RAND EUROPE

Estimating the economic costs of antimicrobial resistance

Model and Results

Jirka Taylor, Marco Hafner, Erez Yerushalmi, Richard Smith, Jacopo Bellasio, Raffaele Vardavas, Teresa Bienkowska-Gibbs, Jennifer Rubin

For more information on this publication, visit www.rand.org/t/rr911

Published by the RAND Corporation, Santa Monica, Calif., and Cambridge, UK

Preface

This report presents the findings of a study on the economic costs of antimicrobial resistance. The study has been commissioned by the Independent Review on Antimicrobial Resistance and supported by the Wellcome Trust.

This report will be of interest to government, industry and civil society actors active or interested in the field of health economics and health care. It will also be of interest to academic audiences interested in epidemiology.

RAND Europe is an independent not-for-profit policy research organisation that aims to improve policy and decision-making in the public interest through research and analysis. This report has been peer reviewed in accordance with RAND's quality assurance standards. For more information about RAND Europe or this document, please contact Jennifer Rubin (jkrubin@rand.org):

RAND Europe

Westbrook Centre, Milton Road

Cambridge CB4 1YG

United Kingdom

Tel. +44 1223 353 329

Executive Summary

Objectives of this study

Antimicrobial resistance (AMR) has increasingly been recognised as a growing global health threat (WHO, 2012), and the urgency of the AMR situation is now well accepted by many policy-makers, scientists, as well as by civil society organisations, including patients' advocacy groups. Despite growing awareness and concern, inertia appears to persist in improving stewardship of existing antimicrobials to prevent a future with more resistant bacteria (Dowling et al., 2013). For instance, in comparison with climate change, while there appears to be increasing scientific consensus about the urgency of countering the impact of global warming, this is perhaps less clear (or at least the emerging consensus is less coherent) for antimicrobial resistance.

An important gap in the evidence base for policy makers is the economic burden of AMR and the cost-effectiveness of changes to stewardship, pharmaceutical and other developments. This is because, in policy terms, it is important to be able to weigh up the range of competing budgetary demands and prioritise investments today that may bring rewards or savings, whether today or in the future. As Smith and Coast (2013a) point out, there is an incentive problem for policy makers with respect to AMR in that the burden needs to be high *now* and needs to be high enough to justify costs associated with solutions, such as restrictions in use of current drugs.

This study, commissioned in the framework of the independent review led by Jim O'Neill, aims to stimulate the discussion on the economic burden of AMR by building the evidence base for understanding that burden in two specific ways:

- First, in contrast with the country-specific examples provided above, this study presents a high-level global estimate of the current economic burden of AMR.
- Second, it assesses the potential global economic impact of AMR, under different future scenarios for the burden of AMR from the present year until 2050.

Conceptualisation of AMR and scope of the study

In our conceptualisation of the economic costs attributable to AMR, we focus on the effect of drug resistance on economic production through its negative impact on the labour supply as AMR may prevent people from engaging in economic activity. In our study AMR affects the supply of effective labour through two mechanisms. Together, these affect the production function through:

1) **Increased mortality** – deaths attributable to AMR permanently reduces the size of the working age population;

2) **Increased morbidity** – prolonged periods of sickness temporarily reduce the size of the global workforce and may, in severe cases, lead to permanent reductions in labour efficiency (productivity). This is a direct effect on the effectiveness of the working age population. In addition, increased morbidity of non-productive people may also affect the supply of labour if their condition requires the attention of a carer who would otherwise be economically productive.

In this research we focus only on the effects that AMR has on the economy through disruption of the supply of labour. We recognize that there are many other effects that could be monetised that are not covered by our pragmatic approach, which likely will result in an underestimation of the potential cost of AMR. Our estimate of the cost of AMR should therefore be considered as a conservative estimate of the cost of AMR. Below we outline the most notable limitations to the scope of our approach.

In terms of other direct costs, our approach would enable us to calculate some of the **health care costs** associated with AMR, such as those resulting from longer hospital stays for individuals with resistant infections.

In addition, it is important to bear in mind that AMR, particularly if resistance rates increase substantially, could result in further **indirect costs**. For example, people may choose *not* to undergo certain medical procedures because of the heightened risks involved. People may also refrain from undertaking certain economic activities, such as travel and trade, or experience general negative psychological effects, such as panic. In this study, we focused on the impact of AMR on overall economic output, i.e. the reduction of global economic output as a direct result of external shocks to the effective labour supply caused by AMR. Due to time constraints, budget constraints and limitations in the availability and quality of data, we do not estimate these wider costs of AMR.

Finally, estimating the **costs of action** required to tackle AMR was beyond the scope of this study.

In our conceptualisation of AMR and its associated costs, it is important to recognise the differences in the role of antimicrobial drugs in health care systems across the world. For example, in low income countries, antimicrobial drugs play an important role in treating severe infectious diseases, such as malaria or tuberculosis (TB), often at the community level, which contribute less to the burden of disease in high income countries due to their comparatively low prevalence. By contrast, health care systems in high income countries are heavily dependent on the use of antimicrobial drugs, not only for the treatment of primary infections, but also for many aspects of secondary health care, such as cancer treatment or prevention of iatrogenic infection in surgical care. Therefore, in high-income countries, hospital-acquired infections are a major concern.

Acknowledging these global differences in the use of antimicrobial drugs, the scope of our study includes both hospital-acquired infections and infectious diseases. In both categories, however, the list of conditions is non-exhaustive and, as is discussed in greater detail below, includes only a subset of

situations where AMR costs may arise.[1] For hospital-acquired infections, we include only infections caused by one of the following bacteria:

- *Escherichia coli (E. coli)*
- *Klebsiella pneumoniae (K. pneumoniae)*
- *Staphylococcus aureus (S. aureus)*

For infectious diseases, we consider only resistance to drugs for the following conditions:

- HIV
- Tuberculosis
- Malaria

The restriction in the scope of this study is necessitated by limitations in the availability and quality of data in that the bacteria and infectious diseases included in the study represent conditions on which the research team was able to identify sufficiently robust data.

Method

We developed a theoretical dynamic general equilibrium model using a system of equations to characterize the economic interactions of individual agents, divided into several AMR-specific regions. The main aim of the introduction of AMR regions in our model is to reflect the differences in the role of antimicrobial drugs in health care systems across the world. As a result, our model consists of the following five regions:

- High (this region includes all OECD, EU and EEA countries)
- Latin America (not including OECD countries in the region)
- MENA (including Middle East and North Africa)
- Eurasia (including countries from Eastern Europe to Western Pacific)
- Sub-Saharan Africa (i.e. original Low region)

In order to input the impact of AMR on the supply of labour through population and labour efficiency projections, four types of data are needed: incidence of conditions caused by the pathogens listed above, rates of resistance, AMR-attributable mortality and morbidity and future projections of incidence and resistance. Table 1 below summarises the data sources used for each of the data categories used for the baseline values of the parameters in our model.

[1] We reiterate that while the term antimicrobial resistance is most commonly associated with resistance to antibiotics, the term encompasses other types of resistance as well. One example is resistance to antivirals, such as antiretroviral drugs for HIV.

Table 1. Overview of data sources for health components of the model

	E.coli *K. pneumoniae* *S. aureus*	HIV	TB	Malaria
Incidence	ECDC reports on HAI WHO report on HAI worldwide World Health Survey	UNAIDS Gap Report	Global Health Observatory Data Repository	Global Health Observatory Data Repository
Resistance	WHO report on AMR surveillance	WHO HIV Drug Resistance Report 2012	WHO Global Tuberculosis Report 2013[2]	WHO Global report on antimalarial drug efficacy and drug resistance
Mortality/morbidity	WHO report on AMR surveillance	WHO HIV Drug Resistance Report 2012, supplemented as necessary by available research literature	WHO Global Tuberculosis Report 2013, supplemented as necessary by available research literature	WHO Global report on antimalarial drug efficacy and drug resistance, supplemented as necessary by available research literature

In order to project rates of future resistance, it is necessary to add three additional parameters to the model: future rates of resistance, future growth rate of resistance and future starting point of increase in resistance. All three are discussed in turn below.

Future scenario rates

We include three future rates of antimicrobial resistance in our projections: low (5%), medium (40%) and high (100%) – across all three bacteria and the three infectious diseases included in our analysis.

Our scenarios are constructed with a view to incorporate several key elements:

- First, following consultations with the commissioning team and external experts, we incorporate as a best case scenario a future rate that corresponds to a situation where resistance rates have been successfully kept at a low rate. To that end, our low scenario assumes 5% resistance rates.
- Second, we aim to build on existing observed rates of resistance, as much as possible. Indeed, the medium rate of resistance (40%) has already been observed in the past, though arguably, for the latest classes of antimicrobial drugs, only in a small number of cases, in a small number of countries.

[2] WHO (2013a).

- Third, we include a worst case scenario with a future rate of 100% resistance. This scenario is primarily useful from a conceptual and theoretical point of view in the absence of a more evidence-based quantified version of the 'apocalyptic' scenario referred to by the CMO.

We acknowledge that a limitation of this study is that we use the same future rates across all included countries, even though the current rates of resistance for each of the included bacteria and infectious diseases differ from each other and across countries. However, given the uncertainty in projecting future rates and the need for a high degree of geographical aggregation, we think this to be both a reasonable and pragmatic approach, which facilitates the understanding of our scenarios and interpretation of our final results. It is important to note that these are a guide, and indicator, of a plausible future, rather than precise estimates or predictions.

Future growth rate of resistance

For the purposes of our scenarios, we assume that resistance rates will increase in a one-off step from one year to another. In other words, we do not include any consideration of an S-shaped epidemic path from a baseline rate of resistance to the scenarios' final values.

Future starting points of increase in resistance: alternative scenarios

We incorporate two different starting points in our future scenarios. Taking Year 0 as the first year in the projection, we model increases in resistance to take place in Year 0 and Year 15.[3] This approach to the alternative scenarios is motivated by the fact that, in addition to expressing the differential costs of *changes* to resistance (that start in year 0), there may also be value in calculating long-term costs associated with differences in the *timing* of the change in resistance.

In addition, we add a pair of absolute resistance scenarios intended to approximate a world without effective antimicrobial therapy. This is in recognition of the fact that mortality rates used in the six basic alternative scenarios allow for some effective therapy even in the event of 100% resistance rates and, as such, these scenarios do not represent the theoretical upper bound of AMR-attributable costs. To construct these absolute resistance scenarios, we used mortality rates based on academic literature on outcomes of untreated conditions and on expert suggestions[4] and applied these to the two original 100% scenarios, i.e. sc3 and sc5, to create sc6 and sc7 respectively.

In total, we include eight future scenarios in our model to allow both horizontal and vertical comparisons. These are captured in Table 2 below.

---

[3] Note that Year 0 refers to the model being calibrated to economic data in 2011. The demographics and labour health components refer to year 2010, which are projected forward at intervals of 5 years. This seeming lack of consistency is due to lack of comparable data. However, assuming that preferences of agents do not change dramatically between 2010 and 2011, and being a calibrated model, we believe that these years are approximately close enough to match.

[4] For a full discussion of the sources of these absolute resistance mortality rates, please refer to Appendix B.

Table 2. Future resistance scenarios

	Rate of Resistance	Starting Year of Resistance	
		Year 0	Year 15
Baseline	0%	sc0	
Alternative	Current Rates	sc00	
	5%	sc1	
	40%	sc2	sc4[5]
	100%	sc3	sc5[6]
Absolute resistance	100%	sc6	sc7

The baseline in this model is 0% resistance rate, i.e. a world with no antimicrobial resistance. This baseline is included so that, in addition to observing any differences in the costs of AMR stemming from differential changes to rates of resistance and the timing of their occurrence, absolute costs of individual scenarios can also be expressed. The baseline is followed by six alternative scenarios.

The first, scenario 00 reflects *current* rates of resistance observed for the three included bacteria and the three included infectious diseases, which are assumed to continue at a constant rate until Year 40. As such, this status quo scenario corresponds to the 'business as usual' situation. Scenarios 1, 2 and 3 increase the current rates from 5% to 40% and 100%, respectively, starting from year 0. Scenarios 4 and 5 assume that the *current* rates of resistance persist until year 15, but increase thereafter to 40% or 100%. In other words, in the first 15 years of the model's projections, the results for scenarios 4 and 5 are identical to those of scenario 00, and thereafter diverge.

Assumptions about future incidence rates

With respect to the incidence of conditions affected by drug resistance, we assume they remain constant until 2050. We recognise that this assumption may be unrealistic as incidence rates will likely change over time. This will affect the overall estimate of the model. However, there is a lack of agreement among health specialists about the future changes to incidence rates and/or their direction and we did not identify any authoritative projections of the most likely changes in incidence rates. Therefore, in the absence of better data, it is necessary to assume that the incidence of conditions affected by resistance remain constant over time. The only exception to this assumption are our projections pertaining to malaria in scenarios that incorporate a substantial rise of resistance, i.e. sc2 and above. In these scenarios, we assume that future changes in resistance will be accompanied by changes in incidence rate and base these changes on available historical data.

[5] Until Year 15, current rates of resistance are assumed.

[6] Until Year 15, current rates of resistance are assumed.

Calibration of the model to economic data

To estimate the cost of AMR, the theoretical model is calibrated to economic data within each AMR zone and its bi-lateral trade flows with neighbouring zones. National level economic data is required to apply the model to the existing economic landscape. Thereafter, it is expected that the increase in antimicrobial resistance will have a negative impact on the economy by diminishing the size of its workforce, and deteriorating the quality of its human capital. The economic data is collected into a Social Accounting Matrix (SAM), which is a square matrix of rows and columns (Pyatt and Round 1985). Each represents a debit and credit account of the various financial transactions in the economy, including trade accounts with other regions. The principle of double-entry accounting requires that for each account in the SAM, expenditures must equal revenues.

Population projections: a cohort-component model

We base the growth of the labour force and its efficiency on current projections of AMR, assuming no change in resistance, as well as demographic projections for the possible future scenarios with varying rates of resistance. We generate the demographic projections using input data from the United Nations and an adapted version of Chapin's cohort-component model (Hunsinger n.d.).

The cohort-component model starts with the base population in 2010 and is categorised for each region by age and gender. The base population subsequently evolves by applying assumptions on mortality, fertility and migration. The outcome of the model is a projection of the population by (5-year) age and gender groups up to 2050, applied to each of the five regions. In essence, the cohort-component model characterises population change according to a 'natural' increase (births minus deaths) and net-migration (in-migration less out-migration).

Labour Efficiency Model

To calculate the AMR-related efficiency units of labour, we draw mainly on morbidity data collected for various AMR related conditions that are prevalent in the five regions. For instance, an episode of drug-resistant malaria will reduce productivity of a unit of labour by keeping workers away from work by a number of additional days. Thus, in our model, labour efficiency is based on subtracting a number of days (normalized to a year) from the baseline yearly efficiency level; AMR-attributable lost days is for a combination of the adult workers and child population.

Findings

To estimate the cost of AMR, we examine six alternative scenarios and two absolute resistance scenarios (as previously discussed) which are compared with a baseline scenario of 0% resistance. In interpreting the results of our model, it is important to keep in mind that the values calculated in each scenario represent how much lower the global (or regional) GDP would be at a particular point of time in comparison with a world that would not be affected by antimicrobial resistance. Since deaths attributable to AMR permanently reduce the size of labour force, which influences future population sizes, the effects of AMR accumulate over time. This explains why the costs of AMR increase over time, even if rates of resistance remain constant.

In year 10, the world working age population would be lower by 2 to 92 million people compared to a world without AMR. By year 40, the total loss in people in productive age rises to a range from 11 million to 444 million. It is worth noting that Eurasia would experience the biggest loss in people (in absolute terms).

Table 3 reports how the working age population in each region evolves over time with different AMR scenarios. In year 10, the world working age population would be lower by 2 to 92 million people compared to a world without AMR. By year 40, the total loss in people in productive age rises to a range from 11 million to 444 million. It is worth noting that Eurasia would experience the biggest loss in people (in absolute terms).

Table 3. Working age population loss relative to 0% resistance, by AMR Zone, in million people, per year

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
10	High	-0.55	-0.13	-1.03	-2.64	-0.55	-0.55	-7.94	-0.55
	Eurasia	-1.11	-0.63	-7.47	-20.29	-1.11	-1.11	-48.31	-1.11
	MENA	-0.07	-0.02	-0.28	-1.41	-0.07	-0.07	-3.07	-0.07
	Sub	-0.75	-0.83	-8.94	-14.40	-0.75	-0.75	-29.74	-0.75
	Latam	-0.06	-0.02	-0.96	-1.52	-0.06	-0.06	-3.21	-0.06
	World	**-2.53**	**-1.64**	**-18.68**	**-40.26**	**-2.53**	**-2.53**	**-92.27**	**-2.53**
20	High	-1.09	-0.26	-2.05	-5.23	-1.34	-2.13	-15.64	-4.79
	Eurasia	-2.57	-1.32	-15.80	-42.87	-6.03	-12.92	-100.55	-28.19
	MENA	-0.21	-0.09	-0.69	-3.46	-0.33	-1.00	-7.47	-1.97
	Sub	-1.92	-2.07	-22.19	-35.13	-7.17	-10.75	-69.50	-19.59
	Latam	-0.15	-0.05	-2.08	-3.32	-0.63	-0.94	-6.86	-1.86
	World	**-5.94**	**-3.79**	**-42.82**	**-90.01**	**-15.49**	**-27.74**	**-200.01**	**-56.39**
40	High	-2.14	-0.65	-4.00	-10.18	-3.32	-7.15	-30.09	-19.67
	Eurasia	-5.47	-3.22	-31.67	-85.60	-23.99	-55.87	-197.52	-127.68
	MENA	-0.50	-0.22	-1.59	-7.78	-1.24	-4.98	-16.72	-10.49
	Sub	-5.55	-6.84	-62.50	-97.54	-42.78	-64.37	-185.94	-114.44
	Latam	-0.34	-0.16	-4.27	-6.81	-2.83	-4.35	-13.80	-8.81
	World	**-14.00**	**-11.09**	**-104.02**	**-207.91**	**-74.17**	**-136.71**	**-444.08**	**-281.09**

In terms of economic costs, sc3 projects the world economy in Year 40 to be 1.2% smaller compared to the baseline. In absolute terms, this equals to an annual loss of 3.9 trillion USD. Broken down by region, sc3 projects the yearly cost range from 0.8% of GDP in High to 5% in Sub-Saharan Africa. The costs are even higher in the absolute resistance scenario with no effective therapy – global annual costs in Year 40 are projected to be 3% of GDP (2.3% in High, 10% in Sub-Saharan Africa).

Table 4. Yearly world GDP loss relative to 0% resistance

Scenario Results								
Percent GDP Loss, per year								
Year	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
5	-0.01%	0.00%	-0.04%	-0.11%	-0.01%	-0.01%	-0.3%	0.0%
10	-0.03%	-0.01%	-0.10%	-0.23%	-0.03%	-0.03%	-0.6%	0.0%
20	-0.06%	-0.02%	-0.22%	-0.52%	-0.11%	-0.21%	-1.3%	-0.4%
30	-0.10%	-0.04%	-0.36%	-0.86%	-0.26%	-0.50%	-2.2%	-1.1%
40	-0.14%	-0.06%	-0.51%	-1.23%	-0.40%	-0.83%	-3.1%	-1.9%
Loss in bn USD 2011, per year								
Year	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
5	-10.9	-3.7	-38.4	-91.1	-10.9	-10.9	-239.3	-10.9
10	-28.6	-9.8	-101.2	-240.2	-28.6	-28.6	-625.2	-28.6
20	-95.2	-32.8	-338.6	-804.9	-177.8	-323.4	-2,055.1	-593.6
30	-224.7	-80.1	-809.9	-1,927.7	-576.9	-1,116.8	-4,860.0	-2,399.7
40	-453.7	-188.0	-1,647.7	-3,926.8	-1,282.0	-2,668.0	-9,807.9	-5,978.0

Table 5. Percent GDP loss relative to 0% resistance, by AMR zone, per year

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
10	High	-0.03%	-0.01%	-0.06%	-0.16%	-0.03%	-0.03%	-0.47%	-0.03%
	Eurasia	-0.02%	-0.01%	-0.11%	-0.30%	-0.02%	-0.02%	-0.72%	-0.02%
	MENA	-0.01%	0.00%	-0.05%	-0.21%	-0.01%	-0.01%	-0.49%	-0.01%
	Sub	-0.06%	-0.07%	-0.77%	-1.22%	-0.06%	-0.06%	-2.62%	-0.06%
	Latam	-0.01%	0.00%	-0.14%	-0.23%	-0.01%	-0.01%	-0.49%	-0.01%
	World	**-0.03%**	**-0.01%**	**-0.10%**	**-0.23%**	**-0.03%**	**-0.03%**	**-0.59%**	**-0.03%**
20	High	-0.07%	-0.02%	-0.13%	-0.34%	-0.09%	-0.14%	-1.03%	-0.29%
	Eurasia	-0.05%	-0.02%	-0.24%	-0.64%	-0.11%	-0.23%	-1.55%	-0.43%
	MENA	-0.05%	-0.02%	-0.15%	-0.52%	-0.06%	-0.13%	-1.23%	-0.23%
	Sub	-0.14%	-0.14%	-1.55%	-2.45%	-0.88%	-1.69%	-5.05%	-2.32%
	Latam	-0.03%	-0.01%	-0.30%	-0.51%	-0.10%	-0.15%	-1.10%	-0.27%
	World	**-0.06%**	**-0.02%**	**-0.22%**	**-0.52%**	**-0.11%**	**-0.21%**	**-1.33%**	**-0.38%**
40	High	-0.16%	-0.05%	-0.31%	-0.78%	-0.25%	-0.52%	-2.31%	-1.40%
	Eurasia	-0.13%	-0.06%	-0.54%	-1.39%	-0.42%	-0.92%	-3.37%	-2.04%
	MENA	-0.12%	-0.04%	-0.36%	-1.18%	-0.26%	-0.72%	-2.80%	-1.53%
	Sub	-0.30%	-0.34%	-3.14%	-4.97%	-2.52%	-4.17%	-9.99%	-6.88%
	Latam	-0.08%	-0.03%	-0.67%	-1.17%	-0.45%	-0.73%	-2.55%	-1.50%
	World	**-0.14%**	**-0.06%**	**-0.51%**	**-1.23%**	**-0.40%**	**-0.83%**	**-3.06%**	**-1.87%**

Table 6. GDP loss by AMR Zone, in bn USD 2011, per year

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
	High	-20.1	-4.7	-37.9	-96.8	-20.1	-20.1	-291.7	-20.1
	Eurasia	-5.7	-2.9	-33.6	-89.8	-5.7	-5.7	-217.0	-5.7
10	MENA	-0.7	-0.2	-2.6	-10.1	-0.7	-0.7	-23.3	-0.7
	Sub	-1.5	-1.7	-18.4	-29.2	-1.5	-1.5	-62.7	-1.5
	Latam	-0.6	-0.2	-8.8	-14.3	-0.6	-0.6	-30.6	-0.6
	World	**-28.6**	**-9.8**	**-101.2**	**-240.2**	**-28.6**	**-28.6**	**-625.2**	**-28.6**
	High	-56.1	-13.2	-106.1	-270.7	-68.2	-106.9	-809.3	-225.9
	Eurasia	-27.6	-11.9	-135.0	-354.4	-62.6	-128.7	-858.6	-237.7
20	MENA	-3.7	-1.4	-12.5	-42.5	-5.0	-10.8	-100.1	-18.5
	Sub	-5.3	-5.4	-58.4	-92.5	-33.4	-63.8	-190.6	-87.5
	Latam	-2.5	-0.9	-26.7	-44.9	-8.7	-13.2	-96.5	-24.0
	World	**-95.2**	**-32.8**	**-338.6**	**-804.9**	**-177.8**	**-323.4**	**-2,055.1**	**-593.6**
	High	-200.7	-58.7	-381.3	-970.1	-308.6	-646.6	-2,866.6	-1,731.6
	Eurasia	-192.4	-87.1	-824.0	-2,127.3	-636.9	-1,414.6	-5,163.9	-3,137.1
40	MENA	-21.5	-7.9	-66.7	-217.0	-48.3	-132.0	-514.8	-281.4
	Sub	-25.8	-29.0	-268.4	-424.8	-215.6	-356.8	-854.0	-587.6
	Latam	-13.3	-5.4	-107.3	-187.7	-72.7	-118.0	-408.7	-240.3
	World	**-453.7**	**-188.0**	**-1,647.7**	**-3,926.8**	**-1,282.0**	**-2,668.0**	**-9,807.9**	**-5,978.0**

It is important to stress that the numbers above represent annual costs, rather than one-off costs. Since AMR costs continue to accrue over time as population changes, the annual costs will never be the same in two consecutive years. For instance, in Year 10 in sc3, High countries are projected to lose 97 billion USD. In Year 9 the costs borne by these countries will be lower while Year 11 costs will be higher.

Given this compounding effect, it is possible to calculate the cumulative costs of AMR. Unlike the annual costs presented above, these represent the total of costs over the duration of a given scenario. The cumulative cost associated with the worst-case scenario based on current mortality rates, sc3, is 49.4 trillion USD. To put this value into perspective, this is roughly the equivalent of three quarters of the annual global GDP. In the same scenario in the High region alone, the projected cumulative cost of 14.2 trillion USD is only slightly lower than the current GDP of the entire European Union. The worst absolute resistance scenario results in a cumulative cost of 125 trillion USD, i.e. roughly double the current annual global GDP. Lastly, even the continuation of the current situation, sc00, is estimated to result in a cumulative global cost of 5.8 trillion USD, which is broadly comparable to the current GDP of Germany and the United Kingdom combined.

