Outcomes Research & AMR

Defining the Value of Healthcare Interventions in Antimicrobial Resistance

CIDRAP

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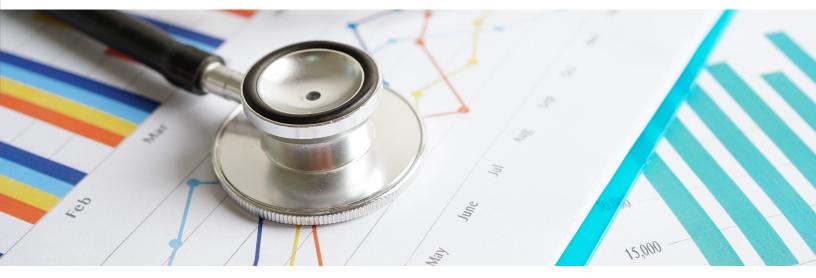
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Acknowledgements

Preamble

The unprecedented health emergency and consequent economic crisis that has swept the world over the past three years have put health systems and society as a whole under incredible pressure, several estimates put global excess mortality due to COVID-19 between 10 million and 20 million deaths (Mathieu 2023). Now more than ever, governments need to manage competing priorities, while ensuring access to health for all and equal distribution of resources among programs to support resilient health systems. A recent Organisation for Economic Co-operation and Development (OECD) report highlights that additional health investments of up to 1.4% of countries' gross domestic product (GDP) will be needed in the near future to equip countries with the ability to respond not only to potential future health emergencies but also to other natural or man-made events (OECD 2022). The report continues to explain that, despite the initial higher expenditure needed on top of the existing health spending—currently amounting to an average of 8.8% of GDP in OECD countries—the return in terms of acquired social benefits will be much higher, and costs will trend lower in the longer term. Resilient health systems are at the core of solid economies and have long-lasting and far-reaching societal benefits (OECD 2022). They protect population health

and equip communities with the necessary tools to respond to emergencies. Global health leaders are increasingly recognizing that health interventions and access to healthcare have broad effects on individuals' quality of life and overall societal well-being. These effects cannot be quantified only through dollars saved and GDP growth. The World Health Organization (WHO) Council on the Economics for Health For All has acknowledged the need for the adoption by countries of frameworks that better recognizes the interplay between human health and well-being, medicine, community foundations and economy (WHO 2022). Outcomes research acknowledges the interconnectivity across clinical, social welfare, and economic outcomes and allows one to measure the overall impact of an intervention in a given context. In global health, where notoriously competing health priorities put governments under incredible decision-making and funding pressure, outcomes research is a necessary tool to measure the impact of health interventions and help policymakers allocate necessary resources.

This three-paper series will explore the emerging role of outcomes research in public health. In this first paper, we will define outcomes research and explore how the concept has evolved over time and can be applied to research. The second paper

will look at specific case studies related to the use of outcome research to quantify the value and cost-effectiveness of the use of diagnostics to inform appropriate prescription of antibiotics in hospital settings. The third paper will explore the impact on patients of these interventions and how they are captured in outcome research.

We will focus primarily on its impact on antimicrobial resistance (AMR). AMR, due to its complexity and reach across human, veterinary, and environmental dimensions of health, has often struggled to secure necessary investments or political attention equally across all sectors. In particular, advocacy for the implementation of prevention measures or the development and use of tools to control the spread of drug-resistant infections across communities has not raised sufficient funds. Outcomes research can help shift the focus on the benefits of action, not only measured as a simple clinical outcome but as the multidimensional interplay between the various factors that make health interventions sustainable.

Introduction

Health outcomes research is a tool to identify the most effective interventions that lead to high-quality care. It can aid healthcare professionals to make strategic decisions to benefit patients and the overall health system and society. When coupled with principles of health economics, it allows policymakers to easily identify the most sustainable and valuable treatments. It is also referred, especially within the life sciences industry, to health economics and outcomes research, or HEOR. However, as outcomes research is inherently connected to the domain of public health, we will refer to it as outcomes research, or OR, in this paper.

