Building the investment case for action against antimicrobial resistance

March 2024

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Abbreviations

LIC	Low-income country
LMIC	Lower and middle-income country
UMIC	Upper middle-income country
HIC	High income country
GDP	Gross Domestic Product
RoI	Return-on-investment
AMR	Antimicrobial resistance
WHO	World Health Organization
OECD	Organization for Economic Co-operation and Development

1. Background

The continued global challenge of antimicrobial resistance (AMR) across the One Health sectors is multifaceted, requiring the attention of a multitude of actors and stakeholders. Increased activities from global actors including the Quadripartite organizations (WHO, FAO, UNEP, and WOAH), the Organization for Economic Co-operation and Development (OECD), and the World Bank have sought to illuminate the continued challenges and act on the growing burden of AMR. Bacterial infections due to antibiotic resistance have increasingly become a major health sector problem. The Institute for Health Metrics and Evaluation (IHME) reported that, as of 2019, 1.27 million deaths were directly caused by bacterial AMR worldwide. At the regional level, the IHME estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 27.3 deaths per 100,000 population (2). As for the European Economic Area (EEA), it was estimated that each year, more than 650,000 infections occur due to antibiotic resistant bacteria and more than 30,000 people die yearly as a result of these resistant infections (1). These negative health outcomes are estimated to cost the health sector more than €1 billion annually in EU/EEA countries alone (1).

In response to a request from the Global Leaders Group, the Quadripartite Joint Secretariat undertook an economic analysis to better understand the costs of AMR and the associated benefits of the AMR response across different sectors. The aim of this work is to inform global, regional, and country action on AMR response and to mobilize appropriate resources. Overall, the workstreams consisted of the following:

- The development of a business-as-usual scenario to estimate the current and projected cost of AMR should no greater action be taken.
- The development of a list of priority AMR interventions across sectors and the sub selection of a package of interventions for which cost-, and effectiveness-related data is available.
- The development of a global AMR investment case to estimate the return-on-investment (RoI) from implementing the package of interventions.

2. Methods

This section addresses the methodology and data used for the development and conduct of the business-as-usual scenario, the consensus-based process used to define a priority list of AMR interventions, and for the investment case to quantify expected returns.

To validate these methodological approaches and to identify any missing data parameters, different groups of experts were consulted. In 2022, each organization of the Quadripartite, in addition to the World Bank, nominated an expert to participate in the meetings of the Core Group on the economics of AMR. The Core Group had oversight of each stage of this project. Additionally, the Quadripartite Technical Group on the economics of AMR (QTG-EA) was formed in early 2023, bringing together twenty selected experts across the globe to advise the Quadripartite organizations on the economic implications of tackling AMR across sectors. Members of QTG-EA provided feedback about the main assumptions, methodology, and inputs of the business-as-usual scenario, the selection of key AMR interventions, and investment case during four main meetings carried out during 2023 and January 2024. Finally, the regional of the Quadripartite organizations provided feedback in relation to the list of priority key AMR interventions and the methodology used to select them.

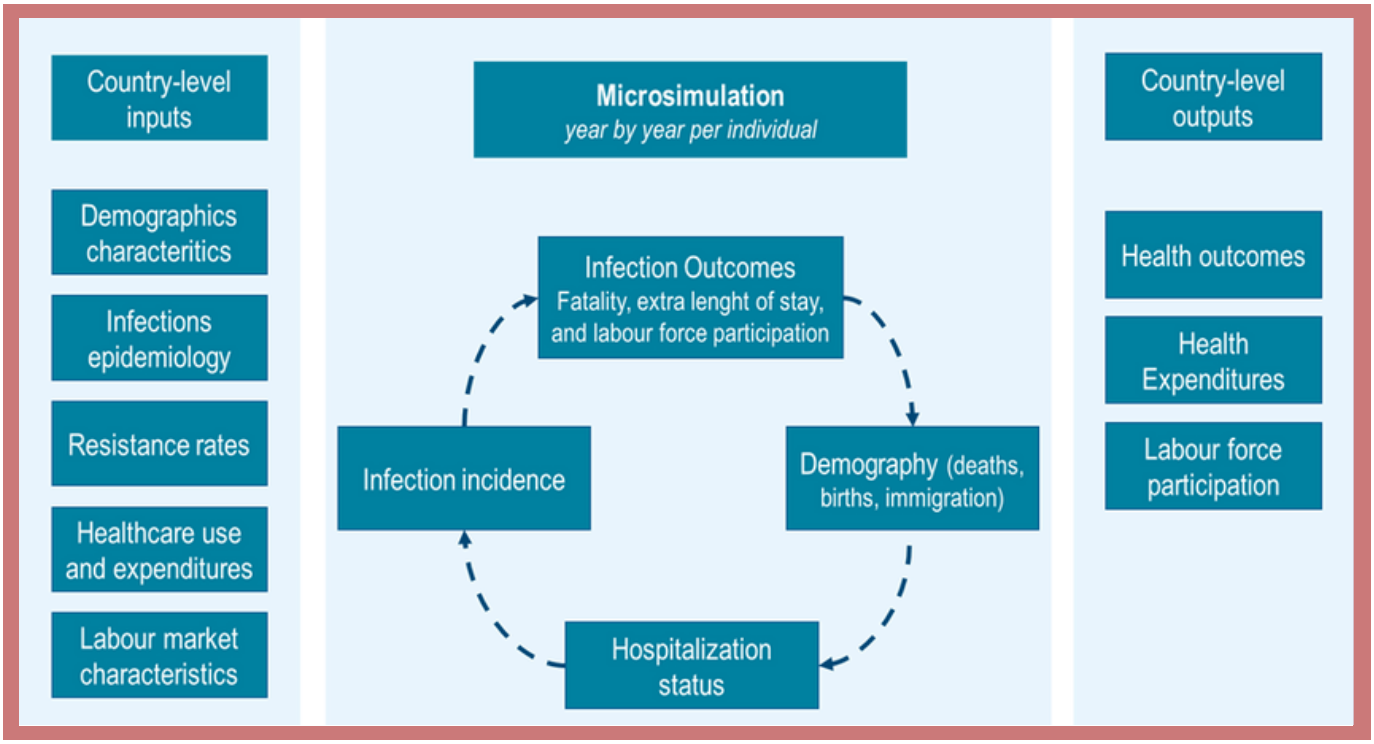
2.1 Estimating AMR losses: Business as usual scenario

The business-as-usual (BAU) scenario was analyzed with a cost-of-illness approach using the OECD Strategic Public Health Planning for AMR (SPHeP-AMR) model (4). The SPHeP for infectious diseases model is an advanced systems modelling tool for public health policy and strategic planning. The model is used to predict the health and economic outcomes of the population of a country or a region up to 2050 (Figure 1).

For each country or region, the model uses demographic and risk factor characteristics by age and gender (Demographic module)(4). From these inputs, the model generates synthetic cohorts in which individuals are assigned demographic characteristics and risk factor profiles. Based on these profiles, individuals are characterized as having a certain annual risk of developing a disease of interest (Disease module). For each year of analysis, a cross-sectional representation of the population is used to calculate health status indicators such as the prevalence of the disease of interest, associated life expectancy and disability-adjusted life years (DALYs)(Calculating disability weights)(4). In addition to considering the epidemiology of a country or region, the model is designed to consider the economic impact. Health care costs of disease treatment are estimated based on a per-case annual cost, which is extrapolated from national health-related expenditure data (Healthcare costs).

The labor market module uses relative risks to connect disease status with the risks of absenteeism, presenteeism, early retirement and employment (Labor market module). Changes in the workforce participation are assessed using the human capital approach, employing national average wages to calculate lost labor market outputs. A more detailed description of the model and technical information on how the analyses were carried out is described in detail in the OECD Strategic Public Health Planning (SPHeP) for antimicrobial resistance (4).

Figure 1. Graphical representation of the SPHeP model



The BAU scenario estimated the current and projected cost of AMR (in terms of healthcare expenditure and productivity loss) should no action be taken and was then used as the benchmark for the development of the investment case. The geographical scope of the economic burden analysis covered 14 regions. These can be further defined as a combination of WHO geographic regions and of World Bank income categories (i.e. low, lower-middle, upper-middle, and high-income). Monetary results presented in the main document are expressed in US$ 2020. Findings are provided for the period 2015-2035 as well as 2015-2050.

The model is designed to incorporate the economic impact of the disease of interest from the societal perspective. The healthcare costs associated with treating the disease are estimated based on an annual cost per case associated with the medical treatment of infections. Medical treatment encompasses both inpatient care and care provided in intensive care units.

The cost of medical treatment was calculated by multiplying the number of hospitalizations attributed to the condition by country-specific estimates of the cost of treatment. The analysis also considered the average duration of hospital stays linked to each pathogen.

2.2. List of priority AMR interventions across sectors

To reach a consensus-based list of priority AMR interventions to be modelled in the investment case, a multi-step approach was implemented, including evidence generation and expert consultation. First, key terminology and the scope of work were defined, which involved the following elements:

- Definition of key terminology: A priority AMR intervention is a broad (policy) intervention that seeks to answer one of the key objectives laid out in the Global Action Plan on AMR (5) or the Quadripartite One Health Joint Plan of Action (6). These interventions are also anticipated to be effective and have an economic impact. The "package" is the subset of interventions for which cost and effectiveness data was available, and therefore included in the economic analysis.

- Definition of sectors: Animal, human, environment, and plant were included. Interventions across sectors were also considered.

- Applicability of interventions: The list of priority AMR interventions takes a global perspective acknowledging the fact that countries are at different stages of readiness to address AMR. The list of priority AMR interventions is intended to be a menu for countries to digest and understand which interventions are relevant per sector and across sectors. The list does not consider local, regional, or national implementation requirements or variation in healthcare settings.

A targeted literature search of peer-reviewed (in PubMed) articles and publications from intergovernmental organizations, non-governmental organizations and research institutions was performed. In addition to the literature search, feedback was received on relevant evidence from the Quadripartite core group as well as from the Quadripartite Technical Group on the Economics of Antimicrobial Resistance (QTG-EA). Literature that met the inclusion criteria were selected and their information was extracted using a predesigned data extraction form. A summary of the included literature can be found in Appendix 1.