Table 7. Cumulative GDP loss over 40 years, trillion USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
High	-2.9	-0.8	-5.6	-14.2	-4.1	-7.6	-42.1	-18.9
Eurasia	-2.1	-0.9	-9.4	-24.4	-6.4	-13.4	-59.2	-28.6
MENA	-0.3	-0.1	-0.8	-2.7	-0.5	-1.3	-6.4	-2.6
Sub	-0.3	-0.3	-3.5	-5.5	-2.4	-4.0	-11.2	-6.3
Latam	-0.2	-0.1	-1.5	-2.5	-0.8	-1.2	-5.5	-2.4
World	-5.8	-2.1	-20.7	-49.4	-14.1	-27.5	-124.5	-58.9

In addition, it is possible to calculate the average GDP loss attributable to AMR over a given period of time. Thus, on average over a forty year horizon, the world GDP loss runs between USD 53 billion to 3 trillion per year (in terms of 2011 values, reported in Table 8) The main regions affected by AMR are Eurasia, the High region and, to a lesser extent due to its comparatively lower income, Sub-Saharan Africa.

The upper bounds of these ranges are driven by costs projected in the absolute resistance scenarios. Their first configuration, i.e. onset at Year 1, results in average global costs of 3.1 trillion dollars, 152% higher than the results of the basic 100% scenario. Interestingly, the size of this increase varies quite substantially across individual AMR zones. By far the biggest increase is observed in the High region (197%), which suggests that the absence of effective therapy could be particularly impactful in areas with comparatively high utilisation of health care services. The other configuration of the absolute resistance scenarios, sc7, results in smaller average costs due to its onset in Year 15. Nonetheless, the costs in this scenario are 114% higher than in the corresponding basic scenario.

Table 8. Per year GDP loss attributable to AMR, by region (average over 40 years)

	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
High	-73.2	-18.9	-138.8	-353.8	-101.7	-189.9	-1,051.9	-473.1
Eurasia	-52.1	-22.2	-234.9	-610.5	-159.6	-334.1	-1,481.2	-714.9
MENA	-6.3	-2.2	-20.3	-67.3	-12.5	-31.9	-159.1	-65.1
Sub	-8.1	-8.3	-86.7	-137.4	-59.6	-100.0	-279.9	-157.8
Latam	-4.1	-1.5	-37.1	-63.7	-19.5	-30.6	-138.1	-60.6
World	**-143.8**	**-53.1**	**-518.3**	**-1,233.9**	**-353.3**	**-687.4**	**-3,112.6**	**-1,472.8**

Discussion

The main message that can be derived from the results of our model is clearly consistent with existing studies, both empirical and theoretical, on antimicrobial resistance. The current costs attributable to AMR are not necessarily large, as such do not represent a sizeable burden on the world economy and therefore may not translate into a sense of urgency. In stark contrast with the current costs of AMR, the estimated future costs of AMR have the potential to be large, imposing a substantial cost to the world economy. This is apparent in all of our scenarios that project the estimated costs of 100% resistance rates, regardless

of timing of the onset of higher resistant rates. These estimated costs are even greater in the two absolute resistance scenarios where no effective drug therapies remain, which would affect all regions of the world.

In conclusion, these findings draw attention to the fact that it is not the current burden of AMR that is driving the urgency to recognise antimicrobial resistance as an important public health issue. Instead, it is the possibility of future costs that are orders of magnitude higher that render AMR a challenge of utmost importance.

Several qualifications should be added to the discussion of this study's results and their interpretation, even though these qualifications do not alter the main message of our modelling work. First and foremost, it is important to bear in mind the limited scope of our study, i.e. hospital-acquired infections caused by three bacteria and three infectious diseases. As such, our final numbers capture only a part of the whole picture and underestimate the likely extent of AMR costs.

Several additional factors further contribute to what may be perceived as surprisingly low current costs of AMR and should be highlighted here. In contrast with existing studies, our model includes only costs resulting from the disruption of the supply of effective labour and does not include any other kinds of costs, such as increased health care costs. Second, our model uses AMR-specific mortality rates, rather than overall mortality from resistant infections. In other words, we do not express how many people die from resistant infections in total. Rather, we consider how many more people die because their infections are resistant compared to if they were susceptible. In general, the guiding principle of setting the parameters for our model and making assumptions (as discussed below) was to adopt the most conservative parameters and assumptions. This may have led to an underestimation of the total costs of AMR. Nonetheless, these estimates are anchored in the most reliable data available and present and can therefore be linked to AMR with a reasonable degree of certainty. Lastly, throughout this study, we had to make a series of assumptions to address data availability issues and uncertainties about the future, which may occur in reality.

Moreover, it is important to keep in mind that the full potential costs of AMR amount to a world without effective antimicrobial drugs, with serious repercussions for modern health care as we know it. This is consistent with the recent recommendations made by Smith and Coast (2013a) to the UK Department of Health, which articulated a perspective in which resistance is not simply an infectious disease issue but rather "a surgical issue, a cancer issue, a health system issue." The removal of effective antimicrobial drugs from health care systems would represent a significant disruption to modern medicine, which would likely provoke behavioural changes among the wider population. Unfortunately, the estimation of these indirect costs was beyond the scope of this study and thus could not be included in our analysis. Therefore, even the estimates from the absolute resistance scenarios in our model should be understood only as part of the overall potential costs of AMR. This is a crucial point to emphasise and further reinforces the main message from our model that current observed costs of AMR are very small in comparison with the potential future ones.

Table of Contents

Figures

Tables

Boxes

Acknowledgements

The authors would like to thank the Review Team and the Wellcome Trust for commissioning this research project.

We would also like to thank Hala Audi and Anthony McDonnell of the AMR Review Team for their helpful and constructive feedback on earlier versions of this report, for their careful reading of interim reports and progress updates and for advice and support throughout the research project.

We are grateful to all those who contributed to the research efforts leading to this publication – Gavin Cochrane, B Raffan Gowar, Kristy Kruithof, Joanna Miler, and Mafalda Pardal.

In addition, we are indebted to the following individuals for their valuable insights throughout the research project: Adrian Alsop (ESRC), Naomi Beaumont (ESRC), Ranjit Roy Chaudhury (National Institute of Immunology), Virander Singh Chauhan (International Centre for Genetic Engineering & Biotechnology), Stephen Dobra (UK Department of Health), N.K. Ganguly (Indian National Science Academy), Courtney Gidengil (RAND Corporation), Jonathan Grant (King's College London), Libby Green (British Embassy in Beijing). Alan Johnson (Public Health England), Rajesh Kapur (Department of Biotechnology, Government of India), KPMG research team led by Yael Selfin (KPMG London), Grace Lang (ESRC China), Ramanan Laxminarayan (Center for Disease Dynamics, Economics & Policy), Nafees Meah (ESRC India), Melinda Moore (RAND Corporation), Himanshu Negandhi (Smolensk State Medical Academy), Piero Olliaro (WHO), Marcelo Pilonetto (Laboratório Central do Estado do Paraná), Sarah Rappaport (AMR Review Team). John Rex (Astra Zeneca), Sukhdeb Sinha (Government of India), Lisa White (Oxford University), Peter Wilson (UCLH), and Neil Woodford (PHE).

Last but not least, we would like to express our thanks to our quality assurance reviewers, Fay Dunkerley and Stijn Hoorens, for their thoughtful comments and suggestions on earlier versions of the draft.

1. Introduction

The term antimicrobial resistance (AMR) refers to situations in which microorganisms are not inhibited by antimicrobial drugs (Davies, 2012). While most commonly associated with resistance to antibiotics, AMR encompasses a range of pathogens, including bacteria, mycobacteria, viruses, fungi, and parasites (Falagas and Karveli, 2006). Drug resistance renders the treatment of patients infected by these pathogens more difficult, or in extreme cases even impossible, and as such results in greater length of illness and higher mortality. Of growing concern is the emergence of multiple drug-resistant (MDR) microorganisms, which are not susceptible to agents from several classes of drugs at the same time (WHO, 2014a).[7]

Resistance occurs as a result of mutations and transfer of DNA in microorganisms. As time progresses, the use of antimicrobial drugs helps resistant organisms grow more dominant through the process of natural selection, as their susceptible counterparts are killed (Davies, 2012). Resistance emerged soon after the introduction of antimicrobials – for instance, first cases of resistance to penicillin were documented as early as the mid-1940s (Chambers and De Leo, 2009). For several decades, the existence of AMR represented a relatively manageable problem because new classes of drugs were developed that were able to replace antimicrobials that had been rendered ineffective by AMR. However, the discovery of new classes of antibiotics has slowed down substantially in recent decades, increasing the possibility that new drug development will no longer be able to stay ahead of trends in resistance (Silver, 2011).[8] This scenario, coupled with the absence of improvements in the stewardship of existing antimicrobials, could result in the eventual unavailability of effective antimicrobial drugs.

Accordingly, AMR has increasingly been recognised as a growing global health threat (WHO 2012), and the urgency of the AMR situation is now well accepted by many policy-makers, scientists and by civil society organisations, including patients' advocacy groups. AMR was identified by the 2013 World Economic Forum as one of the greatest risks globally to human health (World Economic Forum, 2013), and, in 2013, the Chief Medical Officer for England, Dame Sally Davies, dedicated part of her annual

[7] Related terms that are used to capture instances of resistance to multiple drugs include extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria. XDR generally refers to more severe cases of MDR, while PDR refers to instances of non-susceptibility to all drugs in all categories. For a definitional discussion of these terms, see, for example, Magiorakos et al. (2012).

[8] This is not meant to suggest that there have been no advances in new antimicrobial drug development. For a recent example see Eyre (2014).

report to the rise of antimicrobial resistance (Davies, 2013). More recently, Prime Minister David Cameron announced the establishment of an independent review commission, led by economist Jim O'Neill, to "set out a plan for encouraging and accelerating the discovery and development of new generations of antibiotics" (Department of Health, 2014).

1.1. The economics of AMR

Despite growing awareness and concern, inertia appears to persist in improving stewardship of existing antimicrobials to prevent a future with more resistant bacteria (Dowling et al., 2013). For instance, in comparison with climate change, while there appears to be increasing scientific consensus about the urgency of countering the impact of global warming, this is perhaps less clear (or at least the emerging consensus is less coherent) for antimicrobial resistance.

An important gap in the evidence base for policy makers is the economic burden of AMR and the cost-effectiveness of changes to stewardship, pharmaceutical and other developments. This is because, in policy terms, it is important to be able to weigh up the range of competing budgetary demands and prioritise investments today that may bring rewards or savings, whether today or in the future. As Smith and Coast (2013a) point out, there is an incentive problem for policy makers with respect to AMR in that the burden needs to be high *now* and needs to be high enough to justify costs associated with solutions, such as restrictions in use of current drugs.

According to Smith and Coast's assessment of what galvanises action, the economic case for investment has not yet been made as existing estimates of the current economic burden of AMR are comparatively low. For example, the annual cost to the US health care system of antibiotic-resistant infections is currently estimated at between US$ 21 billion and US$ 34 billion (Spellberg et al., 2011). Smith et al. (2005) estimated current losses attributable to AMR in the UK at 0.4% to 1.6% of real GDP. Their estimate included costs that extend beyond the health care system, such as losses in labour supply and labour productivity. These estimates represent substantial costs to governments and communities. However, while these costs are substantial, they do not outweigh those of other important contemporary challenges that governments are striving to address, such as climate change (Smith and Coast, 2013a).[9] It is nonetheless safe to assume that, in the extreme, the potential future costs of a world without effective antibiotics would be much larger than the cost of anti-microbial resistance today; however, it is currently not clear to what extent, or how quickly, the future burden of anti-microbial resistance will grow.

[9] Climate change is often used as a comparison because, similarly to AMR, it represents a collective action problem with a strong intertemporal dimension. In both cases, people's behavior at present affects their ability to behave in a certain way in the future.

1.2. Objectives of this study

This study, commissioned in the framework of the aforementioned O'Neill Review, aims to stimulate the discussion on the economic burden of AMR by building the evidence base for understanding that burden in two specific ways:

- First, in contrast with the country-specific examples provided above, this study presents a high-level global estimate of the current economic burden of AMR.
- Second, it assesses the potential global economic impact of AMR, under different future scenarios for the burden of AMR from the present year until 2050.

In order to achieve these aims, this report is structured as follows: Chapter 2 sets out the scope of the study and describes the different parameters of our approach. Chapter 3 provides a short summary of our methodological approach, and outlines the study's assumptions and limitations. Chapter 4 outlines the individual parameters of the model, which can be broadly divided into two categories – health parameters and economic parameters. Chapter 5 presents the main findings from our economic modelling work. Chapter 6 presents the results of additional calculations and sensitivity analyses conducted to complement the basic scenarios of future AMR trends. Chapter 7 comprises a discussion of the project's findings, the implication of these findings for current and future action and also offers additional comments on the interpretation of this study's findings, bearing in mind its scope, limitations and inherent assumptions. Lastly, Chapter 8 concludes by bringing together the main points from all of the sections of the report. This final chapter recognises that this study is but one contribution to discussions around the economic burden of AMR, though hopefully one that may have a catalysing influence, and suggests areas for further research. Additional information, including detailed descriptions of our methodology and data sources, is presented in appendices annexed to this report.

2. Conceptual approach and scope of the study

2.1. Type of costs covered by the study

In our conceptualisation of the economic costs attributable to AMR, we focus on the effect of drug resistance on economic production through its negative impact on the labour supply as AMR may prevent people from engaging in economic activity. In our model AMR affects the supply of effective labour through two mechanisms. Together, these affect the production function through:

1) Increased mortality – deaths attributable to AMR permanently reduces the size of the working age population;
2) Increased morbidity – prolonged periods of sickness temporarily reduce the size of the global workforce and may, in severe cases, lead to permanent reductions in labour efficiency (productivity). This is a direct effect on the effectiveness of the working age population. In addition, increased morbidity of non-productive people may also affect the supply of labour if their condition requires the attention of a carer who would otherwise be economically productive.

2.1.1. Costs outside of the study's scope

In this research we focus only on the effects that AMR has on the economy through disruption of the supply of labour. We recognize that there are many other effects that could be monetized that are not covered by our pragmatic approach, which likely will result in an underestimation of the potential cost of AMR. Our estimate of the cost of AMR should therefore be considered as a conservative estimate of the cost of AMR. In the remainder of this section, we outline the most notable limitations to the scope of our approach.

In terms of other direct costs, our approach would enable us to calculate some of the **health care costs** associated with AMR, such as those resulting from longer hospital stays for individuals with resistant infections. Interestingly, these increased health care expenditures may, to some extent, offset the overall decrease in economic output associated with AMR. They themselves contribute to GDP because the time in hospital requires work and represents consumption of a good in the form of health care. However, because our approach is designed for a high level, aggregate view of the regions and the world, we are unable to comment further on the extent to which the positive contribution to GDP of increased provision of healthcare services offsets the losses to society from decreased labour productivity as a result of AMR.

In addition, it is important to bear in mind that AMR, particularly if resistance rates increase substantially, could result in further **indirect costs**. For example, people may choose *not* to undergo certain medical procedures because of the heightened risks involved. People may also refrain from undertaking certain economic activities, such as travel and trade, or experience general negative psychological effects, such as panic.

In this study, we focus on the impact of AMR on overall economic output, i.e. the reduction of global economic output as a direct result of external shocks to the effective labour supply caused by AMR. Due to time constraints, budget constraints and limitations in the availability and quality of data, we do not estimate the wider costs of AMR. Nevertheless, the narrative presented in Chapter 7 considers the results of this project in the context of potential wider societal costs and discusses possible future research areas that may result in greater understanding of these indirect costs.

Finally, estimating the **costs of action** required to tackle AMR was beyond the scope of this study.

2.2. Infectious diseases and bacterial infections covered by the study

In our conceptualisation of AMR and its associated costs, it is important to recognise the differences in the role of antimicrobial drugs in health care systems across the world. For example, in low income countries, antimicrobial drugs play an important role in treating severe infectious diseases, such as malaria or tuberculosis (TB), often at the community level, which contribute less to the burden of disease in high income countries due to their comparatively low prevalence. By contrast, health care systems in high income countries are heavily dependent on the use of antimicrobial drugs, not only for the treatment of primary infections, but also for many aspects of secondary health care, such as cancer treatment or prevention of iatrogenic infection in surgical care. Therefore, in high-income countries, hospital-acquired infections are a major concern. The incidence of hospital-acquired infections in low income countries may exceed the incidence in high income countries, but the relative contribution of hospital-acquired infections to the burden of diseases compared to other infectious diseases is much lower in low income countries (WHO, 2011). Middle income countries share some antimicrobial use characteristics with both high and low income countries.

Acknowledging these global differences in the use of antimicrobial drugs, the scope of our study includes both hospital-acquired infections and infectious diseases. In both categories, however, the list of conditions is non-exhaustive and, as is discussed in greater detail below, includes only a subset of situations where AMR costs may arise.[10] For hospital-acquired infections, we include only infections caused by one of the following bacteria:

- *Escherichia coli (E. coli)*
- *Klebsiella pneumoniae (K. pneumoniae)*

[10] We reiterate that while the term antimicrobial resistance is most commonly associated with resistance to antibiotics, the term encompasses other types of resistance as well. One example is resistance to antivirals, such as antiretroviral drugs for HIV.

- *Staphylococcus aureus (S. aureus)*

For infectious diseases, we consider only resistance to drugs for the following conditions:

- HIV
- Tuberculosis
- Malaria

The restriction in the scope of this study is necessitated by limitations in the availability and quality of data in that the bacteria and infectious diseases included in the study represent conditions on which the research team was able to identify sufficiently robust data. We recognise that this will necessarily result in an underestimation of the overall costs of AMR. For example, the WHO has identified seven bacteria as being of international concern[11] but gaps in data do not allow us to incorporate all of them in our model.

However, we are reasonably confident that the conditions covered in our work yield a good representative picture of the burden of AMR. Our selection includes bacteria that have been frequently identified as major public issues in the available academic literature and have featured prominently in the policy debate surrounding AMR. While methicillin-resistant *S. aureus* (MRSA) might now be considered as a somewhat lesser threat than in recent years, it remains a high-profile health issue. In addition, our inclusion of *K. pneumoniae* and *E. coli*, i.e. two Gram-negative bacteria, ensures that our approach takes into account types of bacteria that have been described as being of utmost priority (Nicasio et al, 2008; Kollef et al., 2011).

Similarly, for infectious diseases, our scope is also driven by data availability and we consider resistance to treatment for HIV, tuberculosis and malaria. All three conditions are recognised as major sources of ill health and contributors to weak economic growth (Global Fund, 2014; Bhutta et al., 2014). And represent three of four disease-specific programmes noted by the 2014 WHO report on AMR (WHO, 2014a).[12] However, as above, this restriction to the consideration of antimicrobial resistant for only three conditions will result in an underestimation of the overall costs of AMR.

[11] These are: *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae, Nontyphoidal Salmonella, Shigella species, and Neisseria gonorrhoeae*.

[12] The fourth one is influenza.

3. Method: A dynamic general equilibrium model

We developed a theoretical dynamic general equilibrium model using a system of equations to characterize the economic interactions of individual agents. A CGE model approach is the most accurate way to capture the effects of policy changes on the economy as it incorporates the inter-dependencies between the different components of an economic system. In essence, this type of model views the many markets of goods and inputs as an interrelated system, whereby values at equilibrium for all variables are simultaneously determined. Its aim is to mimic the interactions between the main components of an economic system, including consumption, production, investment, trade, as well as labour and capital inputs (for further information, see Dervis et al. (1982); Shoven and Whalley (1992); Lofgren et al. (2002) and many others). Our model is based on three types of weak inequality conditions that are satisfied simultaneously: zero profit, market clearance and income balance. These are solved as a mixed complementarity problem with Arrow–Debreu equilibrium (Mathiesen, 1985; Rutherford, 1995, 1999).

General equilibrium models are now widely used tools for empirical analysis. They are predominantly used for analysing policy issues, such as income distribution, trade policy, environmental policy, structural adjustments to external shocks, growth and structural changes, government tax (subsidy) policy, and others. They have also gained ground recently in Health Economics in application to HIV/AIDS, Malaria, anti-microbial resistance (AMR), pandemic influenza and non-communicable disease (Borger et al., 2008; Dixon et al., 2004; Kambou et al., 1992; Rutten and Reed, 2009; Smith et al., 2009; Yerushalmi et al., 2014).

There are other modelling approaches, such as partial equilibrium models (e.g., total factor productivity approaches) that may, in principle, be sufficient modelling the economic costs of AMR. However, these models only examine the *direct* effect of a component while keeping all other effects fixed. If we, however, believe that the endogenous inter-linkages between the various markets are an important element in the analysis, and that the *indirect* effects are sizeable, then general equilibrium models are needed. For example, partial equilibrium techniques do not include issues such as decreasing returns to effective units of labour. In those cases, additional deaths occurring as a result of AMR might not be matched with the increase in demand for labour. GDP and consumption per capita could, therefore, rise in the event of an even faster growth in wages due to non-linear labour market pressures. Alternatively, changes to AMR in one region will have spill over effects on other regions, even though other regions may not be directly affected, as a result of the interdependence between the regions. These kinds of issues cannot be accounted for with partial equilibrium models.

3.1. Overview of the model

We developed a multi-region model that is divided into AMR-specific regions r. As we discuss in the next section, the purpose of having different AMR regions is to enable a more realistic characterisation of how AMR affects the population, labour efficiency, production and hence, welfare.

Generally speaking, general equilibrium models view the many markets for goods and inputs as an interrelated system, whereby all values at equilibrium for all variables are simultaneously determined. Figure 1 illustrates the general layout of our model.

In each AMR region, there are two main types of agents (shown as orange squares): (1) firms that produce goods, and (2) representative agents that consume goods. There are also three main markets (shown as green circles): (1) a product market for buying/selling goods and services, (2) a factors market for hiring/renting labour and capital inputs,[13] and (3) capital markets that generate investment for the next period. Finally, arrows show the direction of demand.

For example, in each AMR region, profit maximizing firms demand inputs from the factor markets (i.e., labour and capital) and compare these costs with the revenue they expect to earn from selling final goods in the product market or exporting to markets abroad. This forms the production-side of the economy.

Simultaneously, consumers in the AMR regions are endowed with labour and capital, which they offer as inputs in the factors markets. Consumers demand a bundle of goods and services produced in the AMR regions or imported from abroad to maximize their utility, subject to their budget constraint. This forms the demand-side of the economy for goods and services. In equilibrium, prices adjust so that equilibrium must hold and demand equals supply.

To simplify the model and limit the number of necessary assumptions, we aggregate the consumption and production of the public sector (including healthcare services) with that of the private sector.[14] Our focus is to link the different AMR scenarios and the effective-labour supply for each AMR region, which will affect the production and consumption in that region. Furthermore, each AMR region has a different sensitivity to the various AMR scenarios.

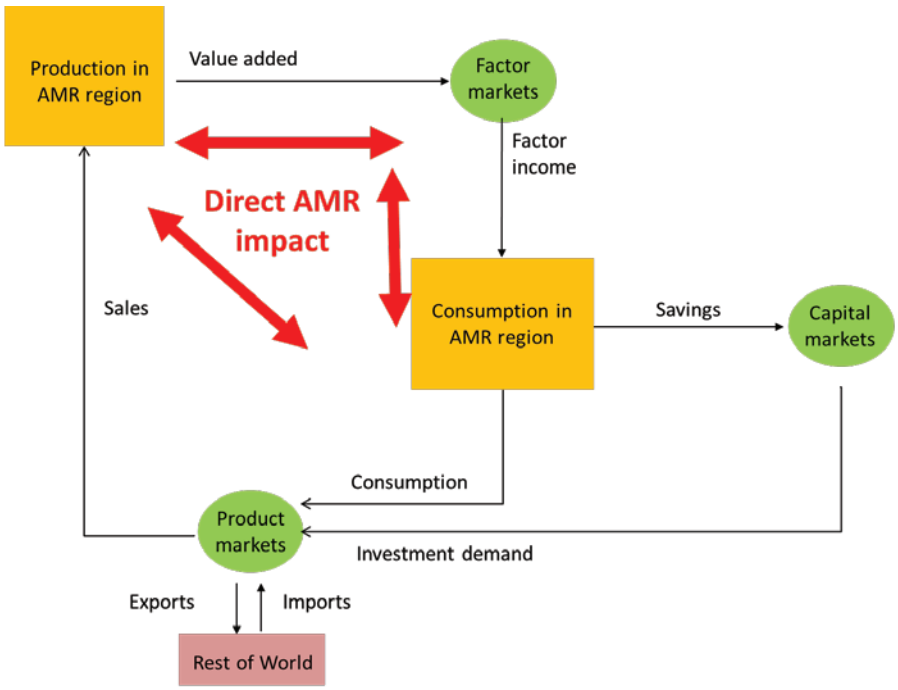
As a general equilibrium model, the model captures both the direct and indirect economic effects of AMR. The key feature of our model (shown as the red arrows in Figure 1) is the introduction of AMR health status by region. A reduction in the labour efficiency means that a region loses labour resources, which directly reduces the production possibilities of an economy. Firms will, therefore, produce less and consumers will consume less, resulting in decreased welfare overall. There are, however, also indirect effects that are captured in this model. First, even though AMR could hit one region, because of the bi-lateral trade linkages between all regions, this could have a detrimental indirect effect on all other regions, simultaneously. Second, an increase in AMR would also indirectly affect investment, which would project

[13] Note these include intermediate demand from other goods/services produced, hence product markets are combined with final (consumer) demand and intermediate (other firm) demand.

[14] There is no need for a government, for example, since we do not focus on healthcare policies that the government might, or might not, adopt to counteract a negative AMR scenario.

a region onto a lower economic growth path, for two main reasons. First, because we assume a Leontief consumption-savings function (i.e., fixed proportion), both directly decline proportionately when, for example, the labour supply of a region falls. Second, investment requires a combination of labour and capital inputs. But when major demographic changes occur, it alters the labour to capital ratios, hence their marginal productivity and relative prices. Optimal investment will therefore adjust accordingly to account for the fall in the production possibility frontier compared to the baseline.

Figure 1. A schematic representation of the Dynamic CGE model



3.2. AMR in the model

As explained in Chapter 2, in our model AMR affects the supply of effective labour and therefore the production in a region through two mechanisms, increased mortality and morbidity.

