Enumerating the Economic Cost of Antimicrobial Resistance Per Antibiotic Consumed to Inform the Evaluation of Interventions Affecting their Use

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Abstract

Background – Antimicrobial resistance (AMR) poses a colossal threat to global health and incurs high economic costs to society. Economic evaluations of antimicrobials and interventions such as diagnostics and vaccines that affect their consumption rarely include the costs of AMR, resulting in sub-optimal policy recommendations. We estimate the economic cost of AMR per antibiotic consumed, stratified by drug class and national income level.

Methods – The model is comprised of three components: correlation coefficients between human antibiotic consumption and subsequent resistance; the economic costs of AMR for key pathogens; and consumption data for antibiotic classes driving resistance in these organisms. These were used to calculate the economic cost of AMR per antibiotic consumed for different drug classes, using data from Thailand and the United States to represent low/middle and high income countries.

Findings – The correlation coefficients between consumption of antibiotics that drive resistance in *S. aureus*, *E. coli*, *K. pneumoniae*, *A. baumanii*, *P. aeruginosa*, and *S. pneumoniae* and resistance were 0·37, 0·27, 0·35, 0·45, 0·52, and 0·62 respectively. The economic cost of resistance per standard unit of quinolones, for example, was estimated at $0·87 in Thailand ($0·2 - $2·6 in best and worse-case scenarios) and $0·83 in the USA ($0·1 - $2·4).

Interpretation – The economic cost of AMR per antibiotic consumed were considerable, often exceeding their purchase cost. Notwithstanding their limitations, use of these estimates in economic evaluations can make better informed policy recommendations regarding interventions that affect antimicrobial consumption and those aimed specifically at reducing the burden of AMR.

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Research in context

Evidence before this study

In 1996, Coast et al. pointed out that the cost of antimicrobial resistance (AMR) is an important social externality that has been ignored in economic evaluations of interventions that affect antimicrobial consumption, a major failing when seeking to inform policy making as to their costs and benefits. Since then virtually no progress has been made in addressing this failing, as indicated by a literature search for articles on MEDLINE published until June 2016, using the following string: **("societal cost" OR "external cost" OR "social cost" OR "externality" OR "economic evaluation") AND (antibiotic resistance OR antimicrobial resistance OR resistance).**

Among the resulting articles, we found one that estimated the costs of AMR per antibiotic consumed in the context of a German hospital, and one cost-effectiveness analysis of antibiotic therapy in respiratory illness in primary care that incorporated a 'cost of resistance' estimate, demonstrating the decisive importance of its inclusion. Apart from these studies, none others were found dealing with the calculation of the costs of AMR associated with antibiotic consumption or incorporating such costs in economic evaluations.

Added value of this study

This study produced a menu of economic costs of AMR per antibiotic consumed for different drug classes and stratified into low/middle income and high income countries. These estimates can be applied in future economic evaluations of interventions that involve or affect antibiotic consumption for a more comprehensive and accurate assessment of the interventions' cost-effectiveness.

Implications of all the available evidence

Evidence-based policy relies on economic evaluations to allocate available resources most efficiently, but this is entirely dependent on the inclusion of pertinent costs and benefits associated with the interventions. In the two decades following the warning by Coast et al. with regards to the negative external effects of ignoring the cost of AMR, there has been little effort to address the methodological challenges pertaining to the calculation. This analysis of the cost of AMR by drug class and national income brackets provides estimates of the cost of AMR to be incorporated in evaluations of interventions affecting antibiotic consumption. This facilitates better informed decisions and policies regarding interventions that include or affect the consumption of antimicrobials and those aimed specifically at reducing the burden of AMR.

Introduction

Human antimicrobial consumption, whether or not clinically warranted, is associated with propagation of antimicrobial resistance (AMR).[1,2] Other key drivers of AMR are listed in Figure 1, notably widespread antibiotic use prophylactically, therapeutically, and as growth promoters in agriculture.[3]

Treatment of resistant infections is associated with higher costs of second line drugs, additional investigations, and longer hospitalisation.[4] Other indirect costs associated with AMR include productivity losses due to excess morbidity and premature mortality. These costs can be conceptualised as a negative externality to antimicrobial consumption accrued by all members of society, and not reflected in the market price of antimicrobials.[5,6]

