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Economic burden of antibiotic resistance: how much do we really know?

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Abstract

The declining effectiveness of antibiotics imposes potentially large health and economic burdens on societies. Quantifying the economic outcomes of antibiotic resistance effectively can help policy-makers and healthcare professionals to set priorities, but determining the actual effect of antibiotic resistance on clinical outcomes is a necessary first step. In this article, we review and discuss the contributions and limitations of studies that estimate the disease burden attributable to antibiotic resistance and studies that estimate the economic burden of resistance. We also consider other factors that are important in a comprehensive approach to evaluating the economic burden of antibiotic resistance.

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Introduction

The introduction of antibiotics, along with public health improvements in sanitation, hygiene, and safe drinking water, was associated with an accelerated decline in infectious disease-related mortality in the USA during the 20th century [1,2]. Clinical studies have shown that the mortality reduction with antibiotics ranges from 10% for skin infections to 75% for bacterial endocarditis [3]. Antibiotics have been pivotal in treating and preventing common infections, but their overuse and misuse have contributed to an alarming increase in antibiotic resistance worldwide. With a declining choice of antibiotics, we have entered a 'post-antibiotic' era [4,5].

Several studies have shown that antibiotic-resistant infections are associated with increased morbidity and mortality as compared with antibiotic-susceptible infections; however, quantifying the disease burden with any degree of accuracy has proven difficult, and existing studies have major methodological limitations and biases [6–9]. Accurately quantifying the effect of antibiotic resistance on clinical outcomes is essential for estimating the associated economic burden. In this article, we review the existing estimates of disease and economic burdens attributable to antibiotic-resistant bacterial infections (excluding tuberculosis). We summarize the limitations of these studies, and discuss ways to more accurately quantify the disease and economic burdens attributable to antibiotic resistance.

Limitations and Reasons for Variability in Studies Estimating the Disease Burden of Antibiotic Resistance

Estimating the morbidity and mortality burden attributable to antibiotic-resistant infections is necessary before evaluating the economic burden of antibiotic resistance, as the economic burden is directly related to the disease burden. Existing cohort studies focusing on the disease burden are subject to methodological limitations, however, and these limitations make it difficult to accurately assess the true burden of disease. Previous reviews [6–9] have discussed these drawbacks in detail: they include failure to adjust for important factors such as length of hospital stay prior to onset of infection, severity of underlying illness, comorbidities, and effective antibiotic therapy (Table 1).

TABLE 1. Methodological limitations in studies assessing the disease burden attributable to antibiotic-resistant infections

Weakness	Description	Example
Failure to adjust for hospital stay prior to onset of infection	Prolonged hospitalization increases the risk of antibiotic-resistant infections and death. Lack of adjustment for LOS prior to onset of infection could result in an overestimation of the effect of resistance on clinical outcomes	Schlugen *et al.* [83] showed that excess LOS decreases when patients with hospital-acquired pneumonia are matched by LOS prior to onset of infection
Failure to adjust for severity of underlying illness and comorbidities	Patients with antibiotic-resistant infections often have underlying illnesses and comorbidities, which lead to adverse outcomes independently of resistance. Lack of adjustment for these variables could result in an overestimation of the effect of resistance on clinical outcomes	Thom *et al.* [84] showed that adjusting for severity of illness decreased the impact of appropriate therapy on in-hospital mortality
Failure to adjust for effective antibiotic therapy	The likelihood of receiving appropriate empirical antibiotic therapy may be low for patients with antibiotic-resistant infections. Inappropriate antibiotic therapy alone can have adverse clinical outcomes. Not adjusting for appropriate antibiotic therapy could result in an overestimation of the effect of antibiotic resistance on adverse clinical outcomes	In a meta-analysis, Rottier *et al.* [85] assessed the impact of inadequate antibiotic therapy on mortality associated with ESBL-producing *Enterobacteriaceae*. Studies adjusting for inadequate empirical therapy had lower ORs of mortality than those that did not (OR 1.37, 95% CI 1.04–1.82 vs. OR 2.77, 95% CI 2.13–3.60)
Failure to consider exposure as time-dependent	Time-dependent bias occurs when the time-varying nature of antibiotic-resistant infections is ignored. This can result in an overestimation of the effect of resistance on clinical outcomes	Beyersmann *et al.* [86] studied the effect of nosocomial pneumonia on LOS in ICU patients by considering nosocomial pneumonia as a time-dependent vs. a time-fixed variable. In both cases, nosocomial pneumonia prolonged LOS; however, in time-fixed analysis, the effect was overestimated (HR 0.75 vs. HR 0.36)