It is clear that the traditional view of research solely evaluating the safety and efficacy of treatments can no longer take into account the complexity of many global health issues. Interventions need to be studied and evaluated in the broader context of where they are deployed, incorporating health system resilience, patient diversity, contextual factors, and social and economic determinants of health. OR provides evidence for the value of specific medical treatments and interventions that can help clinicians make informed decisions. For instance, data help healthcare

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professionals select the most appropriate treatment options for individual patients while accounting for their specific needs and situations. Additionally, the data can be used to determine gaps in interventions and/or any interventions that are over- or underused by population groups in order to help providers develop evidence-based treatment strategies that bring value-added care (Jefford 2003).

OR can be effective only if data can be used to integrate evidence-based interventions and policies into routine healthcare and public health settings. Although this is an obvious next step, the collection, use and translation of evidence-based data into practice is still relatively new and challenging, especially in many resource-limited settings (Barlow 2018).

A diverse and growing number of stakeholders, including employers, healthcare organizations, insurance and pharmaceutical companies,

and governments currently use real-world data provided by health OR to guide their decisions about different treatment options and interventions. Health outcomes data coupled with cost-effectiveness analyses can guide the decision-making process both in clinical practice and in policymaking. OR should be seen not just as a tool to measure the value of every dollar spent on healthcare, but also as an instrument to guide implementation research across different contexts, particularly those in which governments must develop health goals and budgets for their achievement. Interventions need to demonstrate value for money and bring substantial improvements to patients' lives and provision of quality healthcare. In May 2015 the World Health Assembly adopted a global action plan on antimicrobial resistance, including five objectives for countries to contain the increasing spread of drug-resistant infections. Countries were tasked with the development of AMR national action plans (NAPs), including specific actions aimed at ensuring access to appropriate and quality-assured treatments and development of prevention measures that would limit the spread of infectious diseases (68th World Health Assembly 2015). Nearly 7 years later, while many NAPs have been developed, countries have faced challenges in securing the necessary funding for a reasonable NAP implementation budget. The development of a budgeting tool by the WHO and targeted developed loans by the World Bank are providing much needed support, especially in low-resource settings, to strengthen AMR NAPs. However, there is a clear need to invest more in research that can provide a clear outlook on beneficial health interventions (World Bank 2022).

Outcomes Research

What Is Outcomes Research?

There is no standard accepted definition for OR, and the term is often used to identify research related to measuring the effectiveness of public health interventions. Many in the field cite the definition used by the US Agency for Healthcare Research and Quality (AHRQ). According to the AHRQ, OR aims to understand the results of public health interventions: *"End results include effects that people experience and care about, such as change in the ability to function. In particular, for individuals with chronic conditions—where cure is not always possible— end results include quality of life as well as mortality. By linking the care people get to the outcomes they experience, outcomes research has become the key to developing better ways to monitor and improve the quality of care."* (Gunter 1999). Thus, OR does not focus solely on the efficacy and safety of treatments in the manner of clinical trials,

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but it also measures patient health-related quality of life, behaviors, and preferences, and it includes an analysis of healthcare delivery by accounting for cost-effectiveness, health status, and disease burden.

A brief history of OR development

The term "outcomes research" related to healthcare delivery and quality was first used in 1966 in a framework built on the model of structure (health systems), process (patients receiving treatments), and outcome (measured clinical impact) (Donabedian 1988). These efforts were further expanded by John Wennberg and Paul Ellwood, who emphasized the central role of patients in clinical decision-making and highlighted the measurement of related outcomes as reported by patients and clinicians (Elwood 1988, Wennberg 2014;). Outcomes studies might evaluate the rate of reduction of hospital-acquired infections after an intervention to increase handwashing, the expenses saved by the hospitals, and patient morbidity. For instance, a study conducted in a teaching hospital in Taiwan during the implementation of the WHO Hand Hygiene strategy estimated savings equal to $940,000 and 3,564 admission patient days per year (Chen 2016).

