Outcomes Research & AMR

A human-centered perspective on a biosocial problem

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Introduction

Translating public health interventions into measurable effects is a necessary step to contextualize problems and their solutions, especially when outcomes need to be translated outside a medical or scientific domain. The challenge is creating and using tools that can effectively measure the overall impact of an intervention on the patients and communities they live in to predict whether these interventions will be sustainable long term. "Real-world" studies have been increasingly used to justify the need for a more comprehensive design of public health interventions that take into account patients' needs and contexts' unique characteristics. Given the complexity of antimicrobial resistance (AMR) and its spread across the human, animal, and environmental domains of health, well-rounded tools are needed to capture the overall impact of interventions.

A Socioeconomic Perspective on AMR Outcomes Research: Learning from Indicator Bacteria, Maternal Sepsis, Tuberculosis, and Malaria

Few examples or studies exist that demonstrate how the drivers and consequences of AMR can be measured at a societal level, yet, in recent years, viewpoints and studies that incorporate a society-wide viewpoint of cost-effectiveness have gained traction. A 2018 study of the economic burden of AMR in Thailand and the United States assessed indirect costs of AMR as a proxy for society-wide effects, finding that productivity losses associated with deaths attributable to AMR in five bacterial species (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*) far outweighed direct clinical costs. For instance, indirect costs attributable to methicillin-resistant S aureus in Thailand and the US were estimated to be $151 million and $5.9 billion USD, respectively, in comparison with the direct costs of $29 million and $114 million USD, respectively. The study found that total direct and indirect costs associated with resistance from only the five bacteria can be estimated at $500 million USD in Thailand and $2.8 billion in the US (Shrestha 2018).

Maternal sepsis following childbirth is an important public health problem worldwide, disproportionately affecting women in low- and middle-income countries (LMICs) and those who are socioeconomically disadvantaged in high-income countries. A recent study conducted in seven low-resource countries found that a single oral dose of azithromycin—an antibiotic which is affordable, available in generic form, does not require refrigeration, and has not been associated with the development of resistance when used as a single prophylactic dose—taken during labor and delivery lowered the incidence of maternal sepsis by 35% and resulted in fewer re-hospitalizations (Tita 2023). Although socioeconomic data and population-level effects of the intervention and its cost-effectiveness were not measured, studies of population-wide prophylactic azithromycin present many opportunities to identify socioeconomic metrics that may lead to ground-breaking outcomes research on the balance between the costs and burdens of AMR and the benefits of interventions.

Although research into the socioeconomic burden of malaria often tends to be limited, as in AMR societal research, to outcomes associated with labor and productivity, it may help to illuminate a way forward for thinking about AMR as a biosocial problem in the design of outcomes and cost-effectiveness studies.

In the context of rising rates of multidrug-resistant tuberculosis (TB) and stalled efforts to end TB during the COVID-19 pandemic, advocates of new TB vaccines are also building on a growing base of society-level cost-effectiveness models to spur investment in research and development. The World Health Organization's (WHO's) investment case for new vaccines uses an economic model to stratify TB outcomes by income and estimate long-term economic effects on countries' gross domestic product, asserting that every $1 invested in new TB vaccines will return $7 globally over 25 years. The case also notes that new TB vaccine rollout in children and adolescents will avert 66% of catastrophic costs borne by the poorest 40% of the global population, which, if accurate, will create massive societal improvements in health and well-being and narrow the equity gap between wealthy and poor households and nations (WHO 2022a).

Research into malaria prevention, drivers, effects, and economic burden—especially in the context of shifting rates of and geographies associated with artemisinin resistance—has historically taken a society-level view. Malaria researchers have been asserting for decades that malaria is not only a consequence, but a cause, of poverty (Tefera 2020). Although research into the socioeconomic burden of malaria often tends to be limited, as in AMR societal research, to outcomes associated with labor and productivity, it may help to illuminate a way forward for thinking about AMR as a biosocial problem in the design of outcomes and cost-effectiveness studies.

