



# Modelling the Future Clinical and Economic Burden of Antimicrobial Resistance: The Feasibility and Value of Models to Inform Policy

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## Abstract

Due to the increasing threat to public health and the economy, governments internationally are interested in models to estimate the future clinical and economic burden of antimicrobial resistance (AMR) and to evaluate the cost-effectiveness of interventions to prevent or control resistance and to inform resource-allocation decision making. A widely cited UK report estimated that 10 million additional deaths will occur globally per annum due to AMR by 2050; however, the utility and accuracy of this prediction has been challenged. The precision of models predicting the future economic burden of AMR is dependent upon the accuracy of predicting future resistance rates. This paper reviews the feasibility and value of modelling to inform policy and resource allocation to manage and curb AMR. Here we describe methods used to estimate future resistance in published burden-of-disease models; the sources of uncertainty are highlighted, which could potentially mislead policy decision-making. While broad assumptions can be made regarding some predictable factors contributing to future resistance rates, the unexpected emergence, establishment and spread of new resistance genes introduces substantial uncertainty into estimates of future economic burden, and in models evaluating the effectiveness of interventions or policies to address AMR. Existing reporting standards for best practice in modelling should be adapted to guide the reporting of AMR economic models, to ensure model transparency and validation for interpretation by policymakers.

## Key Points for Decision Makers

The overuse and inappropriate use of antimicrobials, and the consequent impact on the risk of antimicrobial resistance, extends well beyond the individual recipient of the antimicrobials, however the wider consequences are difficult to quantify.

Consideration of the cost-effectiveness of interventions to address antimicrobial resistance must take a One Health perspective and incorporate the costs and benefits to all sectors, including human health care, animal health care and the health of the environment.

Methods and assumptions used to model future resistance rates should be transparently and consistently reported to assist interpretation by policymakers who must determine whether the models are credible and clinically relevant.

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## 1 Introduction

“All models are wrong, but some are useful” [1]. This quote from renowned statistician George Box encapsulates the concept that no mathematical model can perfectly simulate real-life, but some well-structured and adequately populated models may estimate future scenarios with sufficient accuracy to usefully inform decision making.

Cost-effectiveness models are used to inform healthcare resource allocation by providing decision-makers with quantitative estimates of the future costs and benefits of alternative health technologies and health policies [2, 3]. Cost-effectiveness models constructed to inform funding decisions typically extrapolate healthcare resource use and health outcomes over an appropriate time horizon, based on the results of clinical trial data or non-trial data (real-world data/observational data). Forecasting models are used to estimate the impact of near-term expenditure on interventions that will prevent or reduce future economic burden due to a particular disease or public health concern [4].

This narrative overview examines the methodologies and limitations of existing models of the clinical or economic burden of antimicrobial resistance (AMR), and reflects on the value and potential role of such models in informing policy and practice. A literature search of peer-reviewed literature (Medline and Embase) was conducted in 2018 and updated in October 2021, and included the search terms ‘antimicrobial resistance’ or ‘antibiotic resistance’ (and associated MeSH terms) in addition to any of the following terms: models, modelling, cost of illness, cost-benefit analysis, cost-effectiveness models or economic models. The search was supplemented with searches of the grey literature, and included the websites of both the UK AMR review (<https://amr-review.org>) and DRIVE-AB ([drive-ab.eu](http://drive-ab.eu)), an international collaboration of 12 countries developing economic models to promote antibiotic innovation. Reference lists of relevant papers were searched to identify additional evidence sources. No date limits were set for the literature search.

## 2 The Potential Role of Burden-of-Disease Models to Inform Antimicrobial Resistance (AMR) Policy and Resource Allocation

AMR is the natural adaptation of micro-organisms to resist those medicines designed to inhibit their growth [5]. AMR is associated with increased clinical and economic costs due to suboptimal treatment or treatment failure [6–10]. Although it is agreed that AMR is becoming an increasing

burden on the healthcare system and society in general, published estimates of the clinical and economic burden vary significantly [9, 11–17]. While modelled estimates of burden would be useful for all levels of government, the ability to do this is constrained by substantial uncertainty about the future evolution of resistance in different bacterial species, and the multifarious nature of the epidemiology and transmission dynamics of antimicrobial resistance, including multidirectional relationships between human and animal health and the environment (Fig. 1) [18–21].

