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Economic Burden of Antimicrobial Resistance on National Health Budgets: A Cost-of-Illness Study

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ABSTRACT

Background: Antimicrobial resistance (AMR) is increasingly recognized as a direct fiscal threat to national health budgets, as resistant infections require costlier second-line therapy, longer hospitalization, and greater intensive care utilization than susceptible infections. Objective: This review synthesizes peer-reviewed cost-of-illness evidence on the economic burden of AMR, organized around direct medical costs, indirect and productivity costs, and national and macroeconomic budget-impact estimates. Methods: A narrative synthesis was conducted using PubMed/MEDLINE and Crossref-indexed sources, with every candidate reference individually verified against publisher or DOI-registry records before inclusion; studies were grouped thematically into direct-cost, indirect-cost, national cost-of-illness, and macroeconomic burden domains. Findings: Resistant infections are consistently associated with higher direct medical costs than susceptible infections, driven primarily by excess hospital length of stay and intensive care use rather than antimicrobial acquisition cost alone, with per-episode excess costs reported across pathogens including ESKAPE organisms, methicillin-resistant Staphylococcus aureus, and resistant Escherichia coli. Indirect productivity costs from morbidity and premature mortality are reported far less consistently and, where estimated, are of comparable or greater magnitude than direct costs. National-level estimates vary by more than an order of magnitude across studies, but consistently indicate a rising, multi-billion-dollar annual burden in high-income settings, with a disproportionately high relative burden in lower-income settings despite lower absolute per-episode costs. Conclusions: AMR imposes a measurable and apparently structural excess burden on national health budgets, but the strongest attributable-cost evidence remains concentrated in a small number of high-income health systems; standardized, locally derived cost-of-illness studies are needed to support realistic budget planning elsewhere, including in Central and Eastern Europe.

Keywords: *antimicrobial resistance; cost of illness; health economics; healthcare expenditure; budget impact*

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Introduction

Antimicrobial resistance (AMR) has moved, over the past decade, from an infection-control concern confined to hospital microbiology laboratories to a first-order threat to the fiscal sustainability of national health systems. When a pathogen no longer responds to first-line antibiotics, clinicians are compelled to substitute broader-spectrum, more expensive, and often more toxic second-line or last-resort agents, to prolong diagnostic work-up, and to manage a materially higher probability of treatment failure, complication, and death. Each of these clinical consequences carries a directly measurable price tag, and cost-of-illness methodology — long used to quantify the economic footprint of cancer, cardiovascular disease, and diabetes — has increasingly been applied to AMR as a way of translating a biological phenomenon into a budget line that health ministries and payers can act on [1,2].

The global projections that have done the most to place AMR on national policy agendas originate largely outside the peer-reviewed journal literature — most notably the 2014-2016 UK Review on Antimicrobial Resistance chaired by Jim O'Neill, which projected that drug-resistant infections could cause 10 million deaths annually by 2050 and cumulative global economic output losses of USD 100 trillion, and the World Bank's 2017 report modelling AMR's potential drag on gross domestic product (GDP) under high- and low-impact scenarios. These estimates have been highly effective at mobilizing political attention, but they rest on extrapolations and scenario modelling rather than empirically measured cost-of-illness data, and the peer-reviewed

literature has both scrutinized their assumptions and produced an independent, more granular evidence base built from hospital-level and national administrative datasets [3,4]. The Global Burden of Antimicrobial Resistance (GRAM) collaboration's 2022 analysis, for instance, estimated that bacterial AMR was directly responsible for 1.27 million deaths and associated with 4.95 million deaths globally in 2019, a mortality burden on the same order as HIV/AIDS or malaria, but expressed in disability-adjusted life-years and deaths rather than in the currency units that finance ministries budget in [5].