While clinical outcomes still occupy an important part of the results, there is a growing interest in measuring other outcomes related to health-related quality of life, costs for the health institution, etc. During the evolution of thought about OR, it became clear that one outcome could influence many other outcomes. Kozma, Reeder, and Schulz developed a model which measures balanced outcomes to ensure no outcomes are maximized to the detriment of other outcomes (Kozma 1993). For instance, it avoids the so-called bubble effect, wherein use of a new intervention or the cost of treatment will outweigh the benefits to patients. Their framework, called ECHO, includes three dimensions of outcomes: clinical, economic, and humanistic (Gunter 1999). Clinical outcomes measure the medical events, while economic outcomes are measured as direct, indirect, and intangible costs compared with the consequences of alternative medical treatments. Humanistic outcomes are the effects of the intervention on patients that might include health-related quality of life, satisfaction, adherence, etc. This framework acknowledges the interplay between these three dimensions and informs an equal distribution of resources.

Overview of OR advantages

The benefits of using OR are multiple and affect patients, healthcare workers, health systems, governments and the overall society, as summarized in Table 1. It therefore has the benefit of combining the viewpoints of many different stakeholders. OR focuses on the result of healthcare interventions, making it simpler to measure and compare their effectiveness and immediate clinical benefits. As the focus is not only on clinical outcomes, survival is often measured together with QALYs (quality-adjusted life-years) and DALYs (disability-adjusted life-years), which is a combined measure of the patient's retained or acquired well-being (or health outcome) and cost-utility of that intervention. Utility provides a summary of quality of life that can be usefully compared across diseases, conditions, and populations. Cost-utility analyses are generally expressed in terms of dollars per QALYs/DALYs gained. Other cost analyses can include the effectiveness of the intervention as compared to existing treatments and cost outcomes (See Focus Box 1).

Table 1. Advantages of Outcomes Research (OR)

Stakeholder	Advantage
Patients	• Increased participation in clinical decision-making • Increased choice regarding hospital/practitioner/treatment options • Better understanding of the effectiveness of interventions • Interventions improve both well-being and survival
Healthcare professionals	• Clearer understanding of the benefit of an intervention • Availability of standards/guidelines to guide clinical practice • Shared responsibility with patients in decision-making
Healthcare systems	• Use of effective interventions • Delivery of quality care • Cost savings
Governments	• Cost savings • Ability to plan health services • Only effective pharmaceuticals and services are subsidized • Targeted research in areas of greatest potential

Note: Information for this table was modified from Jefford 2003.

OR & Antimicrobial Resistance: Progress and Limitations

The Health and Economic Burden of AMR

Though the field of OR applied to AMR is in its infancy, drug-resistant infections have been found to place a significant cost burden on patients, healthcare systems, and societies, threatening global progress toward the United Nations Sustainable Development goals and efforts to end poverty. In 2016, the World Bank published models forecasting AMR costs through 2050, predicting that if rates of AMR rose significantly, global gross domestic product would fall by 3.8% by 2050. Within the same timeframe, healthcare costs attributable to AMR in high-income, middle-income, and low-income countries would rise by 6%, 15%, and 25%, respectively, and collectively reach $1.2 trillion per year (World Bank 2016).

Similarly, a 2018 OECD model of healthcare costs attributable to AMR found that drug resistance accounted for annual expenses of $3.5 billion in 33 primarily high-income countries, predicting that costs across the countries' healthcare systems would reach $134 billion by 2050. Major contributors to AMR-related costs included increased use of second-line or combination antibiotics, diagnostic testing and imaging, monitoring for complications, hospitalization and intensive care length-of-stay and transfers, isolation, and surgery (Ouakrim 2020). Yet the economic case has failed to materialize, and many countries and health systems are still struggling with budgeting for the implementation of AMR countermeasures.

Most AMR research that might fall under the rubric of OR occurs at the healthcare system level. A 2021 model of clinical and economic costs related to AMR among hospitalized patients in Japan found that reducing drug-resistant gram-negative infections could save more than 4 million life-years, about 4.4 million bed-days, and approximately 3.6 million defined daily doses of antibiotics, providing a net benefit of close to $170 billion over 10 years (Matsumoto 2021).