Appendix 2 provides an overview of each identified intervention per sector with a link to the appropriate reference.

2.3. Building the investment case

2.3.1. Investment case – General setting

The SPHeP-AMR model was run with the intention of simulating the impact of the policy package to tackle AMR. The package is assumed to be implemented in 2020 and its effect is calculated for the period spanning 2020-50. A multiplicative approach was used to combine the interventions' effectiveness in the package. A societal perspective was considered in the analysis, accounting for healthcare expenditures avoided and improved workforce participation. Population growth factors reported by the United Nations were considered for each region for future projections. No inflation factors were used. Undiscounted and discounted (3% and 6% annual discount rate) results are presented for both investments and benefits. The following formula was used to estimate the return on investment (RoI) of an intervention package focused on addressing antimicrobial resistance (AMR) across the different sectors.

$$ROI = \left(\frac{\text{Present values (benefits)}}{\text{Present values (investment)}} - 1\right)$$

Where:

- RoI represents the return on investment. Values > 0 show that each invested unit gives a positive return, while values < 0 show a negative return.
- Present values (benefits) represent the present values for the intervention benefits (returns), throughout the analysis.
- Present values (investment) represent the present values for investments (implementation costs of interventions) throughout the analysis.

Scenario analysis was conducted to provide additional information to decision makers and to account for uncertainty surrounding certain key parameters. Given that there is insufficient information about what the distribution of intervention costs would be over time, the base case assumed an equal distribution of investment for all years of analysis.

A separate scenario assumed that 50% of the total investment occurs during the first year, and the rest (maintenance costs) is incurred in the remaining years. For this scenario, an annual discount rate of 3% was applied starting in the second year. The value of 50% was chosen based on the information reported for the WASH intervention investment (39). Additionally, results are presented for different subperiods within the time horizon of the analysis. Detailed information on the effectiveness of the intervention package, total investments and benefits is presented in sections that follow.

2.3.2. Investment case - Defining the final package of priority AMR interventions

For the package of interventions, two literature searches were conducted. The first looked for secondary data analyses including systematic reviews of cost-effectiveness analyses or any other cost-analyses on any of the 52 priority AMR interventions.

The targeted systematic literature review was conducted on cost-effectiveness or cost-analysis estimates of AMR interventions between 2018 - 2023. Appendix 3 gives an overview of the identified studies. Each of the identified systematic literature reviews were then searched for specific primary studies that showed cost-effectiveness or cost-analysis estimates for the interventions of interest.

In a second step, targeted primary studies reporting cost and effectiveness data for each of the 52 priority AMR interventions were identified. The searches were performed in PubMed and specific grey literature databases and were limited to literature in English and published within the last 5 years. The aim was to capture any primary studies that were not captured by the previous systematic reviews. A detailed summary of each search strategy per AMR intervention can be found in Appendix 4. In addition to the literature search, any additional information from relevant studies or projects were added.

The literature searches combined identified effectiveness and economic information for 10 interventions out of 52 list of priority AMR interventions. However, on some occasions, values for cost or effectiveness for more than one activity (component) were identified for a single intervention.. A total of 13 components related to 10 interventions were finally selected.

Information on effectiveness and costs were extracted from all identified studies. Table 1 summarizes the main characteristics of the final package of key AMR interventions sub-selected for the RoI analysis. Detailed information about the resources comprising these interventions is addressed in Appendix 5.

Baseline and target coverage values for each intervention were applied in the model. While baseline coverage was taken to vary in line with reported values, target intervention coverage was assumed to be similar for all regions. Appendix 6 reports information on the target coverage selected for each intervention (Table A6.1), as well as information about the effectiveness, population target, and impact for each intervention included in the package (Table A6.2).

Finally, to estimate the present values for investment (intervention costs), and in light of the complexity of conducting a micro costing for each intervention and each country/region, costs identified in the literature were extrapolated to the different regions, adjusting for PPP index values, using the most recent data from the World Bank. Appendix 7 shows detailed information on costs for each intervention included in the analysis.

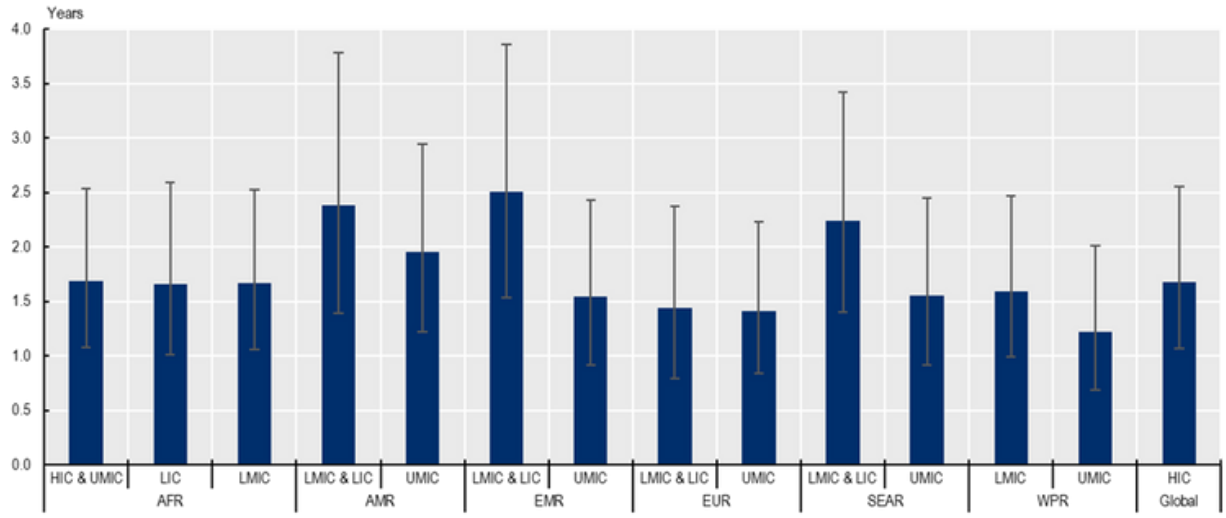
Table 1. Final package of key AMR interventions for the RoI analysis.

Category	Interventions	Specific activity/component	Sector
Improve awareness and understanding of AMR	1. AMR awareness raising, education and behavior change of health workers and the community	1. a. Enhance health worker training 1. b. Scale up mass media campaigns	Human
Improve surveillance AMR/AMU	2. Enhance food-handling practices / biosecurity practices to reduce the risk of AMR spread between humans and animals	2. a. Improve food handling practices	One Health
Invest in new drugs, diagnostic tools, vaccines, and other interventions (R&D)	3. Research into new antimicrobials, diagnostics and vaccines for AMR and behavioral and implementation science	3. a. New antibiotic incentive program	Human
Effective sanitation, hygiene, and infection prevention measures	4. Implementation of biosecurity measures to prevent the introduction and spread of disease in farms	4. a. Improve farm hygiene	Animal
	5. Implementation of infection, prevention, and control core components to mitigate AMR	5. a Enhance hand hygiene	Human
	6. Universal access to improved WASH and waste management to mitigate AMR	6. a. Strengthen access to latrines / improved latrines	Human
	7. Ensure safe and sustainable disposal and treatment of antimicrobials and hazardous waste	7. a. Enhance environmental hygiene	Environment
Optimize the use of antimicrobial medicines in human and animal health (Antibiotic stewardship)	8. Quality laboratory system and diagnostic stewardship to enable clinical bacteriology and mycology testing	8. a. Implementation or scale up of Rapid diagnostic tests (RDTs)	Human
	9. Access to vaccines and expanded immunization to manage AMR.	9. a. Improve vaccination coverage	Human
	10. Up-to-date evidence-based treatment guidelines and antimicrobial stewardship programs.	10. a. Strengthening antimicrobial stewardship programs (ASPs) 10. b. Delayed antimicrobial prescribing 10. c. Financial incentives	Human

3. Results

3.1. Expected losses due to AMR: Business as usual scenario

Figure 2. Loss in life expectancy (years) attributed to AMR by region between 2015 and 2035

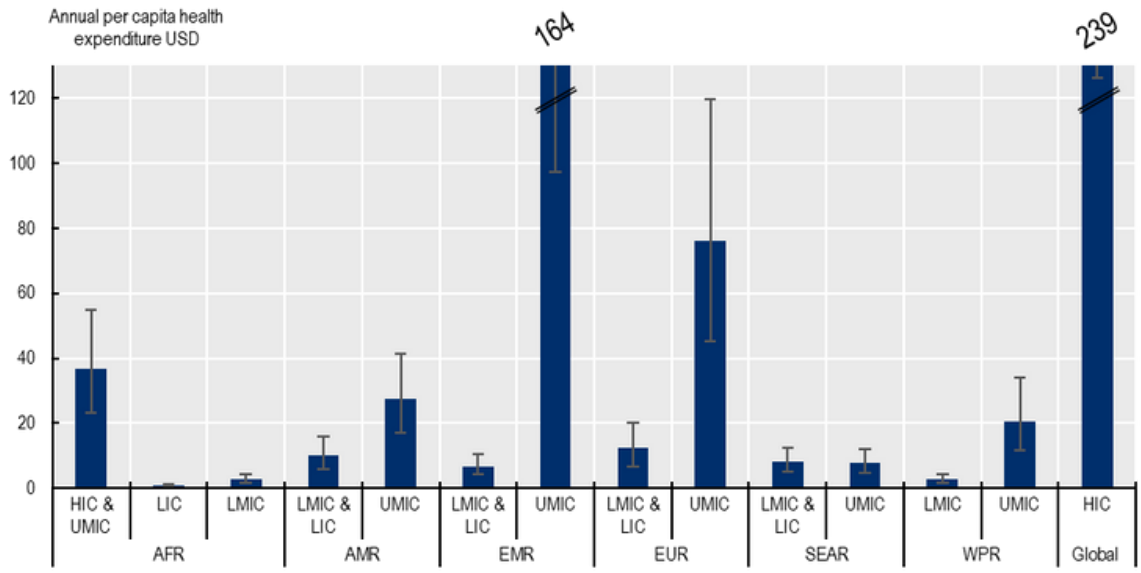


Note. AFR: Africa. AMR: America. EMR: Eastern Mediterranean Region. EUR: Europe. SEAR: South-East Asia. WPR: Western Pacific Region. LIC: Low -income countries. LMIC: Lower middle-income countries. UMC: Upper middle-income countries. HIC: High-income countries.