In addition to curative use in infectious diseases, antimicrobials are widely used presumptively, in mass treatment programmes (anti-helminths, antimalarials), and as prophylactics in surgical procedures and alongside immunocompromising treatments.[2,7] Many other healthcare interventions such as vaccinations, diagnostics, and treatments for infectious diseases affect antimicrobial consumption, and consequently increase or decrease the risks of AMR. Economic evaluations of such interventions, however, have failed to internalise the potential costs of AMR into the analyses, leaving policymakers to intuitively consider these alongside more tangible costs and benefits in the evaluation.[4,8] This can result in uninformed decision making, as the cost of AMR is likely to be under- or over-estimated by policymakers, if it is considered at all.[4,8,9]

Coast et al. argued that the omission of the cost of AMR in economic evaluation is partly explained by the challenges to quantify it,[4] with extensive uncertainties surrounding resistance mechanisms, paucity and poor quality of relevant data, and other methodological challenges.[5,10] The (mis)perception that the impact of AMR will only be felt in future years might also deter analysts from including them in the evaluation, assuming policymakers operate with a myopic view of health gains and costs.

Policymakers and key stakeholders, however, appear increasingly concerned with AMR, with unprecedented funding being allocated to interventions to mitigate its impact. In late 2016 the UN General Assembly held a special meeting on the topic, passing a unanimous resolution from Member States committing to adopt such measures.[11] Without enumerating the cost of AMR per antimicrobial consumed, it will be difficult to determine the allocative efficiency of these investments, and particularly so in LMICs with more tangible causes of ill-health to invest in.

Therefore, despite the challenges, there is a clear need for costing the negative externality of AMR that can be affixed to the consumption of antimicrobials. The rare occasions where this has been done indicate the importance of such efforts. For example, the use of a single defined daily dose of a second or third generation cephalosporin was associated with €5 and €15 respectively in costs of AMR, in a German hospital setting.[6] The current analysis produced a menu of economic costs of AMR per antibiotic consumed for different drug classes, stratified into low/middle income countries (LMICs) and high income country settings. The output can be applied in future economic evaluations of interventions that involve or affect antibiotic consumption.

Methodology

Economic costs of resistance

The economic cost of AMR is narrowly defined as the incremental cost of treating hospitalised patients with resistant infections as compared with sensitive ones, and the indirect productivity losses due to excess mortality attributable to resistant infections. We make a fundamental conservative assumption that resistant infections replace, rather than add to the burden of sensitive infections. We estimate these direct and indirect costs for the following key pathogens:

1. *Staphylococcus aureus* (*S. aureus*) resistant to Oxacillin
2. *Escherichia coli* (*E. coli*) resistant to 3rd generation cephalosporin
3. *Klebsiella pneumoniae (K. pneumonia)* resistant to 3rd generation cephalosporin
4. *Acinetobacter baumanii (A. baumanii)* resistant to carbapenems
5. *Pseudomonas aeruginosa (P. aeruginosa)* resistant to carbapenems
6. *Streptococcus pneumonia (S. pneumonia)* resistant to penicillin.

We focus our analysis on Thailand and the United States as representatives of low/middle and high income country settings, respectively.

Direct cost to the provider: We use the product of the number of resistant infections due to each of the above organisms, and the direct medical cost attributable to resistance in the respective infections (Table 1). The number of infections and deaths per infection for the USA was obtained from the Center for Disease Control and Prevention (CDC).[12] The unit cost per infection was obtained from a detailed costing analysis carried out in a US hospital.[13] We used the most conservative estimates that adjust AMR attributable costs for sensitive infections, severity, and ICU admission. As no estimate was available for the cost of *S. pneumoniae* resistant infections, we derived it using the excess medical cost per year and the number of infections from the CDC.[12] These costs were inflation adjusted to 2016 US$ using the US consumer price index.[14]

Estimates for the number of resistant infections in hospitalised patients in Thailand were available from a 2012 study of the burden of AMR in Thai hospitals.[15] The total number of AMR attributed deaths in this paper was estimated at 38,000 but we opted for more conservative estimates in a recent study reporting approximately 19,000 AMR attributable deaths annually.[16] We obtained the unit cost per infection from the first of these studies. These costs included only those for antibiotics, therefore we used the estimated excess length of stay of 9·2 days from the US study and applied a cost of $38 per bed-day in a secondary hospital in Thailand.[17,18] Costs were adjusted to 2016 US$ by converting to US$ at the year they were reported and inflation adjusted using the World Bank GDP deflator for Thailand.

