.

[15] Tisdell, C., 1982. Exploitation of techniques that decline in effectiveness with use. Public Finance 37, 428–437.

[16] United Nations Office on Drugs and Crime. 2010. The globalization of crime. A transnational organized crime threat assessment. Counterfeit products 2010, pp 183–189. https://www.unodc.org/documents/data-and -analysis/tocta/TOCTA_Report_2010_low_res.pdf and United Nations Interregional Crime and Justice Research Institute. 14 December 2007. Counterfeiting. A global spread, a global threat. 4. The counterfeiting medicines, pp 29, 63–72. http://www.unicri.it/news/article /0712-3_counterfeiting_crt_foundation.

[17] World Health Organization. 1999. Summary of WHO counterfeit drug database as of April 1999, unpublished paper of the WHO Division of Drug Management and Policies. WHO, Geneva, Switzerland. 66. World Health Organization. 2000. World Health Organisation counterfeit drug reports: 1999–October 2000. www.who.int/medicines/services/counterfeit/overview/en/1.

[18] Kelesidis T., Falagas M. E. 2015. Substandard/counterfeit antimicrobial drugs. Clinical Microbiological Review doi:10.1128/CMR.00072-14.

[19] A high prevalence of substandard antibiotics can lead doctors to avoid prescribing them for their patients and to instead opt for broad-spectrum antibiotics. This practice also contributes to AMR because many of the active ingredients in a broad-spectrum drug are, in fact, redundant and not required to treat the infection.

D. Access to Treatment in Developing Countries and AMR

Even as there is overuse and misuse of antimicrobials, some poor populations also still lack access to effective medicines. For example, one million children with untreated pneumonia and sepsis, which can be effectively treated with antibiotics, are estimated to die each year.[20] 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 less access to treatment than when the cheaper, first-line antimicrobials were still working. The current lack of access and expected future declines in access are inequitable. Shrinking access to effective antimicrobials hinders progress toward universal health coverage, which is part of the Sustainable Development Goals for 2030. These goals have been adopted by all countries and, as such, progress toward universal health coverage and the other health targets are an international policy concern.[21]

Individual patients and livestock producers and their families enjoy private benefits from using effective antimicrobials. But there are, in addition, large global and national public benefits from such use. Access to treatment with effective antimicrobials is a textbook example of a public good because untreated infectious diseases can spread within the clinic, hospital, and country, to other countries in the region, and beyond, without regard to borders.

All countries are at risk of importation of infectious diseases; the risk varies across diseases and by country. The risk is higher the greater the interconnectedness and volumes of trade and travel with other countries. The risk of importation of infectious diseases (including those caused by drug-resistant pathogens) by any one country will be reduced if there is adequate access to effective treatment in the countries where travelers and exports may originate, or where a country's residents travel for visits or business. The volume and diversity of trade and travel are dramatically higher now than even just twenty years ago and still growing. Each country thus benefits more today than even in the recent past, if there is access to effective treatment of infectious diseases in all other countries.

Counterfeit and substandard drugs are also a major factor in harming animal health and welfare and producer incomes. 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. Animal disease causes both negative shocks to their owners' incomes and sustained reductions of their welfare.

E. Closing the Governance Gaps

Surveillance of Microbial Threats

Drug-resistant infectious diseases are a subset of the microbial threats to human and animal health and welfare. There is evidence on the extent of AMR, as well as on the accelerating emergence and spread of AMR. With improved disease surveillance, this evidence will become more robust and very likely more definitive. Still, surveillance coverage and quality require resources to build and sustain. Because of very low spending on investments, training, operations, and maintenance of surveillance systems, performance of the core public health function of surveillance of microbial threats has been weak. As a result, vital information about AMR remains unknown. Early warning about AMR emergence is not possible with the existing 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 "blind spots" extend across most of Africa and Asia, as well as parts of other regions, so the world does not yet have sufficient intelligence on microbial threats, including AMR. These vast "blind spots" are not an exogenous or immutable feature, however. Rather, they are a direct result of policy decisions that have over time underestimated the value of information

[20] Ramanan Laxminarayan, Precious Matsoso, Suraj Pant, Charles Brower, John-Arne Røttingen, Keith Klugman, Sally Davies. Access to effective antimicrobials: a worldwide challenge. Lancet 2016; 387: 168–75, http://dx.doi.org/10.1016/.

[21] See Annex 3. Targets for goal #3: Ensure healthy lives and promote well-being for all at all ages. This goal has 13 targets, including universal health coverage.

about our microbial adversaries. It is therefore important that WHO, OIE and partners are setting up the Global Antimicrobial Resistance Surveillance System (GLASS), which embeds AMR in the various tasks that comprise surveillance of microbial threats. Surveillance for AMR can only improve, however, if the capacity of surveillance systems is strengthened in countries for better performance in detecting and assessing the full range of threats to veterinary and human public health. GLASS also 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 also Part IV, including on implementation steps for country participation in GLASS).

Outbreaks of Drug-Resistant Diseases Are Inevitable, but Their Spread Is Optional

When a drug-resistant disease starts spreading in an area where surveillance is weak, economic and health costs will escalate rapidly. If the disease is easily-transmissible, the rate escalation can be exponential. There are several factors at work. The first and the most important reason behind the cost-escalation is the delay in detection. Take the example of a disease that was treatable in animals and humans with antimicrobials. Because of the "blind spot" in surveillance, the drug-resistant pathogen will progress within the animal or human population (or both) resulting in a rising incidence of cases and individuals needing medical care. Where AMR is present but undetected, humans and animals likely do not receive a drug that works against their drug-resistant infection. Uncured animals and patients then may spread the infectious disease further, including in hospitals and in the community. They will probably have a more severe and longer illness, as well as complications, the longer is the lag between the pathogen's emergence and correct diagnosis. The weaker the surveillance system, the less knowledge there is 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. Surveillance can prevent escalating costs because it shortens the time between pathogen emergence and implementation of control measures.

Early effective control measures at the source are the best and most-efficient way to reduce the risk of further spread of drug-resistant infectious diseases. While the probability of further spread can the greatly reduced by prompt control measures, the weak performance of surveillance functions inexorably increases the probability of further spread. The policy and financing choices of governments and their development partners have resulted in inadequate surveillance capacity, which enables undetected spread of pathogens (both drug-susceptible and drug-resistant), which in turn increases the probability of emergence of "AMR epidemics" and pandemics.

The overlap between surveillance "blind spots" and potential "hot spots" for drug-resistant disease emergence is a substantial and growing concern. Investing in capacity to control AMR threats at their onset—at their origin in hospitals and other healthcare, in livestock and other agricultural production, and in low-income countries, for example—has extraordinarily high returns for economies and for public health. The same capacity will serve well to reduce pandemic risks and improve health more broadly.

Possible Waves of Contagion

It is already known that multiple-drug resistance (MDR) in pathogens has emerged and is spreading. The diseases caused by such pathogens have thus become "diseases with no cure" and, too often, also "no vaccine." Such diseases are joining a growing list of other infectious diseases that also have no cure and no vaccine. These include virulent new strains of existing infectious diseases and new infectious diseases, 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, precisely because there is no readily available cure or vaccine to help thwart or slow the spread. Because of AMR, previously controlled infectious diseases may 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. The waves of contagion may overlap and aggravate economic and health impacts. The risks of such outcomes can be significantly reduced by surveillance systems with the capacity to provide

timely warning about microbial threats. A lack of such capacity will give rise to high health and economic costs (discussed in Part II). The chronic neglect of veterinary and human public health systems and, notably their surveillance capacities, is therefore a major governance gap. Containing AMR and similar microbial threats that the world will continue to face is possible, but only with robust veterinary and human public health systems in all countries.

Interdependence among Country Actions

To contain AMR successfully, all countries will need to act in a coordinated way. For instance, prohibiting one kind of misuse of antimicrobials in a country may not be effective unless all countries adopt a consistent approach. Consistent labelling of antimicrobial medicines will reduce scope for confusion and misuse. In the absence of such cooperation, efforts to contain AMR will not succeed. Rules to minimize misuse should be consistent everywhere, or all countries will eventually suffer from drug-resistant pathogens that emerge at the weakest links in the worldwide chain of antimicrobial use. Phasing of implementation of new regulations may need to differ across countries, and low-income countries may require assistance with building capacity for implementation of new regulations.

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 contain AMR—and then benefit from the result without investing in its own actions to contain emergence and spread of AMR on its territory. But because AMR spreads, the success of containment of AMR will be undermined, and all countries will suffer the consequences. Fortunately, international organizations responsible for establishing governance of global public goods already exist both for human public health (WHO), for veterinary public health (OIE), as well as for production of food (FAO). The large benefits that AMR containment will bring to all countries individually and to the global economy as a whole (Part III) provide strong incentives to cooperation that leads to all countries taking measures and contributing to the shared public good.

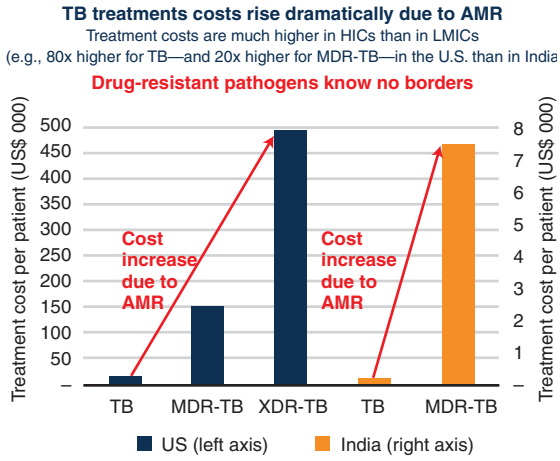
International Coordination of Measures Can Lower Costs and Increase Effectiveness

Infectious disease control has long been considered the quintessential global public good.[22] The risk of AMR further bolsters the economic case for effective and early control of infectious diseases at their source. Dramatic growth in human mobility within countries and internationally, increasing urbanization, and increases in international trade in goods and in services like medical and other tourism have been rapidly expanding the opportunities for pathogens to spread quickly and widely, and these trends are expected to continue. As with preventing and fighting fires, reducing risks at their source is invariably more effective and more efficient over time than a reactive stance of waiting for a crisis to develop before responding. For example, one high cost that can be mitigated by international coordination is that of treating drug-resistant and emerging infectious diseases imported into high-income countries from countries that do not provide effective treatment. Promotion of treatment of infectious diseases in the potential countries of origin is an option that can be both more effective and efficient than coping with imported cases.

The costs of some of the measures that will be required to contain AMR will vary 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. This is already evident in the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of TB. MDR TB and XDR TB infections are far more expensive to treat than TB. Because of the higher costs, effective treatment of drug-resistant cases would be less likely than for TB. Since uncured patients will pass the infection to more people, MDR TB and XDR TB will spread. Controlling the disease will become still more challenging and costly as the number of people with the drug-resistant infection increases (see also Part V).

[22] On priorities among global public goods and practical issues for their provision, see International Task Force on Global Public Goods (2006), Final Report, *Meeting Global Challenges: International Cooperation in the National Interest*. See also World Bank (2007), "*Global Public Goods: A Framework for the Role of the World Bank,*" DC2007–0020, September 28, 2007.

FIGURE 1. AMR Makes TB Far Costlier to Treat



TB = Tuberculosis (infectious disease caused by bacteria)
MDR = Multidrug-resistant
XDR = Extensively drug-resistant; TB caused by bacteria that are resistant to some of the most effective anti-TB drugs

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. For example, it costs 80 times more to treat one TB patient in the U.S. 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 U.S., two-thirds of TB patients are foreign-born (with India among the top source countries). The number of TB patients treated in the U.S. and AMR risks would be lower if effective treatment had been provided to more patients in the countries of origin.

Delays in controlling infectious diseases are extremely costly because contagion can spread at an exponential rate, from one country to another and across continents. The costs of delayed control are higher still in the presence of AMR. As noted, AMR often develops because of inadequate treatment of the original, drug-susceptible,[23] infection. Early disease control at the source thus generates both substantial savings because of avoided spread of disease and lower AMR risks. These two reasons are a powerful rationale for the international community to maintain an unwavering focus on ensuring good performance of veterinary and human public-health systems, especially in countries where they are the weakest. The returns on investment in core public-health functions are especially high in these countries.

[23] A microbe's "susceptibility" to an antimicrobial is the opposite of "resistance."

Economic Impact of AMR

A. Rationale for the Simulations

Given that AMR presents a current and future threat, how much of its economic resources should the world invest in reducing this threat? The answer depends on the economic costs of the impacts that AMR is expected to have. If these expected costs are high, then the world should be willing to spend more than if the expected costs were low. There are of course difficulties in estimating costs that will occur in the future, especially when these costs are caused by an inherently uncertain pace of emergence and spread of AMR in different pathogens. Weak surveillance yields sparse, low-quality information about AMR and pathogens. The simulations of impacts 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 on expectations about its spread. The projection period ends in 2050, or well within the lifetimes of present-day children and young people. Values of impacts in the year 2030 were calculated as well, because of their relevance to the Sustainable Development Goals for 2030.

AMR may be misunderstood because it is not a disease or an organism. It is an abstract concept that describes a property of invisible pathogens. This may help expalin why the threats of AMR and pathogens are inadequately appreciated by the general public and policy makers outside the public health field. A vague understanding of a critical element behind top global catastrophic risks to economies and public health results in low risk-awareness and thus gross underinvestment in public-health systems; moreover, there may be low awareness where risks of AMR emergence and spread are highest. If such cross-country differences remain unmanaged, it will aggravate risk to all countries.[24] Microbial threats are underestimated (and even ignored) in "peacetime," which is evident in gross neglect of preparedness. During disease outbreaks, people, politicians, firms, and others exhibit strong spontaneous avoidance behaviors that are based on a substantial overestimation of risks, and their reactions tend to sharply reduce and otherwise disrupt economic activity.[25] Such behaviors, which are predominantly based on fear, are likely to accompany outbreaks of drug-resistant diseases because there will be no cure available. The simulations prepared for this report aim to contribute to a more complete understanding of the economic implications of AMR and to stimulate further work, such as analyses of country-level economic impacts.

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, however. To do so implicitly assumes future AMR impacts in the country to be zero, and that disease outbreaks and pandemics will never occur. The results of the simulations of global impacts to 2050 that are presented below may serve as an incentive to preparing country simulations. Country policy makers and their 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 among the factors that underpin 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 be therefore safely 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 impacts are not directly related to the amount of resistance *per se*, however. To illustrate: for a dangerous disease with a 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. This report uses "high AMR" to mean "high AMR impact." This said, 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 actions will be inevitably more costly. The firefighting analogy is apt. Buying a fire alarm and extinguishing a fire early on are always and unambiguously more efficient and effective ways to reduce risks than waiting for the fire to engulf the neighborhood before noticing it and taking measures to stop it.

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[24] Otker-Robe, I. 2014. IMF Working Paper No. 14/195: *Global Risks and Collective Action Failures: What Can the International Community Do?* http://www.imf.org/external/pubs/cat/longres.aspx?sk=42416.0.

[25] Milan Brahmbhatt and Arindam Dutta, "*On SARS Type Economic Effects during Infectious Disease Outbreaks,*" World Bank Working Paper Series WPS 4466 (Washington, DC: World Bank, 2008), 48.

Effective antimicrobials are a highly valuable public good that have brought enormous benefits to humanity—and 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 pre-antimicrobial era. This would reduce output because of a lower effective labor supply. This reduction of GDP (modelled 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 (scenario without "shocks") is the economic impact only.

There would be additional reductions in human welfare, however, 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,[26] 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 foregone 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, appendectomy, 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.[27]

The third reason that human welfare would worsen more than in the simulations below are the costs of resorting to inferior treatment methods. Older, more-likely-to-fail treatments may become the best available option if AMR is not contained. For instance, gonorrhea, which is a bacterial infection, is continuing to become 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 installation 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."[28]

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 be invariably more costly and produce worse outcomes for the 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 modelling work carried out for this report ensures that impacts on prices, factors of production, and sector outputs are consistently modelled, 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.