A 2014 study of data primarily from high-income countries also found extra costs to be related to particular drug-resistant pathogens, with costs for treating vancomycin-resistant *Enterococcus* estimated at $16,711 to $60,988, and expenses for drug-resistant *Acinetobacter baumannii* measured between $5,336 and $126,856 (Gandra 2014). Another study found that AMR increased per-prescription costs for treating otitis media by 22% (Jit 2020)

A 2020 review of 110 articles that measured costs associated with AMR found that most were led by hospitals (86%) and approached outcomes measurements from a hospital- or insurance/payer-based perspective (88%), in lieu of studying outcomes as they affect patients, caretakers, or society. Only 12 studies evaluated costs and outcomes from AMR in low- and middle-income settings (Jit 2020).

Research Models for AMR OR

Numerous methodologies are used to link clinical and economic outcomes in AMR OR, with some attention starting to be paid toward using OR to design cost-effective, sustainable interventions. Time is an important variable in almost all AMR OR analyses, as health status and costs associated with microbial infection are usually temporary but may have long-lasting and evolving effects on a patient, healthcare system, and society or result in consequences that can only be predicted by modeling cost-effectiveness into the future. Including time as a variable also can help to resolve the seeming paradox whereby, in many instances, a significant expenditure may be needed upfront before health and cost-savings benefits are realized in the future.

Examples of AMR OR methods include:

Health economic evaluation

At the healthcare level, a health economic evaluation assesses costs and benefits associated with a particular intervention with the understanding that resources are finite and/or may not be available. The intent of a health economic evaluation is to aid in clinical decision-making, especially when resources are scarce. Evaluations compare more than two interventions and assign values to outcomes, with the goal of describing how much a healthcare system must invest before a clinical benefit is realized. The most common types of health economic evaluations are: (1) cost-benefit analyses, which analyze outcomes in terms of cost savings or expenses; (2) cost-effectiveness studies, which measure outcomes as health effects (e.g., clinical cure, hospital length of stay) associated with specific expenditures; and (3) cost-utility frameworks, which are similar to cost-effectiveness

DALYs & QALYs: What are they, and why are they used?

QALYs (quality-adjusted life-years) and DALYs (disability-adjusted life-years) are widely used tools to quantify, evaluate, and compare the cost-effectiveness and risk-benefit of health interventions on quality and length of life. They are not interchangeable and will produce different measures depending on disabilities and conditions. A QALY measures years lived in perfect health. It combines life expectancy with remaining quality of life-years. Standard valuations of different conditions are given a score. Usually 1 is used to indicate perfect health and 0 death, while certain severe disabilities are given negative scores (worse than death) (Sassi 2006). On the other hand, DALY was developed in the 90s as an alternative framework and measures the burden of disease. DALYs sum years of life lost (YLL) due to premature mortality and years lived with a disability or disease (YLD). YLL are calculated as the number of years where deaths occurs earlier than expected. YLD represent the number of years lived with a disease or disability weighted by a disease/disability factor. For DALYs, the scale used to measure health state is inverted; thus, 0 indicates perfect health and 1 equates to death (Sassi 2006, WHO 2022).

DALYs and QALYs have often faced criticisms, because neither measure fully captures the wider effects that stem from interventions and are notoriously difficult to quantify, such as emotional and mental health status, impact of death or disability on families and careers, and other social consequences.

studies but measure health outcomes as they affect quality of life (Turner 2021).

Example: A cost-utility analysis of a pharmacist-led antimicrobial stewardship program at a large hospital in Ethiopia measured expected life-years, QALYs, and program costs, finding that a significant financial investment in implementation costs was later associated with improved health and quality-of-life outcomes and cost savings (Gebretekle 2021).

Investigator-initiated or product development study

AMR-focused OR for antimicrobials or diagnostic and susceptibility tests may begin during product development so that outcomes data can help inform uptake and associated interventions when the product reaches the market (Trevas 2020).

Example: In preparation for US Food and Drug Administration clearance of its biomarker test to distinguish between bacterial and viral infections, a diagnostics company built a model of costs, benefits, and risks for its product compared with the standard of care for community-acquired pneumonia (Schneider & Cooper 2022).