Translating this epidemiological burden into a budget-relevant figure requires cost-of-illness studies that separately identify the direct medical costs attributable to resistance (the incremental hospital, pharmacy, and intensive care expenditure incurred because an infection was resistant rather than susceptible), the indirect costs of lost productivity and premature mortality, and the aggregate macroeconomic burden that these micro-level costs sum to at national and global scale. This review synthesizes the cost-of-illness and economic-burden literature on AMR published in peer-reviewed journals, organizing findings around these three cost categories and around the growing body of country-level budget-impact studies, with particular attention to the methodological choices — comparator selection, attribution of excess length of stay, and discounting of future productivity losses — that account for the wide variation in published cost estimates. The three co-authors' backgrounds in health economics, infectious diseases, and health policy across three Central and Eastern European health systems inform particular attention to how these methods translate to middle-income and transition economies, where the fiscal space to absorb AMR-related cost growth is typically narrower than in the high-income settings that dominate the primary literature.

Methods

This review followed a structured narrative synthesis approach rather than a formal systematic review protocol, appropriate to a topic that spans clinical epidemiology, health economics, and health system budgeting and for which methodological heterogeneity across primary studies precludes meaningful meta-analytic pooling of point estimates. Relevant literature was identified through searches of PubMed/MEDLINE and Crossref-indexed journals using combinations of the terms "antimicrobial resistance," "antibiotic resistance," "cost of illness," "economic burden," "direct medical costs," "hospital costs," "length of stay," "productivity loss," "budget impact," and "attributable cost," restricted to peer-reviewed original research articles and systematic reviews. Every candidate reference was individually verified against its publisher record or the Crossref DOI registry (matching title, author list, journal, volume/issue, pagination, and DOI) before inclusion, and sources that could not be independently verified in this way were excluded regardless of how plausible the citation appeared. Grey literature sources frequently cited in AMR policy discussion — including the O'Neill Review and the World Bank's macroeconomic scenario report — are discussed narratively for context but are not included among the verified reference list, since neither is a peer-reviewed journal article amenable to the verification standard applied here.

Included studies were organized into four thematic domains that structure the Findings section: (1) direct medical costs attributable to resistant infections at the patient and hospital level, including excess length of stay, second-line antimicrobial expenditure, and intensive care utilization; (2) indirect and productivity costs associated with morbidity, premature mortality, and informal caregiving; (3) national and cross-country cost-of-illness estimates that aggregate patient-level costs to the population level; and (4) macroeconomic projections and budget-impact analyses relevant to national health financing. Because attributable-cost estimation is methodologically contested — studies vary in whether they compare resistant infection to no infection, resistant infection to susceptible infection of the same organism, or resistant infection to a matched uninfected control, and whether they adjust for time-dependent bias in length-of-stay estimation — methodological quality and comparator choice are noted narratively alongside each finding rather than used to generate a single pooled effect size.

Direct Medical Costs of Antimicrobial-Resistant Infections

The most consistently replicated finding in the cost-of-illness literature on AMR is that resistant infections generate substantially higher direct medical costs than susceptible infections caused by the same organism, driven primarily by prolonged hospital stay, escalation to broader-spectrum or last-resort antimicrobials, and disproportionate use of intensive care resources. A systematic review and meta-analysis of healthcare-associated infections caused by multidrug-resistant bacteria across high-income health systems found that resistant infections were associated with significantly higher direct costs, longer hospital stays, and higher mortality than susceptible-organism infections, with the excess cost driven predominantly by the additional bed-days rather than by antimicrobial acquisition cost alone [6]. Organism-specific analyses reinforce this pattern: a meta-analysis focused on ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) found consistently positive incremental costs of resistance across all six organism groups, though with wide heterogeneity in the magnitude of the excess attributable to differences in study setting, comparator group, and costing perspective [7]. A systematic review specific to hospital-acquired resistant and multidrug-resistant Pseudomonas aeruginosa similarly found that resistant infections were associated with significantly greater hospital length of stay, cost, and mortality than susceptible-organism comparators, though the authors noted that few included studies adequately controlled for the time-dependent nature of length-of-stay attribution, a methodological limitation that risks overstating the true incremental cost [8].