In a region *r*, output in sector *i* consists of goods and services Y_{ir}, that are produced by capital K_{ir}, other inputs N_{ijr}, (*e.g.*, intermediate inputs from sector *j*), and effective labour L_{ir} (i.e., a labour input adjusted for efficiency units). Thus, production is modelled as a function of $Y = F(K, N, L)$, where subscripts *i* and *r* are omitted for simplicity.

Similar to the method used by Yerushalmi et al. (2014) in a different context for the study of malaria, for each time period *t*, the model assumes that effective labour supply is adjusted for efficiency units by $L_{r,t} = \bar{L}_{r,t} \cdot E_{r,t}$, with the physical supply of labour input $\bar{L}_{r,t}$, and efficiency of labour $E_{r,t}$ growing at a rates of $g_{r,t}$ and $e_{r,t}$, respectively, based on the AMR scenario.

The effective labour for region r therefore progresses over time by:

$$L_{r,t+1} = \bar{L}_{r,0}(1 + g_{r,t}) * E_{r,0}(1 + e_{r,t}) \quad (1)$$

The model then generates long-run GDP and household income projections for the AMR-specific regions, according to changes in AMR levels, which it then compares to a baseline projection of no change to current AMR levels.

Equation (1) shows the two components of the effective labour supply, for each AMR region: demographic factors and labour efficiency. To address the first component (demographic factors), we develop a cohort-component model that estimates the size of the working age population and the overall population, such that changes to AMR levels will have an effect on the size of the workforce and the population, which directly affects the supply of workers in the economy (i.e. a resource). To address the second component (efficiency), we develop a labour efficiency model that links the health status of adults and children in the population with the number of days lost (or gained) by the workers, such that an increase in resistance levels raises the number of lost working days because adults are themselves ill. However, the number of lost working days also rises by the number of days workers are required to care of their ill children. Finally, these two models are inter-linked because increases to resistance levels also change the composition of the population (i.e. the number of adults relative to children). This also affects efficiency because the proportion of lost days caring for a child or for a worker being ill herself changes.

3.3. Additional model description

The model is a multi-regional model whereby each region has bi-lateral trade with all other regions, simultaneously. World prices are, therefore, determined globally by the model, and each region has an effect on all the other regions. Larger regions will have larger effects compared to smaller regions. This is different from the small-open economy (SOE) health models in which countries cannot affect world prices, but rather take them as given (Smith et al., 2005; Yerushalmi et al, 2014).

In each AMR-specific region, firms produce a single good using a multi-level,[15] differentiable, constant return to scale production function that combines factor inputs (i.e. capital and labour) with intermediate goods. The model uses a constant elasticity of transformation function to split production into domestic production and exports. Then, domestic production is combined with imports to form the final Armington good (Armington, 1969).[16]

The representative agent in each AMR region is assumed to be rational with a locally, non-satiated preference and demands for final Armington goods. Thus, subject to disposable income, the representative agent in each AMR region maximizes a continuous, multi-level, utility function. First, we assume a Ramsey type utility function, which imposes a fixed share between savings and a consumption bundle (Ramsey 1928). This is an appropriate function for a recursive dynamic model, because agents are assumed to be myopic and do not alter their consumption-savings behaviour in anticipation of future

[15] Multi-level functions mean that they are a combination of different functions stacked together to form a more complex function. Breaking them into levels makes it simpler to analyze and describe.

[16] The Armington assumption allows for cross-hauling, thus allowing for product differentiation between imports and exports of similar goods.

events. Second, subject to the net-savings disposable income, the representative agent maximizes a typical Cobb-Douglas utility function (Cobb and Douglas, 1928).[17]

As previously discussed, the government has no active role in the model because of our assumption that the government maintains its current methods (i.e., policies) towards providing the public good. Therefore, the public and private sectors are aggregated together, which simplifies the model, reduces the number of assumptions necessary and increases transparency.[18]

Finally, a virtual investment firm "builds" new capital stock for the next period by demanding some Armington final inputs in fixed proportion. Capital is accumulated under the assumption of a competitive capital market. This means that the purchase price of one unit of new capital is equal to the rental earnings of that unit, plus the value of the remaining capital sold in the subsequent period (net of depreciation).

3.4. Model dynamics

We assume that agents are myopic, rather than forward-looking, and solve the model sequentially (i.e. recursively). Stock variables are therefore updated exogenously at each period, based on forecasts from the demographics and efficiency health components. In the application of this study, simulations are based on a total period of 40 years.[19] An exception is the process of capital accumulation, which occurs through endogenous links with previous-period investment.

We use a recursive, rather than a forward-looking model, because we do not believe that agents, in real life, account for the potential AMR scenarios and change their behaviour accordingly today. Instead, we believe that agents act reactively, and need to adapt to a new AMR situation as it arises along the time horizon of the model.

3.5. Model limitation for estimating the AMR costs

In addition to scope limitations, presented in section 2.1.1, there are several assumptions behind our model that have a further limiting effect on its ability to estimate AMR costs. Our model assumes a consistent rational agent with fixed preferences over time. For example, we do not allow for a change the consumption behaviour when a person is sick (e.g., has less appetite for food) but rather change consumption through changes to income and relative goods prices. In 'real life', however, we recognize

[17] This implies a substitution elasticity of one between the various goods in the aggregate consumption bundle, which is a standard assumption in the literature.

[18] This would not be the case if we were to build scenarios in which the government directly reacts to changes in AMR. In this current model, the government continues at business as usual and only indirectly reacts to AMR due to, for example, lower tax revenues or a fall in the supply of goods.

[19] This number of years was selected strategically by the research team in collaboration with the commissioning team in order to a) have enough time to capture a generation of workers with improved health when they were children, and yet b) not be so long as to be irrelevant for policy makers.

that AMR changes could also affect the way in which agents demand goods. As outlined in section 2.1.1, we do not consider changes to behaviour as a result of fear, panic, or different preferences that are a result of changes to risk of illness or mortality.

Our model, furthermore, assumes full employment, and does not consider the interaction between mortality, unemployment and leisure. This is done to simplify the model and reduce the level of complexity.

4. Applying the theoretical model to AMR

This section provides an overview of individual parameters of the model. It is divided into two broad categories: health and economic/demographic variables. Each category is discussed in turn. For detailed discussions please refer to Appendices B and C, respectively.

4.1. AMR regions and their definition

As described in Chapter 2, the main aim of the introduction of AMR regions in our model is to reflect the differences in the role of antimicrobial drugs in health care systems across the world. To reflect this broad typology of countries, our model uses AMR regions with countries grouped according to their reliance on, and patterns of, use of antimicrobials in their respective national health systems, beyond the treatment for primary infections. This initial consideration yielded three types of AMR regions that differ in their reliance on antimicrobials in their national health systems (as discussed in section 2.2): High, Middle and Low reliance. We further divided the Middle region into three regions based on geographical proximity.[20] As a result, our model consists of the following five regions:

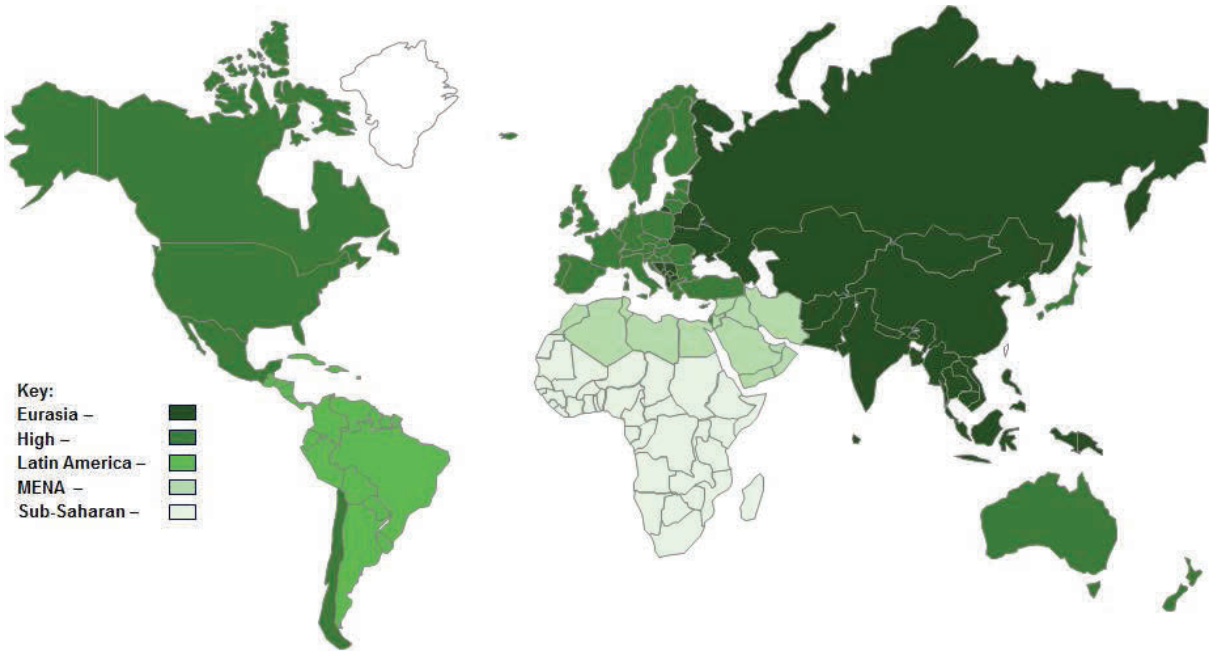
- High (this region includes all OECD, EU and EEA countries)
- Latin America (not including OECD countries in the region)
- MENA (including Middle East and North Africa)
- Eurasia (including countries from Eastern Europe to Western Pacific)
- Sub-Saharan Africa (i.e. original Low region)

To come up with a classification system for countries, we started with the World Bank classification by income level (World Bank, 2014a) and made a series of adjustments to achieve what the research team perceived as a closer alignment.[21] In addition, the adjustments resulted in a closer regional fit, which also facilitated data collection and calibration. A full list of countries included in each AMR region is attached to this report in Appendix A and shown in Figure 2 below.

[20] Concrete country allocation was done in consultation with the commissioning team and is presented in Appendix A.

[21] For instance, according to the World Bank, South Africa is an upper-middle income country. However, we placed it in the Sub-Saharan region along with other predominantly low income countries to reflect the high burden of infectious diseases that South Africa shares with its other Sub-Saharan African countries.

Figure 2. Five AMR regions included in the model



4.2. Health parameters

As mentioned above, due to data availability issues, our study is limited to a small number of bacterial infections and infectious diseases. For individual bacteria, we include infections caused by only the following:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Staphylococcus aureus*

In order to input the impact of AMR on the supply of labour through population and labour efficiency projections, four types of data are needed: incidence of conditions caused by the pathogens listed above, rates of resistance, AMR-attributable mortality and morbidity and future projections of incidence and resistance. Table 9 below summarises the data sources used for each of the data categories used for the baseline values of the parameters in our model.

Table 9. Overview of data sources for health components of the model

	E.coli *K. pneumoniae* *S. aureus*	HIV	TB	Malaria
Incidence	ECDC reports on HAI[22] WHO report on HAI worldwide[23] World Health Survey[24]	UNAIDS Gap Report[25]	Global Health Observatory Data Repository[26]	Global Health Observatory Data Repository[27]
Resistance	WHO report on AMR surveillance[28]	WHO HIV Drug Resistance Report 2012[29]	WHO Global Tuberculosis Report 2013[30]	WHO Global report on antimalarial drug efficacy and drug resistance[31]
Mortality/morbidity	WHO report on AMR surveillance[32]	WHO HIV Drug Resistance Report 2012,[33] supplemented as necessary by available research literature	WHO Global Tuberculosis Report 2013,[34] supplemented as necessary by available research literature	WHO Global report on antimalarial drug efficacy and drug resistance,[35] supplemented as necessary by available research literature

[22] ECDC (2013a).

[23] WHO (2011).

[24] WHO (2013c).

[25] UNAIDS (2014b).

[26] WHO (2014b).

[27] WHO (2014b).

[28] WHO (2014a).

[29] WHO (2012b).

[30] WHO (2013a).

[31] WHO (2010).

[32] WHO (2014a).

[33] WHO (2012b).

[34] WHO (2013a).

[35] WHO (2010).

Incidence rates

Incidence rates are essential for our calculations as they indicate how many cases (usually per 100,000 people) of a given infection there are every year. For a detailed discussion of individual data sources, underlying assumptions behind their use and our approach to data processing, see Appendix C.

Rates of resistance

Rates of resistance are essential for our calculations as they indicate the proportion of individual cases affected by resistance to antimicrobials. For a detailed discussion of individual data sources, underlying assumptions behind their use and our approach to data processing, see Appendix C.

AMR-attributable mortality and morbidity

These data are essential as they indicate the number of additional deaths or days out of the labour force that are associated with each case (or, more precisely, 1,000 cases) of drug-resistant infection. This is different from data on mortality and morbidity associated with the infections in question in general, as this would also include deaths and hospital stays associated with drug-susceptible infections.

The five tables below present meta data tables for the current burden of AMR for each of the AMR zones.

Table 10. Meta data for High

Indicator	E.coli 0-14	E.coli 15+	K. pneu 0-14	K. pneu 15+	MRSA 0-14	MRSA 15+	HIV 0-14	HIV 15+	TB 0-14	TB 15+	Malaria 0-4	Malaria 5+
Incidence rate	99.05	99.05	54.2	54.2	76.62	76.62	0.21	8.26	4.08	19.47	0.34	0.17
Resistance rate	0.2	0.2	0.24	0.24	0.25	0.25	0.05	0.05	0.091	0.01	0.01	0.01
AMR-attributable mortality	129	129	114	114	108	108	100	100	70	70	10	10
AMR-attributable morbidity	2750	2750	8400	8400	4650	4650	0	0	84000	84000	14000	14000

Note: Incidence rates are per 100,000 population. AMR-attributable mortality and morbidity data express the number of additional deaths and days in hospital per 1,000 infections

Table 11. Meta data for Eurasia

Indicator	E.coli 0-14	E.coli 15+	K. pneu 0-14	K.pneu 15+	MRSA 0-14	MRSA 15+	HIV 0-14	HIV 15+	TB 0-14	TB 15+	Malaria 0-4	Malaria 5+
Incidence rate	68.86	26.88	37.68	14.71	53.28	20.8	2.23	15.33	42.91	176.3	1488.2	744.1
Resistance rate	0.33	0.33	0.23	0.23	0.30	0.30	0.051	0.051	0.036	0.036	0.05	0.05
AMR-attributable mortality	129	129	114	114	108	108	100	100	149	149	125	125
AMR-attributable morbidity	2750	2750	8400	8400	4650	4650	0	0	84000	84000	14000	14000

Note: Incidence rates are per 100,000 population. AMR-attributable mortality and morbidity data express the number of additional deaths and days in hospital per 1,000 infections

Table 12. Meta data for MENA

Indicator	E.coli 0-14	E.coli 15+	K. pneu 0-14	K. pneu 15+	MRSA 0-14	MRSA 15+	HIV 0-14	HIV 15+	TB 0-14	TB 15+	Malaria 0-4	Malaria 5+
Incidence rate	64.87	18.36	35.5	10.05	50.18	14.2	2.03	8.17	20.89	43.79	202.93	101.47
Resistance rate	0.39	0.39	0.34	0.34	0.32	0.32	0.05	0.05	0.04	0.04	0.04	0.04
AMR-attributable mortality	129	129	114	114	108	108	100	100	148	148	125	125
AMR-attributable morbidity	2750	2750	8400	8400	4650	4650	0	0	84000	84000	14000	14000

Note: Incidence rates are per 100,000 population. AMR-attributable mortality and morbidity data express the number of additional deaths and days in hospital per 1,000 infections

Table 13. Meta data for Latin America

Indicator	E.coli 0-14	E.coli 15+	K. pneu 0-14	K. pneu 15+	MRSA 0-14	MRSA 15+	HIV 0-14	HIV 15+	TB 0-14	TB 15+	Malaria 0-4	Malaria 5+
Incidence rate	52.16	14.22	28.54	7.78	40.35	11	1.59	30.28	10.18	64.71	308.29	154.14
Resistance rate	0.3	0.3	0.24	0.24	0.37	0.37	0.05	0.05	0.02	0.02	0.01	0.01
AMR-attributable mortality	129	129	114	114	108	108	100	100	88	88	125	125
AMR-attributable morbidity	2750	2750	8400	8400	4650	4650	0	0	84000	84000	14000	14000

Note: Incidence rates are per 100,000 population. AMR-attributable mortality and morbidity data express the number of additional deaths and days in hospital per 1,000 infections

Table 14. Meta data for Sub-Saharan Africa

Indicator	E.coli 0-14	E.coli 15+	K. pneu 0-14	K. pneu 15+	MRSA 0-14	MRSA 15+	HIV 0-14	HIV 15+	TB 0-14	TB 15+	Malaria 0-4	Malaria 5+
Incidence rate	56.69	27.02	31.02	14.79	43.86	20.91	53.24	231.37	65.9	399.5	32009	16005
Resistance rate	0.29	0.29	0.20	0.20	0.33	0.33	0.05	0.05	0.02	0.02	0.04	0.04
AMR-attributable mortality	129	129	114	114	108	108	100	100	138	138	125	125
AMR-attributable morbidity	2750	2750	8400	8400	4650	4650	0	0	84000	84000	14000	14000

Note: Incidence rates are per 100,000 population. AMR-attributable mortality and morbidity data express the number of additional deaths and days in hospital per 1,000 infections

4.2.1. Future projections and scenarios

The three categories of data mentioned above are essential for estimating the current costs of AMR, as defined by our model. However, in order to estimate future costs of AMR, it is necessary to incorporate projections of both incidence rates and resistance rates. In order to project rates of future resistance, it is necessary to add three additional parameters to the model: future rates of resistance, future growth rate of resistance and future starting point of increase in resistance. All three are discussed in turn below.

Future scenario rates

We include three future rates of antimicrobial resistance in our projections: low (5%), medium (40%) and high (100%) – across all three bacteria and the three infectious diseases included in our analysis.

These suggested rates are based on recognition that there are no existing authoritative sources of future resistance rates. This was confirmed by a discussion held at an expert workshop organised by the AMR Review Team in early October 2014,[36] which did not result in any consensus with respect to plausible future rates of resistance. Instead, our scenarios are constructed with a view to incorporate several key elements:

- First, following consultations with the commissioning team and external experts, we incorporate as a best case scenario a future rate that corresponds to a situation where resistance rates have been successfully kept at a low rate. To that end, our low scenario assumes 5% resistance rates.
- Second, we aim to build on existing observed rates of resistance, as much as possible. Indeed, the medium rate of resistance (40%) has already been observed in the past, though arguably, for the latest classes of antimicrobial drugs, only in a small number of cases, in a small number of countries.
- Third, we include a worst case scenario with a future rate of 100% resistance. This scenario is primarily useful from a conceptual and theoretical point of view in the absence of a more evidence-based quantified version of the 'apocalyptic' scenario referred to by the CMO. While we recognise that this rate may not be borne out in reality, any somewhat lower pessimistic projection of resistance (e.g. in the region of 90%) would be arbitrary as well and lack evidence base. Moreover, the likely effects may be similar in practice. In this situation, we prefer to opt for a scenario that is conceptually clear in that it corresponds to a world without effective first-line antimicrobial drugs.

Also, we acknowledge that a limitation of this study is that we use the same future rates across all included countries, even though the current rates of resistance for each of the included bacteria and infectious diseases differ from each other and across countries. However, given the uncertainty in projecting future rates and the need for a high degree of geographical aggregation, we think this to be both a reasonable and pragmatic approach, which facilitates the understanding of our scenarios and interpretation of our final results. It is important to note that these are a guide, and indicator, of a plausible future, rather than precise estimates or predictions.

---

[36] The workshop participants were Hala Audi (AMR Review Team), Stephen Dobra (UK Department of Health), Marco Hafner (RAND), Emyr Harries (KPMG), Alan Johnson (Public Health England), Anthony McDonnell (AMR Review Team), Melinda Moore (RAND), Piero Olliaro (WHO), Sarah Rappaport (AMR Review Team), Yael Selfin (KPMG), Richard Smith (LSHTM), Jirka Taylor (RAND), Hilary Thomas (KPMG), Abhi Vithlani (KPMG), Peter Wilson (UCLH), Neil Woodford (Public Health England), Erez Yerushalmi (University of Warwick).

Future growth rate of resistance

Similarly to future rates of resistance, there does not appear to be robust evidence with respect to the rate or pattern of growth of future rates of resistance. For the purposes of our scenarios, we assume that resistance rates will increase in a one-off step from one year to another. In other words, we do not include any consideration of an S-shaped epidemic path from a baseline rate of resistance to the scenarios' final values. This decision is based on discussions with expert epidemiologists at the workshop described above, who pointed out that notable increases in resistance observed in the past occurred over the course of a short time span. Therefore, we are confident that this assumption does not represent an unreasonable deviation from likely future developments.

Future starting points of increase in resistance: alternative scenarios

Each AMR zone is affected differently by changes to AMR, driven by the different demographic and labour efficiency components. However, based on our evidence review, data collection and consultation with senior experts at the October workshop, increases in resistance do not appear to be more likely to occur at one particular point in the future than another. To address this challenge, we incorporate two different starting points in our future scenarios. Taking Year 0 as the first year in the projection, we model increases in resistance to take place in Year 0 and Year 15.[37] Note that monetary values are in terms of year 2011.

This approach to the alternative scenarios is motivated by the fact that, in addition to expressing the differential costs of *changes* to resistance (that start in year 0), there may also be value in calculating long-term costs associated with differences in the *timing* of the change in resistance. In other words, we feel it is analytically useful to make two types of comparisons – one expressing the cost differentials driven by the absolute value of changes to resistance and another expressing the cost differentials driven by the timing of the changes in resistance.

In addition, we added a pair of absolute resistance scenarios intended to approximate a world without effective antimicrobial therapy. This is in recognition of the fact that mortality rates used in the six basic alternative scenarios allow for some effective therapy even in the event of 100% resistance rates and, as such, these scenarios do not represent the theoretical upper bound of AMR-attributable costs. To construct these absolute resistance scenarios, we used mortality rates based on academic literature on outcomes of untreated conditions and on expert suggestions[38] and applied these to the two original 100% scenarios, i.e. sc3 and sc5, to create sc6 and sc7 respectively.

In total, we include eight future scenarios in our model to allow both horizontal and vertical comparisons. These are captured in Table 15 below.

---

[37] Note that Year 0 refers to the model being calibrated to economic data in 2011. The demographics and labour health components refer to year 2010, which are projected forward at intervals of 5 years. This seeming lack of consistency is due to lack of comparable data. However, assuming that preferences of agents do not change dramatically between 2010 and 2011, and being a calibrated model, we believe that these years are approximately close enough to match.

[38] For a full discussion of the sources of these absolute resistance mortality rates, please refer to Appendix B.

Table 15. Future resistance scenarios

	Rate of Resistance	Starting Year of Resistance	
		Year 0	Year 15
Baseline	0%	sc0	
Alternative	Current Rates	sc00	
	5%	sc1	
	40%	sc2	sc4[39]
	100%	sc3	sc5[40]
Absolute resistance	100%	sc6	sc7

The baseline in this model is 0% resistance rate, i.e. a world with no antimicrobial resistance, in order to capture the absolute costs of AMR, in addition to any relative costs expressed by differences between individual scenarios. This baseline is included so that, in addition to observing any differences in the costs of AMR stemming from differential changes to rates of resistance and the timing of their occurrence, absolute costs of individual scenarios can also be expressed. The baseline is followed by six alternative scenarios.[41]

The first, scenario 00 reflects *current* rates of resistance observed for the three included bacteria and the three included infectious diseases, which are assumed to continue at a constant rate until Year 40. As such, this status quo scenario corresponds to the 'business as usual' situation.

Scenarios 1, 2 and 3 increase the current rates from 5% to 40% and 100%, respectively, starting from year 0. Scenarios 4 and 5 assume that the *current* rates of resistance persist until year 15, but increase thereafter to 40% or 100%. In other words, in the first 15 years of the model's projections, the results for scenarios 4 and 5 are identical to those of scenario 00, and thereafter diverge.

Lastly, differences in the economic fundamentals of the regions also drive the differences in projections. For example, differences in the increases in the productivity of regions or changes in the comparative competitive advantage of regions in production (and trade) may have an impact on the projected costs of AMR. The impact of economic fundamentals, however, is netted out because economic fundamentals are held *constant* throughout the various AMR scenarios, such that differences between individual scenarios are solely attributable to AMR.

[39] Until Year 15, current rates of resistance are assumed.

[40] Until Year 15, current rates of resistance are assumed.

[41] Note that sc0 is calculated by removing current observed AMR effects and is therefore an endogenous function of the models parameters.

Assumptions about future incidence rates

With respect to the incidence of conditions affected by drug resistance, we assume they remain constant until 2050. We recognise that this assumption may be unrealistic as incidence rates will likely change over time. This affected the overall estimate of the model. However, there is a lack of agreement among health specialists about the future changes to incidence rates and/or their direction and we did not identify any authoritative projections of the most likely changes in incidence rates. Therefore, in the absence of better data, it is necessary to assume that the incidence of conditions affected by resistance remain constant over time. The only exception to this assumption are our projections pertaining to malaria in scenarios that incorporate a substantial rise of resistance, i.e. sc2 and above. In these scenarios, we assume that future changes in resistance will be accompanied by changes in incidence rate and base these changes on available historical data (see appendix B for more details).

4.3. Economic components

4.3.1. Calibration of the model to economic data

To estimate the cost of AMR, the theoretical model (as discussed previously) is calibrated to economic data within each AMR zone and its bi-lateral trade flows with neighbouring zones. National level economic data is required to apply the model to the existing economic landscape. Thereafter, it is expected that the increase in antimicrobial resistance will have a negative impact on the economy by diminishing the size of its workforce and deteriorating the quality of its human capital, which is defined as the stock of skills, education, physical abilities, competencies and other productivity-enhancing characteristics embedded in labour (Acemoglu, 2009).