ESBL, extended-spectrum β-lactamase; HR, hazard ratio; ICU, intensive-care unit; LOS, length of stay; OR, odds ratio.

In addition, current estimates of disease burden vary widely because of heterogeneity in study populations, control groups, causative pathogens with different virulence and pathogenic potential, locations of infection site, definitions of resistance, and variation in follow-up time (Table 2). Recent studies [10–12] have addressed these methodological limitations by using a matched-cohort design to match patients infected with resistant strains to control patients infected with susceptible strains who have similar hospital exposure. Although these matched study designs increase the comparability of the risk profiles between infected and control patients, they do not consider the time-dependent nature of antibiotic-resistant infections.

Time-dependent bias occurs when the exposure (infection) varies over time but is analysed as though the exposure was a fixed event. Thus, patients are labelled as either 'infected' or 'uninfected' even before outcomes of interest occur [13]. Previous studies have demonstrated that disregarding the time-dependent nature of hospital-acquired infections results in overestimation of the morbidity (measured by excess length of stay (LOS)) attributable to these infections. For instance, Beyersmann *et al.* [14] studied the effects of nosocomial pneumonia LOS in intensive-care units (ICUs) by considering nosocomial pneumonia as a time-dependent vs. time-fixed variable. In both cases, the nosocomial pneumonia prolonged LOS. However, in the time-fixed analysis, the effect was overestimated: the hazard ratios considering pneumonia as time-dependent vs. time-fixed for ICU LOS were 0.75 vs. 0.36. Similarly, Barnett *et al.* [15] looked at the effects of nosocomial infection on excess LOS in a large prospective cohort study of

TABLE 2. Reasons for variability in outcomes of antibiotic-resistant infections

Variable	Description
Heterogeneity in study population	Estimates of clinical outcomes resulting from antibiotic-resistant infections vary by study population. For example, in a meta-analysis [20] comparing mortality associated with MRSA vs. MSSA bacteraemia, the pooled OR was significantly higher for MRSA. However, subgroup analysis showed that the OR varied according to the characteristics of study subjects (e.g. percentage with nosocomial infections, endocarditis, and line infections)
Inadequate sample size	Studies with small sample sizes can have wide CIs for estimating clinical outcomes
Type of control group	Estimates of the clinical outcomes of antibiotic-resistant infections differ greatly by control group. If the control group comprises uninfected patients rather than those infected with susceptible strains, adverse outcomes resulting from antibiotic resistance will be more frequent
Causative pathogens	Different pathogens vary in their virulence and pathogenic potential, which can directly affect clinical outcomes
Location of infection site	Outcomes of antibiotic resistance depend on the primary source of infection. For example, patients with bacteraemia resulting from endocarditis or intra-abdominal infection have more adverse outcomes than patients with line infections
Definitions of resistance	Definitions of resistance for certain pathogens (such as MRSA, VRE, and ESBL-positive *Enterobacteriaceae*) are straightforward. However, definitions of resistance for *Pseudomonas* or *Acinetobacter* species vary. Outcomes may differ with extent of resistance (multidrug-resistant vs. extremely drug-resistant vs. pan-drug-resistant) because treatment options differ
Follow-up time	Outcomes of antibiotic-resistant infections differ in studies with varying follow-up times: greater follow-up time makes it more likely that long-term effects of resistant infections can be assessed. For example, studies considering mortality three months after onset of infection may have higher mortality rates than studies considering in-hospital mortality only

CIs, confidence intervals; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; OR, odds ratio; VRE, vancomycin-resistant *Enterococcus*.

patients admitted to a hospital in Argentina by considering nosocomial infection as a time-dependent vs. time-fixed variable. The results demonstrated that the excess LOS attributable to nosocomial infection decreased from 11.23 days to 1.35 days after adjustment for timing of infection.