Single-institution and national administrative-data studies provide more granular, budget-relevant detail. An early and widely cited analysis of a large U.S. teaching hospital found that antimicrobial-resistant infections were associated with significantly higher hospital and societal costs than susceptible infections, and that a substantial share of these excess costs were attributable to increased length of stay in medical and intensive care wards rather than to antibiotic acquisition cost itself, a finding that has informed the subsequent literature's general emphasis on bed-day costs as the dominant driver of AMR's direct fiscal footprint [9]. Methicillin-resistant Staphylococcus aureus (MRSA), among the most extensively studied resistant organisms, has been shown in matched case-control analyses to generate significantly higher direct medical costs than methicillin-susceptible S. aureus infection, driven by longer hospitalization and more frequent readmission [10,11].

National-level administrative cohort analysis of Escherichia coli bacteraemia in the English hospital system similarly found that resistant bloodstream infections carried a measurably higher cost and mortality burden than susceptible infections, providing a rare example of attributable-cost estimation performed at true national administrative-data scale rather than in a single sentinel hospital [12]. Community-associated resistant infections have received comparatively less attention than hospital-acquired infections, but available evidence indicates that community-onset resistant infections requiring subsequent hospitalization also carry a measurable cost premium over susceptible-organism community infections, extending the direct-cost burden beyond the hospital's own patient population [13]. Table 1 summarizes representative per-episode excess cost and length-of-stay estimates drawn from this literature, and Figure 1 illustrates the relative magnitude of reported excess direct costs by pathogen group.

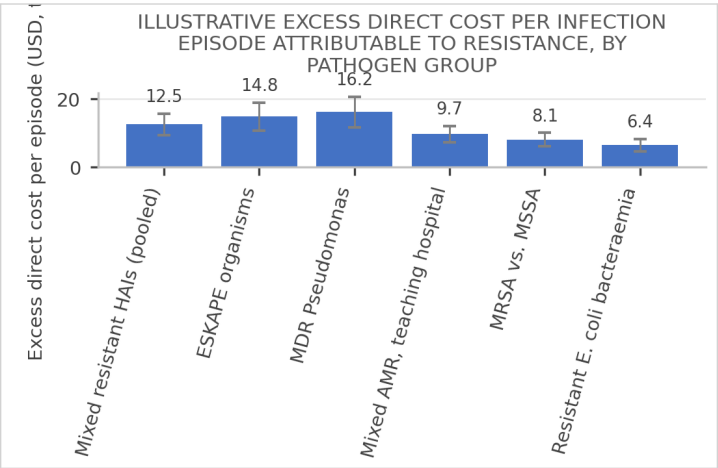
Representative per-episode excess direct medical cost and length-of-stay estimates attributable to antimicrobial-resistant infection.

Pathogen / infection type	Setting	Comparator	Reported excess direct cost or length of stay	Key reference
Mixed resistant bacterial HAIs	Multi-country hospital meta-analysis	Susceptible-organism infection	Significantly higher direct cost, longer stay, higher mortality (pooled)	Serra-Burriel et al. 2020
ESKAPE organisms (pooled)	Multi-country systematic review	Susceptible-organism infection	Positive incremental cost across all six organism groups; high heterogeneity	Zhen et al. 2019
Multidrug-resistant Pseudomonas aeruginosa	Hospital-acquired, systematic review	Susceptible P. aeruginosa infection	Significantly greater length of stay, cost, and mortality	Nathwani et al. 2014
Mixed antimicrobial-resistant infections	U.S. teaching hospital	Susceptible-organism infection	Higher hospital and societal cost, driven by excess ward/ICU length of stay	Roberts et al. 2009
MRSA bloodstream/wound infection	Matched case-control, single center	Methicillin-susceptible S. aureus	Significantly higher direct cost via longer hospitalization, readmission	Zhen et al. 2020; Filice et al. 2010
Resistant Escherichia coli bacteraemia	English national hospital cohort	Susceptible E. coli bacteraemia	Measurably higher cost and mortality burden, national administrative data	Naylor et al. 2019