Budget impact and cost models

Models that assess budget impact in terms of linked AMR-related expenditures and clinical metrics (e.g., antimicrobial defined daily doses, rate of drug-resistant infections, therapy-related adverse events, advanced diagnostic or susceptibility testing) are usually performed at the hospital level and are occasionally used to build estimates of AMR costs and outcomes at the regional or national level by linking costs from individual hospitals to rates of AMR across a region (Dick & Schneider 2021). Cost-modeling techniques are used frequently in AMR OR, often taking the forms of decision trees (i.e., visual representations of decisions, strategies, costs, and outcomes over time), regression models (i.e., models that incorporate many different variables and examine cost-effectiveness in increments to ascertain how individual variables influence cost-effectiveness), and Markov models (i.e., models that measure cost-effectiveness with their ability to map changes in risk or health status over time) (Carta & Conversano 2020).

Example: A budget impact model that assessed health and cost outcomes for biomarker-guided treatment for suspected sepsis and upper respiratory tract infection across Argentina's health system found that procalcitonin testing was associated with avoidance of AMR, prevention of *Clostridioides difficile*, and cost savings for providers and the country's health system (Garay 2021).

Costing framework

A costing framework is similar to a budget impact model and is also typically done at the local or hospital level, though it includes local epidemiologic data on actual and probable colonization and infection. It breaks down AMR-related expenditures into direct and indirect costs, thus making it easier to extrapolate results to the national level and inform policy and practice decisions (Morel 2020).

Example: The WHO's Costing and Budgeting Tool for National Action Plans on AMR encourages a costing framework approach (WHO Budgeting Tool), and, in 2020, the Global Antimicrobial Resistance Platform for ONE-Burden Estimates (GAP-ON€) network carried out a costing framework to enable a local assessment of all costs incurred by a WHO priority pathogen in human healthcare, animals, the environment, and across society (Morel 2020).

Patient cohort study

Many AMR OR studies are conducted at the hospital level and use a matched patient cohort model, where health and economic outcomes are compared between groups of patients with antibiotic-resistant and antibiotic-susceptible infections. Metrics may include diagnosis, severity-of-illness scoring (e.g., SOFA), and hospital length-of-stay (Jit 2020). Matched cohort studies tend to lack validity when extrapolated to a different setting or to the national level (Morel 2020).

Example: A 5-year patient cohort study in Sweden measured the costs of two different antibiotics and the costs of AMR development in febrile urinary tract infections to find the most cost-effective treatment (Larsson 2022).

Regression analysis

A variation of a patient cohort study that may more closely link health and economic outcomes is a regression analysis, in which treatment costs (inclusive of testing, adverse event management, isolation precautions, and need for intensive care or surgery) or hospital length-of-stay are linked to the incidence of drug-resistant infection (Jit et al 2020)

Example: A regression analysis assessed the costs associated with *Staphylococcus aureus* bacteremia in Canadian hospitals, illuminating the fact that cost increases were significantly associated with staffing and care for patients with drug-resistant infections (Thampi et al 2015).

Surveillance database review

Surveillance databases that include patient data on antimicrobial prescribing, rates of antimicrobial susceptibility, and healthcare costs may aid in OR that can more easily be used to inform policy. Surveillance-based studies, however, tend to favor high-income countries or countries that have robust central healthcare and AMR reporting mechanisms.

Surveillance studies that lack patient data take a similar approach as regression analyses or cohort studies by linking rates of AMR to healthcare costs (Jit 2020)

Example: A model to assess cost-effective treatments for ventilated hospital-acquired and ventilator-associated bacterial pneumonia used the "Program to Assess Ceftolozane/Tazobactam Susceptibility" global surveillance database to analyze costs and benefits that could be attributable to different therapies (Naik 2021).

Implementation science

Implementation science examines ways in which evidence-based interventions can be implemented and used regularly in healthcare settings. In other words, it seeks to bridge the gap between scientific knowledge and clinical action by identifying barriers and facilitators to activities that benefit both providers and patients. The inclusion of economic data in implementation science is rare, but it represents an area of opportunity for understanding how expenditures and cost savings affect the uptake of interventions likely to reduce AMR, especially in resource-limited settings (Barnett 2020; Jit 2020; Ouakrim 2020).