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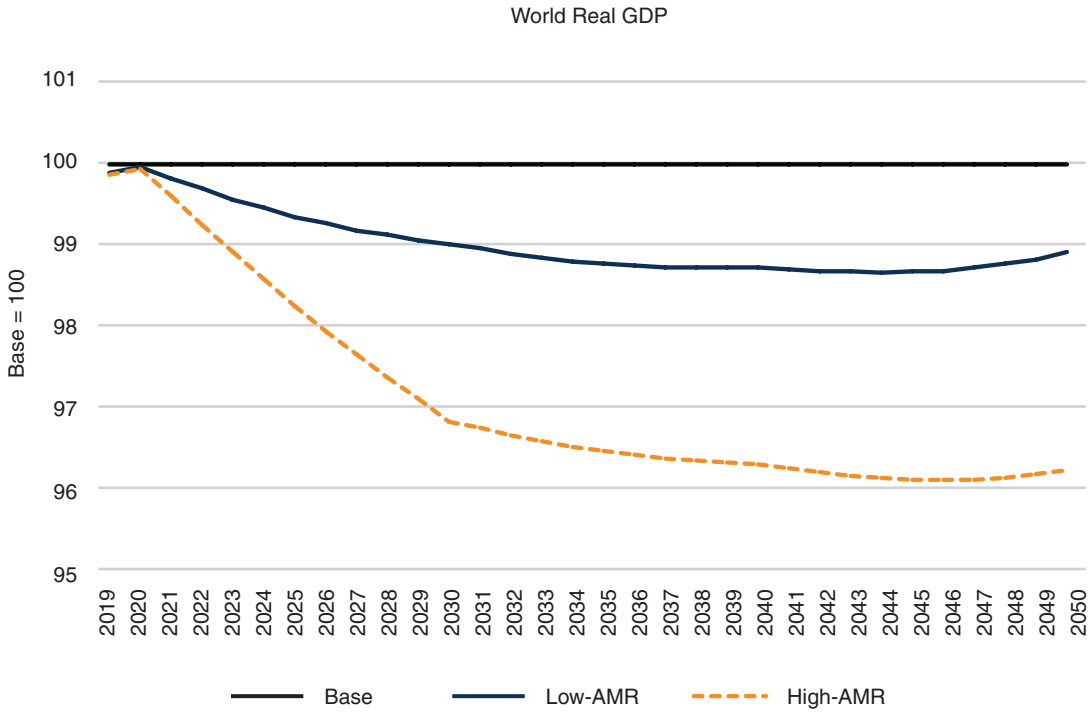
[26] Jamison D. T., Summers L. H., Alleyne G., et al. *Global Health 2035: A World Converging within a Generation.* Lancet 2013; published online Dec 3. Valuation of changes in mortality rates, Supplementary appendix 3. http://dx.doi.org/10.1016/S0140-6736(13)62105-4.

[27] Analyses of the impact of AMR on the availability of such procedures and on the costs of treatment would be more relevant in medical facilities, communities, or country health care systems, than on a global basis. Such procedures generate primarily private goods or, at most, if public provision is involved, national public goods. Such analyses could improve awareness of AMR and help promote antimicrobial stewardship programs.

[28] Vanessa Allen, chief of medical microbiology at Public Health Ontario in Toronto, Canada, quoted in "The world may soon run out of drugs to treat gonorrhea," by Kai Kupferschmidt. *Science,* Aug. 30, 2016, www.sciencemag.org/news/2016/08/world-may-soon-run-out-drugs-treat-gonorrhea.

FIGURE 2. Substantial and Protracted Shortfalls in Global Economic Output



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.[29] In the pessimistic "high-AMR" scenario, global economic output would be 3.2 percent lower in 2030 and then fall short further, so that in 2050, world GDP would be 3.8 percent smaller than in the base case.[30] 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 to be severe, especially since the costly impacts endure over time.

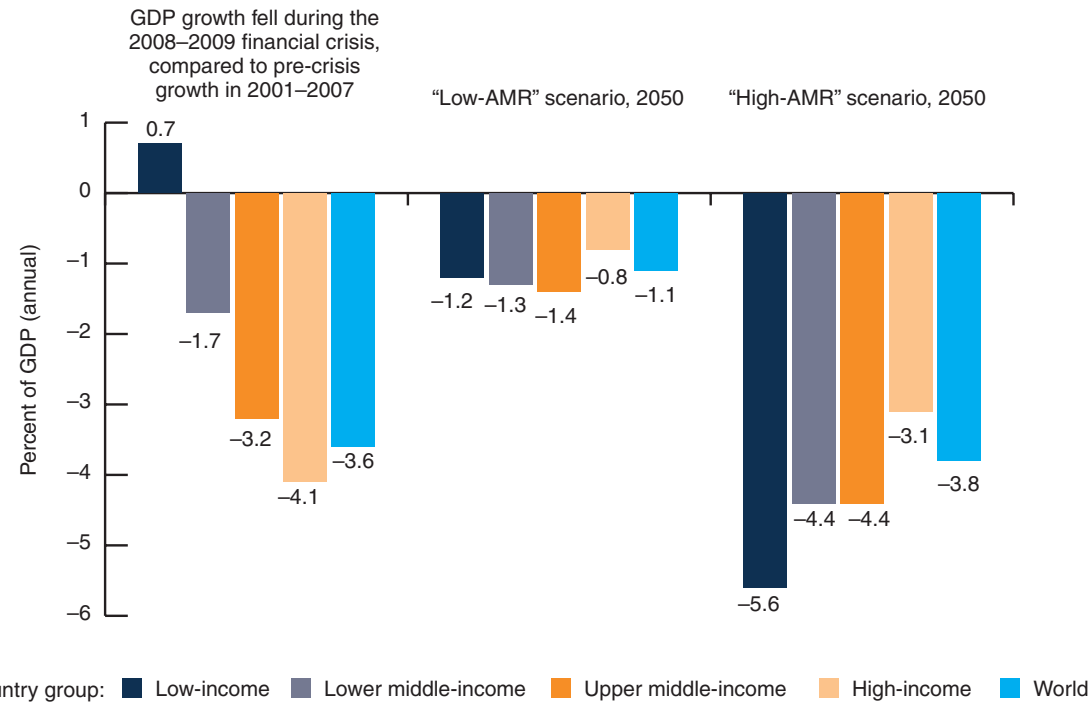
Given that the simulations for this report were done using a dynamic, multicountry, multisector, general equilibrium model with neoclassical growth features, economies do adjust to price signals caused by the AMR shocks. These adjustments lead to a reallocation of resources and to new investments (capital 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 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 was not included in the modelling work. As noted, the scenarios prepared for this report are not predictions but illustrations of some of the plausible impact patterns that could materialize.

[29] The base case is the standard World Bank long-term projection and excludes AMR from the model.

[30] The "high-AMR" case presented here is similar to the results of the modeling done for the UK Review on AMR, *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations,* December 2014: including (1) Taylor, Jirka, Marco Hafner, Erez Yerushalmi, Richard Smith, Jacopo Bellasio, Raffaele Vardavas, Teresa Bienkowska-Gibbs and Jennifer Rubin. *Estimating the Economic Costs of Antimicrobial Resistance: Model and Results.* Santa Monica, CA: RAND Corporation, 2014. http://www.rand.org/pubs/research_reports/RR911.html and (2) KPMG, *The global economic impact of anti-microbial resistance,* December 2014.

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

AMR could reduce GDP substantially—but unlike in the recent financial crisis, the damage could last longer and affect low-income countries the most
(annual costs as % of GDP)



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 as well as 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 would set back progress in economic convergence, possibly by decades.

How large are the potential economic impacts of AMR? To provide a point of reference, Figure 4. 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.[31] In the "high-AMR" scenario, the absolute levels of losses are

[31] All absolute amounts from the simulations for this report are in constant 2007 US$ terms.

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), and even if successful, such new products would take time to reach markets in low- and middle-income countries. The protracted 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 and this recovery continues). 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, setting back progress in economic convergence, possibly by decades.[32]

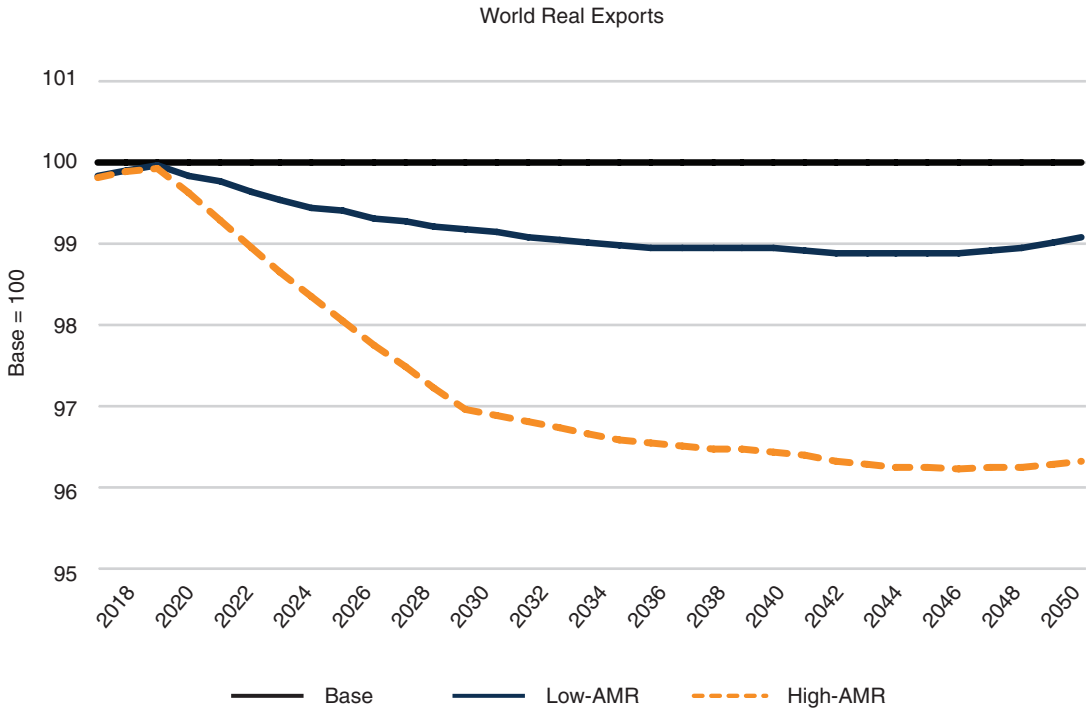
C. Impacts on Select Components of the World Economy

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 are vulnerable to AMR impact not only because of impacts on productivity of untreatable disease, but also because of the "fear factor" results in disruptions of trade (such as bans on imports) in response to disease outbreaks. These effects do not materially affect the simulations of

[32] Convergence refers to the expectation that economic growth in poorer countries would tend to be higher than in high-income countries, so their wealth and level of development become increasingly similar over time. It's also known as "the catch-up effect."

FIGURE 4. AMR Impact on World Trade



trade flows, however, 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 modelled 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. This could include a so-called "fear factor" and contributes to the 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, and this is expected to reduce these benefits 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 the levels of income 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, 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 would be 8 percent higher than in the base case in 2050. 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 would be $0.33 trillion annually in 2050. Since the modeling ensures that these

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

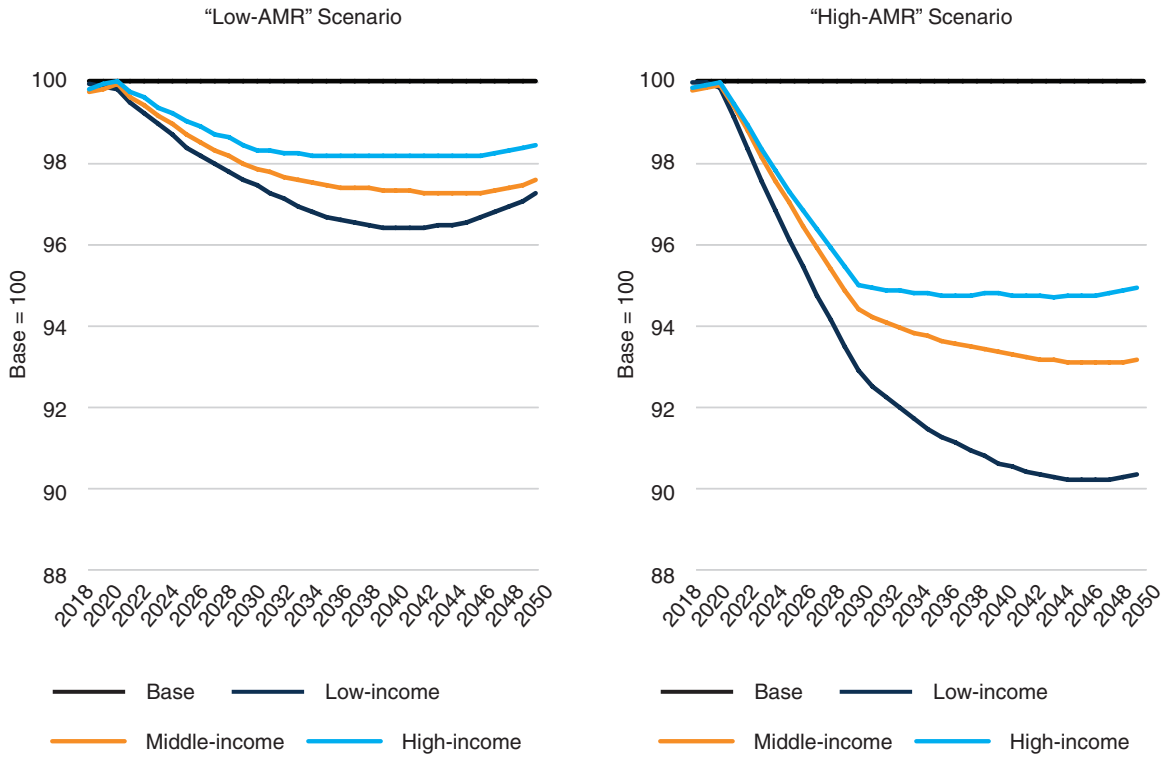
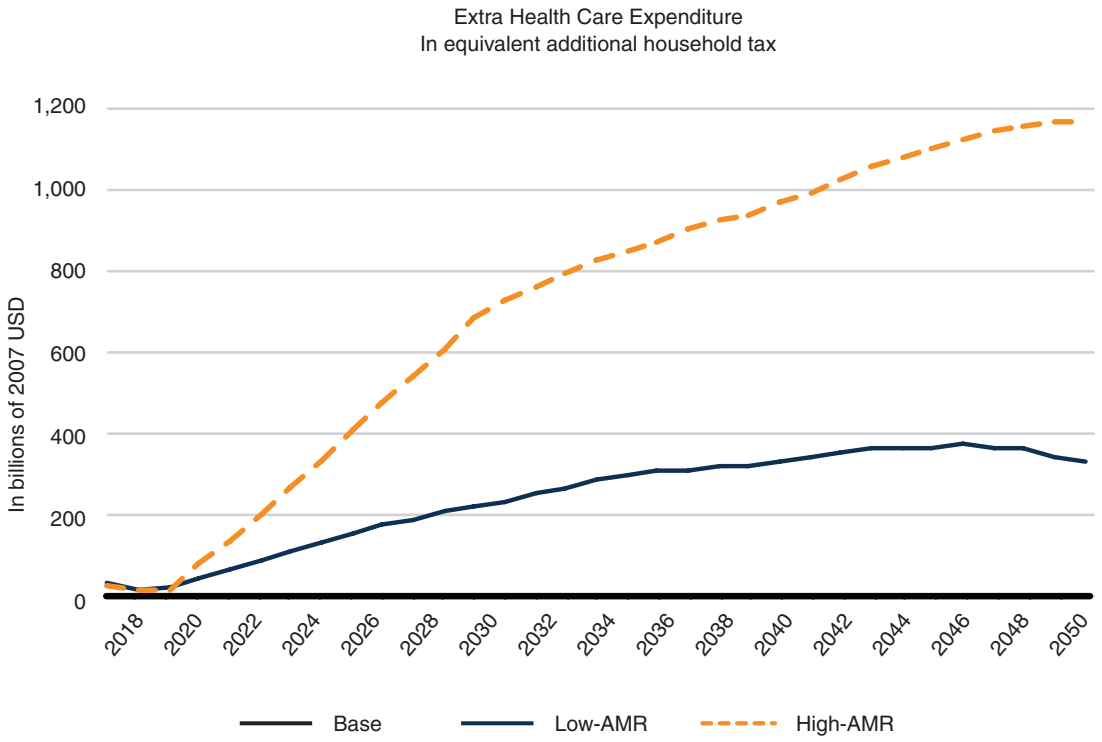


FIGURE 6. Health Care Costs Reach Nearly $1.2 Trillion in the "High-AMR" Case



expenditures are not made unless they are financed, there would be a decline in consumption. This will mean a reduction in other population well-being, because resources that could have been devoted to reduce poverty or 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 they would have to reduce their consumption in order to pay the additional taxes.

Already by 2030, extra health care expenditures would rise to $0.22 trillion annually in the "low-AMR" scenario. This is thirty times the amount needed in annual investments to contain AMR (see Part III). Thus, the amount of extra health care expenditures in just this one year would suffice to finance 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 on the other measures required to contain AMR (see Table 1, page 34) is a highly-justified expenditure just from the narrow perspective of the human health sector.

More broadly, containment of AMR is 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. The expected benefits from avoided extra health care expenditures are much higher than the costs of investing in AMR containment. For instance, 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.

The cumulative savings of extra health care costs during the entire projection period are $4 trillion if the "low-AMR" case is avoided and $11 trillion if the

"high-AMR" case is avoided.[33] This is the range of the order of magnitude of the benefits in the health sector. How do these expected benefits compare to the costs of investments and other measures to achieve AMR containment? These costs are $0.2 trillion. Thus the net present value is positive—and enormous. 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 enjoy a cumulative total net gain ranging between $3.8 trillion and 10.8 trillion—thanks to avoiding the impacts of the "low-AMR and "high-AMR" cases, respectively. These substantial resources could then be invested in improved health care. These resources will not be available, however, if investments in AMR containment are not made.

[33] Both are the present values of extra health care expenditures in the simulations, cumulative total in 2017–2050, and using a 3.5% 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 is in a relatively distant future, the present value is $0.35 trillion, which is the amount that is included in the $11 trillion total.