Reductions in incidence and mortality attributable to malaria have slowed since 2015 and were further threatened by resource allocation toward COVID-19. In 2020, the global incidence of malaria was 241 million cases, 627,000 of which were fatal. Paradoxically, global spending on

malaria prevention and disease management increased by almost 9% annually from 2000 to 2016, reaching more than $4 billion USD total in 2016 (Andrade 2022). Because of ongoing increases in spending, disappointing gains toward the goal of malaria elimination, rising artemisinin resistance, and the difficulty in comparing costs across national economies, cost-effectiveness outcomes research plays a vital part in examining the indirect societal burden of malaria in diverse settings and identifying resource allocation and spending priorities for policymakers and global funders (Shretta 2016).

Because malaria has been associated so closely with poverty and has attracted the attention of global philanthropic agencies, estimates of its socioeconomic impact on household and national economic growth are widely available, though still premised on a limited set of metrics (e.g., labor and productivity loss, loss of educational opportunities). It is estimated that Africa loses $12 billion annually because of malaria treatment costs, time spent away from work and school, loss of work and ability to learn in school attributable to neurologic damage, reductions in agricultural production related to selection of land and crops that will not attract mosquitoes, and loss of global investment and tourism. Losses are forecast to grow with the recent emergence and spread of artemisinin-resistant malaria in some African regions (European Alliance Against Malaria 2007).

A selection of studies that have assessed the indirect costs of malaria at the societal level, along with the metrics and outcomes used, are presented in Table 1.

Like malaria, AMR is a biosocial problem connected to many different elements of society, yet AMR outcomes research is complicated by the fact that it is a manifestation of many diseases. Its socioeconomic drivers and consequences can neither be measured nor compared easily across diverse economies and cultures, yet this complexity is precisely why cost-effectiveness outcomes research must broaden the scope of its inquiry to engage multidisciplinary partners and develop analyses that reflect the reality of AMR's clinical, economic, and social burden. Only when outcomes research reflects the ways in which AMR intersects with all areas of life can economic and clinical models claim that their interventions are truly cost-effective and sustainable.

Table 1. Outcome measures and societal costs associated with malaria cases and interventions

Study	Location	Outcome Measures	Societal (indirect) costs (USD)
Alonso et al (2019)	Mopeia district, Mozambique	Total expenditures (as proxy for societal economic burden)	Mean societal cost: $22 per uncomplicated case and $195 per complicated case Total annual economic burden: $332,286
Sanchez-Castro et al (2022)	Peru	Years of life lost Years lived with disability Disability-adjusted life years (DALYs) Economic burden of productivity loss (EBPL)	Years of life lost: 937 in 2019 (uncertainty interval of 19–5,399) Years lived with disability: 1,032 (uncertainty interval of 558–1,749) DALYs: 1,969 in 2019 (uncertainty interval of 752–6,328) EBPL: $8.3 million in 2019 (uncertainty interval of $2.9 million USD to $30.4 million)

Sicuri et al (2013)	Ghana, Kenya, and Tanzania	Potential future earnings lost due to premature death Productivity loss attributable to caretaking for severe malaria	Potential future earnings lost due to deaths in Ghana: • Infants ages 0–1: $11,800 • Children ages 1–4: $13,800 Potential future earnings lost due to deaths in Kenya: • Infants ages 0–1: $7,600 • Children ages 1–4: $8,900 Potential future earnings lost due to deaths in Tanzania: • Infants ages 0–1: $6,900 • Children ages 1–4: $8,100 Indirect costs associated with productivity loss associated with caretaking for malaria cases with neurological sequelae: • Ghana: $70 • Kenya: $90 • Tanzania: $212
Tefera et al (2020)	Chewaka District, Ethiopia	Days of work lost due to illness Percentage of annual household income spent on malaria management Socioeconomic predictors of economic burden (e.g., gender, education, proximity to healthcare, means of transportation, prior village experience with and expenditures on malaria management)	Total household economic burden of malaria management: $12,243, $9,513 of which was associated with indirect (i.e., non-clinical) costs High economic burden was associated with female heads of households, low educational status, having to travel a longer distance to access healthcare, living in a village that had experienced a malaria epidemic during the previous year, and using a motor bike or car to access treatment.