Healthcare systems across the 14 geographic regions are estimated to spend, on average, about US$ 44 per capita per year up to 2035. There is great variability across regions, reflecting the differences in the levels of access to health care services and the cost of delivering health care services. Figure 3 shows the average healthcare expenditures per capita per year between 2015 and 2035 by region that could be attributed to AMR.

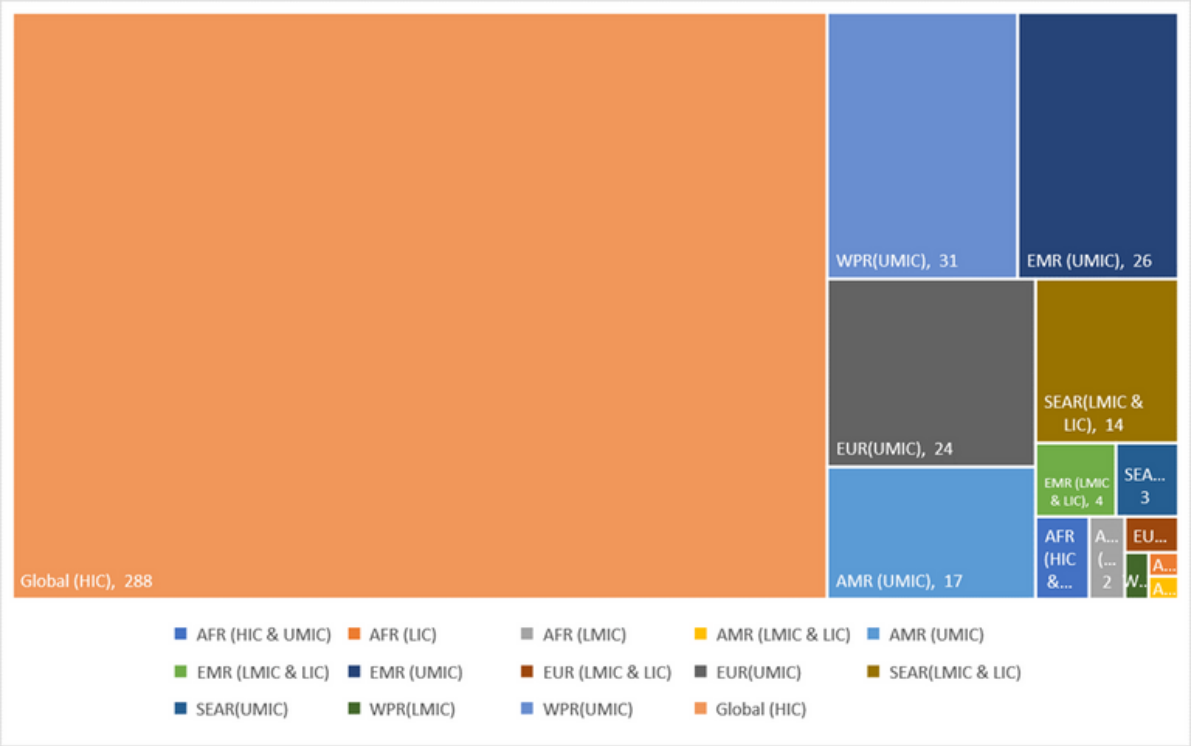
Overall healthcare systems are expected to spend up to around US$ 412 billion per year between 2015 and 2035 due to AMR. Figure 4 shows the average healthcare expenditures attributed to AMR per year between 2015 and 2035 expressed in billion US$ across the 14 geographic regions. The contribution of each geographic region to the total is also highlighted.

Figure 3. Healthcare expenditure (US$ per capita) per year that could be attributed to AMR, by region between 2015 and 2035



Note. AFR: Africa. AMR: America. EMR: Eastern Mediterranean Region. EUR: Europe. SEAR: South-East Asia. WPR: Western Pacific Region. LIC: Low -income countries. LMIC: Lower middle-income countries. UMC: Upper middle-income countries. HIC: High-income countries.

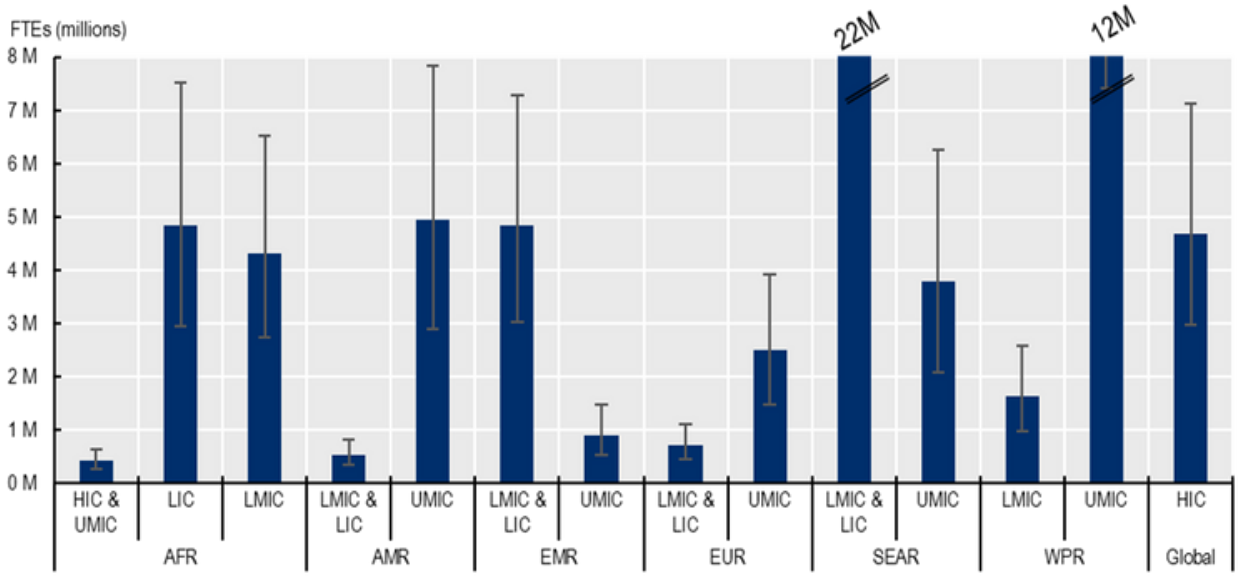
Figure 4. Healthcare expenditures (billion US$) per year that could be attributed to AMR. Results by region between 2015 and 2035



Note. AFR: Africa. AMR: America. EMR: Eastern Mediterranean Region. EUR: Europe. SEAR: South-East Asia. WPR: Western Pacific

Beyond the health sector, AMR depresses economic activity through reduced participation in the workforce. Across the 14 regions included in the analysis, losses have been estimated to be more than 68 million full-time equivalents (FTEs) every year, which can be considered as the number of persons with a full-time job. If monetized using average national wages, this equates to a loss of US$ 443 billion per year. Cross-region variability is determined by various factors such as the total number of individuals in each region as well as the demography and the workforce participation. Figure 5 shows the average yearly losses in workforce participation attributed to AMR between 2015 and 2035 in terms of FTEs

Figure 5. Losses in workforce participation (FTEs) per year that could be attributed to AMR. Results by region between 2015 and 2035



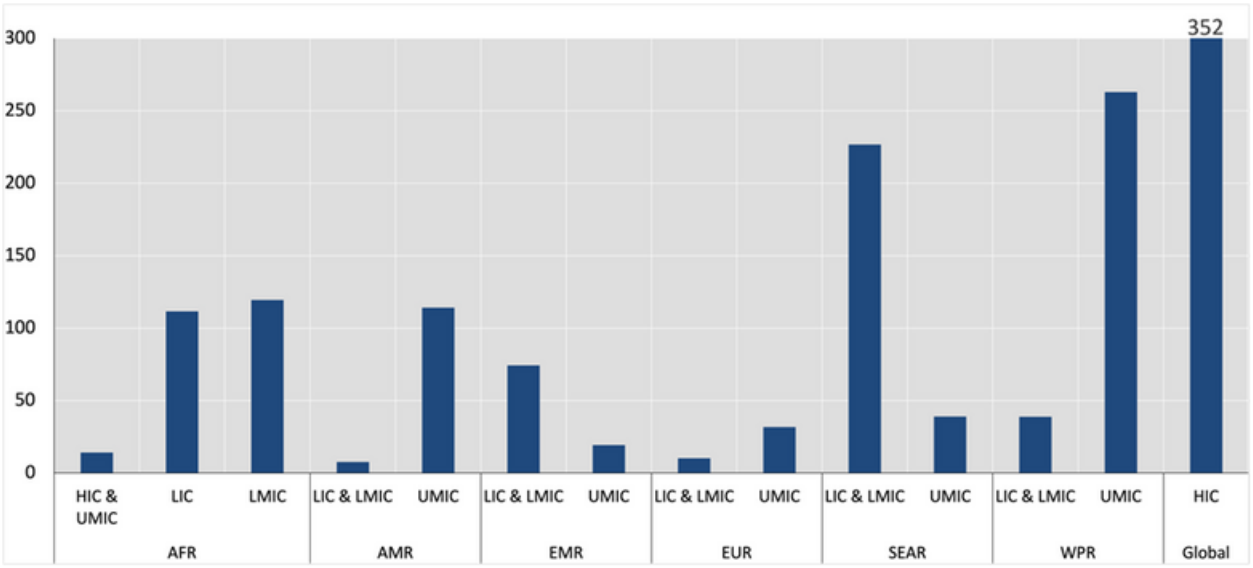
Note. FTE: Full-time equivalents. AFR: Africa. AMR: America. EMR: Eastern Mediterranean Region. EUR: Europe. SEAR: South-East Asia. WPR: Western Pacific Region. LIC: Low -income countries. LMIC: Lower middle-income countries. UMC: Upper middle-income countries. HIC: High-income countries.

3.2. Investment required to implement the package of AMR interventions

When considering the entire period of analysis (2020-2050) the total investment required for the intervention package across the regions was estimated at about US$ 1,420.7 billion. While Figure 6 shows the total investment required per region for 2020-2050 in US$.