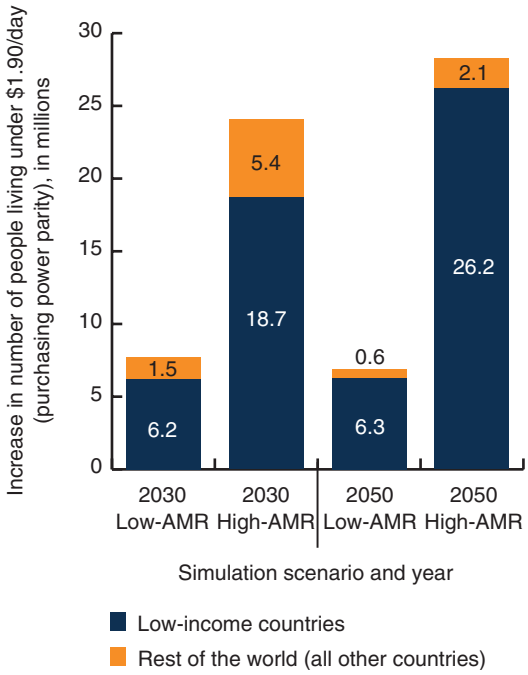
It is possible that even strong AMR containment efforts may not be fully successful. Let us assume a very poor outcome for illustrative purposes: chances of just 1 in 10 that containment will be achieved, or that adverse microbial developments will limit containment to just 10 percent of the full-containment marker. 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 enormity 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.

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 2) which experienced substantial and protracted shortfalls in economic output. 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 (at $1.90/day) by 2030, reaching close to the target of less than 3 percent of people living in extreme poverty. 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

Additional people falling into extreme poverty: nearly 8 million by 2030 in the low-AMR case; more then 28 million by 2050 in the high-AMR case



Source: Simulation results and author's calculations.

Part III. What Will It Take to Contain AMR?

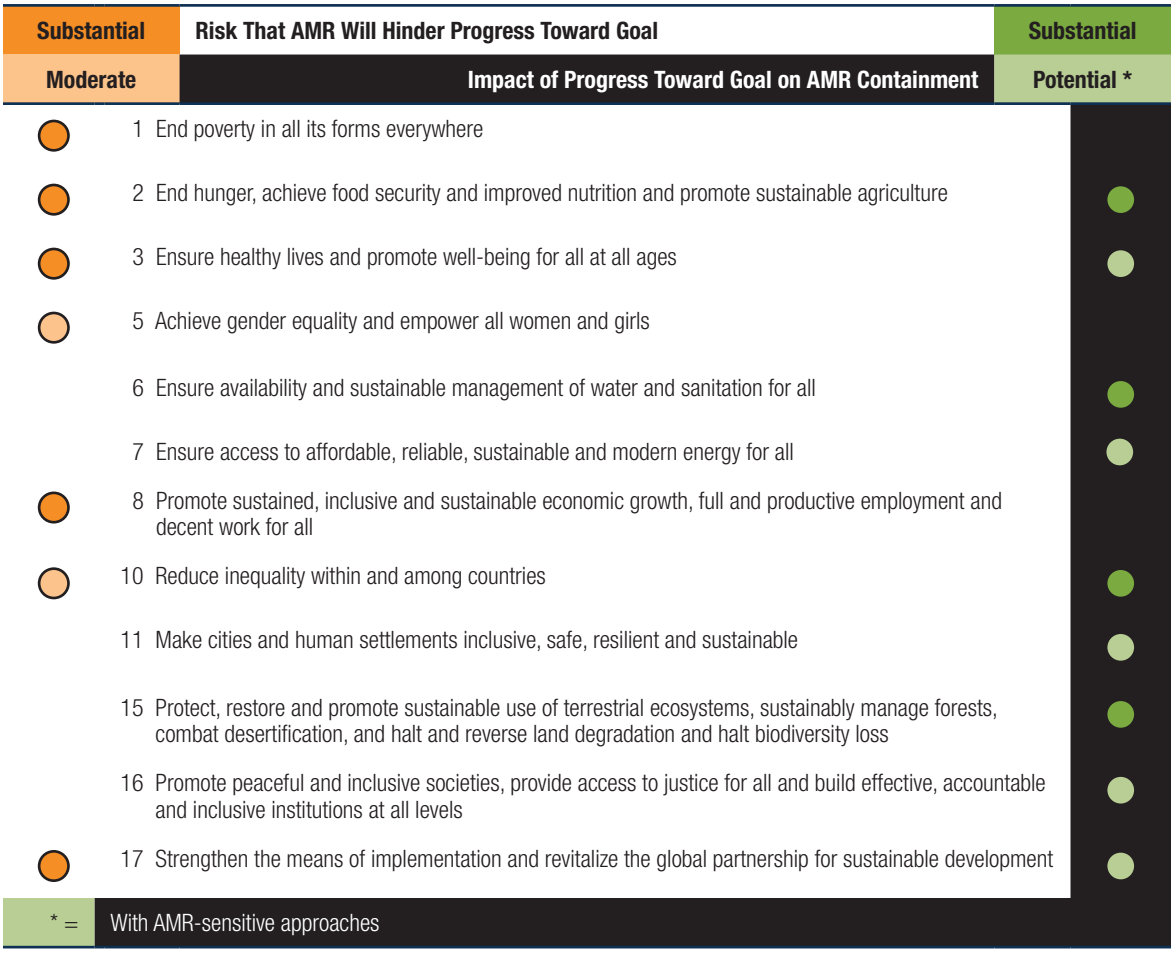
A. International Cooperation

Since AMR does not respect borders, international cooperation is necessary to tackle the problem. Moreover, as shown in Part II, the impacts of AMR will disproportionately fall on lower- and middle-income countries and cause increased poverty. These patterns of the economic impacts of AMR provide additional reasons for international cooperation because AMR puts at risk the achievement of the global development goals.

Containment of AMR and the Global Development Agenda

The simulations results presented in Part II show substantial negative economic impacts both globally and, especially, in low-income countries. 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 8), including ending poverty (the poverty increases that AMR could cause are described above), ending hunger and promoting sustainable livestock, healthy lives and well-being, and sustained economic growth. If the international community does not mobilize the very modest resources required to contain AMR and enable all countries to comply with the International Health Regulations (IHRs), then it will have failed to reach the goal for supporting capacity for implementation and revitalizing global partnerships. Additional, possibly less severe, effects of AMR are to reduce prospects for gender equality (related to women's greater responsibility in caring for the ill as well as their and infants' vulnerability to infectious diseases) and to reach the goal to reduce inequality. The

FIGURE 8. Synergies and Tensions with Global Development Goals for 2030



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).

impacts of AMR on economies are disproportionately more severe in low-income countries than in middle- and high-income countries (Figure 3), which would increase inequality among countries. Progress toward other goals would likely slow as well, to the extent that their achievement requires investments. Reduced global economic growth due to AMR would diminish the resources available for such investments.

While continuing unchecked emergence and spread of AMR will impair progress on the global development agenda, there are a number of entry points for advancing AMR containment within the Sustainable Development Goals framework. For many goals, there are important synergies with AMR containment, as indicated on the right side of Figure 8. When governments and their partners work to determine relative priorities among the goals, they may consider also the impact of progress toward the goal on AMR containment. Water supply and sanitation clearly help reduce infectious disease risks, reducing the need to use antimicrobials and thus contributing to AMR containment. AMR containment is an additional reason to devote resources and attention to reaching the water and sanitation goal.

In some areas the positive co-benefit of contributing to AMR containment is only potential, and it will be worthwhile to consider making investments "AMR-sensitive." This could bring attention to unduly neglected areas. For instance, pursuit of the universal health coverage target should include promotion of infection prevention and control (IPC) in hospitals and clinics. Success in raising performance in IPC in health care facilities will not only substantially contribute to AMR containment, but it can improve the quality of care, increase patient visits for preventive care (fear of infection and low hygiene standards can lead patients to avoid health care facilities), and improve staff morale and productivity. Urban sustainability is higher with lower infectious disease risks, so pursuit of that goal can contribute to AMR containment if municipalities include public health objectives in their development programs. As the results of the simulations presented in Part II indicate, AMR is not just costly but also impoverishing—AMR containment is equalizing. Another example of an opportunity for synergies is in the pursuit of revitalized global partnership, which includes efforts to improve 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 not an exhaustive list; there will be additional opportunities in specific country contexts.

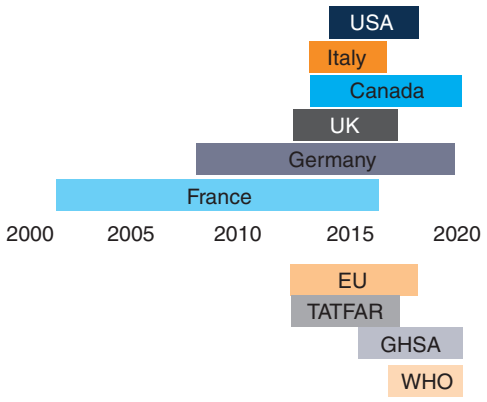
Organizing for International Collective Action

International cooperation is challenging to organize, fund, implement, and monitor because it requires that national public health and other authorities cooperate. This is difficult without capable and adequately-funded international organizations. Nevertheless, there is growing experience in international efforts to contain AMR; such efforts have existed for nearly 20 years. A resolution adopted by the WHO's World Health Assembly[34] in 1998 urged countries to contain the use of antimicrobials and improve relevant legislation. 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 both across different agencies within the EU (i.e., the European Centre for Disease Prevention and Control (ECDC), the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), the European Antimicrobial Resistance Surveillance Network) and with other countries (e.g., China and Russia). The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) has engaged both Europe and the U.S., while the Global Health Security Agenda (GHSA), which was launched in January 2014, now extends to more than 60 countries. These international initiatives and implementation of a number of country plans (which also have international components) are currently ongoing till 2017 (Figure 9).

Implementation of actions has been uneven and, in some areas, modest at best, however. International plans and country plans to contain AMR have listed measures in low- and middle-income countries, but implementation and financing implications have not been sufficiently considered. These aspects have also been unduly neglected following adoption of the revised International Health Regulations in 2005, with the result that the public health capacities that are needed for both IHR compliance and AMR containment have not yet been built. In the context of two major international efforts to improve the world's

[34] Ministers of Health of all countries participate in the World Health Assembly.

FIGURE 9. National and International Plans to Tackle AMR: Year of Implementation and Duration



Source: OECD (2015), p. 29.

economic security, such dual neglect may signal that collective action can, again, founder in the absence of stronger international institutions.

In low- and middle-income countries, and especially in low-income countries, AMR containment has not been able to compete for attention and funds with the many other initiatives that external partners have, nor with the other pressing priorities of governments in the human health sector. Veterinary public health is possibly the most neglected and least financed public good, especially in low-income countries, and actions to contain AMR in agriculture in those countries have been accordingly nil. More broadly, as a senior G20-country official said at a public seminar in Washington, DC in 2016: "In government, we have at any time about 20 top priorities. AMR is number 25, maybe." But the issue has received only modest attention in high-income countries, as well. Thus, in 2010, the Center for Global Development called for a reversal of "a decade of neglect" of drug resistance. The same year, the U.S. Institute of Medicine described AMR as "both a global public health and environmental catastrophe." That they were not "crying wolf" is supported by scientific consensus on evolution, the enormous expected economic costs that will affect all sectors, and substantial poverty impacts (Part II).

Sustaining Leadership of Containment of AMR

Public leadership at the international level has emerged in the last several years. There is a significant risk that this leadership will not be sustained over the decades ahead without stronger, permanent mandates to international organizations that institutionalize responsibilities and accountabilities for containment of AMR. Containment of AMR will not be sustained if it is vulnerable to political cycles in leading countries and to fluctuations in annual budgets of governments. It would make significant sense to confer durable mandates on global institutions, strengthen their capacity to deliver on these mandates, and establish transparent, predictable, and adequate long-term financing mechanisms for a permanent public task that is in the interest of all countries. The inefficient and ultimately highly ineffective cycle of public health crises and neglect of preparedness and prevention are a well-established pattern in the health sector. AMR containment, facing similar incentive and governance problems, may not succeed without arrangements that can span over inevitable periods of "AMR fatigue" and neglect of prevention. The need for arrangements that establish accountability is evident. The continuing emergence and spread of AMR is now a stark and potentially very costly manifestation of poor governance of public health, despite 70 years of warnings based on scientific consensus about AMR.

Improved governance of public health and AMR containment can be seen as a single, joint challenge. Both can improve if at least three things happen: risk awareness, international leadership, and adequate, stable, and fairly burden-shared financing. Looking at the distribution of benefits from AMR containment could be helpful for risk awareness and for establishing long-term, fairly burden-shared financing arrangements. As seen in Part II, economic impacts (measured by percentage shortfalls of GDP relative to the base case) largely depend on the prevalence of infectious diseases and labor intensity of production; both are generally higher in low-income countries than high-income countries. Low-income countries would suffer the largest proportional shortfalls in GDP because of AMR impacts (Figure 3). However, the economic losses would be much higher in absolute terms in high-income countries, where workers affected by higher mortality and morbidity have much higher productivity and wages than workers in low-income countries.

Distribution of AMR Containment Benefits

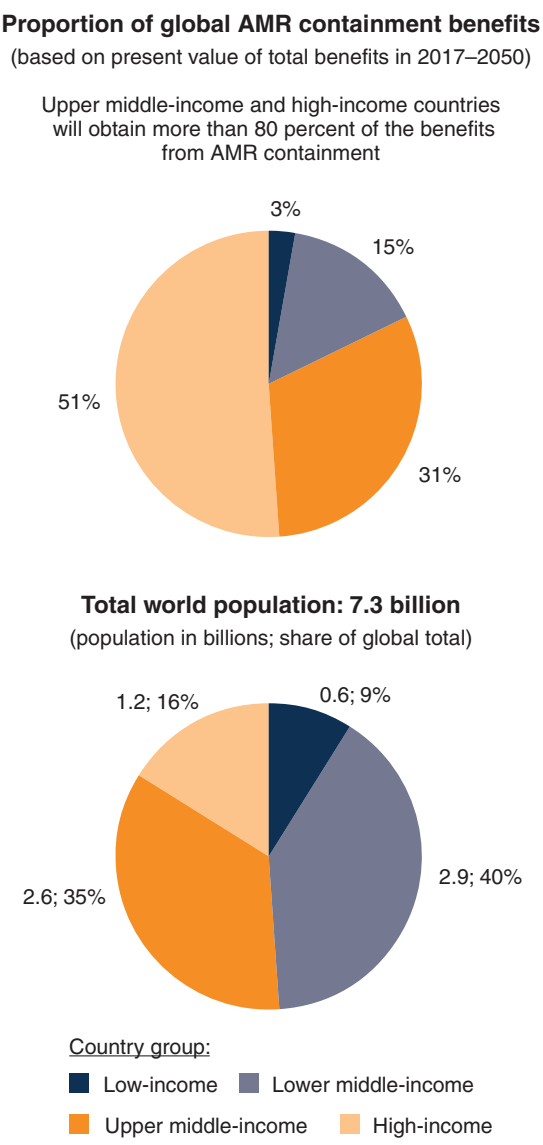
This report cannot answer the question of which countries will contribute to finance the investments needed to contain AMR. Instead, it presents the results of the simulations that indicate the levels of the expected benefits from AMR containment and the

distribution of these benefits across country groups. These results could inform consideration of long-term financing arrangements for containment of AMR. For example, some countries or groups of countries may benefit to such an extent that they will find it in their interest to finance measures to contain AMR not only in their countries, but also in all other countries.[35] The expected benefits from containment of AMR for high-income countries, with a total population of 1.2 billion people, illustrate this point. Using the discount rate of 3.5 percent and assuming that the AMR containment efforts would succeed in reducing the economic costs of AMR by 50 percent, the populations and economies of high-income countries 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, the two groups of countries would obtain about 80 percent of the global economic benefits from full or partial AMR containment (Figure 10). The expected benefits of even partial AMR containment are clearly far more than the total cost of the measures that need to be implemented between now and 2050. The estimate of these costs is $9 billion annually (Part III). The present value of the cumulative cost of the measures during the simulation period is $0.2 trillion. The measures are tested, developed by global experts and based on settled science, and their effectiveness is known in most cases. Without spending $9 billion annually, no AMR containment will occur and this will impose large costs on all countries. High- and upper middle-income countries could thus suffer cumulative losses as high as $15 trillion (if the "low-AMR" scenario materializes) or even $44 trillion (if the high-AMR scenario materializes). Even a partial success in reducing these costs will require the world's leading countries and official financial institutions to make robust arrangements for investing $0.2 trillion in AMR containment over the coming 34 years. The expected net benefit of actions to contain AMR is enormous. Should the actions prove inadequate and AMR continues to increase even as they are implemented, the magnitude of the expected benefits from AMR containment offers a scope for funding the development and implementation of additional measures.

FIGURE 10. High-Income and Upper Middle-Income Economies Stand to Benefit the Most from AMR Containment, Both in Absolute and per Capita Terms



[35] See discussion of single best-effort approach to financing of global public goods, in Barrett, Scott (2007) *Why Cooperate? The Incentive to Supply Global Public Goods,* Chapter 2.