Example. A proposed implementation science approach for launching antimicrobial stewardship programs in Kenyan hospitals uses a cost-benefit analysis to understand how training and incremental evidence- and practice-based updates to antibiotic guidelines will improve health and cost-savings in health facilities and at the country level (Gitaka 2020).

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Top-down and Bottom-up Approaches to AMR OR

AMR OR generally takes one of two approaches: (1) top-down, in which large datasets are used to understand the links between costs and AMR at the national or global level, informing policy and practice changes at the local or healthcare level; or (2) bottom-up, in which cost and AMR data from hospitals or other healthcare facilities are used to estimate and forecast AMR-related expenditures and health outcomes more broadly. The strengths and limitations of each OR approach are illustrated in Table 2.

Table 2. Strengths and limitations of top-down and bottom-up approaches to AMR OR.

Level of Approach	Strengths	Limitations
Top-down	• The availability of large funding schemes enables clinical and economic outcomes data to be collected during antimicrobial or diagnostic test development, and data can then be used to drive uptake and reimbursement strategies when the product has entered the market. • OR-based forecasts of the effects of AMR can guide resource allocation and the priorities of National Action Plans. • Regional or national OR estimates of disease prevalence can draw connections between AMR-related clinical and economic outcomes when patient-level data are unavailable. • Large surveillance systems can capture disease that occurs outside of hospitals and highlight the clinical, economic/labor, and societal repercussions of AMR in the community.	• Global, national, or regional data used to inform OR estimates (healthcare use, antimicrobial prescribing, susceptibility testing, healthcare and societal cost measures) are fragmentary, likely do not provide a full or nuanced picture of the economic or clinical burden of AMR, and are unreliable for making economically beneficial decisions or understanding opportunity costs. • Global AMR surveillance datasets lack representation from low- and middle-income countries and are subject to bias and confounding in reporting mortality and costs attributable to AMR. Also, data from low- and middle-income countries may overestimate the rates of drug-resistant infections when diagnostic testing is performed only when patients do not respond to treatment. • Large multicenter initiatives require significant funding.

Bottom-up	• The use of local data to inform OR can create a framework in which local epidemiology, clinical and economic outcomes metrics, and interventions can be compared across settings and used to more accurately assess the global health and economic burden of AMR. • Local data have the specificity to demonstrate the effects of AMR in different settings and regions. • The comparison of OR data across localities and nations can inform global and national allocation of funds. • Because local or hospital-based studies are easy to conduct and do not require significant funding, local data have contributed to significant understanding of the clinical and economic impacts of AMR.	• High-income countries are significantly overrepresented in hospital-level estimates of costs associated with AMR. • Local metrics used to inform OR tend to include only direct healthcare-associated costs (rather than indirect costs, such as loss of income and out-of-pocket payments), which may make it difficult to design interventions that demonstrate a wide array of health and economic benefits. • Hospital-based metrics cannot reliably be used to understand the effect of an intervention on rates of AMR and thus are of limited value for designing OR-informed interventions or policies. • Local data do not measure the societal value of accessible antimicrobial therapy, ability to earn income, and the value of avoiding suffering, thus likely underestimating the linked health and economic effects of AMR.

Note: The data in Table 2 are from: Gandra 2014, Jit 2020, Morel 2020, and Ouakrim 2020.

AMR OR Outcome Measures

The application of OR to AMR is a developing field. Before practitioners can link health and economic outcomes to cost-effective interventions, they must develop outcomes metrics that accurately connect and predict AMR and expenditures at the patient, healthcare system, and societal levels. Table 3 shows potential outcomes measures that may be useful in OR, though not all will be appropriate for every setting or circumstance.