The economic data is collected into a Social Accounting Matrix (SAM), which is a square matrix of rows and columns (Pyatt and Round, 1985). Each represents a debit and credit account of the various financial transactions in the economy, including trade accounts with other regions. The principle of double-entry accounting requires that for each account in the SAM, expenditures must equal revenues (the SAM used to calibrate this model is presented in Appendix C).

The SAM contains data on the value of intermediate inputs, capital, and labour used as inputs into production. It also contains the consumption patterns of each of the representative agents in an AMR zone, and their respective endowment of labour and capital. Finally, the SAM accounts for the gross capital formation (i.e. investment), and the bilateral trade matrix between all five AMR zones.

The SAM is developed by combining data from various sources, mainly from the World Bank and the International Monetary Fund (IMF), on different elements of economic activity: production, consumption, capital formation, savings, and labour/capital ratios. Data from the World Bank and the IMF have the advantage that they are comprehensively available on an annual basis for most countries. This allows us to make accurate aggregations of the economic input data in the five AMR regions. A summary of the inputs to the SAM and the corresponding data sources can be found in Table 16. A more detailed discussion of individual components is offered in Appendix D. Unless otherwise stated, all data refers to the year 2011 and is expressed in current value US Dollars.

Table 16. Social Accounting Matrix (SAM): Summary of main inputs and sources.

Input Category	Data Source
GDP Data	World Bank DataBank.[42]
Intermediate Consumption	World Input-Output Database.[43] IFPRI SAMs. Academic papers.[44]
Gross Capital Formation	World Bank DataBank.
Import / Export (I/E) of Goods & Services	International Monetary Fund, DoTS data.[45]
Labour / GDP Ratio	IFPRI SAMs. Eurostat Database.[46] Various academic papers.

4.3.2. Population projections: a cohort-component model

We base the growth of the labour force and its efficiency on current projections of AMR, assuming no change in resistance, as well as demographic projections for the possible future scenarios with varying rates of resistance. We generate the demographic projections using input data from the United Nations (UN)[47] and an adapted version of Chapin's cohort-component model (Hunsinger, n.d.).

The cohort-component model starts with the base population in 2010 and is categorised for each region by age and gender. The base population subsequently evolves by applying assumptions on mortality, fertility and migration. The outcome of the model is a projection of the population by (5-year) age and gender groups up to 2050, applied to each of the five regions. In essence, the cohort-component model characterises population change according to a 'natural' increase (births minus deaths) and net-migration (in-migration less out-migration). More formally, the population by age cohort *a* and gender *s* at time *t* can be written as:

$$P(a,s,t_1) = P(a,s,t_o) + B(a,s) - D(a,s) + IM(a,s) - OM(a,s)$$

where *B(a,s)* represents the total births, *D(a,s)* total deaths. *IM(a,s)* and *OM(a,s)* represent inward and outward migration, respectively. The total births in a given period depend on the size of the population, the age structure and the age-specific fertility rates, which vary across the five AMR regions. It is important to stress that we assume in our projections that fertility rates will follow in each region a similar trend within each AMR region as during the last decade. We observe empirically that in the five AMR regions fertility rates across all women in child-bearing age are decreasing, except for women in high-income countries in the age of 35 to 49. Furthermore, it is important to bear in mind that increasing rates

[42] World Bank (2014b).

[43] Timmer (2012).

[44] International Food Policy Research Institute (n.d.).

[45] International Monetary Fund (2011d).

[46] European Commission (2014).

[47] United Nations, Department of Economic and Social Affairs (2014).

of AMR could affect fertility decisions. In our approach, we do not model fertility rates as a function of AMR resistance, even though fertility rates may react to increased rates of morbidity or mortality (i.e. due to conflicts or epidemic outbreaks). Therefore any additional effect of higher resistance on fertility is not captured. However, there is no clear evidence available in the literature on how fertility rates would be affected by increased AMR and therefore we assume them to be an exogenous parameter.

Similarly, the number of deaths in any given period depends on the population size, the age distribution and the age and gender-specific mortality rates. We apply the abridged life tables provided by the UN to calculate age and gender-specific probabilities of surviving from one age group to the next (within five years). Migration is the most difficult component of the model, as there are different determinants of migration, such as employment-related determinants (economic opportunities) or non-employment related determinants (i.e. retirement or forced migration due to conflicts or outbreaks of diseases). The difficulty is that both types of migration are associated with economic growth and may be affected by rising rates of AMR and are therefore endogenously determined in our model. However, to the best of our knowledge there exists no valid approach to take this endogeneity into account. Therefore we calculate the net migration rate for each of our five regions and assume them to be constant over time.

4.3.3. Labour Efficiency Model

To calculate the AMR-related efficiency units of labour, we draw mainly on morbidity data collected for various AMR related conditions that are prevalent in the five regions. For instance, an episode of drug-resistant malaria will reduce productivity of a unit of labour by keeping workers away from work by a number of additional days. Thus, in our model, labour efficiency is based on subtracting a number of days (normalised to a year) from the baseline yearly efficiency level; AMR-attributable lost days is for a combination of the adult workers and child population. Simply put, the yearly efficiency of a worker is:

$$E = 1 - Number\ of\ lost\ days\ normalised\ to\ a\ year \quad (2)$$

where an increase in AMR resistance rates raises the number of lost working days due to illness. At the same time, children are also affected, which results in lost working days for their parents or carers who tend to the sick child. In essence, increasing rates of resistance will have a productivity-reducing effect. (Conversely, there is a possibility that efficiency could rise above one if, relative to the baseline, workers gain days).[48]

In our baseline scenario we assume the AMR rates to be 0 and therefore the household labour efficiency, or relative units of output produced per worker, does not change. Subsequently, for each year and region, under each scenario, we calculate the total number of days lost due to resistance to the three bacteria, HIV, TB and Malaria and relate this to the total number of days actually worked in the economy (assuming a total number of potential working days of 235) in a given year. This gives us the relative labour units.

[48] In this model, there are cases of rising efficiency because it is also subject to the relative weight of adults and children at each moment in time (see Equation 3). As an example, if the weight in the population favours adults, workers will require fewer days off work to care for children, thus raising efficiency relative to the baseline.

To see this formally, let x_i^A be the frequency of clinical episodes per year at time *t*, with *i* being the various health conditions incorporated in this model (e.g., various infectious diseases and hospital acquired infections), and $A = \{\mathrm{a}, \mathrm{c}\}$ for adult worker or children of adult workers, respectively. Furthermore, $p(x_i^A)$ is the probability of having an incident, $f_{sc,t}(x_i^A)$ the probability of an incident that is drug resistant for scenario *sc* at time *t*, and $z(x_i^A)$ a loss function of the number of working days lost per incident of type *i*. Finally, $\phi_{sc,t}$ is the ratio of children to working age adults for each scenario *sc* and time *t*. Therefore, the efficiency parameter per year is:

$$E_t = 1 - \sum_i p\left(x_i^a\right) \cdot f\left(x_i^a\right) \cdot z\left(x_i^a\right) - \phi_{sc,t} \sum_i p\left(x_i^c\right) \cdot f_{sc,t}\left(x_i^c\right) \cdot z\left(x_i^c\right) \tag{3}$$

As discussed in section 4.2, we assume that the rates of infection (incidence) remain constant throughout the time period of the model projection and the different scenarios. We furthermore assume that the loss function of lost days also remains constant. The efficiency parameter is, however, affected by two components: (1) the change in the resistance rate $f_{sc,t}\left(x_i^A\right)$, and (2) the endogenous changes in the ratio of children to adult working population in relation to the demographics cohort-component model that is also affected by the scenario.

5. Results

To estimate the cost of AMR, we examine six alternative scenarios and two absolute resistance scenarios (as previously discussed) which are compared with a baseline scenario of 0% resistance. In interpreting the results of our model, it is important to keep in mind that the values calculated in each scenario represent how much lower the global (or regional) GDP would be at a particular point of time in comparison with a world that would not be affected by antimicrobial resistance. Since deaths attributable to AMR permanently reduce the size of labour force, which influences future population sizes, the effects of AMR accumulate over time. This explains why the costs of AMR increase over time, even if rates of resistance remain constant.

As explained in section 4.2.1 (and especially Table 15), scenario 00 uses the current AMR rates, while scenario 1 to 3 increases resistance from 5%, to 40% and 100% in year 0, respectively. Scenarios 4 and 5 assume that the resistance rates for the first 15 years of the model project follows the *current* rates of resistance (as in scenario 00), but then rises to 40% and 100%, respectively, thereafter. Therefore, of these, scenario 3 is, expected to be the most costly. The two absolute resistance scenarios, sc6 and sc7, build on sc3 and sc5 by using modified mortality rates.

The results of our model are presented in a series of tables and graphs below. Table 17 reports how the working age population in each region evolves over time with different AMR scenarios. In year 10, the world working age population would be lower by 2 to 92 million people compared to a world without AMR. By year 40, the total loss in people in productive age rises to a range from 11 million to 444 million. It is worth noting that Eurasia would experience the biggest loss in people (in absolute terms).

Table 17. Working age population loss relative to 0% resistance, by AMR Zone, in million people, per year

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
10	High	-0.55	-0.13	-1.03	-2.64	-0.55	-0.55	-7.94	-0.55
	Eurasia	-1.11	-0.63	-7.47	-20.29	-1.11	-1.11	-48.31	-1.11
	MENA	-0.07	-0.02	-0.28	-1.41	-0.07	-0.07	-3.07	-0.07
	Sub	-0.75	-0.83	-8.94	-14.40	-0.75	-0.75	-29.74	-0.75
	Latam	-0.06	-0.02	-0.96	-1.52	-0.06	-0.06	-3.21	-0.06
	World	**-2.53**	**-1.64**	**-18.68**	**-40.26**	**-2.53**	**-2.53**	**-92.27**	**-2.53**
20	High	-1.09	-0.26	-2.05	-5.23	-1.34	-2.13	-15.64	-4.79
	Eurasia	-2.57	-1.32	-15.80	-42.87	-6.03	-12.92	-100.55	-28.19
	MENA	-0.21	-0.09	-0.69	-3.46	-0.33	-1.00	-7.47	-1.97
	Sub	-1.92	-2.07	-22.19	-35.13	-7.17	-10.75	-69.50	-19.59
	Latam	-0.15	-0.05	-2.08	-3.32	-0.63	-0.94	-6.86	-1.86
	World	**-5.94**	**-3.79**	**-42.82**	**-90.01**	**-15.49**	**-27.74**	**-200.01**	**-56.39**
40	High	-2.14	-0.65	-4.00	-10.18	-3.32	-7.15	-30.09	-19.67
	Eurasia	-5.47	-3.22	-31.67	-85.60	-23.99	-55.87	-197.52	-127.68
	MENA	-0.50	-0.22	-1.59	-7.78	-1.24	-4.98	-16.72	-10.49
	Sub	-5.55	-6.84	-62.50	-97.54	-42.78	-64.37	-185.94	-114.44
	Latam	-0.34	-0.16	-4.27	-6.81	-2.83	-4.35	-13.80	-8.81
	World	**-14.00**	**-11.09**	**-104.02**	**-207.91**	**-74.17**	**-136.71**	**-444.08**	**-281.09**

In terms of economic costs, Table 18 summarizes the cost of AMR as an annual average GDP loss over a forty years' time horizon. Table 19 reports the yearly GDP loss at a world level at various points in time, while Figure 3 illustrates the projected yearly trends in GDP loss for each of the scenarios, compared to a scenario with 0% resistance. Table 20 reports the cumulative GDP loss over a 40 year period.

Thus, on average over a forty year horizon, the world GDP loss runs between USD 53 billion to 3 trillion per year (in terms of 2011 values, reported in Table 18). The main regions affected by AMR are Eurasia, the High region and, to a lesser extent due to its comparatively lower income, Sub-Saharan Africa.

The upper bounds of these ranges are driven by costs projected in the absolute resistance scenarios. Their first configuration, i.e. onset at Year 1, results in average global costs of 3.1 trillion dollars, 152% higher than the results of the basic 100% scenario. Interestingly, the size of this increase varies quite substantially across individual AMR zones. By far the biggest increase is observed in the High region (197%), which suggests that the absence of effective therapy could be particularly impactful in areas with comparatively high utilisation of health care services. The other configuration of the absolute resistance scenarios, sc7, results in smaller average costs due to its onset in Year 15. Nonetheless, the costs in this scenario are 114% higher than in the corresponding basic scenario.

Table 18. Per year GDP loss attributable to AMR, by region (average over 40 years)

	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
High	-73.2	-18.9	-138.8	-353.8	-101.7	-189.9	-1,051.9	-473.1
Eurasia	-52.1	-22.2	-234.9	-610.5	-159.6	-334.1	-1,481.2	-714.9
MENA	-6.3	-2.2	-20.3	-67.3	-12.5	-31.9	-159.1	-65.1
Sub	-8.1	-8.3	-86.7	-137.4	-59.6	-100.0	-279.9	-157.8
Latam	-4.1	-1.5	-37.1	-63.7	-19.5	-30.6	-138.1	-60.6
World	**-143.8**	**-53.1**	**-518.3**	**-1,233.9**	**-353.3**	**-687.4**	**-3,112.6**	**-1,472.8**

It should be noted that there is a time dimension to the costs presented. The effects of AMR compound over time because reductions in labour force compared to the baseline are reflected in all subsequent years of a given scenario (i.e., the death of a worker does not only affect the year the death takes place but continues to be a part of AMR costs in subsequent years because it also involves the death of all future offspring). To illustrate, Table 19 reports the economic losses relative to the baseline. The costs in year 10 range from USD 10 billion to 625 billion. But by year 40, the range rises from 188 billion to 9.8 trillion (in terms of 2011 values).

Table 19. Yearly world GDP loss relative to 0% resistance, USD PV 2011

Scenario Results								
Percent GDP Loss, per year								
Year	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
5	-0.01%	0.00%	-0.04%	-0.11%	-0.01%	-0.01%	-0.3%	0.0%
10	-0.03%	-0.01%	-0.10%	-0.23%	-0.03%	-0.03%	-0.6%	0.0%
20	-0.06%	-0.02%	-0.22%	-0.52%	-0.11%	-0.21%	-1.3%	-0.4%
30	-0.10%	-0.04%	-0.36%	-0.86%	-0.26%	-0.50%	-2.2%	-1.1%
40	-0.14%	-0.06%	-0.51%	-1.23%	-0.40%	-0.83%	-3.1%	-1.9%
Loss in bn USD 2011, per year								
Year	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
5	-10.9	-3.7	-38.4	-91.1	-10.9	-10.9	-239.3	-10.9
10	-28.6	-9.8	-101.2	-240.2	-28.6	-28.6	-625.2	-28.6
20	-95.2	-32.8	-338.6	-804.9	-177.8	-323.4	-2,055.1	-593.6
30	-224.7	-80.1	-809.9	-1,927.7	-576.9	-1,116.8	-4,860.0	-2,399.7
40	-453.7	-188.0	-1,647.7	-3,926.8	-1,282.0	-2,668.0	-9,807.9	-5,978.0

The lowest costs are observed in scenarios sc1 (i.e. a 5% resistance rate). This is in line with our expectation as this scenario was included as a best-case example in which sent rates of resistance rates are successfully kept at a relatively low level. However, it is worth noting that, this does not hold for Sub-Saharan Africa where costs in sc1actually exceed those observed in sc00 (i.e. the continuation of current rates). The most likely explanation for this result is that the global incidence of infectious diseases (malaria, TB, HIV) is still relatively high while the current resistance rates are relatively low, in some

settings even below 5%. In our model, which assumes constant incidence rates over time, preventing a modest rise in resistance in areas with high incidence of these diseases appears to be somewhat more important for keeping costs down than reducing resistance rates in HAIs to 5%.

Our model, furthermore, suggests that extremely high rates of resistance (e.g. 100%) would translate into substantial costs. In addition, costs associated with very high rates of resistance quickly outweigh any benefits stemming from any delays in their occurrence. This is evident from the comparison of sc2, which assumes 40% rates occurring immediately, and sc5, which assumes 100% delayed by 15 years. The results show that the estimated costs associated with both scenarios are approximately equal in Year 25, i.e. 10 years after the introduction of the resistance hike in sc5. Thereafter, sc5 costs continue to rise at a much faster pace, reaching approximately 150% of sc2 costs in Year 40.

Please note that the inclusion of the absolute resistance scenarios would distort the visualisation by substantially extending the y-axis and are therefore not included.

Figure 3. World percent GDP loss relative to 0% resistance, per year

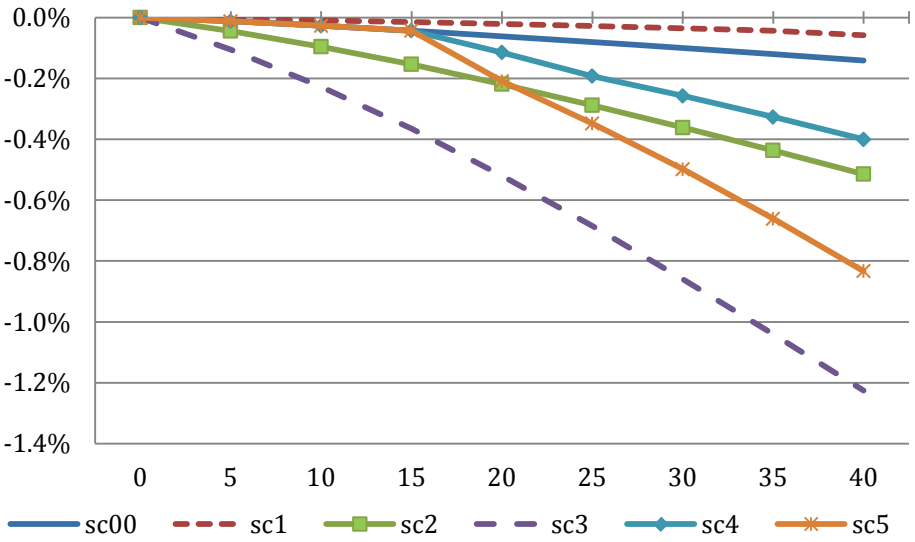


Table 20 reports the cumulative GDP loss over a 40 year period in *trillions* of USD in 2011 value. The cumulative cost associated with the worst-case scenario based on current mortality rates, sc3, is 49.4 trillion USD. To put this value into perspective, this is roughly the equivalent of three quarters of the annual global GDP. In the same scenario in the High region alone, the projected cumulative cost of 14.2 trillion USD is only slightly lower than the current GDP of the entire European Union. The worst absolute resistance scenario results in a cumulative cost of 125 trillion USD, i.e. roughly double the current annual global GDP. Lastly, even the continuation of the current situation, sc00, is estimated to result in a cumulative global cost of 5.8 trillion USD, which is broadly comparable to the current GDP of Germany and the United Kingdom combined.

Table 20. Cumulative GDP loss over 40 years, in trillion USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
High	-2.9	-0.8	-5.6	-14.2	-4.1	-7.6	-42.1	-18.9
Eurasia	-2.1	-0.9	-9.4	-24.4	-6.4	-13.4	-59.2	-28.6
MENA	-0.3	-0.1	-0.8	-2.7	-0.5	-1.3	-6.4	-2.6
Sub	-0.3	-0.3	-3.5	-5.5	-2.4	-4.0	-11.2	-6.3
Latam	-0.2	-0.1	-1.5	-2.5	-0.8	-1.2	-5.5	-2.4
World	-5.8	-2.1	-20.7	-49.4	-14.1	-27.5	-124.5	-58.9

5.1. The cost of AMR by zone

Table 21 and Table 22 report the projected AMR-attributable GDP loss, within ten, twenty and forty years, for each zone. For example, Sub-Saharan Africa will be the most negatively affected by AMR, relative to its GDP. Table 21 reports that the expected AMR attributable GDP loss per year for Sub-Saharan Africa (Sub) will be 0.1% to 2.5%, within twenty years, depending on the scenario. This loss is projected to increase to 0.3% to 5% within forty years.

Table 22 reports these losses in terms of monetary values. In absolute terms, the cost to the High region is the highest until year 10, followed by Eurasia. By year 20, however, Eurasia surpasses the High region mostly because of its relative size in GDP and higher projected economic growth.

Table 21. Percent GDP loss relative to 0% resistance, by AMR zone, per year

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
10	High	-0.03%	-0.01%	-0.06%	-0.16%	-0.03%	-0.03%	-0.47%	-0.03%
	Eurasia	-0.02%	-0.01%	-0.11%	-0.30%	-0.02%	-0.02%	-0.72%	-0.02%
	MENA	-0.01%	0.00%	-0.05%	-0.21%	-0.01%	-0.01%	-0.49%	-0.01%
	Sub	-0.06%	-0.07%	-0.77%	-1.22%	-0.06%	-0.06%	-2.62%	-0.06%
	Latam	-0.01%	0.00%	-0.14%	-0.23%	-0.01%	-0.01%	-0.49%	-0.01%
	World	**-0.03%**	**-0.01%**	**-0.10%**	**-0.23%**	**-0.03%**	**-0.03%**	**-0.59%**	**-0.03%**
20	High	-0.07%	-0.02%	-0.13%	-0.34%	-0.09%	-0.14%	-1.03%	-0.29%
	Eurasia	-0.05%	-0.02%	-0.24%	-0.64%	-0.11%	-0.23%	-1.55%	-0.43%
	MENA	-0.05%	-0.02%	-0.15%	-0.52%	-0.06%	-0.13%	-1.23%	-0.23%
	Sub	-0.14%	-0.14%	-1.55%	-2.45%	-0.88%	-1.69%	-5.05%	-2.32%
	Latam	-0.03%	-0.01%	-0.30%	-0.51%	-0.10%	-0.15%	-1.10%	-0.27%
	World	**-0.06%**	**-0.02%**	**-0.22%**	**-0.52%**	**-0.11%**	**-0.21%**	**-1.33%**	**-0.38%**
40	High	-0.16%	-0.05%	-0.31%	-0.78%	-0.25%	-0.52%	-2.31%	-1.40%
	Eurasia	-0.13%	-0.06%	-0.54%	-1.39%	-0.42%	-0.92%	-3.37%	-2.04%
	MENA	-0.12%	-0.04%	-0.36%	-1.18%	-0.26%	-0.72%	-2.80%	-1.53%
	Sub	-0.30%	-0.34%	-3.14%	-4.97%	-2.52%	-4.17%	-9.99%	-6.88%
	Latam	-0.08%	-0.03%	-0.67%	-1.17%	-0.45%	-0.73%	-2.55%	-1.50%
	World	**-0.14%**	**-0.06%**	**-0.51%**	**-1.23%**	**-0.40%**	**-0.83%**	**-3.06%**	**-1.87%**

Table 22. GDP loss by AMR Zone, in billion USD PV 2011, per year

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
	High	-20.1	-4.7	-37.9	-96.8	-20.1	-20.1	-291.7	-20.1
	Eurasia	-5.7	-2.9	-33.6	-89.8	-5.7	-5.7	-217.0	-5.7
10	MENA	-0.7	-0.2	-2.6	-10.1	-0.7	-0.7	-23.3	-0.7
	Sub	-1.5	-1.7	-18.4	-29.2	-1.5	-1.5	-62.7	-1.5
	Latam	-0.6	-0.2	-8.8	-14.3	-0.6	-0.6	-30.6	-0.6
	World	**-28.6**	**-9.8**	**-101.2**	**-240.2**	**-28.6**	**-28.6**	**-625.2**	**-28.6**
	High	-56.1	-13.2	-106.1	-270.7	-68.2	-106.9	-809.3	-225.9
	Eurasia	-27.6	-11.9	-135.0	-354.4	-62.6	-128.7	-858.6	-237.7
20	MENA	-3.7	-1.4	-12.5	-42.5	-5.0	-10.8	-100.1	-18.5
	Sub	-5.3	-5.4	-58.4	-92.5	-33.4	-63.8	-190.6	-87.5
	Latam	-2.5	-0.9	-26.7	-44.9	-8.7	-13.2	-96.5	-24.0
	World	**-95.2**	**-32.8**	**-338.6**	**-804.9**	**-177.8**	**-323.4**	**-2,055.1**	**-593.6**
	High	-200.7	-58.7	-381.3	-970.1	-308.6	-646.6	-2,866.6	-1,731.6
	Eurasia	-192.4	-87.1	-824.0	-2,127.3	-636.9	-1,414.6	-5,163.9	-3,137.1
40	MENA	-21.5	-7.9	-66.7	-217.0	-48.3	-132.0	-514.8	-281.4
	Sub	-25.8	-29.0	-268.4	-424.8	-215.6	-356.8	-854.0	-587.6
	Latam	-13.3	-5.4	-107.3	-187.7	-72.7	-118.0	-408.7	-240.3
	World	**-453.7**	**-188.0**	**-1,647.7**	**-3,926.8**	**-1,282.0**	**-2,668.0**	**-9,807.9**	**-5,978.0**

Figure 4 to Figure 8 (below) illustrate the same information presented above in graph form, for each scenario and region. The graphs show that trends in AMR-attributable costs are not linear and that their rates of growth may vary over time due to factors such as changes in the share of working age population and related changes in labour efficiency. As above, please note that in the interest of visualisation clarity, the absolute resistance scenarios are not included in the graphs.