Methods for Controlling for Time-dependent Bias

To control for time-dependent bias, recent studies [16–19] have used multistate models—continuous-time models that allow individuals to randomly move among a fixed number of states—such that individuals are not assigned a fixed event time [13]. Individuals move from one state to another when events occur, and thus the composition of infected and uninfected patients changes over time. Studies that control for time-dependent bias by using multistate models report more conservative estimates of morbidity and mortality than studies that do not control for time of infection [16–18]. For instance, Macedo-Vinas *et al.* [18] estimated excess LOS for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections at a single site by using both multistate and matched-cohort models. For the multistate models, the control group comprised MRSA-uninfected patients in the same hospital ward during the same time period as the MRSA-infected patients. For the matched-cohort models, the control group comprised MRSA-uninfected patients from the hospital's administrative database matched for age, sex, and diagnosis. The authors found that excess LOS with a multistate model was 11.5 days, and LOS with a matched-cohort model was 15.3 days. However, neither type of model included adjustments for potential confounders such as severity of illness and empirical antibiotic therapy.

In addition, Lambert *et al.* [16] used multistate models in a European multicentre prospective cohort study to assess the effect of antibiotic resistance on mortality and excess ICU LOS resulting from healthcare-acquired pneumonia and bloodstream infections caused by four pathogens. The results showed that although ICU-acquired pneumonia doubled the risk of death and bloodstream infections tripled the risk, antibiotic resistance alone further increased the mortality risk by only 20%, and resistance did not increase ICU LOS significantly. This study, however, did not adjust for appropriate empirical antibiotic therapy, and the authors did not consider other confounders, such as age, sex, severity of illness, or comorbid conditions, while estimating excess LOS.

Similarly, Wolkewitz *et al.* [17] used a multistate model to assess the mortality associated with in-hospital bacteraemia caused by MRSA and methicillin-susceptible *S. aureus* (MSSA) up to 90 days after hospital admission. Although a previous meta-analyses comparing in-hospital mortality associated with MRSA and MSSA bacteraemia showed that MRSA bacteraemia significantly increased the risk of death compared to MSSA (OR 1.93, 95% CI 1.54–2.42) [20], in the Wolkewitz *et al.* study, the authors found that the odds of mortality for patients infected with MRSA compared to MSSA were not statistically significant (OR 2.45, 95% CI 0.69–8.70). However, the authors adjusted only for age, sex, and comorbid conditions of the patients, discounting other potential confounding factors, such as severity of illness and empirical antibiotic therapy.

Limitations and Reasons for Variability in Studies Estimating the Economic Burden of Antibiotic Resistance

Economic evaluations of antibiotic resistance have thus far focused on healthcare settings in high-income countries. Moreover, they have not attempted to measure the broader societal value of antibiotics, making the true economic burden of antibiotic-resistant infections difficult to quantify accurately. Disregarding the methodological limitations and reasons for variations in estimates of the disease burden attributable to antibiotic-resistant infections, several studies [12,21–57] have reported higher healthcare costs for antibiotic-resistant infections than for susceptible infections, although these estimated cost burdens vary widely (Table 3). Most studies of the economic consequences of antibiotic resistance measure the excess direct costs incurred by hospitals in managing resistant infections. These include the costs of increased hospitalization, diagnostic investigations, treatment, and infection control. However, as previous reviews have discussed [7,9], many of these studies do not adjust for inflation, and they do not consider costs from multiple perspectives (patient, hospital, and society), costs incurred by patients who died, or marginal costs (Table 4).