Indirect cost: Mortality figures were converted into productivity losses taking the human capital approach, by multiplying them by an assumed ten productive life years lost per death, based on a study of survival post ICU admission in Thailand, which reported similar results for high income settings,[18] with a sensitivity analysis of 5-20 productive years lost per death. The number of years lost was then multiplied by GDP per capita to generate the productivity losses per death.

Resistance modulating factor (RMf)

Human antimicrobial consumption is one of a host of factors driving AMR, and different drug classes are implicated in propagating resistance in different pathogens. The Resistance Modulating factor (RMf) approximates the proportional contribution of human antimicrobial consumption towards the total cost of AMR. Correlation coefficients were calculated to study the strength of the relationship between consumption of antibiotics assumed to be implicated in driving resistance in each pathogen, and the rates of resistance observed to their first line treatments. It was assumed that each drug class contributed equally towards resistance[19,20] (Table 2).

Data points for consumption and resistance between 2008 and 2015 were obtained from 44 countries and included total consumption in both hospital and community settings.[21] The ecological association was tested using Pearson's correlation coefficients on log transformations of the data. The lower and upper bounds of the 95% coefficient confidence intervals (CI) were used in the sensitivity analysis.

Model for the economic cost of AMR per antibiotic consumed

Putting together the costs of AMR, the RMf, and the consumption of antibiotics that drive resistance in each pathogen, we established the cost of AMR attributable to the use of a Standard Unit (SU) and a full course of eight antibiotic drug classes, in the context of Thailand and the USA. One SU is a measure of volume based on the smallest identifiable dose given to a patient, dependent on the pharmaceutical form (a pill, capsule, tablet or ampoule).[22] For example, the cost of AMR in MRSA per SU of quinolones, cephalosporins, glycopeptides, broad spectrum penicillins, and narrow spectrum penicillins that are implicated in propagating resistance in *S. aureus*, were calculated as shown in Box 1.

Box 1. The model to calculate economic cost of AMR.

Societal cost per antibiotic consumed (country specific) due to *S. aureus*

$$\frac{\textit{Total economic loss due to MRSA} \quad * \quad \textit{RMf for S. Aureus}}{\textit{Total consumption of antibiotics implicated in propagating MRSA (quinolones, cephalosporins, BSP, NSP, and macrolides)}}$$

The resulting economic costs per SU of antibiotic consumed in each pathogen were then aggregated to calculate the cumulative economic cost per antibiotic consumed for each drug class in each country, including only the infections in which the particular drug class was assumed to propagate resistance.

The outputs of the model are also presented in terms of the cost of AMR per full course of treatment. Table 3 shows examples of the number of SUs per adult full course of antibiotics for listed indications according to the British National formulary (BNF).[23] The calculation of SUs per course for all classes is presented in Supplementary Table 1. Data entry, verification, and analysis were done in Microsoft Excel 2016. Calculation of the correlation coefficients was done in R version 3·2·2 (R Foundation for Statistical Computing, Vienna, Austria). A web interface for the model where readers can vary parameter estimates and test model assumptions was developed using R-Shiny (RStudio, Boston, US).

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Results

The Resistance Modulating factor

As shown in Table 4, a positive relationship was confirmed between consumption of antibiotics assumed to be implicated in resistance, and the average resistance rates in all pathogens with correlation coefficients ranging from 0·27 in *E. coli* (p=0·07) to 0·62 in *S. pneumoniae* (p=0·0001).

Direct and indirect costs of AMR

The direct and the indirect cost due to AMR (the numerator in the model) for each of the organisms in the two countries are shown in Tables 5 and 6 respectively. The direct and indirect annual cost of AMR in Thailand due to MRSA for instance was estimated at $37 million and $165 million, respectively. After adjusting for the relative contribution of human consumption using the RMf, the direct and indirect economic loss was estimated to be $13·7 million and $61 million, respectively.

Economic cost of AMR per antibiotic consumed

Using the consumption data for each of the relevant drug classes in the denominator, the economic cost of one SU of antibiotic for each pathogen was calculated (Table 7). An antibiotic implicated in driving resistance only in *S. aureus*, for example would have an economic cost of AMR of $0·08 per SU in the Thai setting, and if a full course of the same drug consisted of 10 units this would imply a cost of $0·78.