Note: The data in Table 1 are from Alonso 2019, Sicuri 2013, Tefera 2020, Sanchez-Castro 2022, and Barofsky 2015.

Challenges to Incorporating a Societal Perspective in AMR Cost-Effectiveness Outcomes Research

AMR is often described as a "tragedy of the commons," meaning that inequitable access to and misguided use of a precious resource like antimicrobials has contributed to a crisis that affects all levels of society (Bassetti & Giacobbe 2020). Research into the causes, consequences, and interventions associated with AMR, however, has not kept up with this idea, relegating the metrics and outcomes on which it focuses to the biomedical realm.

Socioeconomic considerations of AMR and its possible future impact has been quantified as the effect on the labor market during and following an individual or population-based health crisis. The view of health as a threat to GDP growth is outdated and does not reflect the many ways in which AMR may affect well-being at the intersecting level of individuals, populations, and systems. Modern analyses must account for the effect of drug resistance on labor—not as a means of equating disease and caretaking responsibilities with a threat to production—but with an eye toward the ability of countries and individuals to end poverty, food insecurity, and treatable illnesses on an equal playing field. And they must do so with a series of metrics that acknowledge the socioeconomic forces at play in AMR from an expanded and human-centered perspective (Miller-Petrie & Gelband 2017).

In 2022, the WHO published a draft of a people-centered framework for addressing AMR in healthcare, which focuses on improving equity in access to healthcare and ensuring that patients have a collective voice as they seek and receive care. The framework includes the community level (e.g., homes, schools, access to water and sanitation, ability to pay out-of-pocket for available services), but metrics are largely limited to those that affect an individual's ability to access healthcare. It does not consider the effect of AMR on society and the systems that govern access and equity at the population level (WHO 2022b). While a broader approach to the socioeconomic effects of AMR on society is needed, several challenges affect the development and use of appropriate outcomes research, as outlined below.

A Call for Improved Integration of Social Science Perspectives in AMR Outcomes Research

Many countries' One Health National Action Plans on AMR, which are intended to manage the emergence and spread of AMR across all levels of society, base their objectives on biomedical metrics developed from pathogen data from healthcare, agricultural, and environmental settings. This approach limits the ability of country leaders to make decisions about AMR's effects on society as a whole. Governance based solely on biomedical data will fail to reflect the realities of people's lives and livelihoods, especially as AMR interventions conflict with policies that aim to spur economic growth and improve food security (Wernli 2017).

As part of research priority-setting in 2014, the UK Economic and Social Research Council identified the social sciences as an important contributor in building an understanding of how AMR affects geographically and socially diverse communities, as well as in developing well-rounded and effective AMR interventions. The relative lack of social sciences expertise in AMR governance and AMR clinical education contributes to interventions that may work well initially but lack sustainability, depend heavily on technology or biomedical solutions, and otherwise fail to account for a complex problem that affects—and is affected by—all levels of society (Hofstraat 2021).

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The need for a broad social sciences mindset and accompanying set of metrics also affects the reliability of outcomes studies and economic models. An economic model aimed toward quantifying the drivers or effects of AMR cannot be said to be reliable if outcomes data are limited in their ability to reflect an intervention's performance in real-world circumstances. The vast majority of health economics outcomes research uses biomedical outcomes (e.g., clinical cure rate, length of hospital stay) as signifiers of cost-effectiveness. Failing to incorporate societal metrics that may have an enormous impact on effectiveness and go unseen and unmeasured, however, will contribute to an unreliable economic model (Bassetti & Giacobbe 2020).

In what is perhaps the most robust analysis of current models predicting AMR's societal effects, researchers from two Australian universities describe the urgent need to take a multidisciplinary and population-based approach to assessing the cost-effectiveness of AMR interventions, while also explaining why current models and outcomes associated with evaluating AMR economic burden are fraught with uncertainty and cannot reliably be used to make policy or public health decisions. They conclude, "Very crude models of future economic burden, using hypothetical scenarios of future resistance rates, lack the accuracy to adequately inform governments seeking optimal allocation of resources to limit AMR" (Hillock 2022).