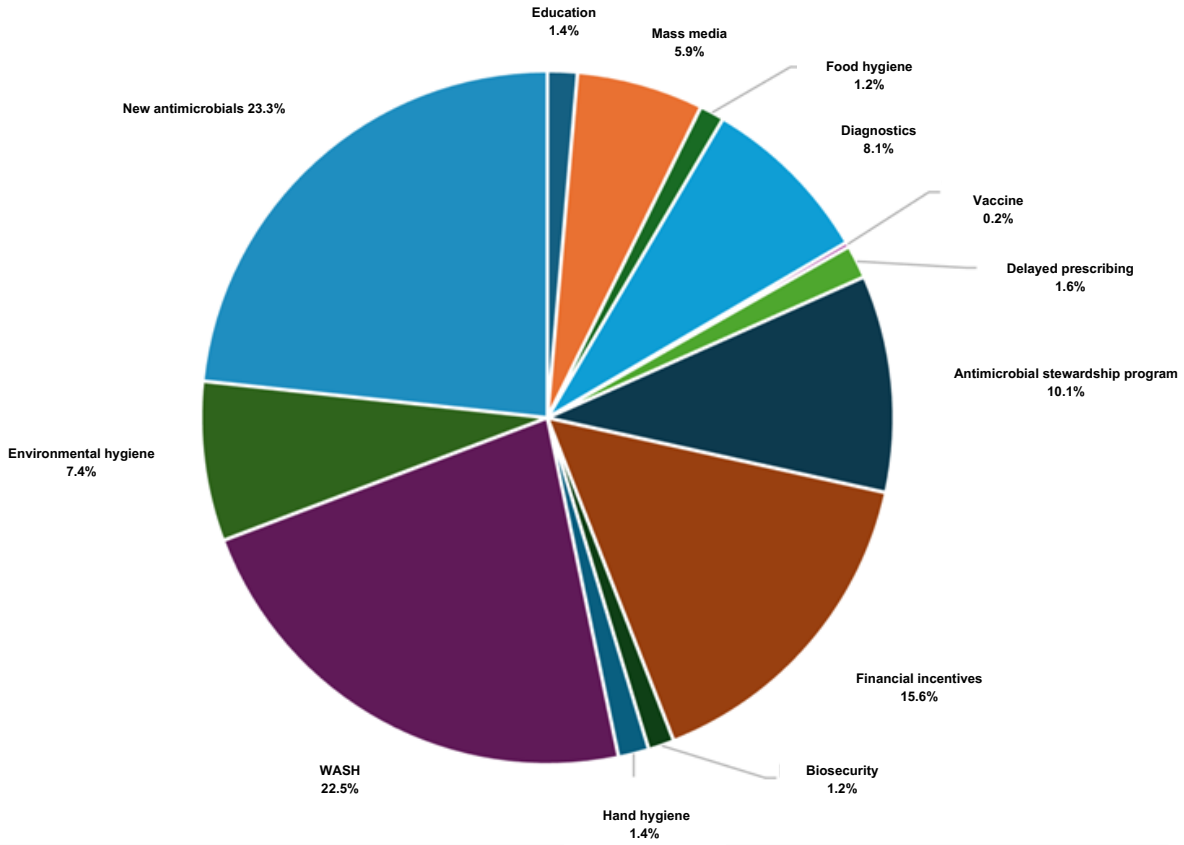
Figure 7 shows the distribution of total costs for the 13 intervention components included in the analysis. The new antibiotic incentive program represents more than a quarter (23.3%) of the total cost of the intervention package. Also, strengthened access to latrines and improved latrines ("WASH intervention") represents 22.5% of the total investment. Given the high percentage of the total investment that the new antimicrobial initiative program represents, Figure A8.1 show the total costs of the intervention package excluding the initiative.

Figure 6. Total investment required for the period of analysis 2020-2050 per region expressed in billion US$, 2020



Note. Values are expressed as billion US$, 2020. AFR: Africa. AMR: America. EMR: Eastern Mediterranean Region. EUR: Europe. SEAR: South-East Asia. WPR: Western Pacific Region. LIC: Low -income countries. LMIC: Lower middle-income countries. UMC: Upper middle-income countries. HIC: High-income countries.

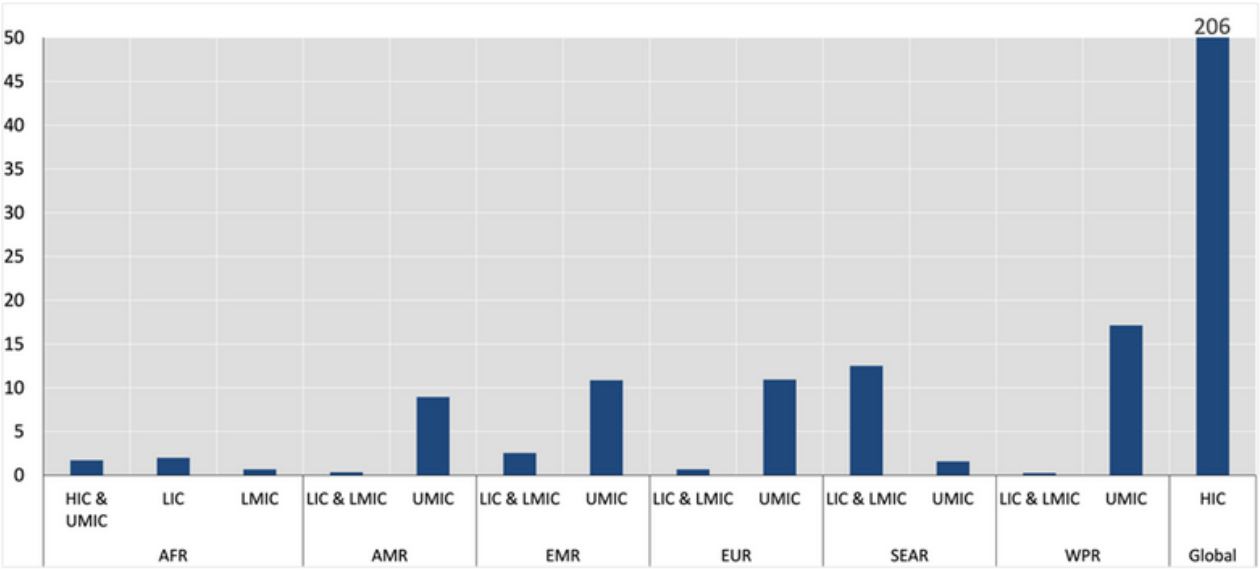
Figure 7. Total investment required for the period of analysis 2020-2050 per region expressed in billion US$, 2020



3.3. Expected benefits from taking action: implementing the AMR Intervention package

The implementation of the package is estimated to produce significant savings to the healthcare systems across the geographic regions (see Figure 8). Globally, cost savings related to healthcare expenditure alone would be about US$ 4,390 billion by 2035 and about US$ 9,141 billion by 2050. The cross-regional differences in savings in healthcare expenditure reflect the variation in the burden of infections, access to and cost of healthcare services. Figure 8 shows the average savings in healthcare expenditure per year, expressed in US$ by region.

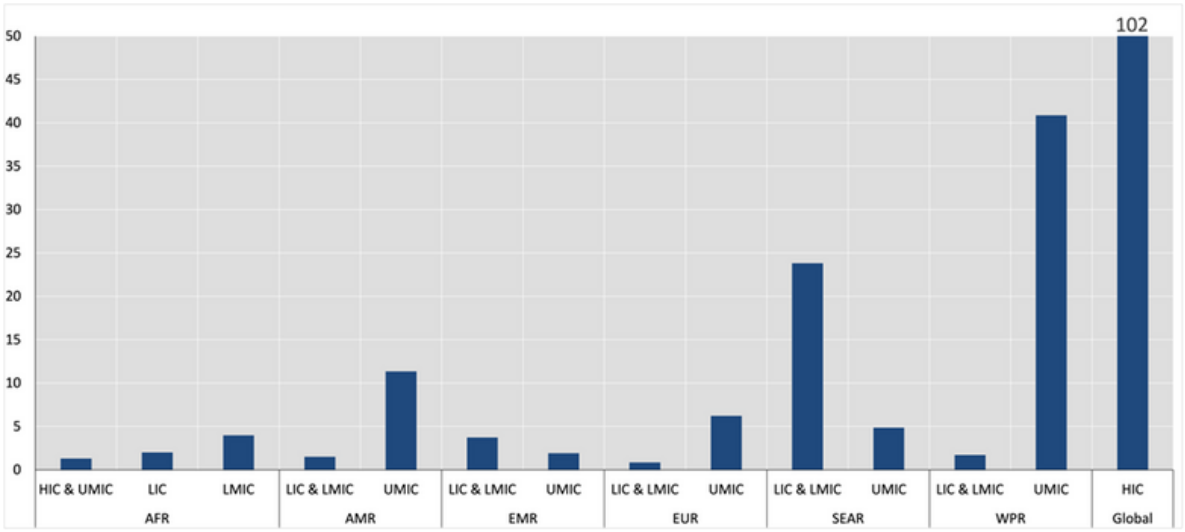
Figure 8. Yearly average savings in healthcare expenditure (in billion US$) produced by the package of AMR interventions, by region between 2020 and 2035



Note. AFR: Africa. AMR: America. EMR: Eastern Mediterranean Region. EUR: Europe. SEAR: South-East Asia. WPR: Western Pacific Region. LIC: Low -income countries. LMIC: Lower middle-income countries. UMC: Upper middle-income countries. HIC: High-income countries.

On the other hand, the reduction in morbidity and mortality produced by the package of AMR interventions also favorably impacts workforce participation. Across the regions included in the analysis the total financial gains produced by the package in terms of workforce participation, would be around US$ 3,293 billion by 2035 and US$ 9,939 billion by 2050. Figure 9 shows the average annual gains that would be produced by the implementation of the package of AMR interventions.