As most antibiotics are assumed to drive resistance in more than one infection, the costs need to be aggregated for all relevant pathogens. For a broad spectrum penicillin that is assumed to drive resistance in all pathogens, for instance, the estimated cost of AMR would be $7·7 per course of 10 SU. The costs in Table 7 were therefore aggregated for each drug class where it was assumed to drive resistance in each of the organisms. Table 8 presents the cumulative economic cost per SU and per full course by drug class in contributing towards resistance in all organism/drug combinations.

Sensitivity analysis

The lower and the upper bound costs of AMR were calculated using the confidence intervals of the RMf (Table 4) and a range of 5-20 productive life years assigned to each excess death for the indirect cost of AMR. Table 9 shows the resulting range of economic cost for a SU and a full course of antibiotic consumed in Thailand and USA. Hence, in Thailand, the best case scenario would see a cost of AMR of $3·2 per course of co-amoxiclav and the worst would be $38·4.

Discussion

Evidence-based policy draws on economic evaluation to allocate available resources most efficiently,[24] but this is entirely dependent on the inclusion of all pertinent costs and benefits associated with the interventions in the analyses. This is, to our knowledge, a first attempt at estimating the costs of AMR per antibiotic consumed by drug class and across national income brackets. We chose simple and transparent methods and restricted our assessment of the costs of AMR to the current burden, rather than more uncertain future projections, and to tangible factors including only direct medical hospital costs and productivity losses due to AMR attributable deaths. Even within this restrictive framework there is much uncertainty surrounding interactions between antibiotic consumption, development of resistance, and its economic implications, but our underlying assumptions and parameter estimates were conservative.

The cost per SU of antibiotic differed between the USA and Thailand primarily as a result of higher direct medical costs and GDP per capita and lower per capita consumption of antibiotics in the USA, and higher incidence of AMR deaths in Thailand. Different epidemiological profiles such as the high burden of *Acinetobacter* associated mortality in Thailand as compared with the USA also explain the differences; these trends vary geographically and by income levels.

The costs for different drug classes also varied substantially; this is driven primarily by the degree to which they were assumed to propagate resistance in the selected infections (e.g. NSPs were only assumed to drive resistance in *S. aureus*, while cephalosporin were implicated in resistance in all pathogens in the analysis). The costs per full course were mostly determined by the number of SU per course, which for glycopeptides for instance were high (a full course of vancomycin being 56 units - four daily over 14 days, as compared with three once daily units for a full course of azithromycin).

Very few attempts have been made to quantify the cost of AMR per antibiotic consumed and internalise them in evaluations of interventions that involve or affect the use of antimicrobials. A recent study by Oppong et al. was one of the first attempts to do so in an evaluation focusing on antibiotic treatment, demonstrating the decisive impact this had on outcomes.[25] An earlier study evaluating the cost-effectiveness of malaria rapid tests used a similarly crude estimate for the cost of antimalarial resistance, also showing the large impact this had in swaying results and conclusions.[26]

Several studies have explored the correlation between antimicrobial consumption and resistance.[27–29] The correlation coefficients in the current study are smaller than prior estimates. For example, the coefficient for resistance in *E. coli* in this analysis was 0·27 (Table 4) in comparison to 0·74 from Goossens et al..[27] This could be explained by the latter using 14 European countries in contrast to 44 countries from different regions in our study. The smaller coefficients imply a conservative assessment of the cost of AMR attributable to human antibiotic consumption.

Kaier et al. derived measures of association between antibiotic consumption and resistance from a time-series analysis using a multivariate regression model with different drug classes.[30] This would be a better approach for calculating the RMf, rather than the ecological associations used here. We were restricted however by limited annual consumption data to only ten years and even sparser and more heterogeneous resistance data.

There were many assumptions and limitations in the analysis (see Supplementary Table 2). One key limitation was the inclusion of a limited number of organisms, while consumption of the same antibiotics could drive resistance in other organisms with additional costs. This and other listed limitations result in a conservative estimate of the economic costs of AMR in our model.