In addition to study design limitations, studies reporting cost estimates vary greatly. Cohen *et al.* [58] analysed the factors leading to variation in cost differences in the literature between patients with antibiotic-resistant infections (cases) and those with susceptible infections or uninfected people (controls). The authors found that cost differences were greater in studies that used uninfected control groups (instead of those with susceptible infections), studies that compared total costs instead of post-infection costs only, studies that did not match cases and controls for LOS prior to infection, and studies that measured costs as median values rather than as

TABLE 3. Excess costs attributable to infections with resistant organisms vs. infections with susceptible organisms

Resistant organism	Control	Range of excess cost[a]
Methicillin-resistant *Staphylococcus aureus*	Methicillin-susceptible *S. aureus*	$695–$29 030 [21,22,24–36]
Vancomycin-resistant *Enterococcus*	Vancomycin-susceptible *Enterococcus*	$16 711–$60 988 [40–47]
Resistant *Pseudomonas aeruginosa*	Susceptible *P. aeruginosa*	$627–$45 256 [48,49]
Resistant *Acinetobacter baumannii*	Susceptible *A. baumannii*	$5336–$126 856 [23,50–52]
Multiple organisms	Susceptible	$9372–$18 990 [12,53,54]
ESBL-producing *Enterobacteriaceae*	Non-ESBL-producing *Enterobacteriaceae*	$3658–$4892 [56,57]

ESBL, extended-spectrum β-lactamase.
[a]Includes both adjusted and unadjusted estimates; includes only studies reporting cost in US dollars.

means. The authors reported that 84% of the variance in cost differences between patients with resistant infections and control patients (either uninfected or those with susceptible infections) is explained by methodological limitations and patient-level characteristics.

Limitations in Current Cost Estimates in Europe and the USA

The overall crude economic burden of antibiotic resistance was estimated to be at least €1.5 billion in 2007 in Europe and $55 billion (http://www.tufts.edu/med/apua/consumers/personal_home_5_1451036133.pdf) in 2000 in the USA, including patient and hospital costs [59] (Alliance for the Prudent use of Antibiotics). Indirect patient costs were estimated on the basis of forgone earnings resulting from illness or premature death. For the European estimates, productivity losses accounted for 40% of the total estimated €1.5 billion, whereas productivity losses constituted 64% of the total estimated $55 billion for the USA.

Both estimates fail to consider costs for patients or payers after discharge from the hospital (except for one outpatient follow-up visit in Europe). Excess healthcare costs for Europe [59] were estimated based on longer hospital stays for patients with resistant infections compared to patients with susceptible infections, and one outpatient follow-up visit with a primary-care physician after hospitalization. The authors estimated excess LOS and mortality rates from previous studies [20,42,48,55,60–63]. These studies, however, did not use time-dependent exposure models, had small sample sizes, and some did not adjust for empirical antibiotic therapy.

Similarly, cost estimates for antibiotic-resistant infections in the USA were estimated based on a single study by Roberts *et al.* [64]. This was a single-centre, retrospective, matched case–control study involving patients infected with antibiotic-resistant organisms from both community and healthcare settings. The overall attributable costs and length of hospital stay resulting from antibiotic-resistant infections were calculated by adjusting for healthcare-associated infections, ICU care, surgery care, and severity of illness, using propensity score and regression models. Healthcare costs were measured from the hospital's perspective and calculated from hospital expenditure reports and patient resource utilization records. The Roberts *et al.* [64] study did not use time-dependent exposure models, did not adjust for LOS before the onset of hospital-acquired infection, and used uninfected patients as the control group, as opposed to patients with susceptible infections.