Figure 9. Gains in average labor market productivity (in billion US$) based on average wages per year produced by the package of AMR interventions, by region between 2020 and 2035

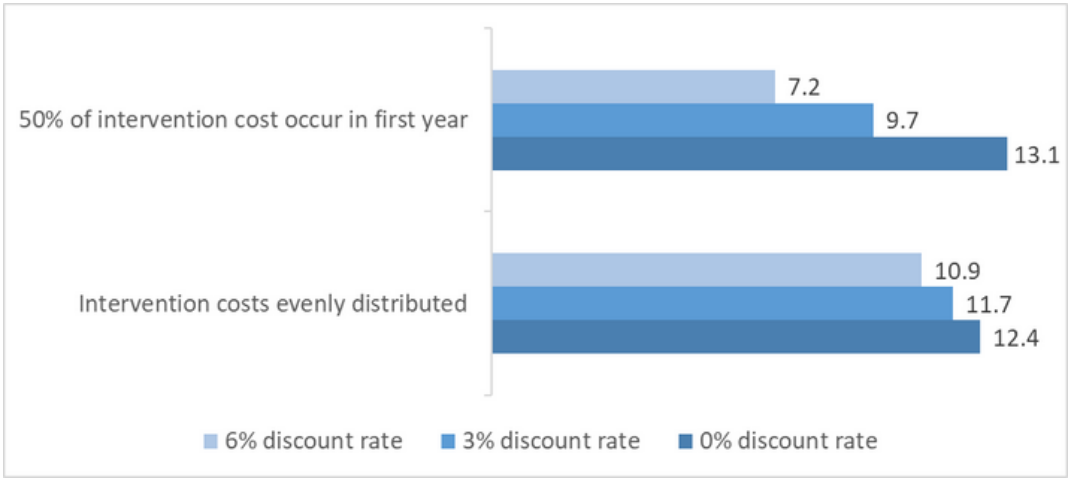


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3.4. Expected return-on-investment for implementing the package of AMR interventions

Return-on-investment (RoI) results are presented for the base case and scenario analysis. When the entire analysis period (2020-2050) was considered, the global RoI, including all regions, was estimated to be between 10.9 and 12.4, applying an annual discount rate of 6% and 0% respectively.

Figure 10: Estimated return on investment from implementing the package of AMR interventions globally (2020-2050)



Note. These results suggest the returns that can be expected from every one dollar spent in implementing the package of AMR interventions.

4. Conclusions

Key messages

- **With the current level of action, it is projected that antimicrobial resistance (AMR) will lead to significantly higher healthcare costs, with annual expenses for treating resistant bacterial infections estimated to reach US$ 412 billion worldwide.**
- **The increase in morbidity and mortality resulting from these bacterial infections will have secondary effects, such as reduced workforce participation, resulting in losses of approximately US$ 443 billion annually worldwide.**
- **Evaluation of a mixed policy of One Health interventions – including awareness raising, surveillance, optimizing antimicrobial use in human and animal health, infection prevention, and new treatments – suggests a potential to avert nearly US$ 7.7 trillion in losses from[BT1] healthcare expenditure and workforce productivity by 2035. Implemented for longer, these interventions would offset another US$ 615.5 billion in losses per year, resulting in cumulative gains of US$ 19.1 trillion by 2050.**
- **The One Health intervention package is estimated to cost US$ 1,420.7 billion worldwide by 2050, or US$ 45.8 billion per year.**
- **For every US$ 1 invested in a mixed policy intervention package, a global net return of between US$ 7.2 and US$ 13.1 is expected**

The present document reports quantitative findings on the disease burden attributable to AMR, its economic implications, and RoI findings for a package of interventions involving different sectors across 14 global regions.

The research findings indicate that the economic burden of AMR is staggering and extends well beyond the healthcare sector. The long-term costs associated with treatment failures, increased healthcare use, and workforce participation losses due to illness are substantial. The business-as-usual case analysis found that, on average, a loss of 1.8 years in life expectancy could be attributed to AMR. In financial terms, US$ 412 billion of healthcare expenditures per year could be attributed to AMR across the countries within the 14 geographic regions included in the analysis. Also, concerning the workforce, a loss of more than 68 million full-time equivalents (FTE) could be attributed to AMR every year.

When the benefits associated with a package of potential interventions were analyzed, the SPHeP-AMR model predicts cost savings related to healthcare expenditure to the value of US$ 4,390 billion in 2035 and US$ 9,141 billion in 2050 across all global regions of analysis.

In addition, the total financial gains produced by the package would be around US$ 3,293 billion for 2035 and US$ 9,939 billion for 2050. These projections highlight potential long-term economic advantages and substantial savings associated with implementing the proposed interventions.

The present analysis reveals that the global RoI of public health interventions for AMR would be particularly high. Even in the most conservative scenarios presented here, a global RoI of 7.2 was estimated for the period of analysis (2020-2050).

The findings from this investment case underscore the need for a collaborative, global effort to address AMR, with a focus on equitable distribution of resources to ensure that vulnerable populations countries benefit from these interventions. Developing countries often face resource constraints and are disproportionately affected by infectious diseases. Allocating funds to AMR interventions such as strengthening healthcare infrastructure, promoting antimicrobial stewardship, and Improving awareness and understanding of AMR can yield significant health and financial benefits, breaking the cycle of infectious diseases and contributing to global health security.

The study also emphasizes the importance of a One Health approach, recognizing the interconnectedness of human, animal, and environmental health. By investing in interventions that promote responsible antimicrobial use in both healthcare and agriculture, we can create a holistic strategy that addresses the root causes of AMR and reduces the emergence and spread of resistant pathogens.

The present study has limitations. Given the lack of information on the effectiveness and costs of interventions from studies conducted in LMICs, much of the information obtained comes from high-income countries. Although an adjustment has been made for PPP index values to extrapolate these values to low- and middle-income regions, the effectiveness values have been assumed to be the same. However, region-specific data on the current coverage (business-as-usual intervention coverage) was used for each intervention.

This study offers a framework within which parameters can be refined as more data become available. It can also help serve as a baseline to track changes in the economic outlook as countries move forward in National Action Plan implementation.

In conclusion, the findings of this investment case make a compelling argument for the prioritization of interventions to tackle AMR across sectors. The high RoI highlights the transformative potential of targeted interventions in mitigating the financial and health consequences of AMR. Policymakers are urged to heed these findings and allocate resources strategically to ensure a sustainable and resilient future in the face of the growing threat posed by AMR.

5.Supplementary Material

Appendix 1. Overview of evidence – Literature review

Table A1.1: Overview of evidence.

Study	Title	Overview and Key Findings
OECD & WHO, 2022 (11)	Addressing the Burden of Infections and Antimicrobial Resistance Associated with Health Care	The report discussed various interventions suggested by the organization in addressing antimicrobial resistance. Evidence behind the interventions suggested were also provided.
Morel et al, 2020 (12)	A one health framework to estimate the cost of antimicrobial resistance	The study created a costing framework that may be utilized by first identifying the most common antimicrobial resistance pathogens and how the epidemiologic pattern of AMR is. This was followed by analyzing the probabilities for each sector (human health, animal health, and others).
World Bank, 2021, unpublished	"Stopping the Silent Epidemic: An Operational Framework for Addressing Antimicrobial Resistance" Working Draft	The document presented a framework in looking at various interventions to address antimicrobial resistance. It divided interventions into AMR-sensitive and AMR-specific.
WHO & World Bank, 2022 (13)	Sustaining Action Against Antimicrobial Resistance: A Case Series of Country Experiences	The report presented case series of several countries, mostly from LMICs with their strengths and weaknesses in implementing their national action plan against antimicrobial resistance as pushed by member countries.
WHO, 2019 (14)	Global Antimicrobial Resistance Surveillance System (GLASS)	The GLASS report was created to boost AMR surveillance among member countries. This was thus a report describing it and discussing key points on surveillance with regards to national action plans of countries.
FAO, 2022 (15)	Tackling Antimicrobial Use and Resistance in Food-producing Animals: Lessons Learned in the United Kingdom	The FAO discussed interventions within the animal health realm in addressing antimicrobial resistance using the United Kingdom as a case study for discussion on national plans for AMR.
OECD & WHO, 2019 (16)	Challenges to Tackling Antimicrobial Resistance	The joint report presented interventions aimed at tackling antimicrobial resistance. It provided a good background on infection control and different approaches to address AMR.
WHO, 2021 (17)	Comprehensive Review of the WHO Global Action Plan (GAP) on Antimicrobial Resistance	The document presented indicators per GAP objective identified to monitor and evaluate efforts for AMR.
WHO, 2022 (7)	People centered framework for addressing AMR ppt	Overview of interventions for human health
Jit et al, 2020 (18)	Quantifying the economic cost of antibiotic resistance and the impact of related interventions: rapid methodological review, conceptual framework and recommendations for future studies	The study proposed a conceptual framework for antibiotic resistance.

Study	Title	Overview and Key Findings
UNEP, 2022 (19)	Environmental Dimensions of Antimicrobial Resistance: Summary for Policymakers	The paper presents environmental impacts of AMR and the causes of the development and spread of resistance in the environment, including the gaps in understanding those impacts and causes.
FAO, 2021 (20)	The FAO Action Plan on Antimicrobial Resistance 2021-2025	This FAO Action Plan on AMR 2021–2025 sets out the five objectives that guide the programming of FAO activities: 1. Increasing stakeholder awareness and engagement 2. Strengthening surveillance and research 3.Enabling good practices 4. Promoting responsible use of antimicrobials 5. Strengthening governance and allocating resources sustainably
OECD, 2018 (21)	Stemming the Superbug Tide: Just a Few Dollars More	In this report, OECD used advanced techniques, including machine learning, ensemble modelling and a microsimulation model, to provide support for policy action in the human health sector.
World Bank, 2017 (3)	Drug Resistant Infections: A Threat to Our Economic Future	This report examines the economic and development consequences of antimicrobial resistance (AMR), using the World Bank Group economic simulation tools to put a price tag on AMR's destructive impacts on the global economy from 2017 through 2050, if adequate measures aren't taken to contain the AMR threat.
Al-Haboubi et al, 2020 (22)	Views of health care professionals and policy-makers on the use of surveillance data to combat antimicrobial resistance	Identified the extent of the use of AMR data to the perceived needs of healthcare professionals and policymakers
PIRU RVC, 2019 (23)	Impact of guidelines and recommendations on the level and patterns of antimicrobial use in livestock and companion animals: Systematic Review	Explored guidelines in Europe and analyzed their impact on AMR relating to farm animals and companion animals
EFSA and EMA, 2016 (24)	EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA)	Assessment and recommendations on AMR interventions in the European region
OECD, 2019 (25)	Evaluating the economic benefits and costs of antimicrobial use in food producing animals	Evaluated on an economic perspective and provided interventions to promote AMR action