For governments to plan their future approach to managing AMR, an accurate estimate of the future clinical and economic burden of resistance could enable better predictions of:

- The cost-effectiveness of policies or programs (such as antimicrobial stewardship (AMS) interventions), infection control procedures, policies regarding animal or environmental use of antimicrobials to curtail the spread of resistance;
- The cost-effectiveness of new rapid diagnostic tests, directing appropriate antimicrobial treatment in a timely manner, and reducing inappropriate antimicrobial use;
- The cost-effectiveness or “value” of new antimicrobials and other types of pharmacological interventions.

## 3 Estimating Future Resistance—Modelling Methodology and Parameter Uncertainty

From the perspective of policy-makers, the validity of the structure of any economic model and its inputs must be clearly described in order for the model’s outputs to be interpreted with clarity in light of any limitations [3]. The scope and perspective of an economic analysis, as well as the type of policy questions requiring answers, are important considerations in determining the type of model required to inform policy [22]. A key aspect of models designed either to estimate the future economic burden of AMR, or to compare the cost-effectiveness of different interventions, is the prediction of future resistance [23–25].

Although there is a correlation between antimicrobial use and resistance, the emergence of AMR is largely unpredictable and can occur either via spontaneous mutations in the bacterial chromosome or much more commonly by acquisition of an existing resistance gene or genes via mobile genetic elements or transformation (gene acquisition) [18]. Acquisition of multiple resistance genes, either sequentially or bundled within mobile genetic elements, means that exposure to one antimicrobial can enable resistance to other antimicrobials, either of the same class or to an unrelated class, a process that