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.[36] 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. There are, in addition, national and regional co-benefits that arise from preventing and controlling disease outbreaks and from improving the quality of health care thanks to surveillance that generates better and more complete information about pathogens (see Part IV).

B. Expert Consensus on Measures to Contain AMR

Momentum toward AMR containment increased in 2013 when WHO convened the AMR Strategic and Technical Advisory Group (STAG). In collaboration with OIE and FAO, the Advisory Group mobilized relevant expertise, including from public health (both human and animal), food safety, and pharmaceuticals industry, to formulate the Global Action Plan on AMR (2015–2019). The Plan was adopted by all countries at the World Health Assembly in May 2015. While the plan is global, the bulk of implementation will need to be by countries. Global institutions like WHO, OIE, and FAO can provide technical guidance and services like global surveillance data and analyses to country authorities, but they have neither the resources nor the mandate to take measures to contain AMR. The government of every country is responsible for leading implementation in the country. The first step is formulating a country action plan that may well follow, depending on country context, the five objectives of the global plan and all the measures associated with each objective (Figure 11).

Implementation of measures to contain AMR in countries will be the most important factor in how much of the benefits of AMR containment will, in fact, materialize. These benefits are enormous, as suggested in Part II. What should be done first? Where should most of the funding that may become available be directed? There are few definite answers that will fit the institutional

[36] National Academy of Medicine (2016). *The Neglected Dimension of Global Security—A Framework to Counter Infectious Disease Crises.* Report of the Commission on a global health risk framework for the future.

FIGURE 11. 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.

and developmental context of all low- and middle-income countries. But some markers emerge from the analysis of economic impacts and from the case studies. It will be helpful to review possible actions from the perspective of whether they are "AMR-sensitive" or "AMR-specific" or "AMR-critical" (some could be a combination). As discussed in Part II, the pursuit of several Sustainable Development Goals (Figure 8. Synergies and Tensions with Global Development Goals for 2030) will clearly help contain AMR—for example, access to clean water and sanitation. Vaccination in humans and livestock is also "AMR-sensitive." Such measures have dual benefits, and it will be appropriate to add the concern to contain AMR to the justification of such programs (if they are more effective than other programs, expansion could be considered).

Some measures are "AMR-specific" such as regulation of trade, distribution, marketing, prescribing, and use of medicines. The governance gaps in this domain are considerable. Still, investing in reforms could generate co-benefits for regulating other medicines and combatting counterfeit and substandard drugs. Wider access to affordable, rapid diagnostics is essential in reducing misuse and overuse of antimicrobials; this will have co-benefits of improved quality of care for patients, since fewer patients will receive inappropriate medications. Antibiotics stewardship programs are an effective, low-cost method to change behaviors that drive excessive use in medical facilities.

"AMR-critical" measures are systematic strengthening of veterinary and human public health systems so they can regulate and monitor effective use of antibiotics and to perform surveillance for AMR and other major threats to public health. The weakness of the veterinary systems is especially dire. As a result, little is known about use of antimicrobials in livestock in low- and middle-income countries. The information basis and veterinary public health service capacity are insufficient for formulating and implementing measures to ensure prudent and responsible use of antimicrobials (see Part VI). The first priority is to invest in veterinary health systems so they rise to an acceptable performance level; it will be only then that many of the supplementary "AMR-specific" actions can be defined and implemented effectively.

Table 1 presents an overview of the costs of the listed measures for AMR containment. The estimated global total is $9 billion annually. About half is for building core veterinary and human public health capacities; these will also reduce pandemic risk, increase preparedness, improve public health, animal health and livestock keepers livelihoods, food safety, food security, economic growth, and resilience. Some expenditures like R&D for new vaccines and medicines may eventually benefit low- and middle-income countries, whereas stronger public health systems will benefit them also already in the near-term. A recent example of the dramatic difference core public-health functions can make was the arrival of an Ebola patient in Lagos, Nigeria, in August 2014, from Liberia, where the Ebola epidemic was spreading fast. The disease could have spread in Lagos, which is a large city, just as it had in Liberia. If it had not been detected promptly and the public-health service in Nigeria had not been prepared, Ebola would have spread further, including to countries with no or minimal capacity to stop it. The savings from the prompt control of Ebola in Nigeria, through swift action at the source, were enormous.

C. Two Principal Risks to Containment of AMR

The first of the two main risks is that support will not be sustained over the timespan of future decades, which is the appropriate duration of efforts to contain the emergence and spread of AMR. (Reducing pandemic risk is likewise a task for many decades.) Building of performing veterinary and human public health systems takes time and perseverance, and this is all the more reason to begin these programs. Filling gaps in response to emergencies that will arise because of neglect of preparedness is always more costly and less effective than reliance on robust capacities for responding. The second risk relates to the gaps between institutions, professions, and capacities for human and veterinary public health. They need to work together to reduce health risks at the animal-human-environment interfaces. Pathogens cross these interfaces with far more ease than highly-educated professionals and public-health organizations. The divides among them generate risks.

Failure to Secure Predictable, Adequate, Long-Term Support for Human and Veterinary Public-Health Systems

The permanence of the threat of AMR reinforces the case for a higher priority of building up robust

TABLE 1. Cost of Measures to Minimize and Contain AMR

INTERVENTIONS AND SERVICES to Implement the Global Action Plan on AMR (2015)	Best Available Estimates, US$ Billion per Year	Approximate Share
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	
Active management of 'antimicrobial commons' for effective, efficient, and equitable access		
As a priority, preventative measures to avoid suffering, costs of disease, and need for health care. E.g., minimize spread of disease in health facilities and harm to patients by reducing hospital acquired infections, promoting infection prevention and control in all facilities receiving public funds, monitoring performance of IPC, improving waste disposal, raising awareness of AMR risks, . . .	1.3	89%
Making 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, sales both for human use and use in animals) Rolling out existing and new **diagnostics and vaccines** both for humans and livestock (initial average proportion 30:70)	2.0	
Global and Regional Interventions (intervention 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	0.3	
(b) promote development of new antimicrobials		11%
Global Innovation Fund supporting basic and non-commercial research in drugs, vaccines,	0.4	
Global **public awareness** campaigns (depends on size of campaign)	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 UK Review on AMR (2016). Estimates of cost of public health system capacities in LMICs are from World Bank (2012); best available estimates.

human and veterinary public-health systems more broadly. The frustration and powerlessness that many policy-makers feel when confronted with the complex and daunting challenges of AMR containment are primarily a reminder that the systems for public health have been neglected for decades. Their functioning is necessary and long overdue—neglect of public health systems has caused recurrent costly crises—most recently, for instance, the Ebola outbreak in West Africa. Such events can stimulate interest of governments in improving core public health infrastructures, but often such interest has been only short-lived, followed by reverting to neglect. The chronic low priority of core veterinary and human public-health functions has long been evident both in countries and in operations of international organizations. If this does not change, AMR containment will be exceedingly difficult to achieve and impossible to sustain.

The long-term nature of the AMR and other infectious threats necessitates careful attention to funding of the systems that need to perform if the threats are to be reduced. As essential infrastructure for veterinary and human public health and components of global defenses against pathogens, every country's public health systems require stable and adequate funding. Weak links in the global system pose a risk that is far greater than the investment and operating costs of public health systems in all countries combined. These weak links can persist in large part because neither governments nor international organizations are accountable for their neglect of public health

systems, even as low and unpredictable funding results in poor system performance. For instance, as noted in Part IV, stock-outs of supplies occur in laboratories. This is highly inefficient since personnel and equipment are then idle, though they still cost money. It is also unproductive, since the intended function of the system (surveillance for vital information on microbial threats) is not delivered because of the stock-outs. While mismanagement of supplies may occur for other reasons than lack of budget, it is certain that inadequate and unpredictable funding will significantly reduce system performance.

Knowledge about measurement of system performance could nudge governments and their partners toward proactively protecting public health and economies by developing the required capacity of core public health systems. Indeed, the World Bank's Independent Evaluation Group (IEG) carried out a review of the avian and human influenza response, covering multisectoral public health projects in 60 countries.[37] Though these were emergency projects, significant efforts were made to improve performance of core public health systems. IEG's review found that, unfortunately, after 2010 the World Bank failed to sustain its support to the public health capacities that are required to reduce pandemic risk *ex ante*. In the expectation that the World Bank would re-engage, IEG also recommended how the World Bank could increase the effectiveness of its support. In particular, IEG found outcome indicators such as disease prevalence and the case fatality ratio, were not sufficient to evaluate progress and, in fact, would be misleading.[38] Instead, reliance on measures of system performance was more appropriate for the core public health functions that are required for AMR containment and prevention and control of public health emergencies. Indicators of system performance may be sometimes called "intermediate" outcomes, which is misleading because the ultimate objective is system capacity and performance, including performance of links to regional and global systems. Such capacity should be tested through exercises and simulations, so outcome indicators may be whether these were carried out. Measuring and rewarding system performance could help end the neglect of core public health functions. Measurement of system performance is central to the OIE Performance of Veterinary Services (PVS) tools as well as in the Joint External Evaluations being introduced by the GHSA. Concerted implementation and priority follow up on remedying the gaps identified in such assessments are important. The consequence of continuing neglect will be tragic and costly failures, such as the four-month delay in detecting and diagnosing Ebola in the 2014–15 outbreak and in AIDS circulating widely, undiagnosed, for more than a decade. The economic impact of the Ebola epidemic was $10 billion; the costs of the AIDS pandemic are still growing. As described in Part II, the costs of inaction on AMR will be on the order of several thousand crises like Ebola.

High-income and many middle-income countries can operate their veterinary and human public health systems independently, drawing on international expert guidance as needed. But in other middle-income countries and especially in low-income countries, the overriding objective of these systems functioning is far from being addressed in a coherent and efficient manner. Satisfactory performance of the systems is required for low-cost, high-impact improvements in public health in the country, for reducing risks to other economies, for compliance with IHR, and for increasing global health security. Containing AMR and reducing pandemic risk are both goals whose achievement requires performing public health systems.

AMR containment and reducing pandemic risk generates extraordinarily high economic returns. As such, investment in public health systems should be at the top of priority lists of governments and organizations disposing with public funds. The lowest estimate of benefits from complete AMR containment alone in the simulations in Part II is $20 trillion. To obtain this benefit, governments need to invest $0.2 trillion. If this investment is made and full AMR containment is achieved, the expected net benefit is $19.8 trillion. All governments that may wish to obtain their share of this net benefit are represented on the boards of international organizations and in negotiations of replenishments of concessional funds for the poorest countries. In those contexts, they consider priorities for investing public funds as well as their contributions. They could decide that the

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[37] See: World Bank Independent Evaluation Group (2014). *Responding to Global Public Bads: Learning from Evaluation of the World Bank Experience with Avian Influenza, 2006–2013.* For disease control and prevention projects, so-called "final outcomes" are driven by multiple unpredictable factors, making attribution especially challenging. Intermediate indicators are warranted, instead, to guide implementation and to assess results.

[38] The challenges of measuring "final outcomes" instead of system performance are evident in Magid Herida, Benoit Dervaux, Jean-Claude Desenclos (2016). *Economic Evaluations of Public Health Surveillance Systems: a Systematic Review.* The European Journal of Public Health, Vol. 26, No. 4, 674–680.

highly-productive investments in AMR containment and related health security objectives would be funded first.

Given the emphasis in the Global Action Plan on AMR and in Parts IV and VI on building capacity for core functions, independent assessments of veterinary and human public health systems in countries will need to become the cornerstone of the global public health agenda. There are good experiences with implementation of the methodology and benchmarks established by OIE for the Performance of Veterinary Services (PVS) pathway, subsequently elaborated jointly by OIE and WHO to include core human public health functions and compliance with IHR, and further developed and tested in the GHSA. AMR containment will more likely succeed and be sustained if WHO and OIE, together with partners, expand their evaluations of system performance to more countries, so that governments and their partners can use the results to guide their decisions on investing in public health systems.

Mitigating Risks of Inadequate and Unpredictable Financing

The financing modalities for AMR containment would be more effective if they were aligned to the characteristic of the required effort: global, multisectoral, long-term, with a predictable and adequate capacity, and appropriately burden-shared (not based on short-term voluntary contributions). A long-term effort to adequately finance capacity-building for core veterinary and human public-health functions is required in all countries, especially in low-income countries. This recognition could prompt a review of the existing global financing institutions that operate in the sectors involved (animal health, human health, environment, disaster risk management) to identify which institutions could be mandated to finance economically more productive projects first, ahead of less productive projects. A pragmatic modification of the existing criteria for allocating multilateral concessional funds could increase incentives for recipient governments and for the managements of global financing institutions to support these investments with multiple benefits. The investments are needed for AMR containment, pandemic risk reduction, compliance with IHR and OIE standards, and achievement of national health and economic objectives. If the modified criteria for allocating public funds prove effective, the arrangement to fund public health system strengthening projects as a priority, could become permanent. The world could thus expect to gain more of the enormous benefits from AMR containment, as well as reduced pandemic risk. The alternative would be to coordinate multiple, fluctuating, and sometimes disparate funding streams from bilateral partners to support investments in AMR containment in some 100 countries. This would have high transactions costs and would not ensure predictable and adequate support to the AMR containment effort that should be sustained during the coming decades.

Basic veterinary and human public health systems should be the first line of defense against AMR and infectious diseases. They are the indispensable bedrock for improved public health and for health and economic security. It bears repeating: Without robust public health systems containment of AMR will be difficult to achieve and impossible to sustain.

As highlighted in the WHO Global Action Plan and in Part IV, surveillance and diagnostic capacities are required for both human and veterinary public health—what public health authorities do not know will invariably harm the population. These systems remain weak in too many low- and middle-income countries, however, and in some failed states they have collapsed entirely. Eight out of ten countries do not comply with the International Health Regulations (IHR) more than a decade after their adoption as binding international law, because they lack the capacity to perform the core functions of detecting, diagnosing, and controlling contagions caused by drug-resistant and other pathogens. In many countries, antimicrobials are widely available, directly or indirectly, practically with no restrictions or controls. According to OIE, the vast majority of countries—110 out of the 130 countries where assessments were made—do not have complete and relevant legislation to ensure appropriate conditions for the import, manufacturing, distribution, and use of antimicrobials and other veterinary medicinal products.

Failure to Adopt One Health Approaches

The second major risk to successful containment of AMR is that it will remain as the responsibility of only the human health sector, which tends to be dominated by medical professionals with an ethic to attend to current patients; with limited resources, there is little attention to tomorrow's far more numerous patients, many of whom may well be ill because of today's ill poultry, for example. AMR risks arise in sectors other than human health,

too, however, so AMR containment will hinge on the capacity of the health sector to work with other sectors to develop effective policies, implement measures, and jointly evaluate results. While competition over budgets is inevitable, in most low-income countries the 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 the weakest and thus give rise to AMR risk, as well as pandemic risk.

The divide between the medical and veterinary domains is a historical, man-made hazard. Collaboration is difficult to achieve, which reduces the prospects for AMR containment considerably. 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, and this gives rise to global risks to health, economies, and societies. Adding AMR to the list of reasons why One Health approaches are needed should be an incentive to the human health sector to advocate for and support such collaboration, since it will not occur by itself. In addition to being indispensable for effectiveness of disease prevention and control, there is also potential for savings from the human and veterinary public health services sharing some functions. For example, the One Health approach is generating large savings in operating cost (estimated at 26 percent annually) at Canada's national laboratory; such efficiencies as well as greater effectiveness could be obtained elsewhere, too (see Annex 2).

D. Economic Justification of Investments in AMR Containment

Investing in containment of AMR is an exceptionally productive use of resources: for very modest investments, accompanied by mandates for international organizations and sustained political support from world leaders, an enormous benefit can be had. This enormous value was not derived subjectively, as in the studies on valuation of life, but it is based on simulations that use market valuations in their calculations. The results of the simulations of economic impacts are telling indicators of the benefits of AMR containment. Benefits of containment will depend on how much of the 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. Because the values arise in the coming 34 years, they need to be discounted, or reduced by a factor that uses the social discount rate. 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[39] and $40 trillion in the "low-AMR" scenario. 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. The report on the economic impacts of climate change by Sir Nicholas Stern (2007) used a discount rate of 1.4%. Table 2 reports the main outcomes of the simulations, using the 1.4% discount rate as well as results with more conventional discount rates of 3.5% and $5.5%.

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 ($6.4 trillion, discounted at 5.5%), to extremely large in the "high-AMR" scenario ($26.8 trillion, discounted at 3.5%), to enormous in the "high-AMR" scenario ($42.2 trillion, discounted at 1.4% annually). 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 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

[39] This result is very close to the outcome of the *UK Review on AMR,* which found $100 trillion cumulative costs due to AMR by 2050.

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-impact AMR scenario	40	30	20	13
High-impact AMR scenario	120	85	54	36
2. Benefits if 50% of costs averted				
Low-impact AMR scenario	20	15	10	6
High-impact AMR 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-impact AMR scenario	19.7	14.7	9.8	5.8
High-impact AMR scenario	59.7	42.2	26.8	17.9

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

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 7 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. 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.

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.