In an interview with North Carolina State University, Boston University Professor of Biomedical Engineering Muhammad Zaman, PhD, said, "I think work in the lab and field must be connected. For example, vaccines are

only possible because of discoveries in the lab. But the reason people in many countries lack access to vaccines is something you couldn't predict solely by working in the lab. So, if you worked only in the field, you wouldn't have vaccines. And if you worked only in the lab, you wouldn't know what challenges exist in getting vaccines to rural parts of the world, which is why both approaches are needed" (North Carolina State University 2022). Because socioeconomic factors drive and result from AMR, and because the complex socioeconomic dimensions of AMR affect all analyses—whether acknowledged or not—an improved incorporation of the social sciences into AMR work is necessary for the reliability of outcomes research and cost-effectiveness models.

Regional Heterogeneity and Diversity

The WHO's recognition of community-associated factors as key determinants of access and equity in AMR prevention and management in its people-centered AMR framework spotlights the fact that AMR is affected by vast differences and disparities at many levels of society (WHO 2022c). This heterogeneity among countries, environmental zones, incomes, healthcare expenditures, antimicrobial regulations and enforcement, food-system security, water and sanitation infrastructure, family and gender norms, social mores, and many other factors means that a set of standardized metrics for measuring society-level effects on and of AMR makes little sense (Wernli). "From the lack of documentation about AMR and antimicrobial use at the global level, to the economics of national healthcare budgets in high- and low-income countries, down to the individual pocketbooks of rich and poor individuals, access to effective antimicrobials at the appropriate time is influenced heavily by social and economic factors" (Miller-Petrie & Gelband 2017).

For instance, health experts predict that LMICs will shoulder much of the future burden of AMR because of low access to necessary antimicrobials, increased inappropriate antimicrobial use as a substitute for healthcare access, and poverty and reduced labor income associated with increased rates of untreatable diseases (Dadgostar 2019). A study of 40 Asia-Pacific countries found that access to fungal diagnostics and appropriate antifungals was significantly associated with a country's gross domestic product, highlighting the role that national economies play in access to care and the importance of including socioeconomic metrics in studies of the risk of AMR on societies (Salmantón-Garcia 2023).

The interplay between food-system transformation and AMR work illustrates why AMR work must consider societal factors in cost-effectiveness and outcomes research. Food systems are changing rapidly across LMICs as countries work to reduce poverty and address growth in population, income, and urbanization. A greater focus on intensive irrigation, livestock production, and access to fresh food, however, may imply a heightened risk of zoonotic disease, foodborne illness, and AMR. In food systems that are undergoing rapid transformation and are associated both with benefits to food and economic security and the risk of rising AMR, interventions that rely on biomedical outcomes alone will not be sustainable. In agricultural economies that are attempting to reduce poverty, unilateral public health interventions can be harmful, as the factors that are increasing the risks of AMR or zoonotic diseases are also enabling people to afford healthcare and reduce risks of poverty-associated or

chronic disease. Societal interventions in these cases must include all stakeholders and consider all risks and benefits of the system to human health and socioeconomic well-being, rather than focusing solely on AMR risk and costs (Waage 2022).

It should also be noted that the many diverse factors affecting socioeconomic analyses of AMR are not static. Social norms, national and individual incomes, climate, food systems, and healthcare systems are changing around the world. So too must outcomes research adapt to changes in the social and economic factors affecting and affected by AMR, in the same way that it has adapted to measuring trends in disease transmission and drug resistance.

A Lack of Systems-based Thinking

Information gaps have historically plagued AMR work, from a lack of AMR surveillance data needed to make decisions to a dearth of information about an intervention's long-term cost-effectiveness and sustainability. The information collected and used to fill these gaps, however, is fairly narrow and usually limited to the biomedical realm, despite the fact that complex socioeconomic dimensions will always affect the results of an analysis. This is true whether the socioeconomic factors are defined, measured, and acknowledged or not. The integration of society-level metrics into outcomes-based cost-effectiveness analyses can help decision-makers avoid unreliable results caused by the socioeconomic ghost in the research machine.