Figure 4. Percent GDP loss relative to 0% resistance, year, High region

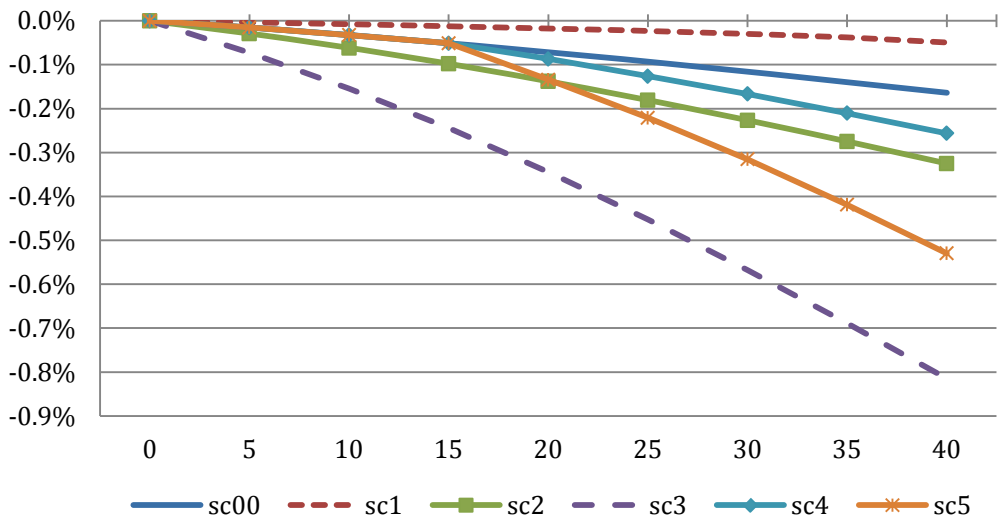


Figure 5. Percent GDP loss relative to 0% resistance, per year, Eurasia

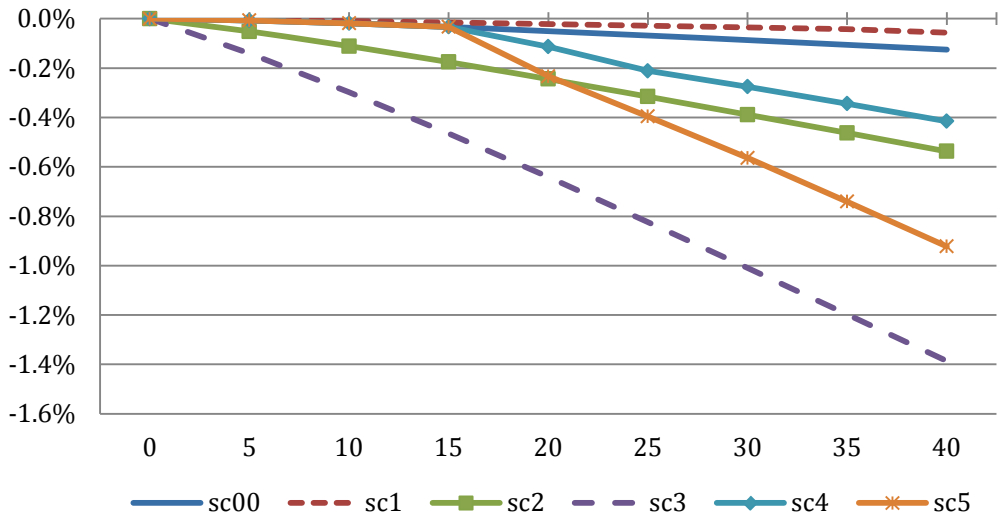


Figure 6. GDP loss relative to 0% resistance, percent per year, Middle East and North Africa (MENA)

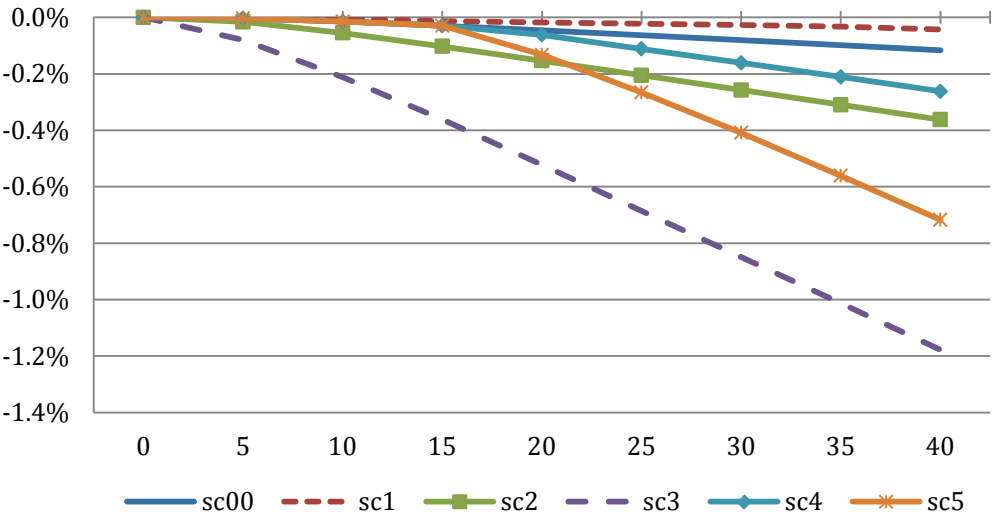


Figure 7. Percent GDP loss relative to 0% resistance, per year, Sub-Saharan Africa

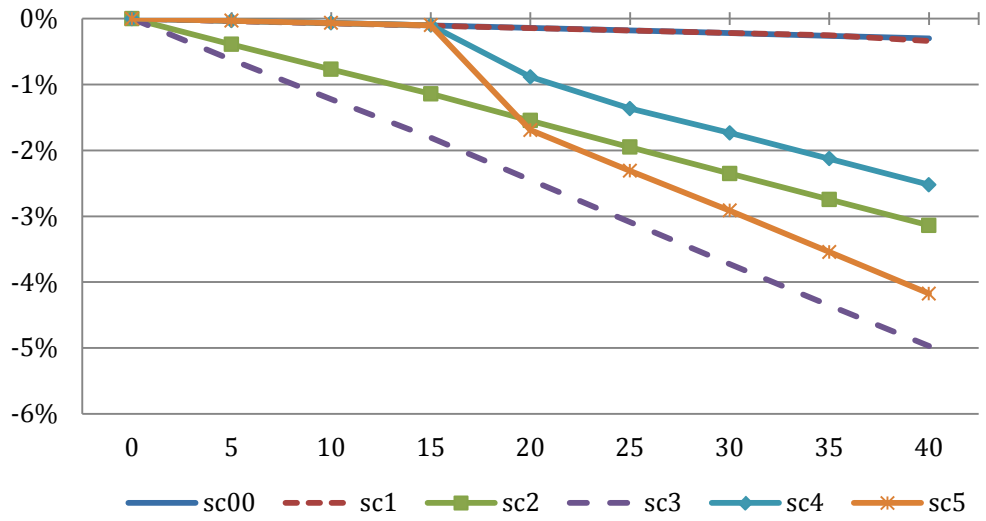
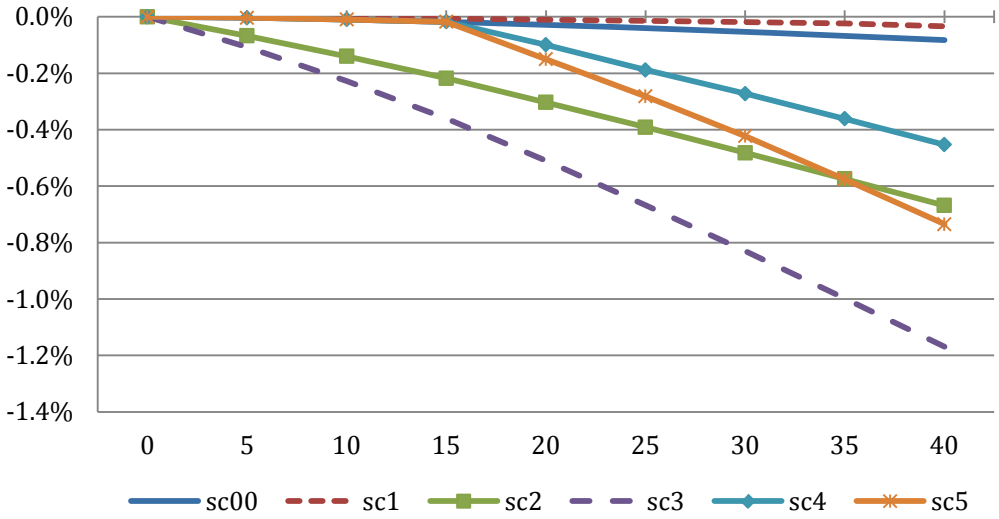


Figure 8. Percent GDP loss relative to 0% resistance, per year, Latin America



5.2. Consumption expenditure

Regional and world utility levels are measured by the expenditure on consumption goods, reported in Table 23 (in terms of percent loss relative to 0% resistance) and in Table 24 (in terms of billion USD lost for values of 2011). Note that these tables closely follow the changes in GDP, because consumption contributes to GDP.

The utility (i.e., consumption) of Sub-Saharan African households is expected to fall the most dramatically.

Table 23. Percent loss in consumption, per year

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
	High	-0.03%	-0.01%	-0.06%	-0.16%	-0.03%	-0.03%	-0.5%	0.0%
	Eurasia	-0.01%	0.00%	-0.05%	-0.14%	-0.01%	-0.01%	-0.3%	0.0%
10	MENA	-0.02%	-0.01%	-0.06%	-0.21%	-0.02%	-0.02%	-0.5%	0.0%
	Sub	-0.06%	-0.06%	-0.69%	-1.10%	-0.06%	-0.06%	-2.4%	-0.1%
	Latam	-0.01%	0.00%	-0.14%	-0.23%	-0.01%	-0.01%	-0.5%	0.0%
	World	**-0.03%**	**-0.01%**	**-0.09%**	**-0.22%**	**-0.03%**	**-0.03%**	**-0.6%**	**0.0%**
	High	-0.07%	-0.02%	-0.14%	-0.36%	-0.09%	-0.14%	-1.1%	-0.3%
	Eurasia	-0.05%	-0.02%	-0.24%	-0.62%	-0.11%	-0.23%	-1.5%	-0.4%
20	MENA	-0.05%	-0.02%	-0.16%	-0.51%	-0.07%	-0.14%	-1.2%	-0.2%
	Sub	-0.13%	-0.13%	-1.39%	-2.22%	-0.79%	-1.52%	-4.6%	-2.1%
	Latam	-0.03%	-0.01%	-0.30%	-0.51%	-0.10%	-0.16%	-1.1%	-0.3%
	World	**-0.06%**	**-0.02%**	**-0.21%**	**-0.50%**	**-0.11%**	**-0.20%**	**-1.3%**	**-0.4%**
	High	-0.16%	-0.05%	-0.33%	-0.82%	-0.26%	-0.55%	-2.4%	-1.4%
	Eurasia	-0.13%	-0.06%	-0.53%	-1.35%	-0.41%	-0.90%	-3.3%	-2.0%
40	MENA	-0.12%	-0.04%	-0.37%	-1.16%	-0.27%	-0.72%	-2.8%	-1.5%
	Sub	-0.29%	-0.31%	-2.86%	-4.56%	-2.29%	-3.81%	-9.2%	-6.3%
	Latam	-0.09%	-0.04%	-0.65%	-1.17%	-0.45%	-0.74%	-2.6%	-1.5%
	World	**-0.15%**	**-0.06%**	**-0.50%**	**-1.17%**	**-0.39%**	**-0.80%**	**-3.0%**	**-1.8%**

Table 24. Loss in Consumption relative to 0% resistance, per year, in billion USD PV 2011

Year	Region	sc00	sc1	sc2	sc3	sc4	sc5	sc6	sc7
	High	-16.4	-4.0	-33.1	-84.0	-16.4	-16.4	-248.3	-16.4
	Eurasia	-3.4	-1.6	-18.5	-48.8	-3.4	-3.4	-118.7	-3.4
10	MENA	-0.5	-0.2	-2.0	-6.8	-0.5	-0.5	-16.1	-0.5
	Sub	-1.1	-1.2	-13.0	-20.8	-1.1	-1.1	-44.9	-1.1
	Latam	-0.5	-0.2	-7.0	-11.7	-0.5	-0.5	-25.4	-0.5
	World	**-21.9**	**-7.2**	**-73.6**	**-172.1**	**-21.9**	**-21.9**	**-453.4**	**-21.9**
	High	-46.7	-11.4	-94.6	-239.2	-59.2	-94.7	-700.7	-196.2
	Eurasia	-15.6	-6.5	-72.3	-187.1	-34.2	-69.0	-456.2	-126.9
20	MENA	-2.5	-0.9	-8.4	-27.0	-3.6	-7.4	-64.5	-13.0
	Sub	-3.9	-3.8	-41.3	-66.1	-23.6	-45.1	-137.1	-62.1
	Latam	-2.2	-0.8	-21.4	-36.8	-7.2	-11.1	-80.2	-20.2
	World	**-70.9**	**-23.4**	**-238.0**	**-556.1**	**-127.8**	**-227.4**	**-1,438.7**	**-418.5**
	High	-171.2	-51.7	-348.4	-876.6	-280.3	-586.0	-2,537.7	-1,533.6
	Eurasia	-102.1	-45.0	-417.7	-1,065.6	-323.2	-710.6	-2,604.5	-1,581.4
40	MENA	-13.9	-5.1	-43.0	-134.1	-31.5	-82.7	-321.6	-178.2
	Sub	-18.9	-20.5	-189.5	-302.7	-152.1	-252.9	-613.1	-420.1
	Latam	-11.6	-4.7	-86.2	-153.6	-58.9	-97.2	-339.1	-200.0
	World	**-317.6**	**-126.9**	**-1,084.8**	**-2,532.6**	**-846.0**	**-1,729.4**	**-6,415.9**	**-3,913.2**

6. Sensitivity analyses and additional calculations

In addition to the basic six alternative and two absolute resistance scenarios presented above, the research team also conducted a series of sensitivity analyses and additional calculations. These can be broadly divided into two groups.

First, we reran the six basic scenarios with modifications to address the uncertainty stemming from the fact that our model assumes incidence rates will stay constant. One modification was designed to approximate a situation where future increases in rates of resistance will result in higher rates of infection and projected that currently observed incidence rates double in Year 1 and stay at that level indefinitely. The second modification in this group attempted to approximate a situation where one of the manifestations of rising welfare in middle income countries is an increased uptake of health care services and a converging trend in hospitalisation rates between middle and high income countries. To model this situation for the purposes of this exercise, incidence rates of HAIs in the Eurasia, MENA and LatAm zones were increased by 25%.

And second, we ran a series of sensitivity analyses to assess how much the model's final results are affected by changes in selected key parameters. In order to perform these, we replaced the original values with the upper and lower bound of available reported confidence intervals for the following parameters:

- Mortality and morbidity for all infections and diseases covered by the model
- Incidence rates of HAIs in the High region

Table 25 below summarises the conducted additional calculations. Their results are discussed in the remainder of this section. Please note that absolute resistance scenarios are not covered by these calculations as they are based on a modified set of basic parameters.

Table 25. Overview of sensitivity analyses and additional calculations

Category	Description
Alternative incidence projections	Incidence rates doubled in Year 1
	HAI incidence rates in Eurasia, MENA and LatAm increased by 25% in year 1
Sensitivity analyses	Upper bound of reported mortality and morbidity confidence intervals applied across all conditions
	Lower bound of reported mortality and morbidity confidence intervals applied across all conditions
	Upper bound of reported HAI incidence confidence intervals applied in High
	Lower bound of reported HAI incidence confidence intervals applied in High

This exhaustive set of sensitivity analysis show that within this stylized AMR framework, our results are consistent and fall within a given range. Thus, even if some of our main health assumptions are not precise, due to lack of available data, having upper and lower bound shows that we are reasonably confident of the range of the results.

6.1. Alternative incidence projections

The following two tables present the results of testing variations in incidence rates. The first approximates the possibility that resistance rates will result in increases in infection incidence rates. The second expresses the possibility that hospitalisations in middle income countries will converge with those in high income countries as a result of economic growth.

Table 26 shows that assuming double incidence rates results in a near doubling of associated costs. Table 27 demonstrates that increases in HAI incidence have a relatively small effect on the overall results of the model. This is a reflection of the fact that the overall incidence rates of HAIs in the three regions is low compared to that of infectious diseases and therefore does not have as high an effect on the overall results as would have been the case if the High incidence rate had been manipulated.

Table 26. Incidence rates doubled in Year 1: Per year GDP loss attributable to AMR, by region (average over 40 years) in USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5
High	-146.5	-37.6	-276.2	-695.9	-203.0	-375.6
Eurasia	-100.2	-39.9	-369.5	-944.8	-265.4	-521.9
MENA	-12.4	-3.9	-32.7	-98.3	-21.6	-47.0
Sub	-11.7	-10.8	-105.7	-184.2	-73.8	-127.2
Latam	-5.7	-1.9	-40.6	-72.5	-22.1	-35.0
World	-276.5	-94.3	-825.4	-1,997.2	-586.4	-1,107.7
World basic	-143.8	-53.1	-518.3	-1,233.9	-353.3	-687.4

Table 27. HAI incidence rates in Eurasia, MENA and LatAm increased by 25% in year 1: Per year GDP loss attributable to AMR, by region (average over 40 years) in billion USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5
High	-73.3	-18.9	-138.9	-353.9	-101.8	-190.0
Eurasia	-57.4	-23.4	-242.0	-628.0	-165.6	-344.7
MENA	-7.0	-2.9	-21.0	-69.1	-12.9	-32.6
Sub	-8.1	-8.3	-86.8	-137.5	-59.6	-100.1
Latam	-4.6	-1.6	-37.9	-65.6	-20.1	-31.6
World	-150.4	-55.1	-527.0	-1,255.4	-360.3	-699.9
World basic	-143.8	-53.1	-518.3	-1,233.9	-353.3	-687.4

6.2. Sensitivity analyses

The following two pairs of tables present the results of our sensitivity analyses using the confidence intervals of two basic health parameters – mortality and morbidity, and incidence of HAIs in High countries.

Table 28 and Table 29 show that applying the available upper and lower bounds of mortality and morbidity data expands the range of average costs by 40% upwards and 30% downwards, respectively. As in other calculations, this effect is not uniform across all AMR regions. In High countries, the application of the upper bound more than doubles projected costs, whereas in Sub-Saharan Africa the increase is only approximately 25%. A similar discrepancy can be observed when comparing the lower bound values to the original scenarios.

Table 28. Upper bound of reported mortality and morbidity confidence intervals applied across all conditions: Per year GDP loss attributable to AMR, by region (average over 40 years) in billion USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5
High	-165.9	-41.8	-306.0	-770.0	-227.3	-419.7
Eurasia	-105.2	-36.8	-344.3	-882.2	-250.5	-498.9
MENA	-13.6	-3.8	-31.9	-96.3	-21.5	-46.9
Sub	-11.5	-9.9	-98.8	-167.2	-70.0	-120.6
Latam	-8.5	-2.6	-45.8	-85.4	-26.4	-42.9
World	-304.6	-95.0	-827.3	-2,002.1	-596.1	-1,129.7
World basic	-143.8	-53.1	-518.3	-1,233.9	-353.3	-687.4

Table 29. Lower bound of reported mortality and morbidity confidence intervals applied across all conditions: Per year GDP loss attributable to AMR, by region (average over 40 years) in billion USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5
High	-34.3	-8.7	-64.6	-168.6	-46.9	-87.9
Eurasia	-26.4	-12.8	-163.8	-433.3	-102.0	-229.2
MENA	-3.1	-1.3	-13.5	-50.4	-7.5	-23.4
Sub	-6.1	-6.9	-76.3	-111.6	-51.5	-84.1
Latam	-2.0	-0.8	-31.8	-50.4	-15.5	-23.2
World	-71.9	-30.6	-350.4	-815.4	-223.7	-448.5
World basic	-143.8	-53.1	-518.3	-1,233.9	-353.3	-687.4

Table 30 and Table 31 show the results of the application of the confidence intervals of reported incidence rates of HAIs in High countries. While there are some effects on all regions due to the interconnectedness of the world economy, the most notable changes can logically be observed in the High region. For costs borne by High countries, the size of the change is in the region of 50% for both the upper and lower bounds.

Table 30. Upper_bound of reported HAI incidence confidence intervals applied in High: Per year GDP loss attributable to AMR, by region (average over 40 years) in billion USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5
High	-120.6	-30.5	-223.7	-565.2	-164.4	-304.4
Eurasia	-65.6	-25.3	-259.1	-670.6	-176.0	-360.2
MENA	-8.4	-2.7	-24.0	-76.6	-15.0	-35.8
Sub	-8.5	-8.4	-87.5	-139.4	-60.1	-100.9
Latam	-4.9	-1.7	-38.6	-67.5	-20.5	-32.2
World	-208.1	-68.6	-633.3	-1,520.1	-436.3	-834.0
World basic	-143.8	-53.1	-518.3	-1,233.9	-353.3	-687.4

Table 31. Lower bound of reported HAI incidence confidence intervals applied in High: Per year GDP loss attributable to AMR, by region (average over 40 years) in billion USD PV 2011

	sc00	sc1	sc2	sc3	sc4	sc5
High	-47.0	-12.4	-91.7	-236.3	-67.0	-126.4
Eurasia	-44.6	-20.5	-221.5	-577.1	-150.5	-319.6
MENA	-5.2	-2.0	-18.2	-62.1	-11.1	-29.8
Sub	-7.8	-8.2	-86.3	-136.4	-59.3	-99.6
Latam	-3.6	-1.4	-36.3	-61.7	-18.9	-29.7
World	-108.2	-44.4	-454.5	-1,074.8	-307.3	-606.0
World basic	-143.8	-53.1	-518.3	-1,233.9	-353.3	-687.4

6.3. Summary of additional calculations

The calculations presented above demonstrate the variation in the model's results and the degree to which these are affected by the manipulation of key parameters. To enable a quick high-level comparison, Table 32 presents an overview of the average yearly costs over 40 years for all the scenarios in each of the configurations described above. Perhaps surprisingly, the highest average costs are associated with one of the absolute resistance scenarios. Noteworthy rises in costs are also observed in an alternative world with doubled incidence rates, which further underscores the risks stemming from the possibility that future increases in resistance may be accompanied by increases in the number of infections.

Table 32. Summary chart of additional calculations and their comparison with original scenarios: Average yearly costs over 40 years (in billion USD PV 2011)

Calculation type	Sc0	Sc1	Sc2	Sc3	Sc4	Sc5
Basic scenarios	-143.8	-53.1	-518.3	-1,233.9	-353.3	-687.4
Absolute resistance scenarios	N/A	N/A	N/A	-3,112.6	N/A	-1,472.8
Double incidence rates	-276.5	-94.3	-825.4	-1,997.2	-586.4	-1,107.7
Eurasia, MENA, LatAm HAI incidence 25% up	-150.4	-55.1	-527.0	-1,255.4	-360.3	-699.9
CI upper bound mortality and morbidity	-304.6	-95.0	-827.3	-2,002.1	-596.1	-1,129.7
CI lower bound mortality and morbidity	-71.9	-30.6	-350.4	-815.4	-223.7	-448.5
CI upper bound HAI incidence in High	-208.1	-68.6	-633.3	-1,520.1	-436.3	-834.0
CI lower bound HAI incidence in High	-108.2	-44.4	-454.5	-1,074.8	-307.3	-606.0

7. Discussion

7.1. The size and urgency of the AMR challenge is primarily driven by potential future exorbitant costs

The main message that can be derived from the results of our model is clearly consistent with existing studies, both empirical and theoretical, on antimicrobial resistance, as outlined in Chapter 1. The current costs attributable to AMR are not necessarily large, as such do not represent a sizeable burden on the world economy and therefore may not translate into a sense of urgency.

In stark contrast with the current costs of AMR, the estimated future costs of AMR have the potential to be large, imposing a substantial cost to the world economy. This is apparent in all of our scenarios that project the estimated costs of 100% resistance rates, regardless of timing of the onset of higher resistant rates. These estimated costs are even greater in the two absolute resistance scenarios where no effective drug therapies remain, which would affect all regions of the world. The most affected areas in terms of per cent of GDP would be those with a high prevalence of malaria, HIV and/or TB, all of which currently have relatively low rates of drug resistance. However, increases in the mortality associated with untreatable hospital-acquired infections would translate into much larger costs in absolute terms in higher income areas. High projected costs were also noted in an alternative scenario where infection incidence rates were doubled to test the impact of the possibility that infection rates would go up in response to increased resistance rates.

In conclusion, while we do not want to dismiss the current impact of AMR, these findings draw attention to the fact that it is not the current burden of AMR that drives the urgency to recognise antimicrobial resistance as an important public health issue. Instead, it is the projected future costs if growing AMR is not addressed that are orders of magnitude higher and render AMR a challenge of utmost importance.

7.2. Caution is required when interpreting the model's results

Several qualifications should be added to the discussion of this study's results and their interpretation, even though these qualifications do not alter the main message from our modelling work. First and foremost, it is important to bear in mind the limited scope of our study, i.e. hospital-acquired infections caused by three bacteria and three infectious diseases. As such, our final numbers capture only a part of the whole picture and underestimate the likely extent of AMR costs.

Several additional factors further contribute to what may be perceived as surprisingly low current costs of AMR and should be highlighted here. First, in contrast with existing studies, our model includes only

costs resulting from the disruption of the supply of effective labour and does not include any other kinds of costs, such as increased health care costs. Second, our model uses AMR-specific mortality rates, rather than overall mortality from resistant infections. In other words, we do not express how many people die from resistant infections in total. Rather, we consider how many more people die because their infections are resistant compared to if these infections were susceptible to antimicrobials. In general, the guiding principle of setting the parameters for our model and making assumptions (as discussed below) was to adopt the most conservative parameters and assumptions. This may have led to an underestimation of the total costs of AMR. Nonetheless, these estimates are anchored in the most reliable data available and can therefore be linked to AMR with a reasonable degree of certainty.