Taking the human capital approach to productivity losses results in much higher estimates than would have been derived using friction costs; given the context of this analysis, trying to capture the full societal costs of AMR, this was deemed appropriate. This is essentially equivalent to the widespread use of GDP/capita as a proxy for the ceiling ratio in cost-effectiveness analyses to classify interventions as cost-effective.

The direct medical costs assigned to resistant infections were derived from a single study in each country;[13] the Thai study used rudimentary costing methods, largely relying on expert opinion, while the US study relied on detailed micro-costing, and has since formed the basis for much of the cited costs of AMR. The study provided different estimates for the costs that are attributable to resistance, of which we selected to use the lowest, controlling for severity, ICU admission, and hospital acquired infections, all independently associated with higher costs.

Drug classes implicated in propagation of resistance in the respective organisms were based on limited available evidence.[20] This might explain some apparent anomalies, like the relatively low costs for NSPs, which were assumed to drive resistance only in *S. aureus*. Another reason for this anomaly relates to the entire framework of the analysis, whereby the cost of AMR is approximated from its current (or recent) estimated burden, rather than projections of what will happen if resistance to last line drugs such as carbapenem were to spread, for which there are alarming early indications. Such an approach is arguably more relevant than focusing on the present burden of AMR, but it requires many more strong and contestable assumptions.

These rudimentary estimates for the economic cost of AMR per antibiotic consumed could be improved upon in several ways in future work as better data become available. For instance, the link between human antibiotic consumption and resistance can be disaggregated into hospital vs. community use. The model can be further extended to other organisms including parasites and viruses and their varying distribution in different health sectors and geographical locations (global/regional/country/hospital/community).

Notwithstanding the numerous limitations and need for further refinements of the analysis, the outputs generated emphasise the considerable economic cost associated with AMR per antibiotic consumed, which in some cases are multiple times their purchase cost. Incorporation of these estimates in economic evaluation will better portray the true costs and benefits of interventions that affect the consumption of antibiotics and subsequently AMR, and could act as a catalyst for more efficient deployment of interventions to mitigate its effects.

Declaration of Interests:

All authors – No conflict of interest

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Tables

Table 1– Incidence and mortality of resistant infections per 100,000 in Thailand and the USA, and the direct cost per infection

	Mortality per 100,000		Infections per 100,000		Direct medical costs per infection	
	Thailand	**USA**	**Thailand**	**USA**	**Thailand (US$)**	**USA (US$)**
S. aureus	4·1	3·5	29·5	25·2	1,977	12,449
E. coli	0·9	0·2	13·3	3·3	1,150	3,108
K. pneumoniae	0·4	0·5	6·5	7·8	1,150	3,108
A. baumanii	22·4	0·2	326·9	2·3	1,944	46,438
P. aeruginosa	0·4	0·1	6·1	2·1	1,796	46,438
S. pneumoniae	NA	2·2	NA	376·3	NA	97

Table 2 - Drug classes implicated in increasing the risk of resistance in each organism

Organism (Resistance)	Drug classes implicated for propagating the respective resistance						
***S.aureus* (Oxacillin)**	Quinolones	Cephalosporins		BSP[a]	NSP[a]		Macrolides
***E. coli* (3GC[a])**	Quinolones	Cephalosporins	Glycopeptides	BSP	Aminoglycoside		Macrolides
***K. pneumoniae* (3GC)**	Quinolones	Cephalosporins	Glycopeptides	BSP	Aminoglycoside	Carbapenem	Macrolides
***A. baumanii* (Carbapenem)**	Quinolones	Cephalosporins	Glycopeptides	BSP	Aminoglycoside	Carbapenem	
***P.aeruginosa* (Carbapenem)**	Quinolones	Cephalosporins	Glycopeptides	BSP	Aminoglycoside	Carbapenem	
***S.pneumonia* (Penicillin)**		Cephalosporins		BSP			Macrolides

[a] BSP – Broad Spectrum Penicillin, NSP – Narrow spectrum penicillin, 3GC – 3rd Generation Cephalosporin.