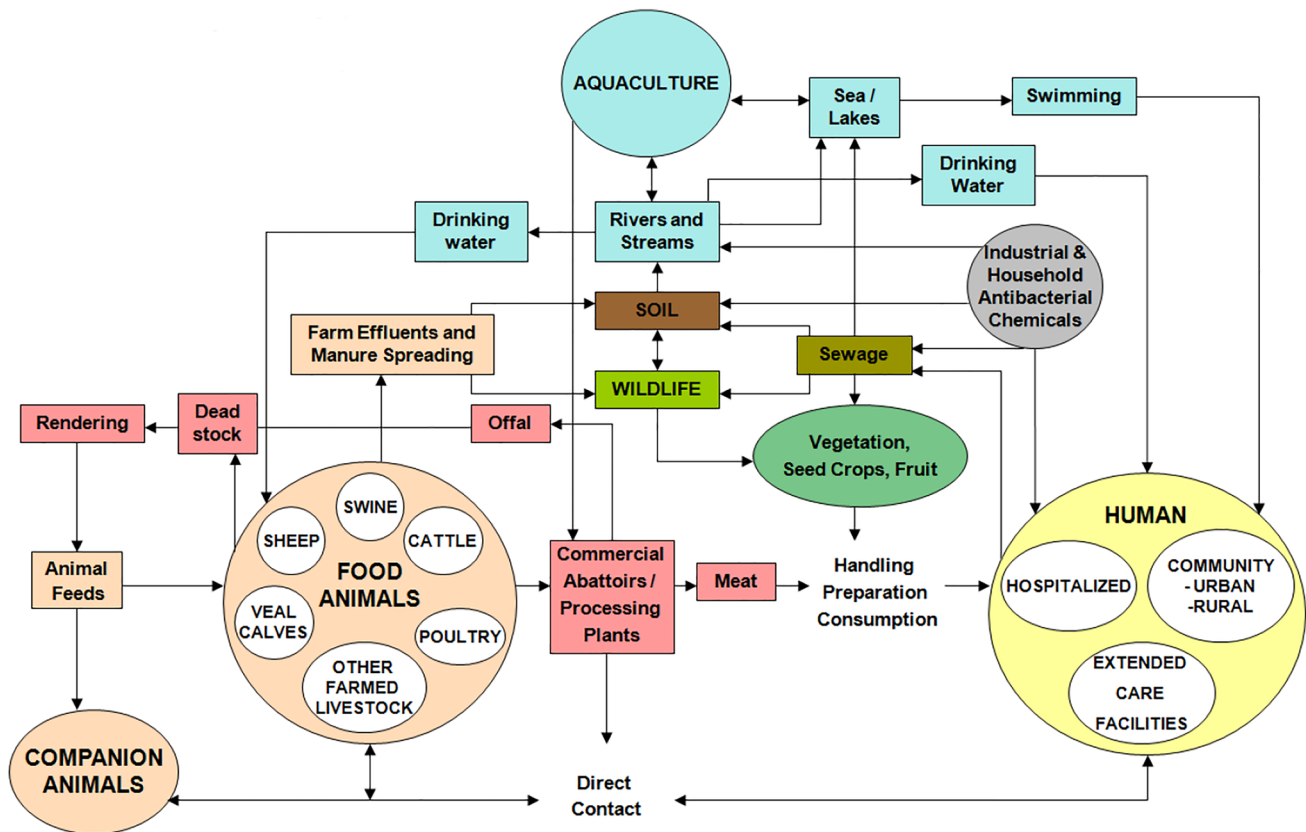


Fig. 1 Epidemiology of antimicrobial resistance. (Source: ACSQHC [18]. Reproduced with permission from the author)

is difficult to predict or model. Transmission dynamics of AMR are complex, with a myriad of factors and multidirectional pathways transferring resistant genes or bacteria between humans, animals, food and the environment [18–21] (Fig. 1).

While the link between antimicrobial use and resistance is complex, the drivers of antimicrobial use and misuse, including the volume and choice of antimicrobials used, are also multifaceted and often unpredictable, and include social, cultural, ethical, economic and political factors [26]. The inter-sector, multi-directional transmission of AMR is acknowledged in the ‘one health’ approach by policymakers in addressing the issue, whereby it is recognised that human health is dependent upon and connected to the health of animals and the environment [27].

Emergent pathogens are also unpredictable and cannot be anticipated with any certainty for the purposes of predictive modelling; their impact on global burden can be illustrated by *Candida auris*, a fungal pathogen that was first isolated from a patient in 2009, but 10 years later is a global health threat causing severe invasive infections with reported mortality rates of up to 72% [28]. The exact number of human pathogens is not known; however, a comprehensive literature survey identified over 1,400 pathogens of which

approximately 40% were bacteria, and of those bacterial species, 10% were considered emerging or re-emerging [29].

Although deterministic or compartmental models have been developed to conceptualise the emergence and spread of resistant pathogens within certain defined settings, for example, in a ward or a hospital, the complexity of transmission described above means these modelling approaches for long-term predictions of rates of resistance at a population level are highly uncertain.

#### 4 Published Models Estimating the Current and Future Economic Burden of AMR

For predictive modelling to accurately inform policy and evaluate the impact of various interventions or policies, it is first necessary to establish the baseline expected costs and outcomes without those interventions or policies in place.

A 2016 report commissioned by the UK government to model the future clinical and economic impact of antimicrobial resistance estimated that with increasing resistance to currently available antimicrobials, drug-resistant infections could kill more than 10 million people globally per year by 2050, including 22,000 per year in Oceania [11]. Although

widely cited, the methodology used in the study and lack of peer review raised questions regarding the accuracy and utility of this estimate [30]. However, despite the questionable model output, the UK report has been a useful reference to highlight the issue of AMR to governments globally.

A 2018 systematic review of published economic burden studies found only six of the 11 identified studies utilised evidence synthesis—a best-practice method for estimating model input parameter values [31]. Two of the identified modelling studies informed the UK *Review on AMR* [11]. RAND Europe, an independent not-for-profit research organisation, and KPMG UK have published overviews of their economic models developed to inform the review [16, 32]. The models projected the economic impact of different future AMR scenarios based on the change in mortality rates and the predicted impact on labour efficiency (productivity) under each scenario with varying resistance rates.