Indirect and Productivity Costs

Direct medical expenditure captures only part of AMR's economic footprint; a substantial and methodologically more contested literature addresses the indirect costs of lost productivity due to morbidity, premature mortality, and informal caregiving. Rapid methodological reviews of the economic-burden-of-resistance literature find that indirect costs are reported far less consistently than direct medical costs across primary studies, both because productivity loss requires assumptions about labor-market participation and discounting of future earnings that vary substantially by country and study design, and because many cost-of-illness studies are conducted from a hospital or payer perspective that structurally excludes patient- and family-borne costs from the outset [14]. Where indirect costs have been estimated, they are frequently found to be of comparable or greater magnitude than direct medical costs once premature mortality among working-age adults is monetized using a human-capital or willingness-to-pay approach, though the two approaches can yield substantially different absolute figures for the same underlying mortality burden [15].

Representative excess direct medical cost per infection episode attributable to antimicrobial resistance, by pathogen group, drawn from hospital and administrative cost-of-illness studies reviewed here (Roberts et al., 2009; Nathwani et al., 2014; Zhen et al., 2019; Naylor et al., 2019).



A conceptual framework developed specifically to standardize how future studies quantify the economic cost of antimicrobial resistance recommends that both the direct cost of treating resistant infection and the indirect productivity cost of morbidity and mortality be estimated per antibiotic course prescribed, an approach intended to make the marginal cost of antibiotic overuse — and hence the return on investment of stewardship interventions — directly comparable across settings and antibiotic classes [16]. Applying this per-prescription framework to representative clinical scenarios, the same body of work found that the expected future cost of resistance attributable to a single antibiotic course, once the probability of resistance emergence and its downstream direct and indirect costs are incorporated, is often small in expectation for any individual prescription but aggregates to a substantial societal cost across the very large number of antibiotic courses prescribed annually — a finding with direct relevance to how antimicrobial stewardship programs should be economically justified to hospital budget holders [16]. Systematic reviews addressing the economic burden of AMR specifically in low- and middle-income countries find that indirect costs, including caregiver time and out-of-pocket household expenditure on second-line therapy, are reported even less consistently than in high-income settings, despite plausible reasons to expect that out-of-pocket financial burden falls disproportionately on households in health systems with lower

public insurance coverage [17].

National and Cross-Country Cost-of-Illness Estimates

Aggregating patient-level attributable costs to the national level requires combining incidence or prevalence estimates of resistant infection with per-episode cost data, a two-step process in which uncertainty compounds at each stage. Systematic reviews of methods used to estimate the economic burden of AMR find that published national-level estimates vary by more than an order of magnitude for comparable settings, driven primarily by differences in whether studies use hospital discharge coding, active surveillance, or modelled incidence to estimate the resistant-infection denominator, and by whether the cost multiplier applied per case is drawn from local administrative data or extrapolated from foreign, typically U.S. or Western European, unit costs [18]. A comprehensive systematic review of the burden-of-AMR literature more broadly reached a similar conclusion, finding substantial inconsistency in study populations, comparator definitions, and reported outcome metrics across the studies it reviewed, and recommending that future national cost-of-illness studies adopt more standardized attributable-cost methodology to allow cross-country comparison [2].

Where standardized national or supranational estimates have been produced, they indicate a substantial and rising cost burden. Population-level modelling for the European Union and European Economic Area estimated that infections with antibiotic-resistant bacteria were responsible for an annual burden comparable to that of influenza, tuberculosis, and HIV combined when expressed in disability-adjusted life-years, translating into direct healthcare expenditure that the same analytical framework has been used to approximate at several billion euros annually across the region [4]. A U.S. national administrative-data analysis estimated that the direct healthcare costs attributable to multidrug-resistant bacterial infections among hospitalized patients exceeded several billion dollars annually, with the largest single contributors being methicillin-resistant Staphylococcus aureus and multidrug-resistant Pseudomonas aeruginosa and Enterobacteriaceae [19]. A separate U.S. claims-based analysis tracking trends over time found that treatment costs specifically attributable to antibiotic-resistant infection had more than doubled between 2002 and the mid-2010s, exceeding USD 2 billion annually by the end of the study period, a trajectory the authors attributed to both rising resistance prevalence and rising per-episode treatment cost [20]. Comparative reviews focused on developing-country settings found that, although the absolute per-episode cost of resistant infection is typically lower in low- and middle-income countries than in high-income countries, the relative economic burden — costs expressed as a share of per-capita health expenditure or gross domestic product — is often disproportionately higher, reflecting the more constrained fiscal space within which these costs must be absorbed [17,21]. Table 2 summarizes representative national and regional cost-of-illness estimates alongside the underlying data source and methodological approach used in each.