Table 3 - Example of standard units (SU) in a prescribed course of antibiotic

Antibiotic (Drug class)	Indication	SUs in a prescribed course
Levofloxacin (Quinolone)	Community acquired pneumoniae	28
Ceftriaxone (Cephalosporin)	Syphilis	14
Co-amoxiclav (Broad spectrum penicillin)	Severe dental infections	15
Amikacin (Aminoglycoside)	Serious Gram-negative infections resistant to gentamicin	20

Table 4 - Pearson's correlation coefficient showing ecological associations between average consumption (2008-14) of drug classes implicated in driving resistance in each organism and corresponding resistance (2008-15)

Organism / resistance	Correlation coefficient (95% CI, p-values)
S. aureus resistant to oxacillin	0·37 (0·08 - 0·61, p = 0·016)
E. coli resistant to 3rd generation cephalosporin	0·27 (-0·03 - 0·53, p = 0·07)
K. pneumoniae resistant to 3rd generation cephalosporin	0·35 (0·06 - 0·59, p = 0·019)
A. baumanii resistant to carbapenem	0·45 (0·15 - 0·68, p = 0·005)
P. aeruginosa resistant to carbapenem	0·52 (0·25 - 0·72, p = 0·0006)
S. pneumoniae resistant to penicillin	0·62 (0·35 - 0·79, p = 0·0001)

Table 5 – Direct cost to the providers due to human antibiotic consumption in each resistant infection

	THAILAND					USA					
	S. aureus	***E. coli***	***K. pneumoniae***	***A. baumanii***	***P. aeruginosa***	***S. aureus***	***E. coli***	***K. pneumoniae***	***A. baumanii***	***P. aeruginosa***	***S. pneumoniae***
Total infections	18,725	11,116	15,239	36,553	6,118	80,461	10,400	24,900	7,300	6,700	1,200,000
Cost per infection	1,977	1,150	1,150	1,944	1,796	12,449	3,108	3,108	46,438	46,438	97
Direct cost (million US$)	37·0	12·8	17·5	71·0	11·0	1001·7	32·3	77·4	339·0	311·1	116·9
RMf	0·37	0·27	0·35	0·45	0·52	0·37	0·27	0·35	0·45	0·52	0·62
Direct cost due to human consumption (million US$)	13·7	3·5	6·1	32·0	5·7	370·6	8·7	27·1	152·5	161·8	72·5

Table 6 – Productivity losses due to excess deaths attributable to resistant infection

	THAILAND					USA					
	S. aureus	***E. coli***	***K. pneumoniae***	***A. baumanii***	***P. aeruginosa***	***S. aureus***	***E. coli***	***K. pneumoniae***	***A. baumanii***	***P. aeruginosa***	***S. pneumoniae***
Excess deaths	2,799	597	288	15,168	270	11,285	690	1,620	500	440	7,000
GDP/capita (US$)	5907					57466					
Indirect Cost (million US$)	165	35	17	896	15	6,485	396	931	287	253	4,023
RMf	0·37	0·27	0·35	0·45	0·52	0·37	0·27	0·35	0·45	0·52	0·62
Indirect cost due to human consumption (million US$)	61	9	6	403	8	2,399	107	326	129	131	2,494

Table 7 - Cost per Standard Unit (SU) and full course antibiotic consumed per resistant organism

	Thailand					USA					
	S. aureus	***E. coli***	***K. pneumoniae***	***A. baumanii***	***P. aeruginosa***	***S. aureus***	***E. coli***	***K. pneumoniae***	***A. baumanii***	***P. aeruginosa***	***S. pneumoniae***
Direct Cost (million US$)	14	3	6	32	6	371	9	27	153	162	72
Indirect Cost (million US$)	61	10	6	403	8	2,399	107	326	129	131	2,494
Total economic loss (million US$)	75	13	12	435	14	2,770	116	353	282	293	2,566
Antibiotics consumed (million SU)	965	774	778	682	682	4,797	4,625	4,646	3,887	3,887	4,028
Direct cost per SU	0·01	0·00	0·01	0·05	0·01	0·08	0·00	0·01	0·04	0·04	0·02
Indirect Cost per SU	0·06	0·01	0·01	0·59	0·01	0·50	0·02	0·07	0·03	0·03	0·62
Cost per SU	0·08	0·02	0·02	0·64	0·02	0·58	0·03	0·08	0·07	0·08	0·64
Cost per full course[a]	0·78	0·17	0·16	6·38	0·21	5·77	0·25	0·76	0·73	0·75	6·37

[a] *Assuming a full course comprises of 10 standard units.*

Table 8 - Cumulative cost per SU and per antibiotic course by drug class (US$)