Further, throughout this study, we had to make a series of assumptions to address data availability issues and uncertainties about the future. These assumptions may not be borne out in reality. For example, changes in future incidence rates, assumed constant in our model,[49] could have a large impact on the model's results. Regrettably, based on conversations with experts in the field, even the direction of the possible error in our assumptions is not clear, as conflicting factors may affect the number of future infections. For instance, the rates of hospitalisation in low and middle-income countries may increase as these countries grow richer, which may results in convergence or rates of hospital acquired infections with rates observed in high-income countries. This would of course result in a greater number of people who could be infected during their hospital stays. At the same time, countries which currently experience a high incidence of infections among hospitalised people may improve their hygiene standards, thereby bringing their infection rates more in line with those observed in high income countries. Similarly in the context of infectious diseases, incidence of infections may be expected to go up in the event of notable rises in drug resistance. At the same time, increased effectiveness of prevention strategies may counter any such developments. The potential error introduced by uncertainties such as these can be considerable. This is particularly applicable to malaria, which, of all conditions included in the scope of our work, affects the largest number of people by far and is the main driver of any results observed in Sub-Saharan Africa.

Mortality rates are also subject to considerable uncertainty, particularly given the possibility of substantial growth in multiple-drug resistant (MDR) and extensively drug resistant (XDR) strains. Our model assumes the continuation of the current mortality rates and also incorporates absolute resistance scenarios where there is not treatment available. These two types of scenarios may represent the lower and upper bound of the range in which any future mortality rates will lie.

Uncertainties surrounding mortality and incidence are the biggest challenges to the extent to which our model is realistic, but are not the only ones. An overview of other noteworthy limitations and assumptions, along with our estimations of their likely impact on our findings, are discussed in Appendix D.

[49] We reiterate that our assumptions with respect to malaria required manipulation of incidence rates. However, these were held constant over the duration of each scenario. For more details see Appendix B.

Lastly, we reiterate that our model assumes the absence of any medical breakthroughs and non-medical interventions that could decrease the burden of AMR and thus to some extent offset costs attributable to AMR. Particularly in the event of high increases in resistance with possible associated increases in incidence/mortality, it is plausible that some form of event or development would occur to alter the course of AMR and therefore diverge from the scenarios presented in this report. We recognise that some of the absolute resistance and alternative exercises presented in Chapter 6 result in very dramatic results (e.g. our most severe scenario projects a world output lower by over 3%), which may be useful as conceptual benchmarks. However, it was beyond the scope of this project to incorporate considerations of medical and non-medical advances, their costs and how they might by brought about in response to various AMR scenarios.

7.3. Full potential cost of AMR extend well beyond direct shocks to the supply of labour

It is important to keep in mind that the full potential costs of AMR amount to a world without effective antimicrobial drugs, with serious repercussions for modern health care as we know it. This is consistent with the recent recommendations made by Smith and Coast (2013a) to the UK Department of Health, which articulated a perspective in which resistance is not simply an infectious disease issue but rather "a surgical issue, a cancer issue, a health system issue." Our model recognises the importance of this perspective and includes two absolute resistance scenarios, which were intended to approximate a world with no effective drug therapy to treat the infections included in the scope of our study. The results of this model are noteworthy as they indicate the magnitude of the potential direct costs of AMR.

However, even the substantial costs estimated in these scenarios do not amount to the full potential impact of AMR. The removal of effective antimicrobial drugs from health care systems would represent a significant disruption to modern medicine, which would likely provoke behavioural changes among the wider population. For example, assuming the current prevalence of hospital acquired infections at 3.5% of hospitalisations (ECDC, 2013a) and a 70% mortality rate from an untreatable condition, such as Ebola (WHO Ebola Response Team, 2014), this would present people with an approximately 2.5% chance of dying every time they were admitted to hospital, as opposed to less than 0.05% today.[50] This likelihood of an extremely adverse outcome may be sufficiently high to dissuade people from pursuing non-essential treatment. Of course, this decision could result in substantial costs from absenteeism due to untreated conditions, or a reduction in productivity from untreated morbidity. The sheer number of hospital-based interventions performed every year suggests that these costs would not be insignificant.[51]

Furthermore, indirect costs attributable to AMR from behavioural changes in response to extremely high rates of resistance and mortality can have an effect on entire economic sectors. For instance, it is

[50] Based on estimated 25,000 deaths due to resistant infections out of ca. 90 million hospital discharges in countries monitored by the ECDC (ECDC, 2013a).

[51] For instance, in the United States alone, the number of inpatient surgeries performed in 2010 was 51.4 million (CDC/NCHS National Hospital Discharge Survey, 2010).

conceivable that faced with the prospect of no existing antimalarials, travel to and commercial relations with certain regions with a high prevalence of malaria would be severely restricted. Drawing another parallel with the aforementioned example of Ebola, this type of effect has been observed in response to the recent outbreak, impacting not only most affected countries but also more broadly elsewhere in Africa (The Economist 2014).

Unfortunately, the estimation of these indirect costs was beyond the scope of this study and thus could not be included in our analysis. Therefore, even the estimates from the absolute resistance scenarios in our model should be understood only as part of the overall potential costs of AMR. This is a crucial point to emphasise and further reinforces the main message from our model that current observed costs of AMR are very small in comparison with the potential future ones.

8. Conclusion

The results of our modelling exercise suggest that the size of current costs associated with AMR effects on the supply of effective labour is dwarfed by their potential increases that could be observed in the event of substantial rises in rates of antimicrobial resistance in the future. Final results vary substantially across all the scenarios included in our model, perhaps unsurprisingly, given the wide variety of projected resistance rates and the duration of their projection. However, they all demonstrate that potential future annual costs of AMR are probably in the region of whole percentage points of GDP (3.1% of global output, ranging from 2.3% in the High zone to 10% in Sub-Saharan Africa in the absolute resistance scenario). Most importantly, this value refers only to direct costs attributable to the impact on the labour supply over time. It is conceivable that the inclusion of additional indirect costs in our calculations would have resulted in significantly higher estimates.

On a final note, it is worth reiterating that the findings of this study should not be understood as a definitive answer to the question of current and future AMR costs, but rather as a building block contributing towards the construction of a more comprehensive estimate. Two areas of future research stand out in particular to further the work undertaken here. First, lack of data with respect to conditions not covered by the scope of this study constitutes an important limitation of our work, and efforts to fill data gaps are necessary to allow a more exhaustive assessment of both current and future AMR costs. Second, and perhaps more importantly, there exists no authoritative attempt to estimate the secondary costs of AMR that may occur as a result of limited or no availability of effective drugs. Filling this gap would go a long way towards communicating and strengthening the case for action in the area of antimicrobial stewardship and new drug development.

List of references

Acemoglu D. (2009). Introduction to Modern Economic Growth. Princeton and Oxford, Princeton University Press.

Ajose, O., Mookerjee, S., Mills, E. J., & Ford, N. (2012). Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: A systematic review and meta-analysis. AIDS, 26(8), 929-938. doi: 10.1097/QAD.0b013e328351f5b2

Al-Ali, H. (2012). The Social Accounting Matrix (SAM) for Jordan, 2006. Available from http://iraqieconomists.net/en/wp-content/uploads/sites/7/2013/11/The-Final-JOSAM-Report-15-April-12.pdf [last accessed: 29 October 2014]

Alkema, L., Raftery, A. E., Gerland, P., Clark, S. J., Pelletier, F., Buettner, T., & Heilig, G. K. (2011). Probabilistic projections of the total fertility rate for all countries. Demography, 48(3), 815-839. doi: 10.1007/s13524-011-0040-5

Armington, P. S. (1969). A theory of demand for products distinguished by place of production. International Monetary Fund Staff Papers, 16(1), 159-178.

Bhutta, Z. A., Sommerfeld, J., Lassi Z. S., Salam, R. A., & Das, J. K. (2014). Global burden, distribution, and interventions for infectious diseases of poverty. Infectious Diseases of Poverty, 3:21, 1-7. doi: 10.1186/2049-9957-3-21

Borger, C., Rutherford, T. F., & Won, G. Y. (2008). Projecting long term medical spending growth. Journal of Health Economics, 27(1), 69-88. doi: 10.1016/j.jhealeco.2007.03.003

Breisinger, C., Thurlow, J., & Duncan, M. (2007). A 2005 Social Accounting Matrix (SAM) for Ghana. Ghana; Washington, D.C.: Ghana Statistical Services (GSS); International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/ghana [last accessed: 29 October 2014]

Bruneel, F., Hocqueloux L., Alberti, C., Wolff, M., Chevret, S., Bédos, J.-P., … Vachon, F. (2003). The clinical spectrum of severe imported falciparum malaria in the intensive care unit: Report of 188 cases in adults. American Journal of Respiratory and Critical Care Medicine, 167(5), 684-689. doi: 10.1164/rccm.200206-631OC

Carter, R. and Mendis, K.N. (2002) Evolutionary and Historical Aspects of the Burden of Malaria. Clinical Microbiology Review 15(4): 564–594

CATIE. (n.d.). Factsheet: The epidemiology of HIV in Canada. Retrieved from http://www.catie.ca/sites/default/files/epi-hiv-can-en.pdf [last accessed: 27 October 2014]

CDC/NCHS National Hospital Discharge Survey, 2010. Summary available at http://www.cdc.gov/nchs/data/nhds/4procedures/2010pro4_numberprocedureage.pdf [last accessed 29 October 2014]

Centers for Disease Control and Prevention. (2012). CDC Factsheet: New HIV infections in the United States. Retrieved from http://www.cdc.gov/nchhstp/newsroom/docs/2012/HIV-Infections-2007-2010.pdf [last accessed: 27 October 2014]

Centers for Disease Control and Prevention. (2014a). 2014 Ebola Outbreak in West Africa - Case Counts. Available from http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html [last accessed 18 November 2014]

Centers for Disease Control and Prevention. (2014b). National and state healthcare associated infections progress report. Retrieved from http://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf [last accessed: 27 October 2014]

Chambers, HF and DeLeo (2009) Waves of Resistance: Staphylococcus aureus in the Antibiotic Era. Nat Rev Microbiol 7(9): 629–641.

Coates, ARM, Halls, G and Hu, Y (2011) Novel classes of antibiotics or more of the same? Br J Pharmacol. 163(1): 184–194.

Cobb, C. and Douglas, H. (1928). "A Theory of Production". American Economic Review 18: 139-165.

Contreras, D., Ramos, J., & Montero, R. (2005). A 1996 Social Accounting Matrix (SAM) for Chile. Washington, D.C.: International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/chile [last accessed: 29 October 2014]

Dalal, R. P., MacPhail, C., Mqhayi, M., Wing, J., Feldman, C., Chersich, M. F., & Venter, W. (2008). Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa. Journal of Acquired Immune Deficiency Syndromes, 47(1), 101-107. doi: 10.1097/QAI.0b013e31815b833a

Davies, R., & Thurlow, J. (2013) A 2009 Social Accounting Matrix (SAM) for South Africa. Washington, D.C.: International Food Policy Research Institute (IFPRI). Available from http://ebrary.ifpri.org/cdm/ref/collection/p15738coll2/id/128029 [last accessed: 29 October 2014]

Davies, S. C. (2013). Annual report of the Chief Medical Officer 2013. Retrieved from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/351629/Annual_report_2013_1.pdf [last accessed: 27 October 2014]

Debowicz, D. (2013). A Social Accounting Matrix for Iraq, 2011. Washington, D.C.: International Food Policy Research Institute (IFPRI). Available from http://ebrary.ifpri.org/cdm/ref/collection/p15738coll2/id/128189 [last accessed 29 October 2014]

Debowicz, D., Dorosh, P. A., Robinson, S., & Haider, S. H. (2012). A 2007-2008 Social Accounting Matrix for Pakistan. Washington, D.C.: International Food Policy Research Institute

(IFPRI)(datasets). Available from http://hdl.handle.net/1902.1/19361 [last accessed: 29 October 2014]

Department of Health (2014). Press release: Prime Minister warns of global threat to antibiotic resistance. Retrieved from https://www.gov.uk/government/news/prime-minister-warns-of-global-threat-of-antibiotic-resistance [last accessed: 27 October 2014]

Dervis, K., {de Melo}, J., Robinson, S., 1982. General Equilibrium Models for Development Policy. Cambridge University Press.

Dewhurst, J., Kerwat, J., & Molana, H. (2011). Constructing a social accounting matrix for Libya. The Journal of North African Studies, 16(1), 143-160. doi: 10.1080/13629387.2010.510635

Dixon, S., McDonald, S., & Roberts, J., (2004). AIDS in Botswana: Evaluating the general equilibrium implications of healthcare interventions. HEDS Discussion Paper 04/07. Retrieved from http://eprints.whiterose.ac.uk/10937/ [last accessed: 17 June 2012]

Dowling, A., O'Dwyer, J., & Adley, C. C. (2013). Alternatives to antibiotics: future trends. In A. Mendez-Vilas (Ed.), Microbial pathogens and strategies for combating them: Science, technology and education (pp. 216-226). Badajoz: Formatex Research Center.

European Centre for Disease Prevention and Control, & World Health Organisation Regional Office for Europe (2013). Joint press release: HIV infections up by 8% across Europe. Retrieved from http://ecdc.europa.eu/en/press/Press%20Releases/press-release-world-aids-day-2013.pdf [last accessed: 27 October 2014]

European Centre for Disease Prevention and Control. (2013a). Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC. Retrieved from http://www.ecdc.europa.eu/en/publications/publications/0512-ted-pps-hai-antimicrobial-use-protocol.pdf [last accessed: 27 October 2014]

European Centre for Disease Prevention and Control. (2013b). Thematic report: HIV treatment, care and support. Monitoring implantation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2012 progress report. Stockholm: ECDC. Retrieved from http://www.ecdc.europa.eu/en/publications/Publications/dublin-declaration-treatment-care-support.pdf [last accessed: 27 October 2014]

European Commission. (2014). Eurostat: Your key to European statistics. Retrieved from http://epp.eurostat.ec.europa.eu/portal/page/portal/esa95_supply_use_input_tables/data/database [last accessed: 29 October 2014]

Eyre, M. (2014) Novel antibiotic class created. Available from: http://www.bbc.com/news/health-29306807 [last accessed 17 November 2014].

Falagas, ME and Karveli, EA (2006) Clinical Infectious Diseases 43:630–3

Fox, M. P., Ive, P., Long, L., Maskew, M., & Sanne, I. (2010). High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa.

Journal of Acquired Immune Deficiency Syndromes, 53(4), 500–506. doi: 10.1097/QAI.0b013e3181bcdac1

Global Fund. (2014). Fighting AIDS, tuberculosis and malaria. Retrieved from http://www.theglobalfund.org/en/about/diseases/ [last accessed: 5 October 2014]

Hosseinipour, M. C., Kumwenda, J. J., Weigel, R., Brown, L. B., Mzinganjira, D., Mhango, B., … van Oosterhout, J. J. (2010). Second-line treatment in Malawi antiretroviral programme: High early mortality, but good outcomes in survivors, despite extensive drug resistance at baseline. HIV Medicine, 11(8), 510-518. doi: 10.1111/j.1468-1293.2010.00825.x

Hunsinger, E. (n.d.). Applied demography toolbox: Tim Chapin's cohort component model spreadsheet. Retrieved from http://www.demog.berkeley.edu/~eddieh/toolbox.html#CohortComponent [last accessed: 1 October 2014]

International Food Policy Research Institute (IFPRI) (2002) Egypt: Social Accounting Matrix, 1997. Washington, D.C.: International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/egypt-0 [last accessed 29 October 2014]

International Food Policy Research Institute (IFPRI) (2003). Brazil: Social Accounting Matrix, 1995-1996. Washington, D.C.: International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/brazil [last accessed: 29 October 2014]

International Food Policy Research Institute (IFPRI) (n.d.). International Food Policy Research Institute home page. Retrieved from http://www.ifpri.org/ [last accessed: 29 October 2014]

International Food Policy Research Institute (IFPRI). (2014a). A 2009 Social Accounting Matrix (SAM) database for South Africa. Washington, D.C.: International Food Policy Research Institute (IFPRI). Available from http://dx.doi.org/10.7910/DVN/24774 [last accessed 29 October 2014]

International Food Policy Research Institute (IFPRI). (2014b). Iraq Social Accounting Matrix, 2011. Washington, D.C.: International Food Policy Research Institute (dataset). Available from http://dx.doi.org/10.7910/DVN/26587 [last accessed 29 October 2014]

International Monetary Fund. (2011). IMF eLibrary – Data. Available from http://elibrary-data.imf.org/DataExplorer.aspx [last accessed: 6 October 2014]

Jiménez, W. (2005). A 1996 Social Accounting Matrix (SAM) for Bolivia. Washington, D.C.: International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/bolivia [last accessed: 29 October 2014]

Kambou, G., Devarajan, S., & Over, M. (1992). The economic impact of AIDS in an African country: Simulations with a computable general equilibrium model of Cameroon. Journal of African Economies, 1(1), 109-130.

Kiringai, J., Thurlow, J., & Wanjala, B. (2006). A 2003 Social Accounting Matrix for Kenya. Nairobi; Washington, D.C.: Kenya Institute for Public Policy Research and Analysis (KIPPRA); International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/kenya-social-accounting-matrix-sam-2003 [last accessed: 29 October 2014]

Kollef, M. H., Golan, Y., Micek, S. T., Shorr, A. F., & Restropo, M. I. (2011). Appraising contemporary strategies to combat multidrug resistant gram-negative bacterial infections: Proceedings and data from the gram-negative resistance summit. Clinical Infectious Diseases, 53(suppl 2), S33-S55. doi: 10.1093/cid/cir656

Laens, S. (2005). A 1995 Social Accounting Matrix (SAM) for Uruguay. Washington, D.C.: International Food Policy Research Institute (IFPRI)(datasets). Available from http://www.ifpri.org/dataset/uruguay [last accessed: 29 October 2014]

Lofgren, H., Harris, R.L., Robinson, S., 2002. A Standard Computable General Equilibrium (CGE) Model in GAMS.

Lubell, Y., Staedke, S. G., Greenwood, B. M., Kamya, M. R., Molyneux, M., Newton, P. N., … Whitty, C. J. (2011). Likely health outcomes for untreated acute febrile illness in the tropics in decision and economic models; A Delphi survey. PLOS ONE, 6(2), 1-9. doi: 10.1371/journal.pone.0017439

Lundgren, C. (2010) Wage policy and fiscal sustainability in Benin. Washington, D.C.: International Monetary Fund, 2010.

Magill, S. S., Edwards, J. R., Bamberg, W., Beldavs, Z. G., Dumyati, G., Kainer, M. A., … Fridkin, S. K. (2014). Multistate point-prevalence survey of health care-associated infections. The New England Journal of Medicine, 370(13), 1198-1208. doi: 10.1056/NEJMoa1306801

Magiorakos, AP et al. (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 18(3):268-81.

Maskew, M., MacPhail, P., Menezes C., & Rubel, D. (2007). Lost to follow up: Contributing factors and challenges in South African patients on antiretroviral therapy. South African Medical Journal, 97(9), 853-857.

Mathiesen, L. (1985). Computation of economic equilibria by a sequence of linear complementarity problems. Mathematical Programming Studies, 23, 144-162.

Mendis, K., Sina, B. J., Marchesini, P., & Carter, R. (2001). The neglected burden of Plasmodium vivax malaria. American Journal of Tropical Medicine and Hygiene, 64(1), 97-106.

Mishra, S. K., Panigrahi, P., Mishra, R., & Mohanty, S. (2007). Prediction of outcome in adults with severe falciparum malaria: A new scoring system. Malaria Journal, 6, 24-27. doi: 10.1186/1475-2875-6-24

Mohanty, S., Mishra, S. K., Pati, S. S., Pattnaik J. , & Das, B. S. (2003). Complications and mortality patterns due to Plasmodium falciparum malaria in hospitalized adults and children, Rourkela, Orissa, India. Transactions of the Royal Society of Tropical Medicine and Hygiene, 97(1), 69-70. doi: 10.1016/S0035-9203(03)90027-7

Molinas, J. R., Cabello, C., & Corvalán, J. R. (2005). A 1998 Social Accounting Matrix (SAM) for Paraguay. Washington, D.C.: International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/paraguay [last accessed: 29 October 2014]

National Bureau of Statistics of China (2013). China Statistical Yearbook 2013. Beijing: China Statistics Press. Available from http://www.stats.gov.cn/tjsj/ndsj/2013/indexeh.htm [last accessed: 31 October 2014]

Nicasio, A. M., Kuti, J. L., & Nicolau, D. P. (2008). The current state of multidrug-resistant gram-negative bacilli in North America. Pharmacotherapy, 28(2), 235-249. doi: 10.1592/phco.28.2.235

Oppong, R., Jit, M., Smith, R. D., Butler, C. C., Melbye, H., Mölstad, S., & Coast, J. (2013). Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. British Journal of General Practice, 63(612), e465-e471. doi: 10.3399/bjgp13X669185

Petri, G. L., & Parra, M. M. (2005). A 2000 Social Accounting Matrix (SAM) for Argentina. Washington, D.C.: International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/argentina [last accessed: 29 October 2014]

Phu, N. H., Tuan, P. Q., Day, N., Mai, N. T. H., Chau, T. T. H., Chuong, L. V., … Hien, T. T. (2010). Randomized controlled trial of artesunate or artemether in Vietnamese adults with severe falciparum malaria. Malaria Journal, 9, 97-106.

Pyatt and Round (1985) Social Accounting Matrices: A Basis for Planning, The World bank.

Ramsey, F. (1928). A Mathematical Theory of Saving. Economic Journal 38 (152):543-559.

Rutherford, T.F. (1995) Extension of GAMS for complementarity problems arising in applied economic analysis. Journal of Economic Dynamics and Control, Journal of Economic Dynamics and Control 19, 1299–1324.

Rutherford, T.F., (1999) Applied General Equilibrium Modeling with MPSGE as a GAMS Subsystem: An Overview of the Modeling Framework and Syntax. Computational Economics 14, 1–46.

Rutten, M., & Reed, G. (2009). A comparative analysis of some policy options to reduce rationing in the UK's NHS: Lessons from a general equilibrium model incorporating positive health effects. Journal of Health Economics, 28(1), 221-233. doi:10.1016/j.jhealeco.2008.10.002.

Sarkar, P. K., Ahluwalia, G., Vijayan, V. K., & Talwar, A. (2010) Critical care aspects of malaria. Journal of Intensive Care Medicine, 25(2), 93-103. doi: 10.1177/0885066609356052

Sertkaya, A., Eyraud, J., Birkenback, A., Franz, C., Ackerley, N., Overton, V., & Outterson, K. (2014). Analytical framework for examining the value of antibacterial products. Report prepared for the U.S. Department of Health and Human Services. Retrieved from http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm

Shoven, J.B., Whalley, J., 1992. Applying general equilibrium. Cambridge University Press.

Silver, L.L. (2011) Challenges of Antibacterial Discovery. Clinical Microbiology Reviews 24:71-109.

Smith, R. D., Keogh-Brown, M. R., Barnett, T., & Tait, J. (2009). The economy-wide impact of pandemic influenza on the UK: A computable general equilibrium modelling experiment. British Medical Journal, 339, b4571. doi:10.1136/bmj.b4571

Smith, R. D., Yago, M., Millar, M., & Coast, J. (2005). Assessing the macroeconomic impact of a healthcare problem: The application of computable general equilibrium analysis to antimicrobial resistance. Journal of Health Economics, 24(6), 1055–1075. doi:10.1016/j.jhealeco.2005.02.003

Smith, R., and Coast, J. (2013a) The economic burden of antimicrobial resistance: Why it is more serious than current studies suggest. Independent research commissioned and funded by the Department of Health Policy Research Programme (Economic burden of antimicrobial resistance: a rapid paper, 0410035).

Smith, R., and Coast, J. (2013b). The true cost of antimicrobial resistance. British Medical Journal, 346, f1493. doi: 10.1136/bmj.f1493

Snow, R. W., & Giles, H. M. (2002). The epidemiology of malaria. In D. A. Warrell and H. M. Gilles (Eds.), Essential Malariology (4th ed.) (pp. 85-106). London: Arnold Publishers.

Spellberg, B., Blaser, M., Guidos, R. J., Boucher, H. W., Bradley, J. S., Eisenstein, B. I., ... Gillbert, D. N. (2011). Combating antimicrobial resistance: Policy recommendations to save lives. Clinical Infectious Diseases, 52(S5), S397-S428. doi: 10.1093/cid/cir153

Stadeli, K. M., & Richman, D. D. (2013). Rates of emergence of HIV drug resistance in resource limited settings: A systematic review. Antiviral Therapy, 18, 115-23. doi: 10.3851/IMP2437

The Economist (2014) The ignorance epidemic. November 15th, 2014.

The UK Collaborative Group on HIV Drug Resistance, & UK CHIC Study Group. (2005). Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. AIDS, 19(5), 487-494.