Projected Macroeconomic Burden and Budget Impact

Beyond retrospective cost-of-illness accounting, a distinct body of work has projected the future macroeconomic and health-budget burden of AMR under continued resistance growth. Systematic reviews of AMR burden-estimation methodology note that most rigorous, empirically grounded burden estimates to date have been produced for high-income countries with strong surveillance and administrative-data infrastructure, while projections for low- and middle-income countries — which the World Bank and O'Neill Review analyses suggest will bear a disproportionate share of future AMR-attributable mortality and GDP loss — rely more heavily on extrapolation from these high-income data sources, introducing substantial uncertainty into exactly the settings where budget-impact information is most needed for health financing planning [2,1]. The GRAM collaboration's global mortality and morbidity estimates, while not themselves an economic-burden study, provide the epidemiological foundation on which several subsequent macroeconomic-burden and budget-impact projections have been built, given that mortality and disability-adjusted life-years lost are the principal drivers of both the direct healthcare-cost and indirect productivity-cost components of any national AMR budget-impact model [5].

Representative national and regional cost-of-illness and macroeconomic burden estimates for antimicrobial resistance.

Geographic scope	Metric	Reported magnitude	Data source / method	Key reference
European Union / EEA	Attributable burden of antibiotic-resistant infections	Comparable to combined burden of influenza, tuberculosis, and HIV (DALYs)	Population-level modelling, EU surveillance data, 2015	Cassini et al. 2019
United States	Direct healthcare cost, hospitalized MDR bacterial infections	Several billion USD annually	National hospital administrative/claims data	Nelson et al. 2021
United States	Antibiotic-resistant infection treatment cost trend	More than doubled 2002 to mid-2010s, exceeding USD 2 billion/year	National claims-based trend analysis	Thorpe et al. 2018
Low- and middle-income countries (pooled)	Relative economic burden vs. per-capita health expenditure	Disproportionately higher relative burden despite lower absolute per-episode cost	Systematic review and meta-analysis	Founou et al. 2017
Global (pooled, multi-organism)	Per-patient excess cost of resistant infection	Consistently positive across virtually all included studies	Systematic review and meta-analysis	Poudel et al. 2023

A systematic review and meta-analysis synthesizing the global economic-burden literature found that, despite considerable heterogeneity, per-patient excess costs attributable to resistant infection were consistently positive across virtually all included studies and organism groups, and that pooled estimates — despite the authors' explicit caution against over-interpreting a single pooled figure given study heterogeneity — supported the qualitative conclusion that AMR imposes a measurable and non-trivial excess burden on health system budgets across income settings [22]. This is consistent with earlier reviews

concluding that, notwithstanding wide variation in absolute figures, the direction and consistency of the evidence supports treating AMR-attributable cost growth as a structural, rather than transient, pressure on national health budgets that health financing projections should explicitly incorporate rather than treat as a residual uncertainty [21,1]. For health systems in Central and Eastern Europe specifically — the regional focus most relevant to this review's authorship — national cost-of-illness data remain markedly sparser than for Western Europe or North America, and the methodological reviews summarized above suggest that, absent country-specific attributable-cost studies, health ministries in this region are currently obliged to extrapolate budget-impact projections from Western European or U.S. unit costs that may not reflect local wage levels, length-of-stay norms, or second-line antimicrobial pricing, a gap this review identifies as a priority for future primary research.