Antimicrobial resistance: How outcomes research can redefine the value of diagnostics

Antimicrobial resistance (AMR) is a growing public health concern, causing significant mortality and morbidity worldwide. It happens when microorganisms, such as bacteria, fungi, or viruses, no longer respond to the antimicrobials previously used to treat them (Christaki 2020, Foucalt 2007). The inability to treat infections threatens the practice of modern medicine and could hamper the delivery of even simple clinical procedures. Recent efforts to quantify the spread of drug-resistant infections have put deaths associated to bacterial AMR at 4.95 million in 2019 (Antimicrobial Resistance Collaborators 2022).

 A key cause in the spread of AMR is the misuse of antimicrobials in people, animals, and the environment. Misuse is compounded by multiple factors, some driven by human behavior, while others are context specific (Klein 2018, Sweileh 2021). Discussing every issue related to AMR is beyond the scope of this brief; however, we will focus on how quick and efficient diagnosis can limit and guide the specific use of antimicrobials when and where they are needed. In particular, lack of access to diagnostics and absence of specific diagnostic tools drives empirical use of antimicrobials. Empirical use depends on the availability of local or regional data and on guidelines that can inform medical decisions on the best course of treatments. Data availability is often an issue, especially in low-resource settings. The second brief in this series will take a closer look at case studies that support the cost-effectiveness of the use of diagnostics to aid antimicrobial prescriptions.

There is a need to stratify antibiotic and alternative treatments in terms of the actual benefit for the patient, improving patient outcome and limiting the impact on AMR. High-quality, effective, and appropriate diagnostic tests to guide appropriate use of antibiotics are available. In particular, rapid diagnostic testing can allow for quick diagnosis and choice of the most appropriate treatment (Pliakos 2018, Timbrook 2017). Data have shown the benefit of using diagnostics at the point of care improve the quality of antibiotic prescription and reduce the number of prescriptions (Antoñanzas 2021). However, implementation of these tests into daily healthcare practice is challenging owing to lack of insight into their medical and economical value. Although the upfront cost of using a diagnostic test might be higher than prescribing an antibiotic, the overall long-term savings to the health system could be far reaching. In fact, identifying the most appropriate treatment earlier in the diagnosis could translate into quick resolution of the condition, fewer treatments needed, and shorter hospital stays. The benefits are obvious for clinicians, the health system, and patients. OR is increasingly used in this sector to characterize the value and barriers to adoption of diagnostics in clinical practice. Due to its breadth, it can generate insights into the development of policies for their routine use. In 2019, the initiative Value-DX (Value-DX Initiative) was launched with the purpose of conducting modeling studies into the use of diagnostic tests for respiratory tract infections. The project, including collaborators from academia, industry and other international funding organizations, is collecting evidence across multidisciplinary sectors to create a framework for the adoption of diagnostics into routine clinical practice.

Table 3. Potential AMR OR outcome measures at the patient, healthcare system, and societal levels.

Level of OR Outcomes Measurement	Direct	Indirect
Patient	• Cure and response to treatment • Time to hospital discharge • Bed days • Side effects and ability to tolerate second-line therapies • Rehabilitation, home health, or long-term care costs	• Ability to earn income, measured to end of treatment • Life-years and QALYs • Funeral costs • Transportation to and from a healthcare facility • Caretaking (including basic living expenses and lost productivity for caretakers who must travel to be with a patient) • Loss of productivity due to post-infection or post-treatment sequelae that require ongoing medical care or surgeries • Lost leisure time • Mental health impact
Healthcare system	• Defined daily doses of antimicrobials used • Diagnostic codes • Severity-of-illness scores • Cost of antimicrobial treatment, potentially factoring in changes in guidelines to respond to changes in resistance levels	• Defined daily doses of antimicrobials avoided • Loss of bed availability and patient revenue due to possible need for isolation or longer hospital stays