To estimate the impact of AMR on productivity, the authors of both models published their estimates of the reductions in the ‘working age’ population due to resistance-attributable mortality [16, 32]. The authors of the RAND model stated that AMR-attributable mortality is dependent upon the incidence of infections caused by the included pathogens, as well as current and future resistance rates, but they are not explicit in their calculations. They acknowledged there was limited data to estimate future AMR-attributable mortality, which was a limitation of their model. KPMG modelled mortality as a function of infection rate, resistance rate and attributable mortality rate, but justification for the attributable mortality rate was unclear, with the two scenarios for increased resistance rates being arbitrary (40% or 100% resistance across all countries for the six pathogens modelled). The uncertainty regarding the magnitude of these estimates (e.g., confidence intervals) was not provided in either model [16, 32].

The scope of both models included only three pathogens that are common causes of community- and hospital-acquired infections (*E. coli*, *K. pneumoniae* and *Staph. aureus*), in addition to HIV, tuberculosis and malaria. Future resistance rates were not based on historical AMR data, rather three arbitrary future resistance rates were projected (5%, 40% and 100%) and compared to baseline (0%). The growth rate of resistance was assumed to be a ‘one-off step’ in year 0 to year 15 for all six pathogens, rather than an increase from baseline over time based on statistical modelling of available surveillance data. Although not stated explicitly, it appears that the models assumed resistance to be defined as non-susceptible to *all* possible available treatment options when used as either monotherapy or combination therapy.

How to model the impact of AMR on the future incidence of infections is also unclear. Notably, both models informing the UK AMR review explicitly excluded costs

associated with stewardship and infection control [16, 32]. For the three common hospital pathogens, and for transmissible infections, HIV and TB, two scenarios were modelled in the KPMG model, one where incidence rates remain constant until 2050, and another scenario where current infection rates doubled between 2014 and 2050 [32]. The RAND model also assumed no change to future incidence as “there is a lack of agreement among health specialists about the future changes to incidence rates and/or their direction” [16]. The potential impact of resistance on the prevalence of HIV and TB was not discussed [16, 32].

A 2019 systematic review of economic studies reporting the additional burden of antimicrobial resistance identified 12 peer-reviewed studies in addition to the two reports by RAND and KPMG [33]. All 12 studies reported attributable costs associated with AMR from a healthcare system or hospital perspective, rather than from a societal perspective [33].

Kaier (2012) published a model that aimed to determine the economic impact of the recovery of antibiotic effectiveness, simulating different scenarios to model the burden of AMR as an externality of antimicrobial use (where reduced usage led to a decrease in AMR) [34]. The model was limited to a single hospital setting and was based on the assumption that a reduction in antibiotic use would result in a decline in the frequency of resistant bacteria. The authors themselves acknowledged that the recovery of antibiotic effectiveness differs between bacterial species; in some cases, even where a reduction in use occurs, an increase in resistance is observed [34].

In 2017, the World Bank published a report estimating the possible impact of AMR on the global economy from 2017 to 2050 [14]. A narrative description of the structure of the economic model is provided in the report, describing it as a “dynamic, multi-country, multi-sector, general equilibrium model”, with two scenarios described as “low AMR impacts” and “high AMR impacts”; however, the definition and methodology for these scenarios was not provided. No graphical representation of the model variables and their relationship was provided, nor were any details of the simulations of future resistance rates. The report estimated that without effective containment, AMR will likely reduce annual global GDP by between 1.1% and 3.8% by 2050 [14].

## 5 Using Current Data to Estimate Future Resistance Rates and Future Economic Burden

The use of currently available data to inform and forecast the future clinical and economic burden of a disease is a common approach to inform policy decision-making. There are, however, many gaps in the currently available surveillance

data of antimicrobial use and antimicrobial resistance in humans, animals and the environment. Diverse approaches have been used in published studies to estimate future resistance, and reiterated the lack of comprehensive data to inform predictive models [33].

To estimate the future economic burden associated with AMR, accurate data are needed to quantify the marginal health costs associated with the treatment or prevention of multi-drug-resistant infections (compared to treatment of susceptible infections), as well as more comprehensive surveillance data of antimicrobial use and resistance.