Factors that Affect Estimates of the Economic Burden of Antibiotic Resistance

Many factors that could influence cost estimates associated with antibiotic resistance are not considered in existing

TABLE 4. Limitations of studies assessing the economic burden of antibiotic-resistant infections

Limitation	Description
Failure to use multiple perspectives	Studies examining economic burden from only one perspective can underestimate the total effect of resistance. Such perspectives include: 1) Patient and/or payer perspective. Expenses are often incurred after discharge from hospital. Expenses include: rehabilitation costs; home health services; physician visits; travel costs for healthcare visits 2) Hospital perspective. Hospitals bear costs associated with infection control activities. Costs include: private rooms for isolation; supplies for isolation measures; delayed discharge to rehabilitation or nursing home because of requirement for private room 3) Societal perspective. Productivity losses, such as lost wages resulting from premature death or absence from work, are generally estimated in two ways [87]: (i) the human capital approach assumes no unemployment, and captures all lost productivity attributable to disease mortality by assuming that individuals who died prematurely worked full-time until the end of their working lives; this could lead to an overestimation of productivity losses; (ii) the friction cost approach captures lost productivity costs only until a worker would probably be replaced by someone currently unemployed plus transaction costs associated with identifying a replacement worker
Failure to include costs of patients who died	Existing studies typically use excess LOS to calculate costs. However, when a patient dies, costs are often truncated, and lost wages attributable to premature death are not considered. Costs are then underestimated
Failure to measure long-term marginal costs	Marginal costs are incurred by adding units of service. Unlike fixed costs, marginal costs are not easily observable
Failure to adjust for inflation	Cost estimates from different years should be adjusted for inflation by using a standard currency year and a standard currency unit if currency type varies

LOS, length of stay.

studies, including the rising prevalence of antibiotic resistance, the consequences of the unavailability of effective antibiotics where they are most commonly used, and the effect of antibiotic resistance on broader economic indicators such as national income, labour supply, and economic growth.

Existing studies estimating the economic burden of antibiotic resistance do not consider the changing epidemiology of resistance and may therefore underestimate the cost. Widespread resistance in either community or healthcare facilities prompts changes in empirical treatment options, and adverse health outcomes could lead to extreme financial constraints on the healthcare system and on society. For example, the rise in the incidence of infections caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* (mainly *Escherichia coli*) and carbapenem-resistant *Enterobacteriaceae* (CRE) is a major concern, as is the emergence of ceftriaxone-resistant *Neisseria gonorrhoea*.

E. coli is the most frequent cause of urinary tract and bloodstream infections people of all ages worldwide [5]. The Study for Monitoring Antimicrobial Resistance Trends programme, which assessed the epidemiology of ESBL producers in ICU and non-ICU patients with urinary tract infections (UTIs) between 2010 and 2012 in 55 countries, found that global ESBL rates for *E. coli* and *Klebsiella pneumoniae* exceeded 20% in both community and hospital patients (3rd Inter science Conference on Antimicrobial Agents and Chemotherapy, abstract E-1687). Similarly, the European Antibiotic Resistance Surveillance System, which includes data from 28 countries for *E. coli*, showed that the proportion of third-generation cephalosporin-resistant (surrogate marker for ESBL production) *E. coli* bloodstream infections increased from 2.7% in 2003 to 8.3% in 2009 [65]. As the proportion of UTIs caused by ESBL-producing *E. coli* increases in the community, UTI-associated bloodstream infections caused by ESBL-producing *E. coli* will also rise, requiring changes in empirical treatment choices for community-acquired bloodstream infections to carbapenems (which are currently considered to be the 'last resort' drugs for the treatment of Gram-negative infections) [66]. This will probably result in substantial cost increases just for treatment, without considering the excess costs resulting from associated morbidity and mortality. In addition, the widespread use of carbapenems for ESBL-producing organisms will augment the CRE incidence, which could further increase the economic burden, as treatment options for CRE are limited.