Appendix 2. List of priority AMR interventions

Table A2.1. List of priority AMR interventions: Animal, Human, Environment and Plant sectors

Objectives	Animal (20-22, 26, 27)	Human (28)	Environment (19, 28,29)	Plant
Improve awareness and understanding of AMR	Improve awareness, education, and behavior/perception change programs incl. learning experiences for farmers, veterinarians, veterinarian students, pet owners, regulators, and the general public.	AMR awareness raising, education and behavior change of health workers and the community.	Education and awareness of key source pollution emitters for appropriate and point-source waste prevention and treatment, and protection of source waters.	Communicate with, educate, and provide training to farmers on AMR, integrated pest management (IPM), and the appropriate use and disposal of pesticides / herbicides/ molluscicides.
			Education and awareness of environmental and other relevant-sector authorities on the role of the environment in AMR development, transmission and spread.	
Strengthen knowledge and evidence-based through surveillance and research	National AMR surveillance to inform development and allow assessment of effectiveness of interventions and policies at national level.	National AMR surveillance network to generate quality data to inform patient care and action on AMR.	Implement systems for transparent and swift collection and reporting of the production, sales, use, and disposal of unused antimicrobials.	National surveillance of AMR data in food and agriculture and AMU data in crops through enrolling in the International FAO Antimicrobial Resistance Monitoring (InFARM).
	National AMU surveillance to inform development and allow assessment of effectiveness of interventions and policies at national level.	Antimicrobial consumption and use surveillance to inform patient care and action on AMR.	Integrate environmental monitoring data (e.g., from monitoring of surface water, solid waste, and airborne particulate matter) with existing AMR surveillance and pollutants data.	
			Document the safety of bioproducts (e.g., biofertilizers, bioplastics, biosolid and manure applications, and plant growth promoters) and novel agricultural practices, as well as key sources of pollution that indicate an impact on AMR in the environment.	
Reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures.	Implementation of biosecurity measures to prevent the introduction and spread of disease in farms.	Implementation of infection, prevention and control (IPC) core components to mitigate AMR.	Improve integrated water management and promote water, sanitation, and hygiene (WASH) to limit the development and spread of AMR in the environment as well as to reduce infections and need for antimicrobials.	Incentivize farm assurance or certification benchmarking schemes in farms.
	Ensure good animal husbandry and farm management practices linked to the Five Freedoms of animal welfare.	Universal access to improved WASH and waste management to mitigate AMR.	Ensure safe and sustainable disposal and treatment of antimicrobials and hazardous waste from healthcare facilities, pharmacies, veterinarian centers, animal and crop production, and households (e.g., creating, strengthening and promoting take-back programs).	
			Implement an integrated zoonotic disease surveillance system to detect disease emergence in human/animal population.	

<table>
<tr><th>Objectives</th><th>Animal (20-22, 26, 27)</th><th>Human (28)</th><th>Environment (19, 28,29)</th><th>Plant</th></tr>
<tr><td rowspan="8">Optimize the use of antimicrobial medicines in human and animal health</td><td>Increase veterinary laboratory capacity (including ability to transport, store and process samples appropriately).</td><td>Quality laboratory system and diagnostic stewardship to enable clinical bacteriology and mycology testing.</td><td rowspan="2">Optimize strategies and resources, to include minimum standards such that adequate laboratory and human resource capacity can be established to maintain quality integrated surveillance at scale.</td><td>Establish regional, central BSL (Biological Safety Level) 3 and 4 laboratories for detection of zoonotic and infectious diseases.</td></tr>
<tr><td>Promotion of use of viable / natural alternatives (e.g., prebiotic, probiotic) to reduce AMU (e.g., vaccines in salmon farming or alternatives to growth promotion).</td><td>Access to vaccines and expanded immunization to manage AMR.</td><td>Reduce the secondary use of AMU as growth promoters in agriculture (e.g., avoid mention of this use on labels).</td></tr>
<tr><td>Create prescribing guidelines and stewardship programs at national level for targeted AMU including indication, line of therapy, dose, administration route and course of treatment of antimicrobials (e.g. switch from broad-spectrum to appropriate narrow-spectrum antimicrobial substances) with no perverse incentives (e.g. delinking prescribing with remuneration).</td><td>Up-to-date evidence-based treatment guidelines and antimicrobial stewardship programs.</td><td rowspan="4">Implement management options to prevent and address releases, effluent, and waste from intensive animal and crop production and from healthcare facilities and pharmaceutical manufacturing.</td><td>Promote integrated pest management to reduce the use of antimicrobial pesticides.</td></tr>
<tr><td>Phasing out over-the-counter (OTC) should be coupled with ensuring the availability of quality and affordable antibiotics.</td><td>Implementation of regulation to restrict non-prescription antimicrobial sales.</td><td rowspan="3">Reduce the need to use antimicrobial pesticides through the Reduce the Need for Antimicrobials on Farms (RENOFARM) initiative.</td></tr>
<tr><td rowspan="2">Ensure accessibility and affordability of AMR diagnostics.</td><td>Uninterrupted supply of essential health products for AMR.</td></tr>
<tr><td>AMR diagnosis and management health services are made affordable for all</td></tr>
<tr><td rowspan="2">Increase investment in new medicines, diagnostic tools, vaccines and other interventions</td><td>Research and development of novel, cost-effective, and affordable vaccines.</td><td rowspan="2">Research into new antimicrobials, diagnostics and vaccines for AMR and behavioral and implementation science.</td><td>Develop new methods/technologies to remove antimicrobial residues from the flows of wastewater, manure, and agricultural run-off.</td><td rowspan="2"></td></tr>
<tr><td>Develop veterinary/animal/farm-appropriate diagnostics.</td><td>Develop soil/water/air-appropriate diagnostics.</td></tr>
</table>

Abbreviations: AMR = Antimicrobial Resistance, AMU = Antimicrobial use, BSL = Biological Safety Level, INFARM = International FAO Antimicrobial Resistance Monitoring, IPC = Infection, Prevention, Control, IPM = integrated pest management, OTC = over-the-counter, RENOFARM = Reduce the Need for Antimicrobials on Farms, WASH = Water, Sanitation and Hygiene

Table A2.2. List of priority AMR interventions across sectors (One Health, cross-cutting interventions)

Objectives	Cross-cutting interventions
Enhance policy, legislation, advocacy and financing.	Set up a functional multisectoral national coordination group to tackle AMR / One Health national platforms, engaging relevant stakeholders and organizations, and considering inequities associated with gender and vulnerable populations.
	Guarantee financing of AMR National Action Plans (NAPs) including the implementation of the recommended interventions e.g., in national budgets.
	Enhance food-handling practices / biosecurity practices to reduce the risk of AMR spread between humans and animals e.g., appropriate personal protective equipment (PPE) and hand hygiene.
	Address AMR in National and Subnational Emergency Preparedness and Response Plans.
Strengthen organizational development, implementation and sectoral integration	Capacity building in all areas of the above-mentioned interventions as well as in data management.
	Advocacy and education to raise awareness of AMR as a holistic OH issue, that can affect humans, animals, plants, and the environment. In particular, provide information about the interconnection and potential transmission routes between humans, animals, plants and the environment such as through soil, water and food.*
Implement data, evidence, and knowledge	Implement high quality, robust data collection, analysis and reporting and sharing systems to periodically review and analyse data on antimicrobial resistance and antimicrobial use across sectors in an integrated fashion and disseminate findings for sector specific and joint action.
	Implement pollution and residue controls for pharmaceutical production, human health systems, animal health systems (including aquaculture), plant production and protection, and municipal waste and wastewater at scale linked to Environmental, Social, and Governance (ESG) principles and conditionalities.
	Collaborative surveillance that covers human and animals, and where possible plant/environment.

Abbreviations: AMR = Antimicrobial Resistance, ESG = Environmental, Social, and Governance, HP=CIAs = Highest Priority Critically Important Antibiotics (HP-CIAs), JPA = Joint Plan of Action, NAP = National Action Plan, OH = One Health, PPE = Personal Protective Equipment, QJS = Quadripartite

* This includes the intervention “AMR advocacy, governance, and accountability in the human health sector in collaboration with other sectors.” As mentioned in the WHO People-Centred Framework

Appendix 3. Systematic literature reviews reporting cost-effectiveness or cost-analysis information of AMR interventions

Table A3.1. Overview of systematic literature reviews (2018-2023) reporting cost-effectiveness or cost-analysis information of AMR interventions

Human	One Health
Ananthakrishnan A, et al. A protocol for a systematic literature review of economic evaluation studies of interventions to address antimicrobial resistance, 2021 (30)	Naylor, NR, et al. Quantitatively evaluating the cross-sectoral and One Health impact of interventions: A scoping review and case study of antimicrobial resistance, 2020 (31)
Poudel AN, et al. The economic burden of antibiotic resistance: A systematic review and meta-analysis, 2023 (32)	Quadripartite One Health Return on Investment (6)
Befikadu L Wubishet et al. Economic evaluation of antimicrobial stewardship in primary care: a systematic review and quality assessment, 2022. (33)	Aluzaite, K, et al. Economic evaluation of interventions to reduce antimicrobial resistance: a systematic literature review of methods. Unpublished.
Painter, C., Faradiba, D., Chavarina, K.K. et al. A systematic literature review of economic evaluation studies of interventions impacting antimicrobial resistance, 2023. (34)	
D'hulster E, et al. Cost-effectiveness of point-of-care interventions to tackle inappropriate prescribing of antibiotics in high- and middle-income countries: a systematic review, 2023. (35)	
Carla Cuevas et al., Improving antibiotic use through behaviour change: a systematic review of interventions evaluated in low- and middle-income countries, 2021. (36)	
Nathwani, D. et al. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review, (2019) (37)	