### 5.1 Data to Inform Marginal Costs Associated with Drug-Resistant Infections

Most published studies investigating the incremental costs of resistant infections are hospital based and have focused on a specific disease or pathogen [9]. Costs assessed in published studies have included additional investigations, drug costs, costs associated with side effects from more toxic drugs or drug combinations, length of hospital stay and increased mortality rates. A 2015 modelling study investigated the additional surgical-site infections and deaths likely with increasing resistance to antimicrobials used for surgical prophylaxis [17]. To our knowledge there are no studies that model the societal cost impact of scenarios with no effective antibiotics for procedures or interventions where antibiotics are currently used routinely, such as prophylaxis in surgery, to quantify the impact on the workforce or economy due to being unable to perform these interventions safely.

In 2014, the WHO conducted a systematic review of evidence relating to the health and economic burden of three multi-resistant organisms: *Escherichia coli* (*E. coli*)—resistant to third-generation cephalosporins and fluoroquinolones, *Klebsiella pneumoniae*—resistant to third-generation cephalosporin and carbapenems, and *Staphylococcus aureus*—resistant to methicillin (MRSA) [21]. The review found there was a lack of published studies collecting healthcare resource consumption concurrently with clinical outcomes for *E. coli*, and none for *K. pneumoniae*. Limitations in the methodology used to capture cost data were identified: data collection on healthcare resource use were mostly retrospective, often not done at the same time as the collection of clinical data, and limited to an estimate based on length of stay in hospital and the proportion requiring treatment in intensive care [21]. The magnitude of marginal costs associated with resistance is likely underestimated due to the paucity of definitive cost evidence available, especially with regard to the global and regional impact of specific multi-resistant pathogens [21].

A 2019 systematic review found data were available to allow justifiable estimates of the AMR-associated economic burden for healthcare-associated *Enterobacteriaceae* and

methicillin-resistant *Staphylococcus aureus* bloodstream infections. For all other infections, and settings, there was insufficient data to generate accurate estimates of the costs attributable to resistance [33].

### 5.2 Data on Antimicrobial Resistance and Usage Data for Statistical Forecasting Models

Extrapolating future resistance rates from available surveillance data has been used as a method to forecast the health and economic burden of resistance [24, 35, 36]. Statistical modelling methods such as interrupted time series regression are a practical modelling method using historical data and current observations to investigate the relationship between antimicrobial utilisation and resistance over time. However, this method is also limited by the comprehensiveness and completeness of available surveillance data. In addition to data gaps regarding emergence and transmissibility, there is also a lack of standardisation regarding defining and measuring AMR, further complicating the interpretation of the available data [37].

A recent statistical modelling paper suggested that an autoregressive linear model with consumption as an independent parameter was the most appropriate approach to a predictive model of future resistance [38]. Further validation of this model is required using different ‘drug-bug’ combinations, as it is not always clear that the relationship between antimicrobial use and resistance is linear for different ‘drug-bug’ combinations. Emerging research suggests a non-linear relationship is more probable, with selection pressure increasing once antimicrobial use exceeds a certain threshold [39]. Non-parametric time-series models using historical surveillance data have been used to identify non-linear relationships between population antimicrobial use and resistance burdens [39]. These methods may enable prediction of thresholds of antimicrobial consumption above which resistance to particular pathogens increases. Validation of these methods may enable improved estimates of burden in the future, in addition to setting targets for reductions in antimicrobial use.

## 6 Dynamic Transmission Models and Incorporation of Antimicrobial Consumption as an Externality

Dynamic modelling methods are used to develop mathematical representations of non-linear systems, incorporating feedback loops and multiple interdependent variables that evolve over time [40]. Dynamic models can be used to simulate the impact of an intervention at a systems level and are used increasingly to inform policy making [41–43]. They provide an explicit method to synthesise available



evidence regarding the effectiveness and costs of alternative healthcare interventions or strategies [44]. A 2018 scoping review investigated the range of published studies that used dynamic models to analyse the problem of AMR, identifying 81 studies in relation to human or animal use [45]. Only two of the 81 studies incorporated multiple host species in a shared environment, highlighting the lack of a ‘one health’ approach to modelling in the literature. The use of an antimicrobial in an individual person, a human population, or multiple animal species potentially impacts the risk of drug-resistant pathogens in that individual, or in other human or animal populations. Ideally, dynamic modelling of AMR needs to include consumption as an ‘externality’, that is, a cost or benefit associated with one person’s activity (e.g., consumption of an antimicrobial) that impacts the population who did not choose to incur that cost or benefit [46]. For example, stewardship interventions that result in prescribers utilising narrower-spectrum antimicrobials instead of broader-spectrum ones may potentially reduce the selection pressure for resistant organisms in the population.