Discussion

Three broad conclusions emerge from this synthesis of the cost-of-illness literature on antimicrobial resistance. First, the direct medical cost premium associated with resistant relative to susceptible infection is one of the most robust and consistently replicated findings across organism groups, health systems, and study designs, and is driven predominantly by excess hospital length of stay and intensive care utilization rather than by antimicrobial acquisition cost alone [6,9,12]. This has a direct budget-impact implication: interventions that reduce length of stay for resistant infections — including faster diagnostics enabling earlier appropriate therapy — are likely to capture a larger share of the addressable cost burden than interventions targeting antimicrobial procurement cost in isolation. Second, indirect and productivity costs remain markedly under-measured relative to direct medical costs, both because of the methodological difficulty of monetizing morbidity and premature mortality and because most primary studies are conducted from a hospital or payer perspective that excludes patient- and household-borne costs by design [14,15]. Health budget-impact analyses that rely solely on the direct-cost literature therefore likely understate AMR's true societal economic burden, particularly in health systems with substantial out-of-pocket cost-sharing. Third, the quality and standardization of national-level cost-of-illness evidence varies enormously by country income level, with the strongest attributable-cost evidence concentrated in a small number of high-income health systems with mature administrative-data infrastructure, and comparatively little country-specific evidence available for the low- and middle-income and transition economies that global macroeconomic projections suggest will bear a disproportionate share of AMR's future burden [18,17].

These findings carry direct implications for national health budget planning. Ministries of health and social insurance funds seeking to incorporate AMR into medium-term budget projections should treat resistant-infection cost growth as a structural rather than residual line item, given the consistency of the qualitative direction of effect across the reviewed literature even where point estimates vary widely [22,21]. Where country-specific attributable-cost data are unavailable — a gap this review finds to be particularly acute in Central and Eastern Europe — health economists should prioritize locally derived length-of-stay and second-line antimicrobial cost data over direct extrapolation from Western European or U.S. unit costs, since wage levels, hospital bed-day costs, and antimicrobial pricing differ substantially enough to materially affect the reliability of an extrapolated national estimate. Investment cases for antimicrobial stewardship and infection-prevention programs would also benefit from routinely incorporating the per-antibiotic-course expected-cost framework proposed in the methodological literature, which more directly connects prescribing behavior to downstream budget impact than aggregate national cost-of-illness figures alone [16].

This review is subject to several limitations. As a narrative rather than systematic synthesis, the search strategy, while targeted and every included source individually verified, cannot guarantee exhaustive coverage of a literature that spans health economics, infectious disease epidemiology, and health policy journals with heterogeneous indexing. The underlying primary literature itself is heterogeneous in costing perspective, comparator definition, discounting assumption, and currency-year, such that the point estimates cited here should be read as illustrative of a consistent qualitative pattern rather than as directly comparable figures suitable for pooling into a single global or regional cost estimate. Widely cited global projections such as the O'Neill Review and World Bank macroeconomic scenario analyses were deliberately excluded from the verified reference list because they are not peer-reviewed journal articles, but they remain influential in shaping the policy discourse this review situates the peer-reviewed evidence within, and their scenario-based methodology differs fundamentally from the empirical attributable-cost methodology of the studies reviewed here. Finally, because AMR prevalence and treatment cost are both evolving rapidly, cost-of-illness estimates drawn from studies published earlier in the past decade may understate current cost levels in settings where resistance prevalence has continued to rise.

Conclusion

Cost-of-illness methodology applied to antimicrobial resistance consistently demonstrates that resistant infections impose a measurable, non-trivial, and apparently structural excess burden on national health budgets, driven primarily by prolonged hospitalization, intensive care utilization, and second-line antimicrobial expenditure, and compounded by an indirect productivity-cost component that remains comparatively under-measured in the primary literature. The strength and consistency of this direct-cost evidence base, however, is concentrated in a small number of high-income health systems, leaving national budget planners in many low-, middle-income, and transition economies to extrapolate from foreign unit-cost data whose applicability to local wage levels and health-system financing structures is uncertain. Closing this evidence gap — through locally derived attributable-cost studies, standardized per-antibiotic-course economic frameworks, and more systematic inclusion of indirect and household-borne costs — represents a priority for health economics research if national health budgets are to plan realistically for a burden that the epidemiological evidence indicates will continue to grow rather than plateau.

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