E. Implementation Approaches in Select Areas

The global economic and public health case for investment in containment of AMR is hard to resist. The bulk of measures will have to be implemented in countries, led by governments of the countries. International organizations with mandates for global health (WHO and OIE, together with FAO in the One Health tripartite) and other partners will need to provide technical assistance and guidance on technical standards for functions like surveillance and reporting. As discussed above, there are good reasons for partners to finance investments in

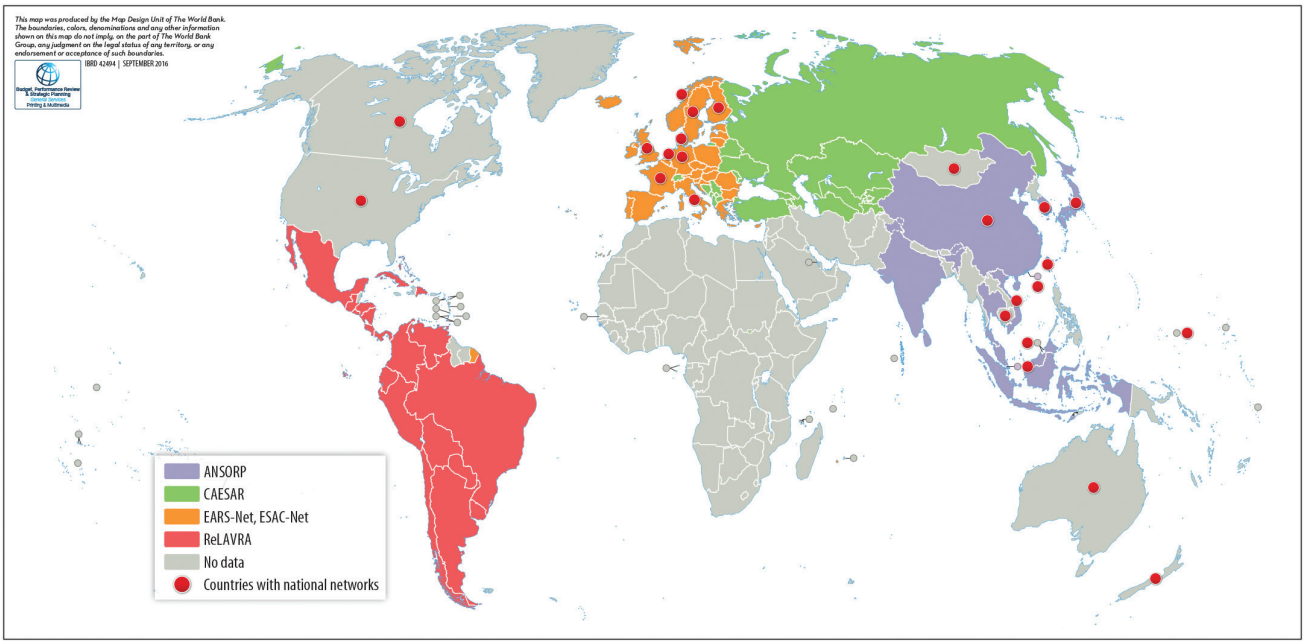
public health systems and other AMR containment measures, including economic self-interest and allocating resources to activities that bring very high economic and development benefits to low-income countries. The implementation challenges should not be underestimated, however. To contribute to narrowing the large knowledge gaps about what kind of specific approaches countries could take to formulate and implement their action plans on AMR, Parts IV, V, and VI below present the main features and findings of three special studies that were undertaken for this report.

Some of the recommendations in the following three sections apply only to the specific countries studied and should be considered as complements to expert technical advice from the relevant authorities like WHO, OIE and FAO. Attention to the "how" of choosing and implementing measures is critical to strengthening the development narrative and framing containment of AMR within the overall development agenda. These studies are by no means a comprehensive treatment of the topics of AMR surveillance, use of antimicrobials in healthcare, and use of antimicrobials in animals. For instance, the substantial overuse and misuse of antibiotics and other antimicrobials in human health care seems to be the result of ingrained behaviors, which are not easily unlearned. Training of physicians, work environment, peer pressure, financial incentives, patient-doctor relationships, access to diagnostics, and so on all appear to be among the drivers, but cannot be addressed in this report.

It should also be noted that the special study on the laboratories (Part IV) 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 short time and with the resources available. Likewise, Part V demonstrates a systematic approach to analyzing a subset of the antimicrobials market; it is limited to the most-pressing problem of misuse and overuse of antibiotics (antibiotics are one important type of antimicrobials). Finally, Part VI on antimicrobial use in animals does not deal with other agriculture sub-sectors, such as crops, that also use antimicrobials.

Part IV. Laboratory-Based Surveillance of AMR

FIGURE 12. Global AMR Surveillance Networks



Antimicrobial resistance surveillance is an indispensable component of the response to a rising tide of antibiotic resistance worldwide. WHO recommends surveillance as part of every AMR national action plan. WHO has developed a global initiative to collect a standard set of AMR data from each country. National-level systems are critical for guiding local and national policy, while regional systems can enhance the value of the data, depicting larger patterns and trends. The following sections present 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 Bank-funded East Africa Public Health Laboratory Networking Project to participate in national and, ultimately, regional AMR surveillance. The section ends with a set of recommendations, which are relevant to both countries in East Africa and other low- and middle-income countries facing similar challenges.[40]

A. Status of Global Surveillance of AMR

WHO defines public health surveillance as the systematic collection, analysis, interpretation and dissemination of data. In 2014, WHO surveyed its member states about their AMR surveillance efforts. They found that AMR among some specific pathogens—such as those that cause tuberculosis, malaria, and gonorrhea—has 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 12). 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 (22, 23). 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 (Box 3) (23).

[40] This section draws heavily on work conducted by the Center for Disease Dynamics, Economics and Policy and the East, Central, and Southern Africa Health Community.

Box 3. Pilot Program of 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.

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 (2). 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 (11). 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 common in community acquired infections such as pneumonia, diarrheal disease, tuberculosis, malaria, and sexually transmitted diseases (1). 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 (1).

B. Benefits and Costs of Surveillance of AMR

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 are 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 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 US$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 US$160,000 annually. Some costs scale to the size of the network (e.g., 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

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 Judgement

One method to estimate the counterfactual scenario is through structured expert judgment. A recent CDDEP study used this method to examine return on investment of an environmental health tracking program in the United States (50). 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.

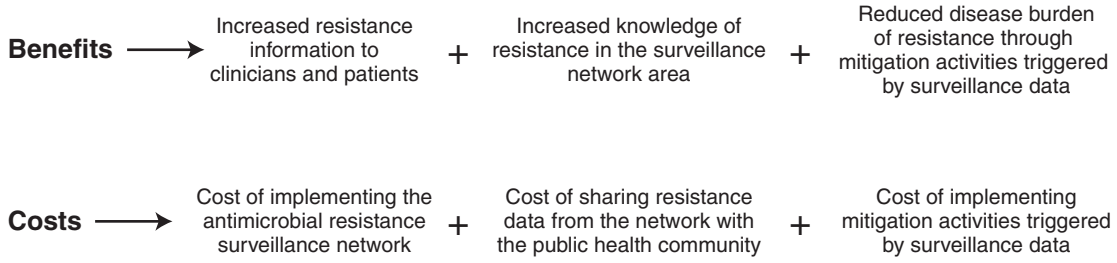
losses. Even if changes are observed, attributing all or some of the changes to a surveillance system is difficult if not impossible, underscoring the complexities and challenges of quantifying the benefits. In fact, even if no changes are seen, the system may be keeping the rates from rising. This is not to suggest that AMR surveillance is not effective, and in fact, all indications suggest that it is.

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 (i.e., 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 and difficult task that has not been satisfactorily carried out anywhere to the best of our knowledge. Box 4 describes the structured expert judgement (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.

FIGURE 13. Theoretical Framework for a Cost-Benefit Analysis of Antimicrobial Resistance



Various techniques are used to value lives lost, which include both direct and indirect costs.[41]

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 (49).[42]

Cost-Effectiveness Analysis of AMR Surveillance

Cost-effectiveness is a tool often used to guide public health decisions in countries at all resource levels (51). 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 (45). Further actions could include public health interventions or educational campaigns, targets for reduction in use, or changes in treatment guidelines or industry practices (Figure 13).

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 (18). If possible, these samples are annotated with patient information such as age, gender, specimen type, date, and geographic location (17). In the laboratory, technicians culture the specimens, identify bacterial isolates, and test isolates for antimicrobial susceptibility (17,18). 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

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[41] 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 Cooperation 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 $US1.5 to 2.5 million (46). 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 (46). The VSL is then multiplied by the number of deaths avoided to estimate the value of reduced mortality.

[42] For example, a 2006 study (47) 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 (48) compared the cost of health care through hospital charges and length of stay for resistant and susceptible infections in New York hospitals.

example, CDDEP's Resistance Map online tool summarizes national and subnational antimicrobial use and resistance and is the largest such repository in existence (20). 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 US$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 (Kenya, Rwanda, Tanzania, Uganda and Burundi). The project is: (i) strengthening diagnostic and surveillance capacity; (ii) expanding training and capacity building; and (iii) 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 a lead in a specific thematic area and provides regional leadership, generating knowledge and sharing experiences and lessons.[43] 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 14). The laboratories are expected to provide specialized services to communities in these regions that are otherwise available only in the national reference facilities.

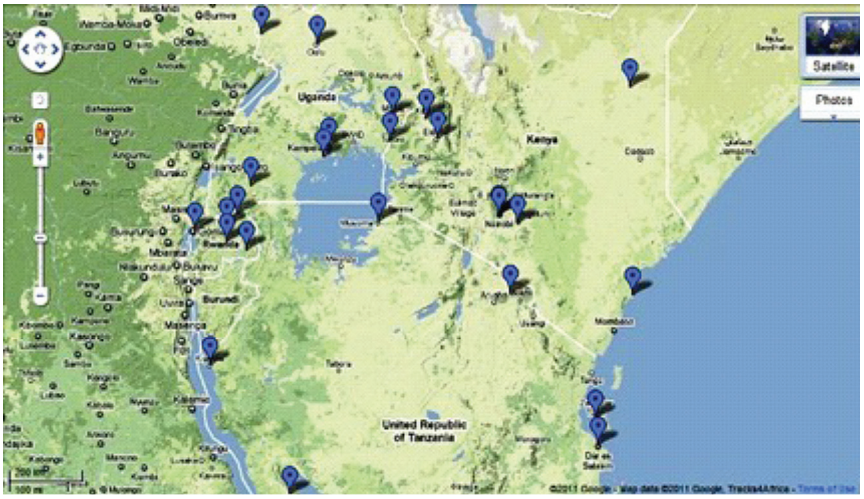
The main achievements include:

- *State-of-the art laboratories*: renovated/ constructed public health laboratories; and rolled out molecular technologies, including GeneXpert for diagnosis of drug resistant tuberculosis that has resulted 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.[44]
- *Regional specialization*: supported Uganda National Tuberculosis Reference Laboratory 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: (i) *joint annual peer audits,* whereby countries assessed each other's laboratories; (ii) *performance*

[43] Kenya leads on surveillance and operational research; Uganda on laboratory networking and accreditation; Tanzania on training and capacity building; Rwanda on information and communication technologies and performance-based financing, together with Burundi.

[44] 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.

FIGURE 14. Location of Satellite Laboratories



based financing, whereby facilities received incentive payments based on progress towards accreditation; and (iii) *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.[45]

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.[46]
- *Organizing a 2-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 (i.e., WHO, CDC, CDDEP).[47]
- *Producing a short film* to improve awareness of the importance of AMR surveillance.
- *Commissioning a technical report* that was 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.[48]

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.

[45] For example, in Kenya the study found substantial levels of drug resistance in Wajir, Malindi, Kitale, Machakos and Busia. Some isolates (*E. coli,* Shigella, and Salmonella) were found to have up to 100 percent resistance to basic antibiotics (ampicillin, erythromycin). Emerging resistance to ciprofloxacin ranged from roughly 14 percent (Wajir) to 50 percent (Machakos).

[46] *Strengthening the Role of Laboratories in Tracking Antimicrobial Drug Resistance in East Africa; Capacity Assessment,* East, Central and Southern Africa Health Community, June 2016.

[47] *Antimicrobial Drug Resistance in East Africa Meeting Report,* CDDEP, ECSA-HC, WB, May 2016.

[48] *East Africa Public Health Laboratory Networking Project: Strengthening the Role of Laboratories in Tracking Antimicrobial Drug Resistance in East Africa,* Center for Disease Dynamics, Economics and Policy, June 2016.

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 is only periodically quality assured (1).
- *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 perform 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 life-saving 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.

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 US$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.

***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 surveillances.
- 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 affect disproportionately 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* (i.e., 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, and routinely share AMR surveillance reports.
- *Maintaining the highest standards and practices* by: (a) relying on proficiency testing from the WHO or other proficiency testing for antimicrobial testing for surveillance; (b) using National Reference Laboratories 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.

Part V. Antimicrobial Use in Human Health Care and AMR

Misuse of antimicrobials (AMs) in humans is prevalent in both low- and high-income countries. There is evidence, for example, that there is a very serious antibiotic overuse of antibiotics for viral upper respiratory tract infection—but underuse of appropriate antibiotics for pneumonia; and serious overuse of antibiotics in acute cases of diarrhea—but underuse of oral rehydration solution.[49] As documented in different studies reviewed,[50] excessive number of AMs in the pharmaceutical market, aggressive pharmaceutical promotion, economic incentives where prescribers gain income from dispensing or selling the medicines they prescribe, poor availability of independent medicine information such as clinical guidelines and drug bulletins, overprescription or irrational prescription in primary health care facilities and hospitals, serious antibiotic misuse, poor adherence to infection prevention control protocols in health facilities (particularly with respect to hospital acquired infections), and treatment withdraw by patients, are among key factors contributing to growing AMR.

Drug stewardship is a huge and complex topic. Rather than aiming to generalize from the findings of the case studies described below or seek to generate (necessarily country-specific) recommendations and analytical findings that would apply also beyond the six countries that participated, this section demonstrates methods and approaches that countries can use to diagnose the functioning of their therapeutic chain and to identify measures that would improve and extend stewardship.

To complement the findings from a literature review conducted for this report, case studies[51] in six low- and middle-income countries (Botswana, Croatia, Georgia, Ghana, Nicaragua, and Peru) were prepared on November 2015 – April 2016 to examine in more detail and provide a cross-country "snapshot" of factors in the health system that may contribute to AMR. In comprehensively examining the AM-use chain, the objective was to identify the "weak links" and factors that may contribute to misuse or overuse of antimicrobial drugs, and possible interventions to promote "prudent use" of AM to prevent the onset of AMR. Figure 15 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 section).

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

Case Study 1—Antibiotic Market Offer

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

Rationale: A reasonable AM offer in the pharmaceutical market could improve the selection of appropriate AMs and how those AMs are prescribed and used. Two specific considerations were:

- The introduction of AMs that have not proven superiority over already marketed products—sometimes referred to as "me-too drugs"—increase the cost of medicines and the unnecessary exposure to promotional activities that contribute to AMR.
- Some fixed-dose combinations (FDCs)[52] which include an AM 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 AMs because prescribers or users are not aware that the product contains an AM.

Findings:

- There were significant differences in the six countries regarding the type and number of

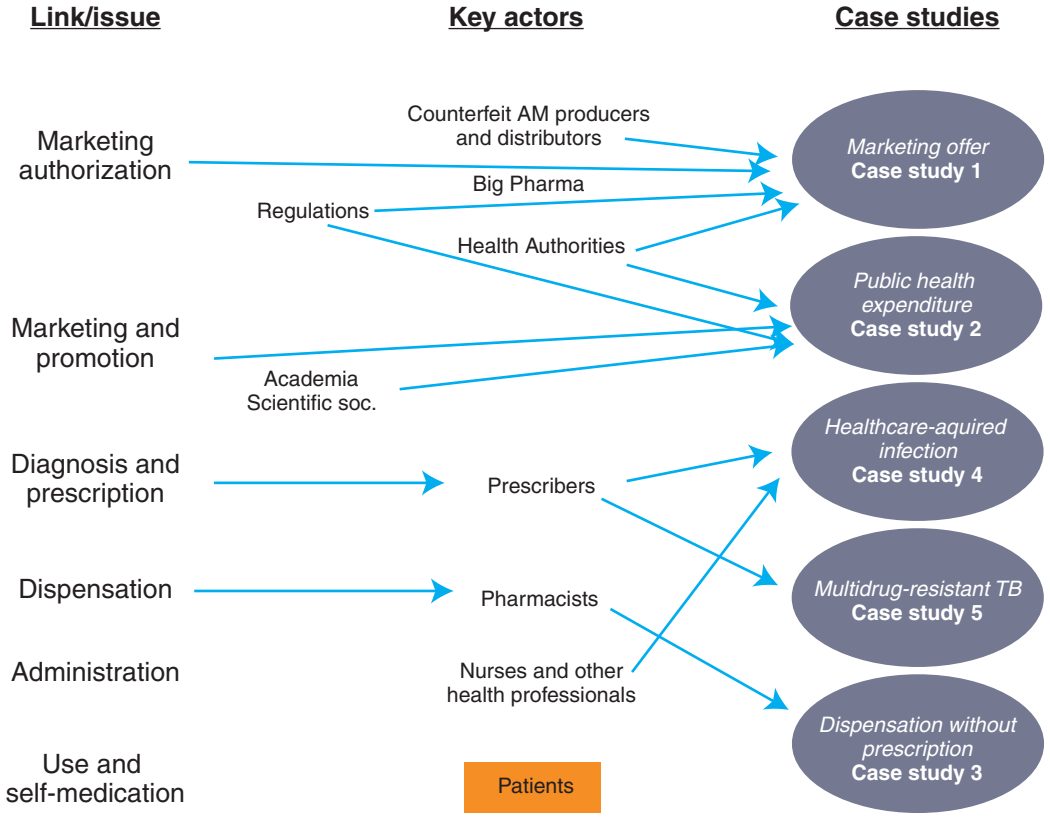
[49] Kathleen, A. H. (2011). "Promoting the rational use of antibiotics." Regional Health Forum—Volume 15, Number 1, 2011.