Appendix 4. Search strategies of the targeted review literature conducted

a.1. Systematic reviews
Search strategy (PubMed):
(Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH]) AND (systematic review[Publication Type])
Filter: Last 5 years;

b.1. Human

b.1.1. AMR awareness raising, education and behavior change of health workers and the community.
Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (Awareness [tiab] OR Education*[tiab] OR Behavior change[tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.2 National AMR surveillance network to generate quality data to inform patient care and action on AMR.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND Surveillance [tiab] AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.3 Antimicrobial consumption and use surveillance to inform patient care and action on AMR.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (Surveillance [tiab] OR consumption [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.
Results: none met the inclusion criteria.

b.1.4. Implementation of infection, prevention and control (IPC) core components to mitigate AMR.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (infect* control [tiab] OR infect* prevention [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.5. Universal access to improved WASH and waste management to mitigate AMR.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (WASH [tiab] OR waste [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.6. Quality laboratory system and diagnostic stewardship to enable clinical bacteriology and mycology testing.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (test* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.7. Access to vaccines and expanded immunisation to manage AMR.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (vaccin* [tiab] OR immunisation [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.8. Up-to-date evidence-based treatment guidelines and antimicrobial stewardship programmes.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (evidence-based [tiab] OR guideline* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.9. Implementation of regulation to restrict non-prescription antimicrobial sales.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (regulat* [tiab] OR prescription* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.10. Uninterrupted supply of essential health products for AMR.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (accessibility [tiab] OR affordability [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.11. AMR diagnosis and management health services are made affordable for all.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (accessibility [tiab] OR affordab* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.1.12. Research into new antimicrobials, diagnostics and vaccines for AMR and behavioural and implementation science.
Search strategy (PubMed):

("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (new [tiab] OR novel [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2. Animal

b.2.1. Improve awareness, education, and behaviour/perception change programs incl. learning experiences for farmers, veterinarians, veterinarian students, pet owners, regulators, and the general public.
Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (farmer*[tiab] OR veterina*[tiab] OR pet owners[tiab] OR regulators[tiab] OR general public [tiab]) (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.2. National AMR surveillance to inform development and allow assessment of effectiveness of interventions and policies at national level.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND Surveillance [tiab] AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.3. National AMU surveillance to inform development and allow assessment of effectiveness of interventions and policies at national level.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (Use [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text; Species: Other Animals.

b.2.4. Implementation of biosecurity measures to prevent the introduction and spread of disease in farms.

Search strategy (PubMed):
biosecurity [tiab] AND farm*[tiab] AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.5. Ensure good animal husbandry and farm management practices linked to the Five Freedoms of animal welfare.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (farm [tiab] OR animal [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.6. Increase veterinary laboratory capacity (including ability to transport, store and process samples appropriately).
Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (veterin* [tiab] OR labo* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.7. Promotion of use of viable / natural alternatives (e.g., prebiotic, probiotic) to reduce AMU (e.g., vaccines in salmon farming or alternatives to growth promotion).
Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (Antimicrobial use [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.8. Create prescribing guidelines and stewardship programs at national level for targeted AMU including indication, line of therapy, dose, administration route and course of treatment of antimicrobials (e.g. switch from broad-spectrum to appropriate narrow-spectrum antimicrobial substances) with no perverse incentives (e.g. delinking prescribing with remuneration).

Search strategy (PubMed):

(Antimicrobial use [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.9. Phasing out over-the-counter (OTC) should be coupled with ensuring the availability of quality and affordable antibiotics.
Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (accessibility [tiab] OR affordab* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.10. Ensure accessibility and affordability of AMR diagnostics.

Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (accessibility [tiab] OR affordab* [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.11. Research and development of novel, cost-effective, and affordable vaccines.
Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab]) AND (new [tiab] OR novel [tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.2.12. Develop veterinary/animal/farm-appropriate diagnostics.
Search strategy (PubMed):
("Drug Resistance, Microbial"[MeSH Terms] OR Antimicrobial resistance* [tiab] OR Antibiotic resistance* [tiab] OR Antimicrobial use[tiab]) AND (diag*[tiab]) AND (animal*[tiab] OR farm*[tiab] OR veterin*[tiab]) AND (costs and cost analysis [MeSH] OR cost savings [MeSH] OR cost-benefit analysis [MeSH] OR economic evaluation [tiab] OR cost analysis [tiab] OR cost-effectiveness [tiab] OR cost control [tiab] OR cost efficiency analysis [tiab] OR cost-effectiveness analysis [MeSH])
Filter: Last 5 years; Full Text.

b.3. Environment

b.3.1. Education and awareness of key source pollution emitters for appropriate and point-source waste prevention and treatment, and protection of source waters.

Search strategy (grey literature, Google Scholar):
Cost AND pollution emitters AND education OR awareness AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.2. Education and awareness of environmental and other relevant-sector authorities on the role of the environment t in AMR development, transmission and spread.

(Search strategy (grey literature, Google Scholar):
Cost AND environment AND education OR awareness AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.3. Implement systems for transparent and swift collection and reporting of the production, sales, use, and disposal of unused antimicrobials.

Search strategy (grey literature, Google Scholar):
Cost AND unused antimicrobials AND education OR awareness AND environment
Filter: Lat 5 years; first three pages.

b.3.4. Integrate environmental monitoring data (e.g., from monitoring of surface water, solid waste, and airborne particulate matter) with existing AMR surveillance and pollutants data.

Search strategy (grey literature, Google Scholar):
Cost AND environment AND data OR surveillance AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.5. Document the safety of bioproducts (e.g., biofertilizers, bioplastics, biosolid and manure applications, and plant growth promoters) and novel agricultural practices, as well as key sources of pollution that indicate an impact on AMR in the environment.

Search strategy (grey literature, Google Scholar):
Cost AND environment AND safety bioproduct AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.6. Improve integrated water management and promote water, sanitation, and hygiene (WASH) to limit the development and spread of AMR in the environment as well as to reduce infections and need for antimicrobials.

Search strategy (grey literature, Google Scholar):
Cost AND environment AND WASH OR water AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.7. Ensure safe and sustainable disposal and treatment of antimicrobials and hazardous waste from healthcare facilities, pharmacies, veterinarian centers, animal and crop production, and households (e.g., creating, strengthening and promoting take-back programs).

Search strategy (grey literature, Google Scholar):
Cost AND environment AND waste AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.8. Implement an integrated zoonotic disease surveillance system to detect disease emergence in human/animal population.

Search strategy (grey literature, Google Scholar):
Cost AND zoonotic AND disease AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.9. Optimize strategies and resources, to include minimum standards such that adequate laboratory and human resource capacity can be established to maintain quality integrated surveillance at scale.

Search strategy (grey literature, Google Scholar):
Cost AND capacity OR surveillance AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.10. Implement management options to prevent and address releases, effluent, and waste from intensive animal and crop production and from healthcare facilities and pharmaceutical manufacturing.

Search strategy (grey literature, Google Scholar):
Cost AND environment AND waste AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.11. Develop new methods/technologies to remove antimicrobial residues from the flows of wastewater, manure, and agricultural run-off.

Search strategy (grey literature, Google Scholar):
Cost AND residues AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.3.12. Develop soil/water/air-appropriate diagnostics.

Search strategy (grey literature, Google Scholar):
Cost AND diagnostic AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.4. Plants

b.4.1. Communicate with, educate, and provide training to farmers on AMR, integrated pest management (IPM), and the appropriate use and disposal of pesticides / herbicides/ molluscicides.
Search strategy (grey literature, Google Scholar):
Cost AND pesticide OR herbicide OR molluscicides AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.4.2. National surveillance of AMR data in food and agriculture and AMU data in crops through enrolling in the International FAO Antimicrobial Resistance Monitoring (InFARM).

Search strategy (grey literature, Google Scholar):
Cost AND surveillance OR data AND food OR agriculture AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.4.3. Incentivize farm assurance or certification benchmarking schemes in farms.

Search strategy (grey literature, Google Scholar):
Cost AND farm AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.4.4. Establish regional, central BSL (Biological Safety Level) 3 and 4 laboratories for detection of zoonotic and infectious diseases.

Search strategy (grey literature, Google Scholar):
Cost AND zoonotic AND laborator* AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.4.5. Reduce the secondary use of AMU as growth promoters in agriculture (e.g., avoid mention of this use on labels).

Search strategy (grey literature, Google Scholar):
Cost AND agriculture AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.4.6. Promote integrated pest management to reduce the use of antimicrobial pesticides.

Search strategy (grey literature, Google Scholar):
Cost AND pest AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.4.7. Reduce the need to use antimicrobial pesticides through the Reduce the Need for Antimicrobials on Farms (RENOFARM) initiative.

Search strategy (grey literature, Google Scholar):
Cost AND pesticides AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.5. Across sector interventions

b.5.1. Enhance policy, legislation, advocacy and financing.
Search strategy (grey literature, Google Scholar):
Cross-sectoral AND Cost AND policy OR legislation OR advocacy OR financing AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.5.2. Strengthen organisational development, implementation and sectoral integration.
Search strategy (grey literature, Google Scholar):
Cross-sectoral AND Cost AND Implement* OR development AND AMR OR AMU
Filter: Lat 5 years; first three pages.

b.5.3. Implement data, evidence, and knowledge.
Search strategy (grey literature, Google Scholar):
Cross-sectoral AND Cost AND data OR evidence AND AMR OR AMU
Filter: Lat 5 years; first three pages.