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Incorporating metrics and outcomes that reflect the drivers and effects of AMR at the society level involves a systems-based approach that can reflect the complexity of the problem, while also empowering multidisciplinary research and solutions across communities (Hofstraat 2021). Such a systems-based approach could include process measures (policy and behavioral drivers of AMR; clinical, social, and economic pressures that spur inappropriate antimicrobial use), outcome measures (the impact of AMR at different levels of society and possible trends), and structural measures (AMR interventions and social transformations, including those that may not directly be related to AMR, such as paid sick and parental leave or sanitation improvements).

The inclusion of a wide array of socioeconomic metrics in AMR outcomes research may help to ensure (1) better reliability of cost-effectiveness and economic models and (2) involvement from professionals, policymakers, and community members in collecting and evaluating outcomes data relevant to the investment decisions they must make for their societies (Wernli 2017).

Recommendations for Incorporating a Societal Perspective in Outcomes Research

Outcomes research that incorporates a societal perspective can inform and enable AMR interventions that have a greater likelihood of being effective and sustainable. Similarly, socioeconomic outcomes and metrics provide policymakers with the most reliable evidence they need to make nationwide and community-wide decisions. A multidisciplinary system of AMR outcomes research that uses up-to-date and realistic metrics; works in the service of equality, access to healthcare, and poverty reduction; and balances economic growth with the need to prevent drug-resistant infections is direly needed, beginning with the following recommendations:

- **Develop broad and inclusive outcome measures.** Cost-effectiveness perspectives on AMR's societal effects have historically focused overwhelmingly on loss of labor and productivity due to illness and death, using quality-adjusted life-years and disability-adjusted life-years as tools to measure outcomes. A societal view of the drivers, effects, costs, and burden associated with AMR should include a wider range of variables, partly to avoid equating human life with a tool of economic production, and partly to reliably define and enumerate the variables that play a role in the effectiveness of any real-world AMR intervention. A multidisciplinary group that includes patients and caretakers must be formed to develop these outcome measures and the priorities that guide their selection and use.
- **Integrate social sciences expertise into AMR research and work.** A social sciences perspective must be included in AMR outcomes research and work, including in infectious diseases clinical education and in diagnostic and antibiotic development. The forces of systemic poverty, access inequality, and market de-incentivizing affect the success of AMR interventions and the ability to develop new tests and treatments; therefore, social sciences expertise incorporated throughout the research, education, and innovation process will aid in planning for and addressing common problems with uptake, access, and widespread engagement.

Societal factors that drive and result from AMR are far more difficult to measure compared with biological factors such as pathogen prevalence and length of hospitalization.

Despite this challenge, socioeconomic factors will affect any analysis, whether measured or not, and they play a key role in helping policymakers make decisions about resource allocation and governance. A broad, inclusive, and multidisciplinary perspective on socioeconomic outcomes research can aid in balancing the benefits and risks of reducing both AMR and the global inequalities that facilitate its emergence, spread, and devastating societal consequences.

References

Alonso S, Chaccour CJ, Elobolobo E, et al. The economic burden of malaria on households and the health system in a high transmission district of Mozambique. Malar J 2019 (published online Nov 11) [Full text]

Andrade MV, Noronha K, Diniz BPC, et al. The economic burden of malaria: a systematic review. Malar J 2022 (published online Oct 5) [Full text]

Barofsky J, Anekwe TD, Chase C. Malaria eradication and economic outcomes in sub-Saharan Africa: evidence from Uganda. J Health Econ 2015;44:118-36 [Full text]

Bassetti M, Giacobbe DR. A look at the clinical, economic, and societal impact of antimicrobial resistance in 2020. Expert Opin Pharmacother 2020;21(17):2067-71 [Full text]

Bull C, Teede H, Watson D, Callander EJ. Selecting and implementing patient-reported outcome and experience measures to assess health system performance. JAMA 2022;3(4):e220326 [Full text]

Dadgostar P. Antimicrobial resistance: implications and costs. Infect Drug Resist 2019;12:3903-10 [Full text]