		Quinolones	Cephalosporin	Glycopeptides	BSP [a]	NSP [a]	Carbapenem	Aminoglycoside	Macrolide
Thailand	**per SU**	0·8	0·8	0·7	0·8	0·1	0·7	0·7	0·1
	per course	21·5	10·8	38·7	11·5	3·1	14·1	13·8	0·3
USA	**per SU**	0·8	1·5	0·2	1·5	0·6	0·2	0·2	1·3
	per course	23·1	20·5	13·9	32·0	23·1	4·7	5·0	3·9

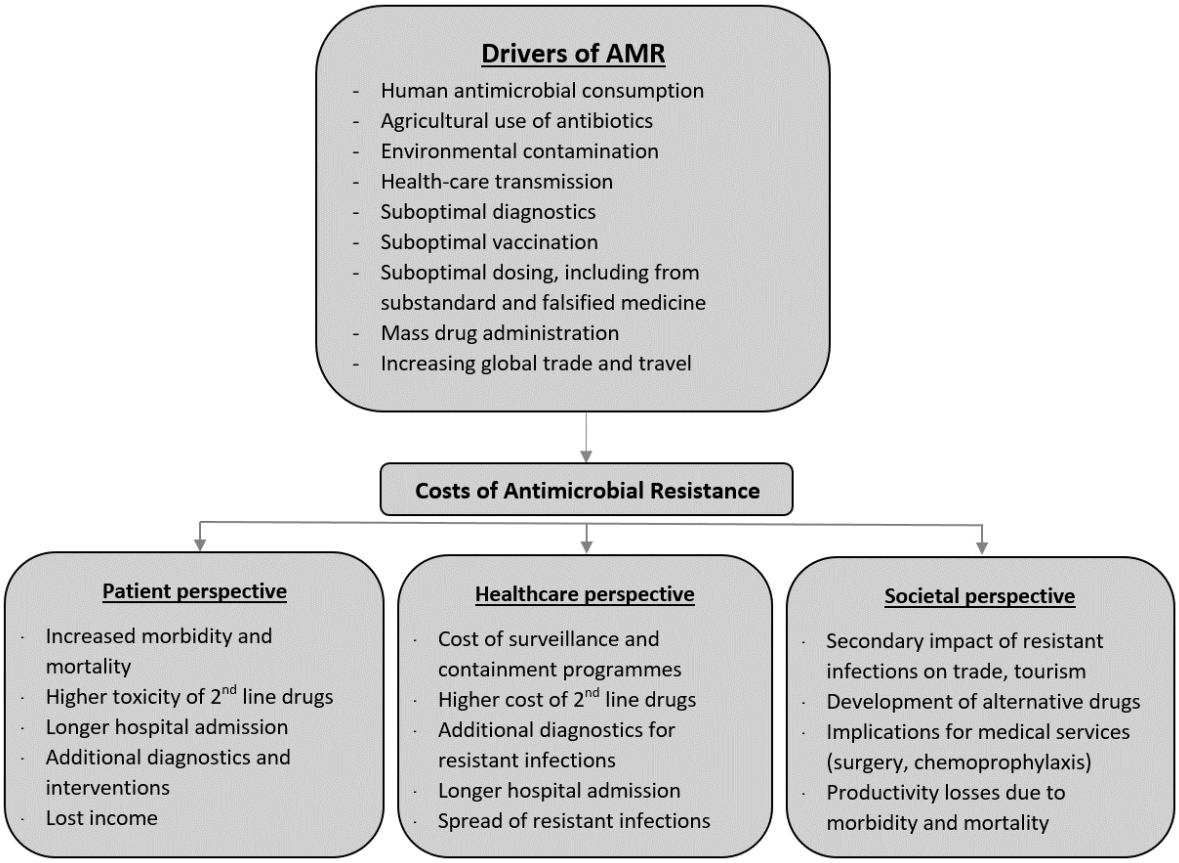
[a] BSP – Broad spectrum penicillin, NSP – Narrow spectrum penicillin.

Table 9 - Range of economic costs per full course of antibiotics using outputs from the sensitivity analysis (US$).