[50] 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 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.

[51] Figueras, A., Premaratne, I., Pérez, P., and Marquez, P. V. (2016). "Approach to Antibiotic Misuse and Resistance in 6 Countries: A Comprehensive Series of Case Studies." Report prepared as a background paper for this report.

[52] 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, R. (2012). "Reducing the "pill burden." CMAJ February 7, 2012 vol. 184 no. 2. First published January 9, 2012, doi: 10.1503/cmaj.109-4076.)

FIGURE 15. A Basic "AM Use Chain"



available AMs (Figure 16). Peru and Botswana have almost the double of different AMs than 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 17), and also to 'me-too' or redundant medicines.
- The proportion of FDCs to single brand name product ranged from less than 20% (Croatia and Peru) to almost 30% (Ghana).
- The proportion of brand names per individual AM also varied significantly among countries, being lower in Croatia (3:1) and higher in Peru (7:1). Such plethora of products with the same ingredients brings about confusion among prescribers and users, complicates AM selection and therapeutic decision making, and increases pharmaceutical promotional pressure (necessary for the manufacturer, but not beneficial and counterproductive for prescribers and users). The 'ideal minimum' of brand names to ensure needs coverage and maintain prices should be promoted and encouraged.
- Some AMs found in the different countries are not sold in the United States and in European Union countries (e.g., sultamicilin, netilmicin, prulifloxacin, or nifuroxazide), and some have been withdrawn from the market due to their toxicity (e.g., 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 AMs in the health system. The combination of market offers and consumption data is helpful to identify appropriate AMs use.

Findings:

- Data on consumption of AMs expressed in units were available in the participant countries,

FIGURE 16. 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 the double of different AM drugs than 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 Croatia.

→ What is the added value of having an average of six different brand names containing the same AM? Besides confusing the prescriber and user, it may contribute to increased pressure on firms to sell more AMs over competitors to preserve and/or expand market share.

FIGURE 17. Top-5 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 or azithromycin are broad spectrum, 2nd choice, expensive AM.

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

→ An unnecessary redundant market offer increases the risk of irrational or inappropriate use of AM.

although the data were not always comparable. Harmonizing information about AMs consumption in terms of defined daily doses (DDDs) helps analyze cross-country consumption patterns.

❇ Consumption in the public health system tended to be higher, in per capita terms, in countries with higher per capita GDP, although the relationship was not statistically significant. The lowest consumption was in Ghana (2015 per capita GDP US$1,381) and the highest in Botswana (2015 per capita GDP US$6,360) and Croatia (2015 per capita GDP US$11,535). Consumption data for private health services providers and self-medication were not available.

❇ The most consumed AM differ among countries. In Botswana, Ghana, and Nicaragua, 4 to 6 different AMs represented 90% of the total consumed units, while in Peru and Georgia, they amounted to 15 and 19 different AMs, respectively. This finding suggests that in the first set of countries the public prescription of AM may be more tightly controlled (either by restricted

FIGURE 18. Top-5 AMs Consumed

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

		SWA	PER	HRV	GHA	GEO*	NIC
Shows broad-spectrum AM or AM used in case of resistance	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**			
Shows a relationship between most consumed AMs and AMs with most marketed brand names for that active ingredient	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 the participant countries, there is an observed relationship between those AMs with more brand names marketed and higher consumption.

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 top consumed AM in units in each country was dominated by those AMs that are sold under different brand names (Figure 18), and differed among countries. The observed difference probably does not reflect different disease profiles because some of these AMs are second-line or broad-spectrum AMs.
- Data on AM expenditures show that amoxicillin was the most consumed AM in all countries (in Croatia, however, it was amoxicillin in combination with clavulanic acid). This uniformity is only for the first top five AMs, as the remaining active ingredients are different in the six countries. The differences in the top five AMs prescribed are not necessarily explained by microbiological differences; on the contrary, the high use of some AMs suggest irrational prescription and use (e.g., among the top prescribed AM are azithromycin, imipenem-cilastatin, dicloxacillin or cefuroxime).
- Examples of potential inappropriate use of AMs that could be discovered by careful analyses of macro prescription and expenditure data are provided by observed practices in some of the countries in the study. In the case of Croatia, the second AM in expenditure was azithromycin (AZM), which has unique pharmacokinetic and pharmacodynamic characteristics that give it unusual clinical properties for an antibiotic, and is used to treat or prevent a range of common bacterial infections including upper and lower respiratory tract infections and certain sexually transmitted diseases. Although azithromycin has become one of the top 15 most prescribed drugs and best-selling antibiotics, a growing body of evidence derived from postmarketing surveillance, including an analysis of the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) over an eight-year period from 2004 to 2011, links

azithromycin to sudden cardiac death risk (Giudicessi and Ackerman, 2013). Researchers have also noted that the risks associated with its use are concerning as it is a widespread pollutant in the water environment, and recommend that AZM be used in situations where well-conducted clinical studies have demonstrated an indisputable superiority over standard treatment or placebo, and by limiting the number of patients treated (Cohen and Grimpel, 2013; Gros, Petrović, Ginebreda, Barceló, 2009).

- Imipenem + cilastatin (second in Peru) and meropenem (third in Peru and fifth in Croatia) are examples of expensive AM that should also be considered as reserve AM. 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; despite this apparently low figure, it was the second most expensive AM. Beyond the high cost, there is the problem of potential irrational use of those restricted AM, as depending on their availability, they tend to be used as empirical treatments.
- Although it is difficult to compare the participant countries, the macro data of the consumption profile in Nicaragua seems more rational. The only AM consumed that attracts attention is dicloxacillin, third in the expenditure ranking of that country with a prescription rate of 593 units/1,000 inhabitants. Dicloxacillin is an example of beta-lactam AMs 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 bacteria."
- These country examples point out 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 to have 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 AMs. 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% of pharmacy visits by the case study's, simulated "self-referred patient" (156 out of 246) AMs were dispensed without a prescription provided after a clinical diagnosis. This practice in five of the six countries studied reflects lack of or limited or no enforcement of health regulations that prevent dispensing of AMs without prescription—Croatia was an exception (only 1 dispensation in 20 visits). See Figure 19.
- In more than 90% of the visits, the simulated "self-referred patient" was not clinically evaluated (for example, patient was not asked by pharmacist about drug allergies), which could place patients at severe risk of developing drug-related complications, including drug ineffectiveness, adverse drug effects, overdosage, underdosage, and multiple-drug interactions.

FIGURE 19. Distribution of "Simulated Self-Referred Patient" Visits That Ended with Dispensation of an AM, by Country

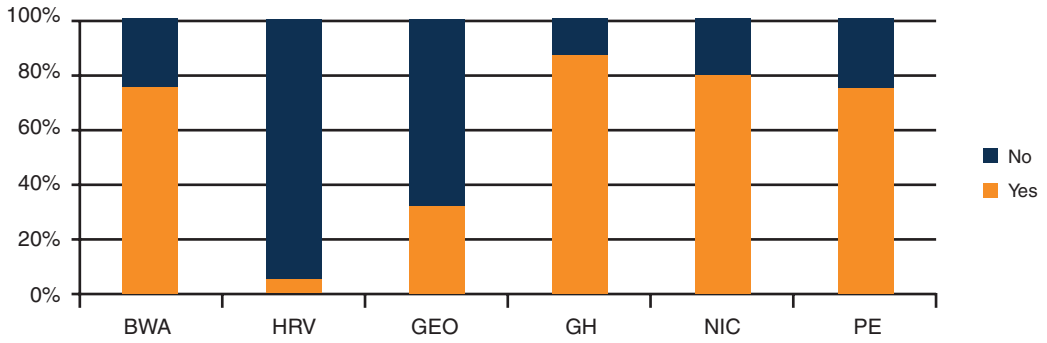


TABLE 5. Antimicrobials Dispensed without Prescription

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

Country	Specific Antimicrobials Dispensed (n 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 AM without prescription in the 6 study countries.

- The pattern of recommended AMs 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, there is an observed relationship between some "redundant" products and high dispensation (e.g., 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 AM was dispensed (53% of cases); the remaining 47% of '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 of medical records or information provided by health care providers on patients with HAI 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 cost, but because of the growing recognition that most HAIs can be prevented.[53]

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

Findings:

- As recorded by health personnel in selected hospitals of the studied countries, 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 and supplies, or poor hand hygiene practices, contribute to observed onset HAIs. This reinforces the need to pay attention and identify both structural factors and health care processes to reduce the risk of spreading strains of resistant microorganisms that cause HAIs in health facilities.
- Adherence to Infection Prevention and Control (IPC) protocols was partial overall, and sometimes poor. However, compliance with IPC protocols is a necessary and highly effective means to prevent infection (infection prophylaxis) in health care facilities.
- Access to patients' information and data quality were poor (incomplete and improperly recorded information, or hospitals requiring fees to provide

[53] Lobdell KW, *et al.* Hospital-acquired infections. *Surg Clin N Am* 2012; 92: 65–77.

data from medical records despite Ethical Committee approvals).

- Sometimes urgency dictates empirical treatment based on experience of health care personnel, as when a dangerous infection by an unknown organism is **treated** with a broad-spectrum antibiotic (in some cases, 'reserve' AMs are prescribed although the microbe could be sensitive to a "less strong" AM) while the results of bacterial culture and other tests are awaited. For example, in Croatia, all 24 analyzed cases received an AM appropriate to the causal bacteria, although in one-third of the patients the bacteria was sensitive to common AMs. So, to know the level of resistance and sensitivity of the microorganisms associated with onset of HAIs is important to improve the precision of empirical treatments and to avoid an unnecessary switch of AMs. It also helps to prescribe 'reserve' AMs only when really needed.
- HAIs tend to complicate the recovery of hospitalized patients. For example, in 7 out of 9 analyzed cases in Georgia, the recovery time varied between 45 and 120 days; additionally, 4 out of 9 patients died because of HAI complications.

Case Study 5—Multidrug-Resistant Tuberculosis

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

Rationale: Multidrug-resistant tuberculosis (MDR-TB) is a growing global public health problem, as noted in Part I. Data from the World Health Organization (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 already in 92 countries.

- Failures along the therapeutic chain increase of the risk of AMR. MDR-TB shows multiple aspects of AMR. Moreover, problems in treating TB can point to a country or institution's readiness to deal with AMR.
- Observation of a discrete number of cases in the countries serve to identify issues at the level of the patient, the final user of AM. Adherence to treatment is especially difficult for diseases that, once controlled, can be asymptomatic.

Findings:

- Multidrug-resistant tuberculosis (MDR-TB) is a growing problem. MDR-TB and XDR-TB depend on gene 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 reference in the medical reports of patients with multidrug-resistant tuberculosis (MDR-TB).
- Specific causes of withdrawal from treatment for MDR-TB (and for other diseases as well) vary and are important to identify, understand, and address.
- For example, in Botswana, the appearance of MDR-TB was attributed to patient's non-adherence to treatment (4 out of 10 cases) and intolerance to prescribed medicines that contributed to treatment withdrawal (3 out of 10 patients).
- 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 to understand the temporal sequence between the initial TB diagnosis and the MDR-TB diagnosis. All patients had at least one relapse, but 3 out of 8 patients had 4, 3 and 2 relapses, respectively. Moreover, 5 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 and religious factors may explain the lack of adherence to treatment.
- Specific causes of poor adherence to treatment or withdrawal from treatment for MDR-TB (and for other diseases as well) vary and are important to identify, understand, and address, as shown by the findings in Peru. Nonmedical causes for poor adherence to treatment or abandoning treatment included failure to come to the treatment center due to long geographical distances from place of residence of patient to a health facility where medications are dispensed, and the associated cost of transportation incurred out-of-pocket by individual patients and families. Medical-related causes include time and 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 DR-TB. Up to 23 patients had one or more relatives diagnosed with TB, including 16 with MDR-TB.

B. Recommendations

Overuse and misuse of AMs 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 AMs. They are outlined in this section.

From Surveillance to 'Surveillance + Action'

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

- **Drug-utilization studies (DUS)**. These can help identify failures in any of the therapeutic chain links. Designing and developing DUS with the active participation of the involved health professionals could also help to identify problems and actions within particular settings to overcome them.
- **Knowledge management.** Local information regarding the use and misuse of medicines are not published in indexed medical journals and remain as "grey" medical literature. Easy access to this source of knowledge would help policy makers identify appropriate context-specific interventions to include in the AMR action plan of countries and increase the general understanding of AM use. To this end, consideration should be given to the establishment of **global, regional or national observatories of grey literature and local studies.** This approach could help design context-specific interventions and increase the general understanding AM use.
- **Greater and better use of information, communications technologies (ICT).** As a tool to increase knowledge on AM consumption and expenditure, and to detect problems of AM overuse or inappropriate use, efforts should be made to promote the transition towards the use of electronic recording of consumption data, and to electronic medical records. This would require the definition of minimum common information to be included in these systems to facilitate analyses and comparisons, and the training of health professionals including health authorities in database research, analyses of results from electronic databases and biases due to the characteristics of that information. Use of electronic records have the potential for helping identify patterns related to AM misuse by health personnel, health care facilities, and among patients, and 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. It also would be important to be able to track different AM after their market introduction to determine their safety and efficacy, and any onset of adverse effects.
- **Antimicrobial Stewardship Programs (ASPs)** have proven efficacy in controlling AMR by improving how AMs are used and in reducing the use of broad-spectrum AM 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 AM 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.

  Core elements of hospital ASPs include:[54]

  - ***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 patient quality-focused hospital committee. Experience with successful programs shows that a physician or pharmacist leader is effective.

[54] U.S. CDC. (2014). Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC. Available at http://www.cdc.gov/getsmart/healthcare/.

- ***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 an ongoing treatment need after a set period of initial treatment (i.e., antibiotic "time-out").
- ***Tracking:*** Monitoring process measures (e.g., adherence to facility-specific guidelines, time to initiation or de-escalation), impact on patients (e.g., infections caused by clostridium difficile bacterium that can infect the bowel and cause diarrhoea in people who have recently been treated with antibiotics, but can spread easily to others; antibiotic-related adverse effects and toxicity), antibiotic use and resistance.
- ***Reporting:*** Regular reporting of information related to these condition to doctors, nurses, and relevant staff.
- ***Education:*** Educating clinicians about disease state management, resistance, and optimal prescribing. Adoption, adaptation, promotion and monitoring to the adherence to treatment protocols and guidelines. Training for a prudent use of AM and clear information on common diseases that should not be routinely or preventively treated with AM 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. These measures could include changes in how health care providers are reimbursed, and disallowing AM sales by prescribers to remove the financial incentive for overprescribing.

'Prevention' of AM Misuse at All Levels

Governance arrangements. AMR is aggravated by AM 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 AMs, a separate legal and regulatory framework and payment/reimbursement modalities could be adopted to promote appropriate use of AMs. Such special arrangements already exist in the pharmaceutical sector for opioids.

Developing new legislation and regulations or revising and updating existing legislation and regulations, including adopting strong legislation and developing enforcement capacity to control or/ and remove any financial incentives to individuals providers and institutions to use antimicrobials indiscriminately for any condition outside accepted protocols and guidelines. Also, the adoption of managerial strategies to guide practice, and strengthen the capacity of national authorities and personnel to adopt, adapt, manage and enforce legal measures in the health system for promoting and ensuring rational use of AMs, merit priority attention by governments. Adequate oversight of the AM market, both supply and demand aspects, also requires effective coordination and work arrangements with non-health sector entities (e.g., in trade and customs, finance, veterinary, and specialized international agencies).

Oversight of offer and prescribing. The continuing increase of AMR, lack of access to effective AM in many poor communities, and evidence of rampant misuse of AM in the health system reinforce the need for sustained political commitment to exercise adequate oversight of AM offers and dispensing practices. Two specific areas where priority focus and adoption of oversight measures are 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 the 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 to decrease unnecessary use of AMs. Measures toward effectively combatting counterfeit/substandard AM, and increasing compliance with the "by prescription only" labeling are also critical actions to be pursued.

Harm reduction from nonprescription sales of AMs is another priority area for action. Obtaining AM without a prescription in pharmacies was a common practice in the studied countries. Widespread training to explain the risks of inappropriate dispensation, strict enforcement of norms and regulation, accompanied by economic fines and legal

consequences may help prevent harm caused by inappropriate use of AM. Croatia is the only country among the six studied that can serve as an example of a good practice.