Healthcare system	• Reimbursement rates • Cost of antimicrobial administration (e.g., intravenous and central lines, infusion) • Cost of diagnostic testing and imaging • Cost of nursing care in a hospital, home health, or long-term care setting • Cost and outcomes related to point-of-care testing • Comparisons between standard of care and an intervention (e.g., diagnostic-guided care) • Rates of and costs related to colonization, including infection prevention and isolation measures, decolonization, ongoing testing, enhanced contact precautions, and admission or visitor screening • Probability of colonization developing into infection • Costs of surgical prophylaxis in patients who are colonized or infected with drug-resistant organisms. • Cost of diagnosing and caring for adverse events and monitoring toxicities related to second-line therapies. • Transfer between settings (e.g., transfer from a general ward to an intensive care unit)	• Care related to the acute and chronic disease aftermath of resistant infections and long-term antimicrobial treatment (e.g., kidney failure, amputation, neurologic issues, mobility impairments) • Costs of changes to or improvements in hospital surveillance systems • Changes in a hospital's reputation that may result in decreased or increased patient revenue • Declines in patient revenue due to cancellations of non-essential procedures • Increase in diagnostic testing and empirical second-line antimicrobial use for patients who do not have drug-resistant infections but who are seen in a hospital or region where AMR is prevalent • Probability of surgical resolution to a drug-resistant infection

Society	• Days of illness (acute and/or chronic) and absenteeism	• Disruptions to international trade
	• Mortality rate	• Reductions in agricultural or industrial production
	• Annual national/regional cost of antibiotics consumed	• Reductions in tourism
	• Research and development associated with antimicrobial innovation, factoring in the potential need for emergency or expedited development	• Progress toward the Sustainable Development Goals
		• Avoidance of medical care and surgeries that require effective antimicrobial prophylaxis
	• Costs of changes to or improvements in regional or national surveillance systems	• Revenue lost and gained across healthcare systems due to changes in reputation or ability to provide care/beds
	• Costs of AMR communication campaigns	• Inability to access healthcare because of increased care for patients with drug-resistant infections

Note: The data in Table 3 are from: Dick and Schneider 2021, Gandra 2014, Jit 2020, Morel 2020, and Ouakrim 2020.

Recommendations for Advancing AMR OR Research

Numerous studies of AMR in healthcare settings include an economic component, though cost and expenditure analyses are often presented separately and not linked to health outcomes. Research into the integration of economic considerations into the field of OR is urgently needed, beginning with the following recommendations:

Standardized OR definitions and protocols

Multidisciplinary committees that include clinicians, economists, epidemiologists, policymakers, patient advocates, sociologists, payers/health insurance providers, and experts from other disciplines, as appropriate, must focus on defining health economics and outcomes research within a clinical, public health, and societal context and develop guidelines for conducting research in this arena (Trevas 2020).

Multidisciplinary involvement

The growing field of OR requires discerning associations between economic and health outcomes, as well as building evidence to understand which outcomes are meaningful in a given situation. Therefore, multidisciplinary research contributions are crucial. Infectious diseases clinicians can offer experiential knowledge on the value

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of diagnostic—including point-of-care—testing among diverse patient populations, with contributions from payers to better understand outcomes associated with testing reimbursement. The involvement of clinical laboratory professionals in AMR OR is crucial in informing policy and interventions related to the applicability, use, costs, and interpretation of diagnostic tests, as well as in the development of laboratory-informed AMR interventions (Trevas 2020, Smith 2023).

Investment in local data management structures

While there are various approaches to establish linkages between the costs (including opportunity costs) and outcomes associated with AMR, many experts agree that research is most accurate and applicable to other situations when carried out locally (Morel 2020, Ouakrim 2020, Trevas 2020), rather than using global databases to extrapolate AMR cost and health burden in different settings. However,

to ensure that local OR research has external validity, investment in multicenter research infrastructure and consistent antibiograms is necessary and should reflect the culture and priorities of health systems. Existing clinical trial structures can be used to develop economic and health outcomes studies that have greater validity and applicability than single-center research. Creating an infrastructure that enables collection and interpretation of locally meaningful data will help to standardize OR and provide an evidence base for funding, research and development, and policy decisions at the national, regional, and global levels.

While the field of OR applied to AMR is in its infancy, significant opportunities exist to build an evidence base that reflects local contexts and priorities while informing global funding and policy. Given the growing body of knowledge on connections between socioeconomic issues and AMR, OR that accurately and carefully connects economic costs and health outcomes attributable to drug resistance can lead to informed decisions for in healthcare settings and all sectors of society.

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