	Thailand		USA	
Antibiotic (Drug class)	**Cost per SU**	**Cost per full course**	**Cost per SU**	**Cost per course**
Levofloxacin (Quinolone)	0·2 – 2·6	5·9– 71·7	0·1 – 2·4	3·5 – 67·7
Ceftriaxone (Cephalosporin)	0·2 – 2·6	2·9– 35·9	0·3 – 4·0	4·3 – 56·2
Vancomycin (Glycopeptide)	0·2 – 2·3	11·2– 130·5	0·1–0·7	3·0 – 36·4
Co-amoxiclav (BSP)	0·2 – 2·6	3·2– 38·4	0·3– 4·0	4·6 – 60·3
Phenoxymethylpenicillin (NSP)	0·0 – 0·2	0·4– 9·3	0·1– 1·8	2·8 – 70·7
Meropenem (Carbapenem)	0·2 – 2·3	4·2– 47·7	0·1– 0·6	1·1 – 11·7
Amikacin (Aminoglycoside)	0·2 – 2·3	4·0– 46·6	0·1– 0·7	1·1 – 13·0
Azithromycin (Macrolide)	0·0 – 0·3	0·0 – 0·95	0·3 – 3·7	0·8 – 11·1

Figure Legends

Figure 1 - Drivers and costs associated with antimicrobial resistance. Adapted from: Holmes et al. [3] and McGowan [17]



Supplementary Material

Table 1 - Standard units per course by antibiotic drug class

Indication	Antibiotic Drug class	Prescribed Dosage	Available form	Number of pill/vial/tablets per day	Duration (Days)	SUs per course
Community acquired pneumoniae	Levofloxacin (Quinolone)	500mg twice daily	250mg tablets	4	7	28
Syphilis	Ceftriaxone (Cephalosporin)	1g daily	1g vials	1	14	14
Severe dental infections	Co-amoxiclav (Broad spectrum penicillin)	250mg thrice daily	250mg tablets	3	5	15
Serious Gram-negative infections resistant to gentamicin	Amikacin (Aminoglycoside)	15 mg/kg daily	250mg/ mL, 2mL vials	2	10	20
Clostridium difficile infection	Vancomycin (Glycopeptide)	125mg four times daily	125mg capsules	4	14	56
Streptococcal infection	Phenoxymethylpenicillin (Narrow spectrum penicillin)	250mg four times daily	250mg tablets	4	10	40
Nosocomial Pneumonia	Meropenem (Carbapenem)	1g IV thrice daily	1g vials	3	7	21
Community-acquired pneumonia, low to moderate severity	Azithromycin (Macrolide)	500 mg once daily for 3 days	500mg tablets	1	3	3

Table 2- Summary of assumptions and limitation

Assumption / Limitation	Discussion	Likely Impact
Pertaining to Cost data		
The model only takes into account the impact of mortality and direct medical costs attributable to resistant infections.	It excludes other possible direct and indirect effects such as the spread of resistant infections, other medical services that will be affected by loss of effective prophylactic treatment	Underestimating the economic cost of AMR
Only present burden is accounted for.	AMR is predicted to continue to spread, incurring ever higher tolls in future years. Models to reliably predict and quantify the future burdens are extremely challenging.	Underestimating the economic cost of AMR
The model takes into account only a subset of resistant infections.	Antibiotic consumption is likely to drive resistance in a host of other pathogens for which mortality estimates are less readily available . Further data on the incidence of other resistant infections and their associated costs could be incorporated if/when available	Underestimating the economic cost of AMR
One death was assumed to result in 10 life years.	Data on mean number of productive life years lost due to an AMR associated death are limited.	Under- or over-estimation of the economic loss data per organism.
Assumption that selected drug classes contribute equally in promoting the resistance.	There are complex mechanisms involving propagation of resistance. Hence, relative contribution intuitively, should be different.	The model can use weighing to incorporate relative contributions once better evidence is available.
The consumption data is up to 2014 and nor always available for all countries.	More recent consumption data and for a broader range of countries would have been ideal.	These data determine the RMf and act as the denominator in the model, therefore they are key drivers of the results.
The consumption data was estimated using retail and/or hospital information.	The actual consumption at the patient-level could be much lower than this estimate.	Could contribute to an underestimation of the economic cost.
The data used for resistance only represents blood samples.	Inclusion of other samples would make the data richer.	Including other samples could increase or decrease the rates and henceforth shift the cost in either direction.