Decreasing the risk of hospital-acquired infections (HAI) is very important, because of the vulnerability of immunocompromised patients and because of the high risk of AMR emergence and spread in health care facilities. HAI fundamentally undermine the functions of hospitals/health facilities when they serve to spread disease, including disease caused by drug-resistant pathogens. Unfortunately, hospitals/health facilities are also the place where multidrug-resistant diseases are most likely to emerge—and this is already occurring. Many structural and care process factors involved in the prevention of HAI 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, cleaning supplies, infection prevention and control measures, and adherence to clinical guidelines and recommendations for the proper use of AM and 'reserve' AMs. The adverse health impacts of HAI are very high as well and substantially diminish quality of care, especially for the poor and for women and infants.

Non-adherence or compliance to treatment regimens is another factor to control since the emergence of numerous cases of drug-resistant pathogens can be traced to limited (or even non-existent) adherence to the recommendations made by physicians or pharmacists. Treatment compliance is important for infectious diseases generally, but is especially important in severe conditions such as TB, as it was documented in the country cases studies and in available literature that was reviewed for this report.

Information, educational, and communications campaigns addressed to both health services personnel and the general population that take into account behavioral and social aspects are also essential. This effort should include the provision of accurate and evidence-based information based on actual clinical practice and not only on data from clinical trials, and publicity campaigns to increase national and local awareness among the general population 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 prudent and appropriate use of medicines in general and AM in particular. Indeed, it is not only important that doctors do not overprescribe AM, but also that patients do not demand them influenced by drug advertisement or supplier induced use as observed in the country case studies.

The Way Forward

In the same way as uncontrolled outbreaks of infectious diseases of animal origin can spread with impunity across national boundaries, causing social and economic havoc, AMR can negatively impact rich and poor countries alike, because patients who remain infectious for a longer period of time pose an increased risk of spreading drug-resistant microorganisms to others. As documented in a recent cross-sectional study in South Asia,[55] a good example for understanding the international transfer of antimicrobial resistant pathogens, is shigellae, particularly as a specific multidrug-resistant (MDR) lineage of Shigella sonnei (lineage III), which is becoming globally dominant. Shigella (a genus of gram-negative enteric bacteria) is amongst the top four most prevalent diarrhoeal in Sub-Saharan Africa and South Asia, accounting for around 125 million cases of diarrhoea annually, with the majority occurring in children in low-income countries. Although shigellosis is typically self-limiting, AM treatment is used to prevent complications, reduce dysenteric discharge, and curb post-symptomatic faecal shedding. As a result, emerging resistance to AM is not only restricting treatment options, putting affected individuals at increased risk of complications and increasing the likelihood of protracted faecal shedding, but also the study findings suggest that a single clone, which is widespread in South Asia, is likely driving the current intercontinental surge of ciprofloxacin-resistant S. sonnei and is capable of establishing endemic transmission in new locations.

To reduce the growing AMR risks, AMs should no longer be considered as 'another drug', but as unique products that have the potential if well administered to contribute to significantly improve the health conditions of the population. The promotion of the "prudent use" of medicines in general and AM in particular should be at the core of efforts in

[55] Chung The, H., Rabaa, M. A., Pham Thanh, D., et al. (2016). "South Asia as a Reservoir for the Global Spread of Ciprofloxacin-Resistant Shigella sonnei: A Cross-Sectional Study." PLOS Medicine | DOI:10.1371/journal.pmed.1002055 (Publ. August 2, 2016). Available at: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002055.

the health system to prevent AMR. Programs and interventions to ensure rational use of AMs, therefore, should be seen as an integral part of continuous quality assurance processes for improving the delivery of safe, efficacious, and effective health and medical care services that benefits all.

The responsibility for promoting rational use of AMs needs to involve politicians, decision makers, administrators, health professionals and service providers, patients and the general population, educators, and pharmaceutical companies as part of a societal-wide effort rooted on scientific evidence to act "everywhere" where AM are used. Indeed, as documented in a recent study focusing on the experience in the Netherlands,[56] it is possible to reduce AMR to low levels, not only by active promotion and effective coordination between the health and agricultural sectors to work together following a "One Health" approach as advocated in this report, but also by implementing policy and operational measures in the health system to create a "different medical culture." For example, in the Netherlands antibiotics must be supplied 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 AM and Dutch patients do not demand them, reflecting a culture of "cautious prescribing" built up over decades through general practitioners' acceptance of strict professional guidance (e.g., indications for use, type, and dosage are issued by the College of General Practitioners (NHG); a 6% decrease was recorded between 2011 and 2014 in daily doses of antibiotics dispensed by pharmacies). The Dutch experience also shows a conscious policy and operational decision to make antimicrobial resistance a priority by decades of work on hospital infection through the Prevention Working Group and promoting prudent antimicrobial use through the Working Party on Antibiotic Policy.[57] The effective application of these measures have helped the Netherlands achieve one of the lowest levels of AMR in the world.

AMR is a global public health threat that if not addressed in a comprehensive and coordinated way at the country level is poised to escalate to ominous levels in the coming years with enormous social and economic consequences as discussed in different section of this report. Besides the wider societal impact and economic cost of AMR assessed in this report, it should be obvious that if nothing is done, AMR has the potential to increase the risk of poor health outcomes and death among patients because it will severely hamper the ability to treat common infectious and viral diseases. This, in turn, can lead to increased spending or waste of limited health care resources, undermining the financial sustainability of health systems and country strategies to expand health care coverage. If not controlled, AMR also threatens the viability of global health programs to reduce the burden of malaria, TB, HIV or other infectious and viral diseases, as well as to expand universal health coverage (UHC).

[56] Sheldon, T. (2016) "Saving antibiotics for when they are really needed: the Dutch example". Br Med J 2016M 354:i4192 (Publ. August 3, 2016).

[57] The Dutch Working Party on Antibiotic Policy website. Accessed at: http://www.swab.nl/english, on September 2, 2016.

Part VI. Antimicrobial Use in Animals and AMR

Issues and Options for Low- and Middle-Income Countries

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

Antimicrobial use in livestock[58] 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 the routine health management. In addition to these therapeutic uses, antimicrobials may also be used as growth promoters, to improve growth rates, based on continuous delivery of sub-therapeutic doses. Overall, at present the benefits of antimicrobials translate into more stable farm incomes and, in some cases, higher incomes for farmers. They also provide greater levels of animal source food production, leading to greater availability and more accessibly priced livestock products for consumers. However, the use of antimicrobials creates evolutionary pressures and leads to the selection of antimicrobial resistant microorganisms. The excessive and inappropriate use of antimicrobials accelerate the emergence of antimicrobial resistant microorganisms (see Box 1). An increasing emergence and spread of AMR will affect the capacity to treat animal infectious diseases and the management of their clinical manifestations. This will undermine current production practices, with impact on disease management, animal welfare, and great uncertainties in food production systems.

The range of species and the animal production systems varies by regions, countries and even by areas within countries. The system for the production, distribution, and usage of antimicrobials of known quality is also subject to standards, regulations and enforcement in well-functioning Veterinary Services,[59] including monitoring of the use of antimicrobials of their residues in animal products, and surveillance for AMR. The role of the veterinary profession and government veterinary services in antimicrobial distribution, use, regulation and enforcement may vary by country, region and production system. The surveillance, monitoring and regulatory infrastructures create costs in the system and significant benefits in terms of managing sustainable

[58] 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.

[59] Defined by OIE as "the governmental and non-governmental 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."

use of antimicrobials, limiting overuse and misuse, and reducing the risk of emergence of AMR.

This report focuses on the following four issues:

1. Costs of the use of antimicrobials in terms of the financial costs at the farm level and the costs of registration, manufacture and distribution by the pharmaceutical industry;
2. Benefits from the use of antimicrobials in livestock in terms of animal health and food production;
3. Impact of AMR on costs of production and productivity in livestock with the collection of data where possible on any linkages to human and environmental health; and
4. Costs of controlling the use of antimicrobials to minimise AMR emergence, including monitoring of the use, authorisation, regulation and enforcement, and the implementation of alternative approaches to livestock production and animal health management.

A. Literature Review and Gaps in Knowledge

There have been a number of extensive reviews of antimicrobial use in livestock and animals with regards to the emergence and spread of AMR.[60] However, much of the literature is focused on antibiotics, being medicines with antibacterial activity, since these are the medicines about which there is currently most concern around the impact of resistance emergence on human health. This terminology—antimicrobial—is often used to mean antibiotics rather than including anthelmintics, antifungals, antivirals, antiseptics and disinfectants, and AMR is often referring specifically to resistance of bacteria to antibiotics.

A review commissioned by OECD, supported by a global estimate of antimicrobial use[61] indicates that much is known about the biology of resistance mechanisms. However, the epidemiology of AMR and its relationship with impact on human and animal health have not been studied in detail, and have generated little concrete information beyond the association between the use of antimicrobials in animals and an increase in the levels of resistance found in those animal production systems.[62] It is noted that most reviews relied on antimicrobial usage data from only a limited number of countries, with estimates of usage in other parts of the world being 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 are based on collection of data.

B. Use and Role of Antimicrobials in Animal Production

Antimicrobials are not only used in livestock, with therapeutic purposes (to treat and prevent infectious diseases); they are also used for non-therapeutic purpose. 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 levels, helping the animals reach full market weight more quickly. Subtherapeutic quantities of some antibiotics (e.g., procaine penicillin, tetracycline) delivered to animals in feed, can enhance the feed-to-weight ratio for poultry, swine, and beef cattle. A number of authors have attempted to compare the overall amount of antibiotic used in humans versus in animals worldwide. One study concluded that quantitatively, by weight of active ingredient, more antimicrobials are used globally in food production these days than in humans. This varies by region and country.

The role of antimicrobials in animal production systems is not only to contribute to improving animal health and welfare, but also to indirectly contribute to human welfare through improving food security, food safety, protection of livelihoods and animal resources and poverty alleviation by improving animal health and productivity.

Quantifying the Use of Antimicrobials Globally

There is a lot of variation in estimates of the total annual global antibiotic consumption in livestock, ranging from around 63,000 to over 240,000 metric tons. With the increasing human populations and increasing demands for food, the quantities

[60] Landers et al., 2012; Rushton et al., 2014; Grace, 2015; Van Boeckel et al., 2015.

[61] Van Boeckel et al., 2015.

[62] van Cleef et al., 2015; Bisdorff et al., 2012.

of antimicrobials used in livestock production is expected to be steadily rising as well. It is suggested that the global consumption of antibiotics in agriculture will increase by 67% from 2010 to 2030, and consumption of antibiotics amongst the five major emerging national economies, Brazil, Russia, India, China, South Africa (BRICS) will increase by 99% in that same period.

It is however difficult to obtain exact figures on the use of antimicrobials, due to a number of reasons, including the lack of capacity of veterinary services to collect data at the country level. It is especially difficult to obtain figures in low- and middle-income countries (low-and-middle-income countries), where the majority of the livestock are kept on small-holdings and where antimicrobials are often sold over the counter, i.e., without prescription, and official controls on their manufacture, importation, distribution, sale and use are often weak.

In addition, there is growing concern over parallel markets, based on the production, distribution and use of illegal, counterfeit, or sub-optimal drugs. The share of such markets in some regions could be substantial.

C. Emergence and Impact of AMR in Livestock

Some types of resistance to antibiotics can spread quickly across different bacterial species, from bacteria in animals to those in humans, and vice versa, and across national borders. A number of medically important antibiotics are also administered to animals via feed or water in agriculture. Out of the twenty-seven different antimicrobial classes used as growth promoters in animals, only nine of these classes are exclusively used in animals. Some second-line antibiotics for humans are being used in animals, with no replacements for human use as yet close to market.

It seems that very little information is available about the impacts of AMR on productivity of livestock production systems. The lack of data, or their aggregation means that the health and economic costs related to AMR are difficult to estimate at this stage. It is known that the consequences of AMR in both HIC 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. Amongst others, if medicines used to prevent and cure diseases no longer work then animals would be less productive and potentially die prematurely. There is potential that AMR could have an impact on trade (for rational and irrational motives), with food consumers being increasingly concerned about contamination risk from imported products and producers concerned about importing animals with resistant microorganisms e.g. livestock-associated MRSA. The impact of AMR extends beyond public health with massive economic repercussions. It is expected that the impact of AMR will be greatest in low- and middle-income countries, with the poorest regions of the world disproportionally affected (see also Part II for details).

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

Knowledge of antibiotic use, the purpose of their use and the factors influencing the decision to use them is important for livestock health management, the prudent and responsible use, and good stewardship of antibiotics; monitoring of antibiotic residues in foods of animal origin and limiting the selection of bacterial resistant to antimicrobials. As stated above, in most low- and middle-income countries, veterinary antimicrobials including antibiotics are available without restriction and sold over the counter without necessary veterinary prescriptions. It can be assumed that use of antimicrobials is likely to be dependent on the predominant livestock species kept in each geographical area. Most sources of information do not specify whether antibiotics are used for growth promotion rather than treatment or prevention of diseases. It is difficult to keep track of antimicrobial use, not only quantities and classes, but also the species in which they are used and whether the use is to prevent or treat diseases versus use for growth promotion.

The increase in demand for animal source food leads to an increase in antimicrobial use. This increase in demand is due to rising populations in developing countries, alongside increasing wealth, urbanisation 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 driving 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 not being adapted to local conditions, either from a physiological point of view and performance, or from the health point of view and susceptibility to infectious diseases. These increases in animal numbers and changes in farming systems, against a background of active endemic and epidemic diseases, is expected to increase the use of antibiotics in low- and middle-income countries animal production systems.

There have been several studies that suggest that AMR is common in agricultural systems in low- and middle-income countries where resistance can be more frequently found to 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 studies they are based on.

Transmission Pathways for AMR

Any use of antimicrobials (in human, animal, plant or environment) creates evolutionary pressures, which can generate AMR. There are different ways in which resistant bacteria and genetic material conferring resistance in bacteria can be transmitted from animals to humans; mainly this can occur through the food chain, from close or direct contact with animals and through the environment. Whether all three are equally important remains unanswered. Despite this, from a public health point of view the initial reaction has tended to be to focus on the food system to ensure that food consumers are not affected.

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, which has been shown to create resistance in soil organisms. Such assumptions would need further specific exploration at scale for environmental impact and transmission pathways. The OIE Terrestrial and Aquatic Codes provide guidance on how to assess risk for AMR arising from use of antimicrobials in animals.[63] 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 in 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 non-pathogenic bacteria, toxicity and carcinogenicity of certain food products. The most important cause for occurrence of antimicrobial residue in animal tissues is an insufficient period of time given for the drug to be eliminated from the body of the animal before slaughter or harvesting of food, such that the 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 Codex Alimentarius Commission internationally recognized standards. It is therefore important that veterinarians, producers and farmers, do respect the prescribed withdrawal times prior to slaughter or harvesting of food products. If these rules are adhered to then the risk of development of AMR through consumption of animal source food products should be significantly minimized.

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 resulted in huge decrease in the number of antibiotic resistance. Other countries also engaged in voluntary re-labelling 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.

[63] Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals (Chapter 6.10 of the Terrestrial code).

Given poor or nonexistent monitoring of use of antimicrobials in livestock and their impacts on production, productivity, public health and environmental health, especially in LMIC, it can be a challenge to gain the interest required to bring about positive changes. An incentive for the setting up of monitoring systems could be that the economic impact of a global ban on antimicrobial use for growth promotion would be higher in lower income countries because of less optimised production systems. A further incentive to raise awareness and get people to engage in the fight against AMR would be to compare benefits from antimicrobial use in animals against both their financial cost and the risks of antimicrobial resistance emergence. That way the problem would become less abstract and it would be easier for people to commit 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 would explain the potentially negative consequences of using antimicrobials to farmers.

It is sometimes suggested that with a lack of resilience of the production systems, the sudden withdrawal of antibiotics for use as growth promoters in LMIC would have major negative consequences. European countries were able to impose a ban on the use of growth promoters without excessive negative impact 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 such 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 else (or as well as) a considerable increase in disease, with consequent mortality and morbidity losses. Similarly, the ban of 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 may be the development of new, alternative treatments, especially since the rate of development of new antibiotics has severely declined over the past 30 years. Several alternatives that could substitute for antibiotics in targeting bacterial infections have been proposed; among others: 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 their alternatives concerning the effectiveness in disease prevention and growth promotion.[64] Currently only a small number of bacterial diseases can be prevented and controlled by the use of vaccines, although anti-viral 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 wide use, and they can still induce bacterial resistance. Meanwhile, proteinaceous compounds, for example, feed enzymes and AMPs that have been put into 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. It is known that the economic impacts of alternative interventions to reduce the use of antimicrobials and/or reduce the risks of AMR emergence and transmission from production animals to people will affect producers differently according to location, farm size, contracting arrangements, production variables, management, 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 sub-optimal. There is little economic research on preventative strategies such as enhanced farm biosecurity and better animal hygiene. It seems that

[64] Cheng et al., 2014.

there are no studies that assess cost-effectiveness of different interventions.