Thurlow, J., Robinson, S., & Evans, D. (2005). A 2001 Social Accounting Matrix (SAM) for Zambia. Washington, D.C.: International Food Policy Research Institute (IFPRI) (datasets). Available from http://www.ifpri.org/dataset/zambia-0 [last accessed: 29 October 2014]

Tiemersma E. W., van der Werf, M. J., Borgdorff, M. W., Williams, B. G., & Nagelkerke, N. J. D. (2011). Natural history of tuberculosis: Duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: A systematic review. PLOS ONE, 6(4), e17601. doi:10.1371/journal.pone.0017601

Timmer, M. P. (Ed.) (2012). The World input-output database (WIOD): Contents, sources and methods. WIOD Working Paper Number 10. Retrieved from http://www.wiod.org/publications/papers/wiod10.pdf [last accessed: 31 October 2014]

Trading Economics. (2014a). Adjusted savings: Gross savings (% of GNI) in Middle East and North Africa. Available from http://www.tradingeconomics.com/middle-east-and-north-africa/adjusted-savings-gross-savings-percent-of-gni-wb-data.html [last accessed 29 October 2014]

Trading Economics. (2014b). Adjusted savings: Gross savings (% of GNI) in Latin America and Caribbean. Available from http://www.tradingeconomics.com/latin-america-and-caribbean/adjusted-savings-gross-savings-percent-of-gni-wb-data.html [last accessed 29 October 2014]

Trading Economics. (2014c). Gross savings (% of GDP) in high income. Available from http://www.tradingeconomics.com/high-income/gross-savings-percent-of-gdp-wb-data.html [last accessed 29 October 2014]

Trading Economics. (2014d). Gross savings (% of GDP) in Sub Saharan Africa. Available from http://www.tradingeconomics.com/sub-saharan-africa/gross-savings-percent-of-gdp-wb-data.html [last accessed 29 October 2014]

UNAIDS. (2014a). Ambitious treatment targets: Writing the final chapter of the AIDS epidemic. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/JC2670_UNAIDS_Treatment_Targets_en.pdf [last accessed 15 October 2014]

UNAIDS. (2014b). The gap report. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf [last accessed: 15 October 2014]

United Nations, Department of Economic and Social Affairs. (2014). World population prospects: The 2012 revision. Retrieved from http://esa.un.org/wpp/ [last accessed: 31 October 2014]

White, N. (1999). Editorial: Antimalarial drug resistance and mortality in falciparum malaria. Tropical Medicine and International Health, 4(7), 469–470. doi: 10.1046/j.1365-3156.1999.00435.x

White, N. J. (2004). Antimalarial drug resistance. Journal of Clinical Investigation, 113(8),1084–1092. doi: 10.1172/JCI21682

WHO Ebola Response Team. (2014). Ebola virus disease in West Africa—The first 9 months of the epidemic and forward projections. The New England Journal of Medicine, 371, 1481-1495. doi: 10.1056/NEJMoa1411100

World Bank. (2014a). Data: Country and Lending Groups. Available from http://data.worldbank.org/about/country-and-lending-groups [last accessed: 30 October 2014]

World Bank. (2014b). World DataBank: Explore. Create. Share: Development Data. Available from http://databank.worldbank.org/data/home.aspx [last accessed 6 October 2014]

World Economic Forum. (2013). Global Risks 2013: Eighth edition. Retrieved from http://www3.weforum.org/docs/WEF_GlobalRisks_Report_2013.pdf [last accessed 19 August 2014].

World Health Organization (2010). Global report on antimalarial drug efficacy and drug resistance: 2000-2010. Retrieved from http://www.who.int/malaria/publications/atoz/9789241500470/en/ [last accessed: 31 October 2014]

World Health Organization (2011) Report on the burden of endemic health care-associated infection worldwide: A systematic review of the literature. Retrieved from http://whqlibdoc.who.int/publications/2011/9789241501507_eng.pdf [last accessed: 31 October 2014]

World Health Organization (2012a) The evolving threat of antimicrobial resistance: options for action. Available from: http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf [last accessed 19 August 2014].

World Health Organization (2012b) WHO HIV drug resistance report 2012. Retrieved from http://www.who.int/hiv/pub/drugresistance/report2012/en/ [last accessed: 31 October 2014]

World Health Organization (2013a). Global Tuberculosis Report 2013.

World Health Organization (2013b). Global update on HIV treatment 2013: Results, impact and opportunities. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130630_treatment_report_en.pdf [last accessed 15 October 2014]

World Health Organization (2013c). WHO Multi-Country Studies Data Archive. Available from http://apps.who.int/healthinfo/systems/surveydata/index.php/catalog/central [last accessed: 14 October 2014]

World Health Organization (2013d). World Malaria Report 2013. Retrieved from http://www.who.int/malaria/publications/world_malaria_report_2013/report/en/ [last accessed: 27 October 2014]

World Health Organization (2014a) Antimicrobial resistance: global report on surveillance 2014. Available from http://www.who.int/drugresistance/documents/surveillancereport/en/ [last accessed 6 October 2014]

World Health Organization (2014b). Global Health Observatory Data Repository. Available from http://apps.who.int/gho/data/node.main [last accessed: 17 October 2014]

World Health Organization (n.d.) Multi-Country Studies Data Archive. Available from http://apps.who.int/healthinfo/systems/surveydata/index.php/catalog/central [last accessed 14 October 2014]

Yerushalmi, E., Hunt, P., Hoorens, S., Sauboin, C., & Smith, R., (2014). Is reducing early childhood malaria an economic benefit, burden or both? Manuscript submitted for publication.

Zhang, Y., & Diao, X. (2013). A 2007 south Matrix for China. Washington, D.C.: International Food Policy Research Institute (IFPRI). Available from http://hdl.handle.net/1902.1/21132 [last accessed: 29 October 2014]

Appendix A: Regional groupings

Table 33. Allocation of countries to individual AMR regions

High	Eurasia	Latin America	MENA	Sub-Saharan
Andorra	Afghanistan	Antigua and Barbuda	Algeria	Angola
Australia	Albania	Argentina	Bahrain	Benin
Austria	Armenia	Bahamas	Egypt	Botswana
Belgium	Azerbaijan	Barbados	Iran	Burkina Faso
Bulgaria	Bangladesh	Belize	Iraq	Burundi
Canada	Belarus	Bermuda	Jordan	Cameroon
Chile	Bhutan	Bolivia	Kuwait	Cape Verde
Croatia	Bosnia and Herzegovina	Brazil	Lebanon	Central African Republic
Cyprus	Brunei	Cayman Islands	Libya	Chad
Czech Republic	Cambodia	Colombia	Morocco	Comoros
Denmark	China	Costa Rica	Oman	Congo
Estonia	North Korea	Cuba	Qatar	Cote d'Ivoire
Finland	Fiji	Dominica	Saudi Arabia	Dem. Republic of the Congo
France	Georgia	Dominican Republic	Syrian Arab Republic	Djibouti
Germany	Hong Kong	Ecuador	Tunisia	Equatorial Guinea
Greece	India	El Salvador	United Arab Emirates	Eritrea
Hungary	Indonesia	Grenada	Yemen	Ethiopia
Iceland	Kazakhstan	Guatemala		Gabon
Ireland	Kosovo	Guyana		Gambia
Israel	Kyrgyzstan	Haiti		Ghana
Italy	Laos	Honduras		Guinea

Japan	Macao	Jamaica	Guinea-Bissau
Latvia	Malaysia	Nicaragua	Kenya
Lithuania	Maldives	Panama	Lesotho
Luxembourg	Marshall Islands	Paraguay	Liberia
Malta	Micronesia	Peru	Madagascar
Mexico	Moldova	Saint Kitts and Nevis	Malawi
Monaco	Mongolia	Saint Lucia	Mali
Netherlands	Montenegro	Saint Vincent and the Grenadines	Mauritania
New Zealand	Myanmar	Suriname	Mauritius
Norway	Nepal	Trinidad and Tobago	Mozambique
Poland	Pakistan	Uruguay	Namibia
Portugal	Palau	Venezuela	Niger
Republic of Korea	Papua New Guinea		Nigeria
Romania	Philippines		Rwanda
San Marino	Russia		Sao Tome and Principe
Slovakia	Samoa		Senegal
Slovenia	Serbia		Seychelles
Spain	Singapore		Sierra Leone
Sweden	Solomon Islands		Somalia
Switzerland	Sri Lanka		South Africa
Turkey	Tajikistan		South Sudan
United Kingdom	Macedonia		Sudan
USA	Thailand		Swaziland
	Timor-Leste		Tanzania
	Tonga		Togo
	Turkmenistan		Uganda
	Tuvalu		Zambia
	Ukraine		Zimbabwe
	Uzbekistan		
	Vanuatu		
	Viet Nam		

Appendix B: Detailed discussion of health data components

Below follows a detailed overview of health data used in the course of the project. It follows the same structure for each of the conditions included in the scope of the study and addresses the following categories of data – incidence rates, resistance rates and AMR-attributable mortality and morbidity.

Hospital acquired infections

Incidence rate

For OECD/EU/EEA countries, we base our analysis on a 2011/2012 point prevalence survey of hospital-acquired infections (HAIs) in European acute care hospitals conducted by the ECDC (2013a).[52] This document estimates that there were approximately 3.2 million patients who acquired an infection (irrespective of type and causal microorganism) during their stay in hospital, which corresponds to an incidence rate of 622.9 HAIs per 100,000 general population. The same document further offers a breakdown of these HAIs by the isolated microorganism in question, which enables us to express bacterium-specific incidence rates. There are presented in the table below.

Table 34. Incidence rates of hospital acquired infections in High region

Bacterium	Incidence rate (per 100,000 population)
E.coli	99.05
K. pneumoniae	54.20
S. aureus	76.62

Source: Own calculations based on ECDC (2013a).

Several comments should be made with respect to this approach. First and foremost, it is likely to result in a slight underestimation of the actual number of HAIs as the point prevalence survey does not cover other

[52] The initial plan to collect data on the incidence of HAIs was to use data collected by national health authorities according to ICD-10 classification. However, upon analyzing collected data, it was clear that this would result in a substantial underestimate as the vast majority of recorded conditions did not specify the causal agent. For instance, while there exists a separate line for Septicaemia due to Staphylococcus aureus (A41.0), numbers recorded under this code are generally dwarfed by those recorded under A41.9 Septicaemia, unspecified. It is likely that some of the cases recorded under the latter code were in fact caused by *S. aureus*; however, there is no reliable way to ascertain how many.

health care facilities where presumably an infection can be acquired. That said, these largely focus on residential care for the elderly, which is why we are confident that their omission is not going to substantially affect our estimation of labour force effects. In addition, this approach is also desirable for the purposes of internal consistency as it matches the scope for calculating the number of HAIs in other world regions.[53]

We apply the findings from the European prevalence survey across all countries in the OECD/EU/EEA region. The reason for this decision is the fact that the survey already covers the vast majority of countries in the region and a desire to avoid issues arising from incompatibility of studies taken from across various other contexts due to factors such as different classification of health care facilities etc. As a validity check, we reviewed a survey of hospital acquired infections conducted by the US Centers for Disease Control and Prevention (Magill et al., 2014) and found the prevalence of HAIs roughly comparable to European data (4% vs 3.5% of hospitalisations). The same was broadly true of the relative frequency of isolated microorganisms, though there were deviations to the order of a few percentage points.

For other world regions, we were regrettably unable to find a similarly systematic source of data, either from an international organization or collected at the national level. Instead, we combine two other WHO sources to arrive at an estimation of the number of hospital acquired infections in non-OECD countries.

First, we use a literature review of studies on the prevalence of hospital acquired infections in lower and middle income countries conducted by the WHO (2011). This review includes data from 20 non-OECD countries on the proportion of hospital patients who acquire an infection during their hospital stay. We allocate the included countries into their respective regions and took an average of the observed infection rates. Unfortunately, this source uses as the denominator the number of hospital admissions recorded in the included studies without indicating the absolute number of recorded HAIs. In order to be able to use the findings of this review, the total number of hospital admissions in non-OECD countries is necessary.

Unfortunately, these data are not collected on a systematic basis in lower- and middle-income countries so we turn to the WHO World Health Survey (WHS), which covers a selection of low-, middle- and high-income countries (WHO, n.d.). The survey asked a randomly-selected person in each household about his or her use of inpatient care, which can be used to arrive at the approximate rate of hospital admissions in non-OECD countries. Applying the average hospitalization rate in a given region to the average infection rate then yields an approximate HAI incidence rate. Since there is no available breakdown of infections by their causal microorganisms, we apply the same relative frequency as in the OECD countries.

Of course, this approach has several limitations. Data are not available for every country, and by splitting available data point across multiple regions, further accentuates the data scarcity challenge. For the relative

[53] It should be added that this is not the only possible approach to calculating the number of HAIs in Europe. Another option is to use the number of isolates with the three microorganism of interest from European laboratories serving hospitals and other health care facilities and adjust the number by the coverage ratio of these laboratories, i.e. the proportion of population they are presumed to cover. The downside of this approach is that the coverage ratios vary substantially across European countries, ranging from as low as 5% to as high as 100%. The ratios for large European countries tend to be on the lower side of the range, which increases the possible error in the calculation.

frequency of individual pathogens there are no data at all. In addition, the latest available WHS data are from 2003, which means they do not capture any changes in health care utilization in the past ten years. And finally, the question on past year's use of inpatient medical care records only binary yes/no answers, i.e. does not indicate the number of contacts by a given respondent and may thus somewhat underestimate the true number of hospitalisations and, by extension, infections.

Resistance rate

Resistance rates are drawn from studies included in a systematic review conducted by the WHO (2014a) and reported in the 2014 global report on AMR surveillance. We are confident that this document represents the best available data as it presents the results of a meta-analysis of published studies on antimicrobial resistance. For EU countries, we complement the WHO Handbook with data from the European database EARSNet for cross-validation purposes. Resistance rates are reported by individual bacteria and by classes of drugs the resistance in question is applicable to. For our model we allocate countries to their respective regions and use an average of studies across each individual class of drugs and then average those out for individual bacteria.[54]

This approach necessitates the research team to make two assumptions. First, we assume resistance data based on a small number of observational studies, often using a small sample, from a series of specific contexts can be broadly applied to individual AMR zones.

Second, in the case of infections caused by individual bacteria in High countries, we are not able to give any special consideration to multiple or extended drug resistance (MDR/XDR). The only available resistance data on the three bacteria included in our study refer to instances of resistance to one class of drugs only. We recognise that, while reported multiple drug resistance is not necessarily very prevalent today, it is frequently cited as a major concern going forward. Therefore, this assumption might result in an underestimation of the true cost of AMR, particularly in its future projections.

AMR-attributable mortality

Data on AMR-attributable mortality are also based on values reported by the WHO (2014) in the latest report on AMR surveillance, which presented the results of a literature review on the differences in clinical outcomes between treating resistant and susceptible infections. For our model, we use the mean value reported for bacterium-attributable mortality, expressed as additional deaths per 1,000 infections. Regrettably, the data cannot be disaggregated by regions and therefore the same rate is applied across all five regions in our model.

For the extreme scenario approximating a world without effective drug therapy, we apply fatality rates observed in another context where there is no treatment available – the 2014 Ebola outbreak in Western Africa. Given the recency of the event, there is not a single authoritative source that could be used; in its

[54] The last step is not necessary for *S. aureus* as the data all referred only to resistance to methicillin.

absence and after consultation with the Review Team and external experts, we use a rate of **40%** and apply it across all hospital acquired infections.[55]

AMR-attributable time outside of labour force

Data on AMR-attributable time outside of labour force are based on values reported by the WHO (2014a), which presented the results of a literature review on the differences in clinical outcomes between treating resistant and susceptible infections. For our model, we use the mean value reported for length of stay, expressed as additional days in hospital per infection. Regrettably, the data cannot be disaggregated by regions and therefore the same rate is applied across all five regions in our model. The main assumption in this area is the same as the one discussed in the section on resistance rates. We assume that mortality and morbidity data based on a small number of observational studies, usually country-specific ones, can be broadly applied to entire AMR zones.

HIV

Incidence rate

Our model assumed that the population that is potentially affected by drug resistance consists of all new HIV cases in a given year that are undergoing antiretroviral therapy (ART). This assumption likely underestimated the number of drug-resistant cases because cases of acquired drug resistance,[56] even after the first year in treatment, have been documented (Stadeli and Richman, 2013). However, data on the extent of drug-resistant cases in later years of the infection are scarce as existing WHO studies on acquired drug resistance generally have follow-up periods of about 12 months.

In order to estimate the baseline incidence per 100,000 people, we used WHO data on new HIV per year, which are available from the Joint United Nations Programme on HIV/AIDS (UNAIDS) Gap report (UNAIDS, 2014b). The breakdown of new HIV cases is available for two age groups – 0-14 and 15 and older. To reflect the fact that not all people diagnosed with HIV receive ART, we adjusted this number by UNAIDS's existing regional estimates of ART coverage (see table below).[57] Please note that the denominator for UNAIDS's estimate is the number of total people living with HIV, rather than the number of new cases, for whom the actual extent of ART coverage may be somewhat different.

[55] We note that this value is very similar to the fatality rate observed by the CDC Case Count as of November 14, 2014, which put the value at 36% (CDC, 2014a).

[56] Acquired resistance can occur throughout the course of treatment, for instance as a result of inappropriate dosage or non-adherence to the treatment regimen. A discussion of the types of drug resistance in HIV follows below.

[57] An additional reduction in the number of people receiving ART, which cannot be quantified for the purposes of this study, is caused by attrition between testing and assessment for eligibility, and assessment for eligibility and initiating therapy (WHO, 2013b).

Table 35. ART coverage by region (2012)

Region	Coverage
Caribbean	41%
Latin America	45%
Sub-Saharan Africa	37%
MENA	11%
South and South-East Asia	33%
Eastern Europe and Central Asia	21%
Europe	45.3%

Source: UNAIDS (2014a); own calculation for Europe.

European data on ART coverage are collected in a different manner, using two indicators: 1) the number of people receiving ART divided by the number of people diagnosed with HIV and known to need ART;[58] and 2) the percentage of people who already need treatment at the time of HIV diagnosis, i.e. those with late HIV diagnosis.[59] As such, ECDC data are not directly comparable with those reported by UNAIDS and presented in the table above. To bring data on ART coverage in line across all regions, we divide the number of people receiving ART in European countries (as reported by the ECDC) by the number of people estimated to be living with HIV (as reported by the WHO) in those countries. Using this approach, we estimated an average ART coverage rate of 45.3%.

Going forward, it can be presumed that ART coverage will continue to increase, as it has in past years. In 2013, UNAIDS introduced a set of targets with respect to HIV treatment (UNAIDS 2014a):

1) By 2020, 90% of all people living with HIV will know their HIV status.
2) By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.
3) By 2020, 90% of all people receiving antiretroviral therapy will have durable viral suppression.

We assumed that the first two goals will be met and project increasing ART coverage so that it reaches 81% of all people estimated to be living with HIV in 2020 and continues the same rate of growth

[58] It is worth noting that even the definition of people in need of treatment differs across countries and between organisations.

[59] ECDC's stated reasons for this difference are concerns that UNAIDS calculations may overestimate the number of people needing treatment and that such system of reporting may conflate two separate challenges of identifying those who need treatment and providing treatment to those identified in need of ART. European Centre for Disease Prevention and Control (2013b).

thereafter. The table below summarises the assumed progression in ART coverage for the purposes of our model.[60]

Table 36. Projected ART coverage

	2013	2015	2020	2025	2030	2035	2040	2045	2050
OECD	45%	55%	81%	100%	100%	100%	100%	100%	100%
LatAm	45%	55%	81%	100%	100%	100%	100%	100%	100%
Subsaharan	37%	50%	81%	100%	100%	100%	100%	100%	100%
MENA	11%	31%	81%	100%	100%	100%	100%	100%	100%
Eurasia	27%	42%	81%	100%	100%	100%	100%	100%	100%

Source: UNAIDS (2014b), ECDC (2013b).

Resistance rates

Drug resistance in HIV patients can be divided into two types. Transmitted resistance refers to situations where a person is infected with a virus that is already resistant, prior to commencing treatment. Acquired resistance can occur throughout the course of treatment, for instance as a result of inappropriate dosage or non-adherence to the treatment regimen. There is no difference in the mechanism through which both types of resistance lead to AMR-related costs as both are strongly associated with treatment failure. However, the relative size of their contribution to the overall burden of HIV drug resistance remains unclear. Faced with this challenge, we turned to WHO studies on acquired drug resistance, which are performed at selected ART clinics and describe the HIV drug resistance present before initiation of antiretroviral therapy. Additionally, these surveys estimate the prevalence of viral load suppression and describe patterns of HIV drug resistance in populations experiencing virological failure 12 months after initiation of first-line antiretroviral therapy. The proportion of people initiating therapy with any drug resistance that is identified at the surveys' endpoint is used as an approximation of the prevalence of overall HIV drug resistance.

This pragmatic approach, necessitated by the absence of concrete data, is likely to underestimate the extent of HIV drug resistance for two principal reasons. First, this proportion of people with confirmed drug resistance, by definition, excludes people who have been lost to follow-up and who stopped antiretroviral therapy, part of whom may have also been affected by drug resistance. Second, it does not take into account people who died before the follow-up endpoint, some of whom may have been affected by existing drug resistance. At the same time, these two sources of underestimation may be partially off-set by the fact that the WHO surveys also include people with prior exposure to antiretroviral drugs, which may have contributed to the levels of resistance existing at baseline and which would not be observable among newly-diagnosed HIV cases, i.e. the baseline population for our calculations.

[60] We acknowledge that this assumption will require ART coverage to grow at different rates in different regions, with some of the highest rates of growth projected in regions that are most resource-limited.

Table 37. Current rates of HIV drug resistance

Region	Resistance rates
Africa	4.7%
South-East Asia	8.9%
Global	5.1%

Source: WHO (2012b).

AMR-attributable mortality

For calculations of deaths resulting from HIV drug resistance, we assumed that every instance of drug resistance results in the failure of first line treatment. In these cases, we apply an average of mortality rate observed in a number of identified studies that commented on therapeutic outcomes associated with the initiation of second-line treatment. This approach assumed that, in the long run, second line treatment remains highly effective and negative therapeutic outcomes associated with the switch from first line to second line treatment predominantly occur early in the aftermath of the start of second line treatment. This assumption is in line with observations made by Hosseinipour et al. (2010), who found that second-line treatment in Malawi was associated with substantial mortality, morbidity and toxicity but, among survivors, virological outcomes were favourable.

To select a mortality rate for second-line treatment, we applied a value based on findings from a Cochrane review (Ajose et al., 2012)[61] of studies that commented on therapeutic outcomes of second-line treatment among patients with first line treatment failure. Based on the information extracted from the studies, and to adjust for the likelihood that some of the lost-to-follow-up cases also died,[62] we applied a rounded up upper bound of the observed second-line mortality rate, i.e. 10%.

It should be stated upfront that our decision is likely to result in an estimate of AMR costs that is somewhat counterintuitively low as HIV/AIDS are commonly associated with higher mortality rates, particularly over a longer period of time. The primary reason for this approach are observations from existing literature, which suggest second-line treatment remains largely effective with minimal long-term effects of first-line treatment failure.

For the extreme scenario approximating a world without effective drug therapy, we applied a relative risk of dying in patients receiving no treatment compared to patients receiving combination therapy and protease inhibitors from an authoritative paper on the impact of ART on HIV mortality. The value of the

[61] Please note that the review is based on studies from resource-limited settings and so values observed in higher-income environments may be somewhat different. However, given the fact that the vast majority of HIV cases can be found in such settings, we are confident that a universal application of the review's findings does not represent an unreasonable assumption.

[62] Fox et al (2010) pointed out that "in many settings being lost means no longer on ART, as most patients who discontinue care will likely die within 1 year of stopping treatment." For illustration, two studies from South Africa reported that the proportion of patients who could be traced after dropping out of treatment at clinics in Johannesburg and who died were 27% and 48% (Maskew et al., 2007; Dalal et al., 2008).

observed relative risk is 4.5 (95% CI: 3.2-6.2) and applying this to the mortality rate above yielded a mortality rate of 45%. As above, this rate is likely to underestimate the true burden of HIV infections without effective therapy. However, the set-up of the model does not allow accommodating higher mortality rates observed over a prolonged period of time.

AMR-attributable time outside labour force

We were unable to identify authoritative sources on time off work that could be attributed to HIV drug resistance and therefore consider only additional deaths as constituting AMR-related costs. Two observations can be offered in further support of this approach. First, the observed causes of death in instances of HIV drug failure are very varied and, even if it was possible to quantify the morbidity associated with these conditions, there appears to be no systematic way of assessing their relative frequency. Second, HIV treatment is often delivered on an outpatient basis, which renders attributing time outside of labour force much more difficult in comparison with instances that would require hospitalization.

We recognize this is a conservative position to take but is in line with our approach in other areas where we tend to opt for approaches that, in the absence of robust sources, may result in an underestimation of AMR costs.

Malaria

Incidence rate

The incidence rates of malaria are based on WHO database of annual new cases (WHO, 2014b). In the absence of reliable and easy to use data that would enable a differentiation of individual cases, we assumed that all malaria cases are potentially subject to drug resistance, although resistance has been well documented so far only in infections caused by *P.falciparum* and *P.vivax* (WHO, 2010). We are confident that this assumption does not result in a large distortion of our model as these two species are generally considered to account for the vast majority of the burden of malaria (Mendis et al., 2001).

It is important to recognize that the burden of malaria in some regions is borne predominantly by children, as evident from the table below.

Table 38. Estimated current age distribution of deaths caused by malaria

Region	Deaths <5 as % of total
African	82%
Americas	27%
Eastern Mediterranean	37%
South East Asia	26%
Western Pacific	46%

Source: WHO (2013d).

Regrettably, WHO data on new malaria cases are not disaggregated by age groups. In order to capture the extent of malaria burden in children and to avoid overestimating the burden of malaria among adult populations, we based our approach on a paper on the macroeconomic implications of reducing early childhood malaria in the Ghanaian context, which, based on collected data, assumed that under five malaria incidence is twice as high as that in people five and older (Yerushalmi et al., 2014). We recognize this is an imperfect approximation; nevertheless, this approach represented the best option to avoid substantial distortion to our calculations that would occur in the event of applying the same incidence rate across all age groups. Similarly, adjusting incidence rates in line with observed death figures and assuming constant fatality rates across age groups was not desirable because children under five are both more likely to be infected with malaria and also more likely to die once they are infected (Snow and Gilles, 2002).

In addition, it is important to keep in mind that not every new case of malaria currently receives ACT. To reflect the fact that only people receiving antimalarial drugs can be affected by resistance, we adjusted out incidence rate by ACT coverage rates, collected from national Malaria Control Programme reports as presented in the latest WHO Malaria report (2013d). Going forward, we assumed the rate of growth in coverage observed in the past five years will continue until reaching 100% coverage in all five regions by 2020. Current and projected rates of ACT coverage are presented in the table below.

Table 39. Projected ACT coverage ratios

	2012	2015	2020	2025	2030	2035	2040	2045	2050
OECD	100%	100%	100%	100%	100%	100%	100%	100%	100%
LatAm	95%	100%	100%	100%	100%	100%	100%	100%	100%
Subsaharan	60%	80%	100%	100%	100%	100%	100%	100%	100%
MENA	75%	95%	100%	100%	100%	100%	100%	100%	100%
Eurasia	80%	100%	100%	100%	100%	100%	100%	100%	100%

Source: National Malaria Control Programme reports cited in WHO (2013d).