Existing studies also do not take into account the economic consequences of the unavailability of effective antibiotics where they are most commonly used. Without effective antibiotics to treat and prevent infections, diverse fields of medicine—including surgery, the care of premature infants, cancer chemotherapy, and transplantation medicine—will be severely hampered, and costs will probably rise. Recent studies have indicated an increasing incidence of infections caused by antibiotic-resistant bacteria among haematology and cancer patients [67], solid organ transplant recipients [68–72], and newborn and paediatric patients [73–78]. With accumulating evidence of worse clinical outcomes, including increased risk of death among patients with antibiotic-resistant infections, the threat of premature death for these groups of immunosuppressed patients is increasing. Increased morbidity and premature death among these patients will impose a significant financial burden on the healthcare system and society.

Similarly, antibiotic prophylaxis plays an important role in preventing surgical site infections. Smith *et al.* [79] calculated that if no antibiotics were available to prevent surgical site infections for patients undergoing total hip replacements, the postoperative infection rate would be approximately 40–50%, as compared with the current rate of 0.5–2% with effective antibiotic prophylaxis. Of the 40–50% of patients who would have postoperative infections, 30% would die. The number of patients undergoing replacement surgery would subsequently drop significantly, greatly increasing overall morbidity associated with hip pain, and leading to potentially large productivity losses.

Broader Approaches to Estimating the Economic Burden of Antibiotic Resistance

Most studies considering the costs of antibiotic-resistant infections take a microeconomic approach that includes health sector costs. However, Smith *et al.* [80] argue for a macroeconomic approach that includes larger economic indicators, such as national income, labour supply, gross domestic product (GDP), and economic growth.

At least one study has hypothesized that an increase in resistant infections has the potential to decrease the quality and quantity of the labour supply, as fewer individuals would contribute to the labour market, hampering production activities [81]. According to this argument, as national output depends on these labour inputs, national output—and subsequently national income—would fall. Similarly, decreased productivity can result in an increase in the cost of productivity, and, as a result, the prices of goods and services can rise, which then can decrease total GDP. With a reduction in demand for goods and services, producers will reduce the use of labour inputs, causing unemployment and reducing household income and overall economic growth.

Using a computable general equilibrium (CGE) approach, Smith *et al.* [80] demonstrated the macroeconomic consequences of MRSA for the UK. A CGE model is a quantitative

method for evaluating the effects of economic and policy 'shocks' on the economy as a whole. The model uses three economic agents to describe the economy: consumers, producers, and the government. Equilibrium represents the prices at which the level of production and consumption within each individual sector confirms that the quantity supplied equals the quantity demanded across all sectors. Antibiotic resistance is introduced into the model as a shock that alters labour supply and input productivity. Assuming that 40% of *S. aureus* isolates are methicillin-resistant, based on previous estimates in the UK, a CGE approach shows that this shock would reduce the labour supply by 0.1% and reduce GDP by 0.4%, equivalent to losses of £3 billion and £11 billion, respectively.

Conclusion

Estimating the economic burden of antibiotic-resistant bacterial infections remains a challenge. Quantifying the disease burden attributable to antibiotic resistance is an important prerequisite. Although resistance has been shown to be associated with adverse health outcomes, existing studies quantifying the disease burden have methodological limitations. Recent studies using multistate models accounting for the time-varying nature of antibiotic-resistant infections have reported more conservative estimates of morbidity and mortality; however, these studies did not address all methodological limitations, leaving the true disease burden still largely unknown. Future studies estimating clinical outcomes of antibiotic-resistant infections should address the methodological limitations by using multistate models with large patient populations in multicentre settings or by using large administrative datasets [84].

Similarly, current economic estimates of antibiotic resistance are limited in scope and do not take into account the wider societal value of antibiotics, thereby likely misestimating the true economic effects of antibiotic resistance. To better quantify the economic repercussions of antibiotic resistance, future studies must use macroeconomic approaches that consider the broader consequences of increasing resistance, including the loss of antibiotic efficacy in modern medicine. Until we overcome these challenges, the true disease and economic burden of antibiotic resistance will remain poorly quantified.

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Transparency Declaration

The authors declare no conflicts of interest.

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