A set of alternatives to the use of antimicrobial agents in pig production[65] were ranked by an expert knowledge elicitation process. The ranking was based on perceived effectiveness, feasibility and return on investment. The top 5 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/optimisation and use of zinc/metals. The top 5 measures in terms of perceived return of investment were: improved internal biosecurity, zinc/metals, diagnostics/action plan, feed quality/optimisation and climate/environmental improvements. This study showed that with rather simple and not too expensive 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 that study highlighted the benefits of an improved internal and external biosecurity status at the farm and are therefore of relevance to finding ways to keep animals healthy with a reduced need for antimicrobials. No study of a similar kind in LMIC was identified but it can be assumed that findings would be similar.

E. Summary of What We Know and of 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. In order to develop a comprehensive set of responses to AMR, there is a need to understand and analyze the use of antimicrobials in animal production systems in different countries, including alternatives to their use.

- 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, more 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 is not limited to the food chain, and is poorly documented;
- While it is difficult to quantify the use of antimicrobials in animal production systems, it is projected that this use will increase, even 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 drawback for positive change;
- There is no or limited information on the cost of alternatives to antimicrobials; and
- Performance of national veterinary public health systems and resilience of animal production systems will be key factors in transition success.

In light of this stocktaking of knowledge relevant to measures to contain AMR in livestock production, this report examined the nature and characteristics of the use of antimicrobials in livestock in order to help to illustrate the magnitude of the potential AMR problem in low- and middle-income countries, with four different 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.[66] The impacts in terms of the costs and benefits of this usage were estimated and weaknesses in the systems of manufacture, marketing authorization, distribution, storage, prescription and end-use of the antimicrobials identified. The study also looked for trade-offs between the benefits of use and the associated costs, including emergence of AMR, and the importance of the institutional environment.
- **OIE global survey—**The OIE conducted a survey of its member countries in late 2015 as

[65] Postma et al., 2015.

[66] 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 (expectations of better data availability in these four countries were disappointing), budget, and short time available for the study. Similar work would be warranted in additional countries.

a part of the OIE's program to develop a system for collecting data on antimicrobial (specifically antibiotic) use in animals at a global level. For the purpose of the study, the analysis focused on data from the LMIC.

- **Regional case study—**The use of antimicrobials should be reported to the animal population it is intended for. Data should be presented per population correction unit, which requires that the livestock sector is properly described and data made available. The study includes a regional case for description and presentation of the animal production systems. The region is South America.
- **Other sources of information—**The study also includes other sources of information identified in the course of the literature review.

Key Considerations for Each of the Case Studies

Country Case Studies

- The country case studies were conducted in four countries, ranging in per capita GDP from approximately US$700 to US$14,500 (PPP current international $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 AM 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, such as 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, 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 purpose versus growth promotion purpose.
- 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 production of livestock products each year were inconsistent and sometimes contradictory from more than one source.
- 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, and facilities for laboratory testing to isolate bacteria and test the sensitivity to antibiotics. 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 better 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 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 be the case in countries with export markets, which drive standards.
- Systems for collecting data on antimicrobials (including antibiotics) sales and use in animals need to be improved in most cases, which accords with the findings of the OIE surveys of 2012 and 2015, recognizing that progress has been observed. It was clear that there were recent efforts to change this situation, with one-off exercises to allow completion of the OIE 2015 survey and in one case a significant program planned in order to establish ongoing monitoring systems. Surveillance systems for AMR were also poorly developed. In all countries there had been studies done of AMR in bacteria from animals but passive surveillance was not observed in the

LMIC studied and active surveillance program 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 and 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 there appears to be much greater investment and effort being made to put in place systems of control, and 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 is around 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 levels of 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 undertake some analysis of whether the countries with both extensive systems and the least control over use of antimicrobials have least to worry about in terms of AMR emergence, or whether effort is 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 LMIC and high-income countries (though these were more acute in the LMIC studied) and the sensitivities that surround such data. It was not possible in any of the case country studies to undertake detailed economic analysis of use of antimicrobials and the impacts of AMR, or to assess the economics of alternatives to use of antimicrobials. In many cases there was a genuine lack of capacity and capability to collect and analyze these data nationally. In other cases it was evident the countries were not willing to share data due to the high profile of the debate on AMR currently and the potential sensitivities of customers.
- It is therefore clear that the basic building blocks for future analyses need to be put in place as a matter of urgency, as well as policy initiatives which give countries confidence to take a transparent approach. The most basic requirements for future analysis would be standardized data collection on 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 needs 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 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 with nearly three-quarters of low- and middle-income countries providing 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 the low- and middle-income countries that reported 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), 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 the livestock information systems in countries and make the generated information understandable and 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 livestock sectors. In turn such growth will benefit the livestock producers, owners of livestock processing industries, consumers and the stability of economies in the continents 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 livestock populations, in order to assess the 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. This information would need to be combined with likely antimicrobial use by species, systems and product to estimate demand. The supply data could be provided by information on antimicrobial manufacture and import and export balance. This process will probably highlight where gaps exist and raise questions on how these will be filled in future interventions. The overall aim will be that by asking questions about the livestock, the systems of production and antimicrobial use will ultimately lead to more critical thinking of how best to apply the antimicrobials.

Other Sources of Information

- A previous study[67] calculated antimicrobials per population correction unit (PCU) based on data from 32 countries that have monitoring systems for the use of antimicrobials, using a Bayesian logistic regression model. They 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 the 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 in the 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 and a high proportion of this was from antimicrobials placed in the feed.[68]
- 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.[69]
- The analysis also concludes that the use of these growth promoters could be stopped with little or no impact on productivity/economic impact. The analysis however makes little or no reference to how the differing hygiene and production systems found in low- and middle-income countries differ compared to the systems where the 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-

[67] Van Boeckal et al., 2015.
[68] Carrique Mas et al., 2013.
[69] Van Boeckal et al., 2015.

2000 are not comparable. Their assumptions on the ability to drop antimicrobials for growth promotion and potentially prophylaxis across low- and middle-income countries needs more careful thought if opportunities are to be provided for smallholder farmers, small-scale traders and of course the urban and rural based consumers in these countries, the majority of whom are poor.

- An assumption would be that the easier targets will be the well-organized large scale multinational companies that span both the HIC and low- and middle-income countries worlds and can invest and act in bringing production systems to a standard where there is less reliance on antimicrobials. A high proportion of pig and poultry farmers in such systems were ignorant of whether they were using antimicrobials or not.[70] In this context, it could be expected that minor changes in production and productivity would occur with a drop in the use of antimicrobials for growth promotion. This would suggest, as has been demonstrated in Europe, that current levels of use of antimicrobials 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 seriously 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 overall benefits in terms of additional livestock production leading to potential (producer surplus due to an improvement in productivity, 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 has a descriptive assessment of the interventions that could be carried out at the country level.

F. Recommendations

Overuse and misuse of antimicrobials in animal production systems can be a source of emergence and spread of AMR. The livestock sectors in low- and middle-income countries could contribute to the effective and sustained containment of AMR. The present study was designed to examine the nature and characteristics of the use of antimicrobials 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. It yields the following 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 done with confidence if the estimates are adequate. This could be achieved by the collaborative efforts to improve WAHIS at OIE and FAOSTAT at FAO. Both international organizations participate to the Tripartite and have networks and possibilities to inform technical services responsible for data collection and analysis in member countries.
- The proposed interventions recognize that there are **major knowledge gaps that require to be further addressed, probably on specific interventions and case-specific for individual countries, including understanding of the institutional environment, human behavior and communication.** There are also major difficulties in low- and middle-income countries in the monitoring of use of antimicrobials and their residues and surveillance of AMR.

[70] Sneeringer et al., 2015.

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 of 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 on the distribution chain Would allow evaluation on management options analysis of productivity change	Short-term low Mid-term low to medium	No risks
Monitoring of antimicrobials 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 on the businesses who depend on antimicrobial sales
Monitoring of 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 AMs for prophylaxsis	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 AMs	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

- **There is a need to strengthen public and veterinary health systems, while being innovative and using economics to demonstrate benefits** to both governments and private sector companies and individuals involved in livestock production, which will help to change attitudes and behaviors around use of antimicrobials in animals.

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

   - **Monitoring and surveillance** at national level
     - Design and implement data collection and capture systems at key **levels of the antimicrobial production, supply and distribution chain** to provide national data on the use of antimicrobials
     - Develop a system for collecting standard **data on animal populations, production and production systems** to enable standardized mg/kg or mg/PCU calculations for each country
     - Develop systems for the **monitoring of antimicrobial residues** in food originating from farmed terrestrial and aquatic animals
     - Design and implement sample collection, testing and data capture systems for national risk based **surveillance of AMR** in the animal production systems
     - Couple monitoring and surveillance with an **assessment capacity of the risks related to the detected emergence,** at the regional level, with the aim to inform decision making process on the use of antimicrobials
   - **National targets for the reduction of the use of antimicrobials**
     - Establish national targets for substantial reduction of the use of antimicrobials in livestock with priority to significantly reduce non-therapeutic usages
     - Establish intersectorial collaboration to jointly **report national data on use of antimicrobials, residues monitoring and AMR**
     - Produce **annual report on progress made against the targets** to be submitted to the Tripartite
   - **Standards** and their role in use of antimicrobials, residues and AMR
     - Perform analysis of legislation, implementation of public and private standards at 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 systems of enforcement when **inappropriate use of antimicrobials, use of suboptimal or counterfeit antimicrobials, residues** are detected and investigate how these could 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 antimicrobials use is highest** and where interventions would have greatest impact in terms of reducing their use
     - Undertake applied **research to investigate alternative approaches to use of antimicrobials** in field conditions e.g., through redesign of systems which would reduce the need for antimicrobials, upgrade of housing, genetic selection, vaccination strategies, dietary adjustments, improved hygiene procedures and staff training
     - Undertake economic assessment and feasibility assessment towards illustrating where **current levels of antimicrobials may be unnecessarily increasing production costs**
     - Recommend **interventions clearly described** in a way that is targeted and appropriate to the audience and easily understood by the people involved in

taking decisions, either at individual, company or government level

- **Manage changes** that could be made in the way animals are kept to significantly reduce disease without compromising food supply and animal health and welfare. For instance, developing insurance against livestock diseases for farmers who do not use antibiotics is definitely impossible with the current and prospective state of veterinary services

❇ **Human behavior and the culture around the use of antimicrobials in livestock**

- Undertake social science research to understand how people are **managing livestock health at the farm level** and how they are using antimicrobials, including drivers for the use. Apply knowledge of their motivations, decision making process to investigate how their behavior could be influenced to reduce reliance on antimicrobials, seek for veterinary advises and change the culture around use of antimicrobials in livestock production
- **Raise awareness and educate professionals and livestock owners** to better understand how antibiotics function and the potential adverse consequences of inappropriate use (including the potential for impacts on their own health), and potential of alternatives to antimicrobials

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

❇ **Rationalization of the use of antimicrobials**

- Undertake applied research to improve **rapid diagnostic methods,** which would reduce the use of antimicrobials either because the sensitivity of the infectious agent to antimicrobials is established before treatment
- 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** with an objective to reduce the use of antimicrobials

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

- Train professionals and livestock owners on the **importance of veterinary oversight, the need for responsible and prudent use of antibiotics and adhering to prescription** including dose rates and withholding periods
- Develop **advocacy messages on the importance of AMR** by guidance on individual actions which could be taken, backed by evidence e.g., of the financial feasibility of adoption of alternative approaches, improved animal husbandry and infection prevention in livestock production systems
- **Strengthen veterinary education and the role of veterinary professional standards** in governing the use of antimicrobials—the extent to which prescribing is required and the veterinarian is involved in treatment decisions (when to treat, dose, duration)
- Use OIE PVS pathway to identify **gaps and training needs in low- and middle-income countries,** to direct available funding and prioritize and to help low- and middle-income countries attract funding

Part VII. Conclusions

The simulations of the economic impacts of AMR carried out for this report point to substantial economic costs of inaction even in the optimistic 'low-AMR impact' scenario. Both international cooperation and country action plans will require consistent attention over time and commitments of substantial resources—these investments are amply justified by the enormous benefits of AMR containment. Given the permanent nature of the AMR threat, the responsibility for such attention should be formally mandated to existing institutions. Containment of AMR makes necessary systematic attention to strengthening of core public health functions in all low-income and many middle-income countries. Progress in containing AMR will be facilitated and can be sustained only when veterinary and human public health systems perform to acceptable standards. Monitoring of this performance is essential for delivery of core public health functions, as well as for compliance with IHR and OIE standards.

Investing in AMR containment will increase the probability that an economic and public health catastrophe will be avoided. If this is not accomplished, it will be low-income and lower-middle-income countries that will suffer the largest economic and human costs. The policy menu has been defined and set out in the WHO Global Action Plan on AMR, which constitutes a robust basis for action both for the international community and for preparing country action plans on AMR in every country.

Major risks are present, however, that the actions needed to contain AMR will not be implemented in an effective and sustained manner. The largest risks are failure of prioritization of AMR containment and, closely related, grossly inadequate funding for public health systems in low and middle-income countries.

Failure of countries to prioritize AMR containment is likely to be an unintended consequence of dismissal of One Health approaches in the human health sector. The World Bank's intersectoral character and convening experience could be brought to bear in supporting country action plans, based on guidance from WHO, OIE, and FAO under the tripartite agreement.

Among the specific challenges that warrant both more funding and technical assistance in low- and middle-income countries are the following:

- Surveillance systems need substantial support that is sustained in the long-term, both for veterinary and human public health. Regular monitoring of the performance of these systems, as part of assessments of compliance with IHR and the OIE standards, will help improve their performance. Consistent use of appropriate standards for sampling, testing and reporting is important as well.
- More judicious use of antibiotics in humans and animals requires understanding of behaviors of actors along the therapeutic chain, and interventions at multiple levels of health systems, in both the public and private sector. Pilot interventions in a large number of countries/regions will be helpful to develop effective approaches in a range of institutional contexts. Strengthening oversight over the marketing, quality, and use of antibiotics would be among the initial priorities in most country contexts.
- More judicious use of antibiotics in animal production systems will also be required. Reducing use of antimicrobials in livestock production requires that capacity of veterinary public health services exist. In addition, interventions at multiple levels of the food production systems will also be required to adapt livestock production to a significantly reduced usage of antimicrobials and render them more resilient to AMR by reducing the need for antimicrobials in animal production.

Annex 1. 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 β-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 2. 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."			
National Public Health Laboratory in Canada. A detailed analysis of the national public health laboratory in Canada 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 3. Targets for 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 4. 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	50,000
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 5. Example of a Laboratory-Improvement Budget to Perform 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

(continues)

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
	40	800	32,000
Yellow pipette tips, non sterile, 1–200µl (5 packs per lab)	800	1,000	800,000
BACTEC blood culture bottles (100 per lab)	80	9,000	720,000
Petri dishes, 100 x 15mm polysterene (10 cartons per lab)	8	80,000	640,000
Test tubes, beakers, flasks (1 set per lab)	20	3,000	60,000
Cryo vials (20 packs for NHPL)	400	1,000	400,000
Cryovial boxes (50 per lab)	80	8,000	640,000
Aluminium plate holders (10 per lab)	16	3,000	48,000
Graduated wire loops with handle (2 per lab)	160	1,000	160,000
Graduated wire loop replacements (20 per lab)	8,000	100	800,000
Inoculating loops and needles, disposable (100 packs per lab)	80	7,000	560,000
Petri dishes, 9cm (10 box per lab)	16,000	25	400,000
Urine collection containers, sterile (2000 per lab)	80	70	5,600
Slides (10 boxes per lab)	1,600	1,000	1,600,000
Slide boxes (20 per lab)	8	12,000	96,000
Polysterene tubes, 75mm (1 carton per lab)			7,001,600
Subtotal			
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 6. 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	Canada Integrated Program on Antimicrobial Resistance Surveillance (CAIPARS)
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
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
Vietnam	Viet Nam Resistance Project (VINARES)

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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	Cote 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 New Guinea	Malaysia	Hungary
	Philippines	Maldives	Iceland
	Samoa	Marshall Islands	Ireland
	Sao Tome and Principe	Mauritius	Isle of Man
	Solomon Islands	Mexico	Israel
	Sri Lanka	Montenegro	Italy
	Sudan	Namibia	Japan
	Swaziland	Palau	Korea, Rep.
	Syrian Arab Republic	Panama	Kuwait
	Tajikistan	Paraguay	Latvia
	Timor-Leste	Peru	Liechtenstein
	Tonga	Romania	Lithuania
	Tunisia	Russian Federation	Luxembourg
	Ukraine	Serbia	Macao SAR, China
	Uzbekistan	South Africa	Malta
	Vanuatu	St. Lucia	Monaco
	Vietnam	St. Vincent and the Grenadines	Nauru
	West Bank and Gaza	Suriname	Netherlands
	Yemen, Rep.	Thailand	New Caledonia
	Zambia	Turkey	New Zealand
		Turkmenistan	Northern Mariana Islands
		Tuvalu	Norway
		Venezuela, RB	

(continues)

Low-Income	Lower Middle-Income	Upper Middle-Income	High-Income
			Oman Poland 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.)