Appendix 5. Detailed information about the resources comprising the interventions

Table A5.1. Detailed information for each intervention included in the package

Interventions	Specific component	Description	Source
1. AMR awareness raising, education and behavior change of health workers and the community	1. a. Enhance health worker training	A training program for health professionals to improve communication skills during consultations with their patients in outpatient care settings.	OECD (2023) (10)
	1. b. Scale up mass media campaigns	The modelled intervention is a nationwide mass media campaign involving mass media and social media platforms to raise AMR understanding and awareness across key stakeholders.	
2. Enhance food-handling practices / biosecurity practices to reduce the risk of AMR spread between humans and animals	2. a. Improve food handling practices	A food safety control training program targets food service workers in food establishments, coupled with visual reminders and regular audits based on checklists.	OECD (2023) (10)
3. Research into new antimicrobials, diagnostics and vaccines for AMR and behavioral and implementation science	3. a. New antibiotic incentive program	New antibiotic incentive program including 18 new antibiotics.	Towse and Silverman. Centre for Global Development (2022) (39)
4. Implementation of biosecurity measures to prevent the introduction and spread of disease in farms	4. a. Improve farm hygiene	The modelled intervention is a procurement program that facilitates the purchase of PPE in farm settings by farmers and professional visitors like veterinarians.	OECD (2023) (10)
5. Implementation of infection, prevention, and control core components to mitigate AMR	5. a. Enhance hand hygiene	A facility-based intervention that aims to enhance hand hygiene practices among health workers.	OECD (2023) (10)
6. Universal access to improved WASH and waste management to mitigate AMR	6. a. Strengthen access to latrines and improved latrines	The intervention phase (community-led total sanitation) included bolstering access to latrines/improved latrines, etc. An improved latrine was defined as a pit-hole of 2 m depth or more, installation of a slab and a pit-hole cover, construction of a wall, door, and roof, and installation of a hand-washing facility with soap within the community-led total sanitation (CLTS) framework.	Cha S et al (2020) (39)

Interventions	Specific component	Description	Source
7. Ensure safe and sustainable disposal and treatment of antimicrobials and hazardous waste	7. a. Enhance environmental hygiene	A bundled intervention that aims to enhance environmental hygiene practices in hospitals.	OECD (2023) (10)
8. Quality laboratory system and diagnostic stewardship to enable clinical bacteriology and mycology testing	8. a. Implementation or scale up of Rapid diagnostic tests (RDTs)	A novel program aims to increase the use of rapid diagnostic tests by increasing the availability of point-of-care (POC) CRP in ambulatory care settings in combination with antibiotic treatment guidelines depending on the CRP levels.	OECD (2023) (10)
9. Access to vaccines and expanded immunization to manage AMR	9. a. Improve vaccination coverage	Scale up of nationwide campaign of 23-valent pneumococcal polysaccharide (PVV23) targeting older adults.	Lu E (Yiwei) et al (2021) (40)
10. Up-to-date evidence-based treatment guidelines and antimicrobial stewardship programs	10. a. Strengthening antimicrobial stewardship programs (ASPs)	The modelled intervention entails scaling up a hospital-based program that involves the creation of multi-disciplinary teams that provide antibiotic stewardship and the scale-up of monitoring and surveillance systems.	OECD (2023) (10)
	10. b. Delayed antimicrobial prescribing	The model intervention is the rollout of antimicrobial prescribing guidelines that promote delayed prescription in primary healthcare settings	
	10. c. Financial incentives	A nationwide pay-for-performance (P4P) program that aims to optimize antimicrobial use in community settings by rewarding bonuses to prescribers for achieving pre-set antibiotic prescribing targets.	

Note. (*) New antibiotic intervention targets deaths due to E. Coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, Streptococcus pneumoniae.

Appendix 6. Target coverage and impact data per intervention

Table A6.2. Effectiveness data, population target, and impact for each intervention (and component) within the package

Intervention	Specific component	Population target	Impact	Effectiveness value	Source
1. AMR awareness raising, education and behavior change of health workers and the community	1. a. Enhance health worker training	Healthcare workers with impact on patients	Resistant community infections	39% reduction in antibiotic prescription	OECD (2023) (10)
	1. b. Scale up mass media campaigns	Whole population	Resistant community infections	7% reduction in antibiotic prescription	
2. Enhance food-handling practices / biosecurity practices to reduce the risk of AMR spread between humans and animals	2. a. Improve food handling practices	Food caterers with impact on the population	Resistant and susceptible enteric infections	28.6% reduction in microbial count	OECD (2023) (10)
3. Research into new antimicrobials, diagnostics and vaccines for AMR and behavioral and implementation science	3. a. New antibiotic incentive program	Patients with resistant infections	Resistant set of infections	5% reductions in deaths attributed to AMR each year: starting from year 10 onward (*)	Towse and Silverman. Centre for Global Development (2022) (38)
4.Implementation of biosecurity measures to prevent the introduction and spread of disease in farms	4. a. Improve farm hygiene	Farmers with impact on the population	Resistant and susceptible community infections	12% reduction in risk of infection among people who use personal protective equipment (PPE) compared to those who do not	OECD (2023) (10)
5.Implementation of infection, prevention, and control core components to mitigate AMR	5. a. Enhance hand hygiene	Healthcare workers with impact on patients	Resistant and susceptible hospital infections	33% reduction in risk of infection among people who comply with enhanced hand hygiene practices compared to those who do not	OECD (2023) (10)
6. Universal access to improved WASH and waste management to mitigate AMR	6. a. Strengthen access to latrines and improved latrines	Children aged 0-5	Resistant and susceptible enteric infections	29% reduction in diarrhea cases	Assumption based on Cha S et al (2020) (39)

Intervention	Specific component	Population target	Impact	Effectiveness value	Source
7. Ensure safe and sustainable disposal and treatment of antimicrobials and hazardous waste	7. a. Enhance environmental hygiene	Healthcare workers with impact on patients	Resistant and susceptible hospital infections	26% reduction in risk of infection among people who are exposed to enhanced environmental hygiene practices compared to those who do not	OECD (2023) (10)
8. Quality laboratory system and diagnostic stewardship to enable clinical bacteriology and mycology testing	8. a. Implementation or scale up of Rapid diagnostic tests (RDTs)	Antibiotic prescribers in the community with impact on patients	Resistant community infections	32% reduction in immediate antibiotic prescribing in adults and 46% in children < 18 years of age	OECD (2023) (10)
9. Access to vaccines and expanded immunization to manage AMR	9. a. Improve vaccination coverage	Children aged 0-5	Resistant and susceptible pneumococcal infections	Reduction in pneumococcal disease cases: - Pneumococcal pneumonia 9.41% reduction. - Pneumococcal meningitis: 42.46% reduction - Pneumococcal acute otitis media (AOM): 8.32% reduction	Lu E (Yiwei) et al (2021) (40)
10. Up-to-date evidence-based treatment guidelines and antimicrobial stewardship programs	10. a. Strengthening antimicrobial stewardship programs (ASPs)	ATB prescribers in hospitals with impact on patients	Resistant hospital infections	25% reduction in antibiotic use	OECD (2023) (10)
	10. b. Delayed antimicrobial prescribing	ATB prescribers in the community with impact on patients	Resistant community infections	60% reduction in antibiotic use	
	10. c. Financial incentives	ATB prescribers in the community with impact on patients	Resistant community infections	8% reduction in antibiotic use	

Note. (*) New antibiotic intervention targets deaths due to E. Coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, Streptococcus pneumoniae.

Appendix 7. Cost data for each intervention included in the package

Table A7.1. Cost data for each intervention included in the package

Intervention	Specific component	Intervention costs	Original currency/year	Country/ region of reference	Source
1. AMR awareness raising, education and behavior change of health workers and the community	1. a. Enhance health worker training	$0.40 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)
	1. b. Scale up mass media campaigns	$0.69 per capita per year	US$ PPP, 2020		
2. Enhance food-handling practices / biosecurity practices to reduce the risk of AMR spread between humans and animals	2. a. Improve food handling practices	$0.24 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)
3. Research into new antimicrobials, diagnostics and vaccines for AMR and behavioral and implementation science	3. a. New antibiotic incentive program	$ 3.83 billion for total country's costs for a 30-year period (*)	US$, 2020	Japan	Towse and Silverman. Centre for Global Development (2022) (9)
4.Implementation of biosecurity measures to prevent the introduction and spread of disease in farms	4. a. Improve farm hygiene	$0.245 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)
5.Implementation of infection, prevention, and control core components to mitigate AMR	5. a. Enhance hand hygiene	$0.48 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)

Intervention	Specific component	Intervention costs	Original currency/year	Country/ region of reference	Source
6. Universal access to improved WASH and waste management to mitigate AMR	6. a. Strengthen access to latrines and improved latrines	$ 45.80 per capita for a 10-year period	US$ PPP, 2016	Ethiopia	Assumption based on Cha S et al (2020) (39)
7. Ensure safe and sustainable disposal and treatment of antimicrobials and hazardous waste	7. a. Enhance environmental hygiene	$2.24 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)
8. Quality laboratory system and diagnostic stewardship to enable clinical bacteriology and mycology testing	8. a. Implementation or scale up of Rapid diagnostic tests (RDTs)	$1.34 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)
9. Access to vaccines and expanded immunization to manage AMR	9. a. Improve vaccination coverage	$0.21 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)
10. Up-to-date evidence-based treatment guidelines and antimicrobial stewardship programs	10. a. Strengthening antimicrobial stewardship programs (ASPs)	$2.3 per capita per year	US$ PPP, 2020	OECD countries	OECD (2023) (10)
	10. b. Delayed antimicrobial prescribing	$0.45 per capita per year	US$ PPP, 2020		
	10. c. Financial incentives	$2.58 per capita per year	US$ PPP, 2020		

Note (*) For this intervention, costs related to improve access to all three types -- Access, Watch, and Reserve antibiotics will also be considered. From the SECURE work, there is an estimate that it will cost approximately 44.3m US$ per 100m population using public health service.

Appendix 8. Regions included in the analysis

Table 8.1. Regions included in the analysis defined by WHO geographic regions and 2024 World Bank income categories

Geographic location	Income Level	Abbreviation
Africa	Upper middle and high income	AFR_UMI_HI
Africa	Low-income	AFR_LI
Africa	Lower middle-income	AFR_LMI
America	Low and Lower middle-income	AMR_LI_LMI
America	Upper middle-income	AMR_UMI
Eastern Mediterranean Region	Low and Lower middle-income	EMR_LI_LMI
Eastern Mediterranean Region	Upper middle income	EMR_UMI
Europe	Low and Lower middle-income	EUR_LMI_LI
Europe	Upper middle income	EUR_UMI
South-East Asia	Low and Lower middle-income	SEAR_LMI_LI
South-East Asia	Upper middle-income	SEAR_UMI
Western Pacific Region	Low and Lower middle-income	WPR_LI_LMI
Western Pacific Region	Upper middle-income	WPR_UMI
Global (*)	High-income	Global_HI

Note (*) Global (HIC) region includes all high-income countries across the globe except the African region.

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