As mentioned in section 4.2.1, for high resistance scenario, we assumed there would be a simultaneous change in incidence, operationalized as a one-off year-on-year movement, in a fashion similar to that of resistance. Following consultation with senior health experts and the AMR Review Team, we modelled the changes in incidence rates based on observed historical rates, as reported by Carter and Mendis (2002). Each scenario in our model was designed to approximate varying degrees of malaria burden and so rates from different points in time are taken for different scenarios. For sc2 and sc4, i.e. future 40% resistance rates, we used data from 1970, i.e. a period when the availability of antimalarials and the introduction of vector control measures were beginning to take effect. For absolute resistance scenarios, we used data from 1950, i.e. a period prior to both systematic eradication efforts and chloroquine anti-malarials. Finally, for sc3 and sc5, i.e. future 100% resistance to first-line therapy, we used the average of the two.

Resistance rates

For our basic scenarios, we used an average of resistance rates currently reported for artemisinin-based combination therapies (ACT). This is in line with current WHO's recommendations to use artemisinin in combination with other drugs that have different mechanisms of action and longer half-lives to maximize the effectiveness of artemisinin and its derivatives. It also reflects the fact that most malaria-endemic countries have shifted their national treatment policies to ACTs (WHO, 2010) though we recognize that in some places, monotherapies may still be used for the treatment of uncomplicated malaria.

Resistance rates are based on the WHO global database on antimalarial drug efficacy, as reported in WHO's latest Global Report on Antimalarial Drug Efficacy and Drug Resistance (2010). The database includes data on treatment failures, which we use as a proxy for resistance. This assumption is likely to lead to an overestimation of the true resistance rates because, while every case of drug resistance qualifies as treatment failure, not every treatment failure is caused by drug resistance but may be due to other factors, such as lack of adherence. However, there are no data available on the proportion of treatment failures attributable to drug resistance.

WHO's global database is organized by regions and drug types – these are summarized in the box below. In the absence of data on the relative frequency of individual drug types given as part of antimalarial therapy, we take an average of reported median rates of treatment failure across all artemisinin derivatives.

Box 1. List of included artemisinin derivatives

Artemether 5-day treatment
Artemether–lumefantrine
Artemisinin–piperaquine
Artesunate 5-day treatment
Artesunate 7-day treatment
Artesunate–amodiaquine
Artesunate–doxycycline
Artesunate–mefloquine
Artesunate–pyronaridine
Artesunate–sulfadoxine–pyrimethamine
Artesunate–sulfalene–pyrimethamine
Dihydroartemisinin 5-day treatment
Dihydroartemisinin 7-day treatment
Dihydroartemisinin–piperaquine

AMR-attributable mortality

The WHO does not offer any authoritative data on mortality and morbidity resulting from resistance to antimalarial drugs. For our model, we base our assumptions in this area on observations made in academic literature. It appears useful to differentiate between usual and severe forms of malaria, which have been found to be associated with substantially different mortality rates. White (2004) noted that while the mortality associated with this presentation is approximately 0.1%, if effective drugs are readily available, in the case of severe malaria mortality despite treatment rises to 15–20%. In light of this, it is plausible

that the biggest mortality and morbidity increases associated with drug resistance will not stem from ineffective treatment of severe malaria, but because of ineffective first-line oral treatment, which causes an increasing proportion of patients to develop severe disease (White 1999).

It should be noted that, due to unavailability of more recent data, these assumptions are based on observations made in a context where resistance to chloroquinine and sulfadoxine–pyrimethamine, i.e. currently, drugs used increasingly rarely on their own, were the biggest concern and resistance to artemisinin was comparatively rare.

In practice, following consultations with senior external experts we assume an AMR-attributable mortality rate of **1%** and apply it across all scenarios in our model.

AMR-attributable time outside labour force

Sarkar et al (2010) observe that therapy for severe malaria should be administered for at least 5-7 days. In addition, a 7-day course of tetracycline or doxycycline is administered to adults and clindamycin to children or pregnant women. For our calculations, we assume that each case of severe malaria requires at least **two weeks** of treatment and thus absence from economic activity.

Tuberculosis

Incidence rate

Incidence rates of TB per 100,000 people are derived from WHO data (n.d.), available from the Global Health Observatory Data Repository (variable name "e_inc_100k"). Age distribution of TB incidence is calculated on the bases of regional aggregations from the latest WHO Global Tuberculosis Report (2013a).

It is likely that not everyone with TB receives treatment. In fact, the WHO estimates that the difference between the total estimated number of TB cases and the number reported to national monitoring amounts to 2.9 million each year (WHO, 2013a). Some of these represent cases that have been diagnosed but were not subsequently reported and some of these were not diagnosed in the first place. In the absence of data on how big a share of the missing cases the latter category accounts for, we do not make any adjustments to the incidence rates reported by the WHO.

Resistance rates

Resistance rates by region are taken from the 2013 WHO Global TB Report, as presented in the table below.

Table 40. Current MDR-TB resistance rates by region

Region	Estimated % of new TB cases with MDR-TB
Africa	2.3%
Americas	2.2%
Eastern Mediterranean	3.5%
Europe	16.0%
South-East Asia	2.2%
Western Pacific	4.7%
Global	3.6%

Source: WHO (2013a).

The WHO regions do not always perfectly overlap with the geographical regions chosen for our study so we had to make the following amendments:

- For High countries, we took an average of Europe, Americas, Eastern Mediterranean and Western Pacific resistance rates, weighted by the populations of OECD countries in those four respective regions, yielding a resistance rate of 8.9%. This enabled our approach to capture the markedly higher rates of resistance in Europe.
- For Eurasia, we used the global rate of 3.6%.

AMR-attributable mortality

In 2013, the WHO commissioned a systematic review to estimate MDR-TB mortality. The review included 25 studies from countries with both high and low burdens of MDR-TB and HIV and produced a global estimate of the relative risk of dying from MDR-TB of 2.36 [CI: 1.67-3.05]. Regrettably, according to the WHO, the data available were not sufficiently robust for the review to produce region-specific estimates of RR so our calculations assume the same relative risk in all regions (WHO, 2013a).

To convert this relative risk into an MDR-specific mortality rate, we assume that the current number of deaths is a product of both drug-susceptible and MDR TB:

$$\begin{aligned} &Total\ number\ of\ TB\ deaths \\ &= Total\ number\ of\ new\ susceptible\ cases * susceptible\ mortality\ rate \\ &+ Total\ number\ of\ new\ resistant\ cases * susceptible\ mortality\ rate * 2.36 \end{aligned}$$

Please note that this calculation carries the risk of a slight imprecision in that some TB cases may last longer than one year, in which case the number of new cases per year may not be a completely accurate denominator.

Also, we bear in mind there exists substantial co-morbidity between TB and HIV. In line with the practice of the ICD-10, which classifies TB deaths among HIV-positive people as HIV deaths, we do not include deaths in HIV-positive people in our TB calculations and assume any deaths arising from this comorbidity are expressed in our HIV calculations. This is in line with the studies on which our HIV-specific mortality rate is based, which have noted TB as one of the causes of deaths observed among their

study populations. In addition, the distinction between TB and HIV deaths is echoed by the WHO, which presents estimates of deaths from TB in HIV-positive people separately from those in HIV-negative people.

Table 41. Calculation of MDR-TB-specific mortality rates

Region	Incidence per 100,000 people	Deaths per 100,000 people	Resistance rate	Susceptible mortality rate	Resistant mortality rate
High	16.63	0.96	0.089	0.052	0.122
Latin America	49.91	3.35	0.022	0.065	0.153
MENA	37.01	4.21	0.035	0.109	0.256
Eurasia	143.30	16.50	0.036	0.110	0.259
Sub-Saharan	255.37	26.69	0.023	0.101	0.239

Source: WHO (2013a); WHO (n.d.).

For the extreme scenario approximating a world without effective drug therapy, we use data from a systematic review of studies on case fatality of untreated pulmonary tuberculosis in HIV negative patients from the pre-chemotherapy era (Tiemersma et al., 2011). The review indicates a rate of 70% for smear—positive cases and 20% for smear-negative cases. Weighting the two by the frequency of each of the two types of new cases, we arrive at a mortality rate of 48.5%.

AMR-attributable time outside labour force

According to the WHO TB report, there is wide variation in the extent to which patients with MDR-TB are hospitalized. In Africa, this ranged from 10% of patients (Democratic Republic of the Congo) to 100% (Ethiopia and Nigeria). The hospital length of stay in hospital with MDR-TB reported by the WHO ranged from 7 to 240 days (WHO, 2013a). We use the median value **84 days** to express the time spent outside of labour force attributable to drug resistance in TB.

Appendix C: Detailed description of the economic data: social accounting matrix

Social accounting matrix components

As laid out in section 4.3.1, in our approach we disaggregate the world into five AMR regions, whereby the model is calibrated to the 'world' social accounting matrix (SAM), which contains information on the flows of the economic transactions within and between the five AMR regions. In Table 42 we reiterate a summary of the inputs to the SAM, followed by a more detailed discussion below. Unless otherwise stated, all data refers to the year 2011 and is expressed in current value US Dollars.

Table 42. Social Accounting Matrix (SAM): Summary of inputs and sources.

Input Category	Data Source
GDP Data	World Bank DataBank.[63]
Intermediate Consumption	World Input-Output Database.[64] IFPRI SAMs. Academic papers.[65]
Gross Capital Formation	World Bank DataBank.
Import / Export (I/E) of Goods & Services	International Monetary Fund, DoTS data.[66]
Labour / GDP Ratio	IFPRI SAMs. Eurostat Database.[67] Various academic papers.

GDP Data

To calculate the Gross Domestic Product of the five AMR regions selected for this study (see Appendix A), we collated accordingly all GDP country-level data available through the World Bank Databank.[68]

[63] World Bank (2014b).

[64] Timmer (2012).

[65] International Food Policy Research Institute (n.d.).

[66] International Monetary Fund (2011).

[67] European Commission (2014d).

[68] World Bank (2014b).

Intermediate Consumption

Due to the lack of an overarching dataset covering all countries or regions selected for this study, to calculate levels of intermediate consumption in the five AMR regions selected, we had to employ a multiplicity of sources. For the 'High' region, we referred to the World Input-Output Database (WIOD) which reports intermediate consumption levels in US dollars for the year 2011 (Timmer, 2012). WIOD country-level data points were used to calculate a reliable regional average for the 'Intermediate Consumption to GDP' ratio in the 'High' region. The ratio obtained was subsequently applied to country-level GDPs for all the 'High' region countries not covered by the WIOD. We then summed all intermediate consumption levels reported by the WIOD for countries in the 'High' region with the intermediate consumption levels calculated through our regional average ratio for remaining countries unreported in the database, thus obtaining the absolute value of intermediate consumption for the 'High' region inputted in the SAM.

A similar procedure to the one outlined above was then employed to calculate levels of intermediate consumption in the four remaining AMR regions. However, the WIOD grants only a limited coverage with regards to countries outside of the 'High' and 'Eurasia' regions. To overcome this problem and calculate reliable regional 'intermediate consumption to GDP' ratios, we used additional data points derived from supplementary sources, namely International Food Policy Research Institute (IFPRI) SAMs and academic papers. Since these SAMs and academic papers refer to different currencies and years, we employed them only to calculate regional averages for 'Intermediate Consumption to GDP' ratios and did not use the absolute values they report. Regional ratios were then applied to previously calculated regional-level GDP for the year 2011 so as to obtain the absolute Intermediate Consumption values inputted in the SAM. When possible, data points for calculating averages were selected by picking countries that accounted for the largest regional population and/or economic output. For the Sub-Saharan Africa region, we referred to SAMs compiled by the IFPRI for Kenya, Ghana and Zambia (Kiringai et al., 2006; Breisinger et al., 2007; Thurlow et al., 2005). For the Latin America region, we referred to SAMs compiled by the IFPRI for Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay (Petri et al., 2005; Jimenez et al., 2005; IFPRI, 2003; Contreras et al., 2005; Molinas et al., 2005; Laens, 2005). For the Middle East and North Africa region, we referred to an academic paper presenting a SAM of Libya. The rationale behind employing Libya's intermediate consumption lies in the fact that, despite the country's small population, this would offer an account in line with that of the major regional economies which have a reliance on the hydrocarbon sector similar to that of Libya (Dewhurst et al., 2011).

Gross Capital Formation

To calculate the Gross Capital Formation of the five AMR regions selected for this study, we collated all Gross Capital Formation country-level data available through the World Bank Databank (2014b).

Import / Export of Goods & Services

To calculate import and export flows of goods and services between the five AMR regions selected for this study, we collated accordingly data on Directions of Trade (DoTS) available from the International Monetary Fund (2011). Since our selected regions cover virtually the whole world, we assumed that data

for exports could be mirrored in the SAM's entries accounting for imports and that no entries accounting for flows to/from the rest of the world (ROW) would be needed in the SAM.

Labour / GDP Ratio

Due to the lack of an overarching dataset covering all countries or regions selected for this study, to calculate regional ratios between Labour and GDP in the five AMR regions we had to employ a multiplicity of sources. For the 'High' region, we referred to data available from the Eurostat database to calculate a Labour to GDP regional average on the basis of data available for the Eurozone (European Commission, 2014). The ratio obtained was then used to calculate the Capital to GDP ratio in the region (see Table 43). With these ratios, we then calculated the absolute values in US Dollars for Labour and Capital by multiplying them for GDP data reported by the World Bank.

The same procedure outlined above for the 'High' region was then employed to calculate Labour to GDP ratios in the four remaining AMR regions selected for this study. However, due to the limited coverage of countries outside of the 'High' region granted by the Eurostat database, to calculate reliable ratios we obtained further data points by employing additional sources, namely IFPRI SAMs and academic papers. Where possible, data points for calculating averages were selected by picking countries that accounted for largest regional population and/or economic output. For the Eurasia region, we referred to SAMs compiled by the IFPRI for China and Pakistan (Zhang and Diao, 2013; Debowicz et al., 2012). For the Sub-Saharan Africa region, we referred to SAMs compiled by the IFPRI for Ghana, Kenya, South Africa and Zambia (Breisinger et al., 2007; Kiringai et al., 2006; Davies and Thurlow, 2013; Thurlow et al., 2005). For the 'Latin America' region, we referred to SAMs compiled by the IFPRI for Argentina, Brazil and Uruguay (Petri et al., 20005; IFPRI, 2003; Laens, 2005). For the Middle East and North Africa Region, we referred to SAMs compiled by IFPRI for Iraq and Egypt and to a publicly available SAM for Jordan (Debowicz, 2013; IFPRI, 2002; Al-Ali, 2012).

Additional Indicators

Further components of the SAM were calculated using formulas referring to the above listed inputs. A summary of indicators plugged through previously inputted data and of the formulas used to calculate them can be found in Table 43.

Table 43. Social Accounting Matrix (SAM): Summary of calculated indicators and formulas.

Input Category	Formula
Total Output	GDP + Intermediate Consumption
Consumption (Household + Government)	GDP + Exports – Imports – Gross Capital Formation
Capital / GDP Ratio	1 – (Labour / GDP Ratio)
Labour	GDP * (Labour / GDP Ratio)
Capital	GDP * (Capital / GDP Ratio)
Labour / Capital Ratio	Labour / Capital
Savings Rate	[(Labour + Capital - Consumption) / Total Output] * 100

Validity Check

To verify the adherence of our SAM to real-world data, we cross checked saving rates obtained through our SAM to those reported by the World Bank Databank. A first test SAM compiled with the above described methodology, but using only data from one test countries per region and adding entries accounting for trade flows to/from ROW, resulted in SAM-calculated savings rate that were equivalent to those reported by the World Bank with an error of ±1%. Furthermore, looking at the savings rate obtained throughout the five regions SAM accounting for the world economy, we can see that the results obtained are in line with savings rate calculated for similarly structured regions on the basis of World Bank, as shown in Table 44.

Table 44. Social Accounting Matrix (SAM): Regional Saving Rates Comparison.[69]

Region	SAM-Calculated Saving Rate	World Bank Saving Rate
High Income	18.4%	19.8%[70]
MENA	32.7%	36.9%[71]
Sub-Saharan	20.9%	19.3%[72]
Latin America	19.8%	21.1%[73]

[69] Due to the ad-hoc composition of the Eurasia region employed in this study, no external sources presenting average economic indicators for similarly structured regions were available for comparison to our SAM-calculated saving rate.

[70] Trading Economics, (2014c).

[71] Latest data point available refers to 2007. Trading Economics, (2014a).

[72] Trading Economics, (2014d).

[73] Trading Economics, (2014b).

Figure 9 is the resulting social accounting matrix that is used to calibrate the model. Table 45 is a summary of the main economic indicators as previously discussed.

Figure 9. Model social accounting matrix

World SAM, USD Billion, 2011

		High	Eurasia	MENA	Sub	Latam	High	Eurasia	MENA	Sub	Latam	High	High	Eurasia	Eurasia	MENA	MENA	Sub	Sub	Latam	Latam	High	Eurasia	MENA	Sub	Latam	High	Eurasia	MENA	Sub	Latam	
		a1	**a1**	**a1**	**a1**	**a1**	**c1**	**c1**	**c1**	**c1**	**c1**	**lab**	**cap**	**lab**	**cap**	**lab**	**cap**	**lab**	**cap**	**lab**	**cap**	**inc**	**inc**	**inc**	**inc**	**inc**	**inv**	**inv**	**inv**	**inv**	**inv**	**exp**	**exp**	**exp**	**exp**	**exp**	**Total**
High	**a1**						88732																										88732
Eurasia	**a1**							36895																									36895
MENA	**a1**								4206																								4206
Sub	**a1**									2222																							2222
Latam	**a1**										7954																						7954
High	**c1**	41465																				38556					9482					1761	1740	372	155	350	93882
Eurasia	**c1**		22203																				8668					5625				2267	7662	218	103	139	46887
MENA	**c1**			1326																				1938					561			592	372	132	29	12	4962
Sub	**c1**				744																				1170					286		203	96	7	43	14	2563
Latam	**c1**					3551																				3533					901	328	121	26	10	143	8614
High	**lab**	23167																																			23167
High	**cap**	24099																																			24099
Eurasia	**lab**		5840																																		5840
Eurasia	**cap**		8851																																		8851
MENA	**lab**			974																																	974
MENA	**cap**			1906																																	1906
Sub	**lab**				793																																793
Sub	**cap**				685																																685
Latam	**lab**					2097																															2097
Latam	**cap**					2306																															2306
High	**inc**											23167	24099																								47266
Eurasia	**inc**													5840	8851																						14692
MENA	**inc**															974	1906																				2880
Sub	**inc**																	793	685																		1478
Latam	**inc**																			2097	2306																4403
High	**inv**																					8710										0	526	220	48	-22	9482
Eurasia	**inv**																						6024									-526	0	154	-7	-18	5625
MENA	**inv**																							943								-220	-154	0	-22	14	561
Sub	**inv**																								308							-48	7	22	0	-4	286
Latam	**inv**																									870						22	18	-14	4	0	901
High	**exp**						1761	1740	372	155	350																											4379
Eurasia	**exp**						2267	7662	218	103	139																											10390
MENA	**exp**						592	372	132	29	12																											1138
Sub	**exp**						203	96	7	43	14																											363
Latam	**exp**						328	121	26	10	143																											629
	Total	88732	36895	4206	2222	7954	93882	46887	4962	2563	8614	23167	24099	5840	8851	974	1906	793	685	2097	2306	47266	14692	2880	1478	4403	9482	5625	561	286	901	4379	10390	1138	363	629	471116

Table 45. Economic description of the AMR zones

Production Approach		High	Eurasia	MENA	Sub	Latam	Total
Total Output		88,732	36,895	4,206	2,222	7,954	140,009
Intermediate Consumption	-	41,465	22,203	1,326	744	3,551	69,289
GDP	=	**47,266**	**14,692**	**2,880**	**1,478**	**4,403**	**70,719**
Expenditure Approach		**High**	**Eurasia**	**MENA**	**Sub**	**Latam**	**Total**
Consumption (House & Gov)		38,556	8,668	1,938	1,170	3,533	53,865
Gross capital formation	+	9,482	5,625	561	286	901	16,855
Exports	+	4,379	10,390	1,138	363	629	16,898
Imports	-	5,150	9,992	756	341	659	16,898
GDP	=	**47,266**	**14,692**	**2,880**	**1,478**	**4,403**	**70,719**
Income Approach		**High**	**Eurasia**	**MENA**	**Sub**	**Latam**	**Total**
Employment		23,167	5,840	974	793	2,097	32,872
Capital	+	24,099	8,851	1,906	685	2,306	37,848
GDP	=	**47,266**	**14,692**	**2,880**	**1,478**	**4,403**	**70,719**
Labour / GDP		0.490	0.398	0.338	0.536	0.476	
Capital / GDP		0.510	0.602	0.662	0.464	0.524	
Labour / Capital		0.961	0.660	0.511	1.157	0.909	
Zone Savings Rate		18.4%	41.0%	32.7%	20.9%	19.8%	

Appendix D: Summary of assumptions and limitations

This appendix presents a summary overview of assumptions and limitations inherent in our study approach, along with an estimate, where possible, of their likely impact on the final results. The points below are categorised by their relevance to three aspects of this study – scope, health components, and economic components.

This appendix presents a summary overview of assumptions and limitations inherent in our study approach, along with an estimate, where possible, of their likely impact on the final results. The points below are categorised by their relevance to three aspects of this study – scope, health components, and economic components.

Assumptions and limitations pertaining to the study's scope and conceptual approach

Assumption /limitation	The scope of the study (hospital-acquired infections and infectious diseases of HIV/TB/malaria) leaves out other possible instances of AMR
Discussion	Driven by unavailability of data on AMR-attributable mortality and morbidity for other bacteria. Based on consultations with experts, these are the most commonly discussed and *E.coli* and *K. pneumoniae* as Gram-negative bacteria are considered part of the most serious threat.
Likely impact	Final estimate of AMR costs too low

Assumption /limitation	For hospital-acquired infections, our work includes only the following bacteria: *E.coli* *K. pneumoniae* *S. aureus*
Discussion	Driven by unavailability of data on AMR-attributable mortality and morbidity for other bacteria. Based on consultations with experts, these are the most commonly discussed and *E.coli* and *K. pneumoniae* as Gram-negative bacteria are considered part of the most serious threat.
Likely impact	Final estimate of AMR costs too low

Assumption /limitation	For infectious diseases, our work includes resistance only in the context of the following conditions: *HIV* *Tuberculosis* *Malaria*
Discussion	Driven by desire to differentiate the health impact of AMR in various world regions and data unavailability with respect to resistance in other contexts.
Likely impact	Final estimate of AMR costs too low

Assumption /limitation	Regional grouping does not match precisely any given existing classification
Discussion	Driven by the need to have a limited number of regions and associated data aggregations for our model. Proposed grouping roughly in line with WB income categories, modified slightly to reflect public health realities such as geographical distribution of infectious diseases.
Likely impact	Introduces some degree of error but impossible to say how much, although likely minimal compared to overall error.

Assumption /limitation	Only economic costs in terms of reduced supply of labour are included in the scope of the study
Discussion	Other possible costs of AMR include health care costs and secondary/indirect costs
Likely impact	Final estimate of AMR costs too low, particularly when assessing the costs of potential large increases in future resistance rates

Assumptions and limitations pertaining to the study's health components

Assumption /limitation	Baseline resistance rates are based on average values from a studies of varying quality and of incomplete geographical coverage
Discussion	We base our work on the best existing data. While patchy, it's still the most rigorous approach possible given the limited availability of sufficiently valid data and the timeline of the project.
Likely impact	This point introduces additional degree of error but not likely substantial.

Assumption /limitation	Mortality and morbidity rates attributable to AMR in HAIs are based on a very small number of observational studies. Also, these data cut across various conditions caused by individual bacteria.
Discussion	Driven by unavailability of data. We base our work on the best existing data.
Likely impact	This point introduces additional degree of error but not likely substantial.

Assumption /limitation	Infection incidence rates of HAIs in non-High countries is based on a limited number of survey data points
Discussion	Driven by unavailability of data.
Likely impact	This point introduces additional degree of error. Impossible to assess the size and direction of the error.

Assumption /limitation	Incidence rates going forward are remain constant
Discussion	Driven by unclear evidence on future infection rates and lack of time to run a transmission model. It may also be desirable to have only one variable to manipulate in the model (resistance rates).
Likely impact	This is one of the assumptions that are surrounded with much uncertainty. It is likely that incidence rates might increase in the event of high resistance rates, particularly in the case of infectious diseases, which would mean our final estimate is too low.

Assumption /limitation	Projections of resistance rates until 2050, including their rates of growth and starting points, may not be borne out in reality
Discussion	There's little existing data on projections and what does exist has often been proven wrong by subsequent developments. Suggested scenarios based on experts suggestions and on considerations about their conceptual analytical value.
Likely impact	Impossible to assess

Assumption /limitation	Existing data on mortality and mortality still allow for some effective therapy
Discussion	Driven by data availability. Included as part of our sensitivity analysis mortality rates that approximate situations without effective therapy.
Likely impact	Degree of error impossible to assess

Assumption /limitation	HIV and malaria coverage ratios will continue to increase approximately at the same rate as they have in the past five years
Discussion	Driven by data unavailability. In the HIV context, this assumption reflects publically stated goals by relevant authorities
Likely impact	This point introduces additional possibility of imprecision but not likely substantial.

Assumptions and limitations pertaining to the study's economic components

Assumption /limitation	Fertility rates are not affected by increasing rates of AMR.
Discussion	Driven by unavailability that literature on the effects of AMR and fertility and need for simplicity in the model.
Likely impact	If in reality fertility rates are negatively affected by increasing AMR, population estimates will be overestimated.

Assumption /limitation	Inter-region migration not included in our model.
Discussion	Driven by unavailability of authoritative projections and desire not to increase complexity of the model.
Likely impact	Difficult to assess