## 7 Discussion

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. Governments globally are seeking ‘better models’ for a more accurate estimate of country-specific future burden; however, it is questionable whether sufficiently accurate estimates are possible given the substantial uncertainties regarding the transmission dynamics of AMR. The National Institute for Health and Care Excellence (NICE) in the UK is currently undergoing wide consultation in order to seek consensus among stakeholders on other methods and models for evaluating antimicrobials given the limitations highlighted here [47].

As illustrated in this review, the feasibility and accuracy of estimating long-term cost-effectiveness of new antimicrobial drugs or stewardship interventions is dependent upon being able to correlate the effect of that drug or intervention with long-term effects on resistance rates, and therefore on public health. Compared to other medication use, antimicrobial treatment is unique in that its use generates a negative externality, antimicrobial resistance, reducing the effectiveness of that drug into the future.

At a national level, antimicrobial utilisation has been used as a surrogate outcome measure for policy or stewardship interventions, with the assumption that reduced antimicrobial consumption will lead to a reduction in future resistance rates and therefore reduce the risks of treatment failure and improve clinical and economic outcomes. Comprehensive surveillance data measuring consumption across all sectors

(human, animal and the environment) is required to reduce the uncertainty regarding the correlation between usage and future resistance rates. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) has grown from 729 surveillance sites when it was established by the WHO in 2015 to 24,803 surveillance sites in 70 countries [48]. As surveillance data improves, the precision of statistical forecasting models will improve, allowing further exploration of non-linear relationships between use and resistance, as well as further research to identify possible thresholds of usage at which resistance emerges [39].

While broad assumptions can be made regarding some predictable components of resistance rates, the unexpected emergence, establishment and spread of new resistance genes limits the feasibility of models to provide governments with accurate predictions regarding the long-term cost-effectiveness of AMR policies or interventions. While models may crudely predict the immediate clinical and economic impact of antimicrobial failure in a particular clinical area, the complexity of AMR limits the utility of dynamic models in predicting future resistance rates. Even if more comprehensive antimicrobial usage and resistance surveillance data were available, there are multiple unpredictable behavioural and social factors that introduce uncertainty into dynamic models of future AMR, such as patient compliance with antimicrobial treatment and compliance with infection control methods.

The COVID-19 pandemic has illustrated how models estimating the future economic burden of a particular disease can divide political opinion, resulting in contrasting policy decisions, based on political trade-offs between economic and health outcomes. Like COVID-19, future AMR risks at a patient and population level are dependent upon both policies implemented by governments but also by human compliance and behaviour. However the COVID-19 pandemic has also illustrated that complex models that incorporate behavioural and social factors can be developed [49, 50]. Improved surveillance may reduce the uncertainty in statistical forecasting of resistance, which in turn could be used as inputs into dynamic models in the future. Expert elicitation methods have been investigated to address the fundamental challenges of predicting future resistance, with experts demonstrating relevant knowledge not captured in statistical forecasts [51]. Future modelling frameworks could employ such methods to (a) design parsimonious model structures and (b) estimate uncertain parameters.

One issue that can be fairly easily addressed is that the methods and assumptions used in models to estimate the burden of AMR, or in cost-effectiveness analyses, should be transparently reported. Without these, the policy maker is unable to judge whether the assumptions and inputs used to inform the model are credible and clinically relevant. Existing reporting standards for best practice in modelling

should be adapted to guide the reporting of AMR economic models [3].

Without consistency in reporting and transparency regarding the level of uncertainty about future resistance rates and transmission dynamics, and the future incidence of drug-resistant infections, the value of modelling to guide decision-making on which interventions will be the most cost-effective use of resources for managing AMR is limited.

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