Dawson J, Doll H, Fitzpatrick R, et al. The routine use of patient reported outcome measures in healthcare settings. BMJ 2010;340:c186 [Full text]

European Alliance Against Malaria. Malaria & Poverty. 2007 [Website]

Hillock NT, Merlin TL, Turnidge J, et al. Modelling the future clinical and economic burden of antimicrobial resistance: the feasibility and value of models to inform policy. Appl Health Econ Health Policy 2022;20:479-86 [Full text]

Hofstraat K, Spaan VF, de Vries DH. The limited state of training on the social dimensions of antimicrobial resistance. JAC Antimicrob Resist 2021 Dec;3(4) [Full text]

Manary MP, Boulding W, Staelin R, Glickman SW. The patient experience and health outcomes. N Eng J Med 2013;368(3):201-3 [Full text]

Miller-Petrie M, Gelband H. Socioeconomics, antimicrobial use and antimicrobial resistance. AMR Control 2017 Aug 2 [Website]

Murray CJ, Salomon JA, Mathers C. A critical examination of summary measures of population health. Bull World Health Organ 2000;78(8):981-94 [Full text]

North Carolina State University. The future of antimicrobial resistance. Applied Ecology News 2022 Sep 16 [Website]

OECD. Patient-reported indicators for assessing health systems. Measuring what matters: the patient-reported indicator survey. Paris: Organisation for Economic Development and Cooperation, 2019 [Full text]

Salmanton-García J, Au W-Y, Hoenigl M, et al. The current state of laboratory mycology in Asia/Pacific: A survey from the European Confederation of Medical Mycology (ECMM) and International Society for Human and Animal Mycology (ISHAM). Int J Antimicrob Agents 2023;61(3) [Full text]

Sanchez-Castro EE, Cahuana GM, García-Ríos CJ, et al. Health and economic burden due to malaria in Peru over 30 years (1990–2019): findings from the global burden of diseases study 2019. Lancet Reg Health Am 2022 (published online Aug 18) [Full text]

Sassi F. Calculating QALYs, comparing QALY and DALY calculations. Health Policy Plan 2006;21(5):402-8 [Full text]

Shrestha P, Cooper BS, Coast J, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. Antimicrob Resist Infect Control 2018 (published online Aug 9) [Full text]

Shretta R, Avanceña ALV, Hatefi A. The economics of malaria control and elimination: a systematic review. Malar J 2016 (published online Dec 12) [Full text]

Sicuri E, Vieta A, Lindner L, et al. The economic costs of malaria in children in three sub-Saharan countries: Ghana, Tanzania and Kenya. Malar J 2013 (published online Sep 3) [Full text]

Tefera DR, Sinkie SO, Daka DW. Economic burden of malaria and associated factors among rural households in Chewaka District, western Ethiopia. Clinicoecon Outcomes Res 2020;12:141-52 [Full text]

Tita ATN, Carlo WA, McClure EM, et al. Azithromycin to prevent sepsis or death in women planning a vaginal birth. N Engl J Med 2023 (published online Feb 9) [Abstract]

Waage J, Grace D, Fèvre EM, et al. Changing food systems and infectious disease risks in low-income and middle-income countries. Lancet Planet Health 2022;6(9):e760-8 [Full text]

Wernli D, Jørgensen PS, Harbarth S, et al. Antimicrobial resistance: the complex challenge of measurement to inform policy and the public. PLOS Med 2017 (published online Aug 17) [Full text]

Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull 2010;96:5-21 [Full text]

World Bank. Cost effectiveness analysis of results-based financing programs. A toolkit. Washington: World Bank, 2015 [Website]

WHO. Valuing Health for All: Rethinking and building a whole-of-society approach. Geneva: World Health Organization, 2022a [Website]

WHO. An investment case for new tuberculosis vaccines. Geneva: World Health Organization 2022b Dec 8 [Website]

WHO. People-centred framework for addressing antimicrobial resistance in the human health sector: draft for public consultation. Geneva: World Health Organization 2022c [Website]