Burden of disease associated with antimicrobial resistance

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Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteraemia: Estimating the burden of antimicrobial resistance in Europe

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Abstract

Objectives

This study determined the excess number of deaths, bed-days and hospital costs associated with BSI caused by MRSA and G3CREC in 31 countries that participated in the EARSS.

Methods

The number of BSIs caused by MRSA and G3CREC was extrapolated from the EARSS prevalence data and national health care statistics. Prospective cohort studies, carried out in hospitals participating in the EARSS in 2007, provided the parameters for estimating the excess 30-day mortality and hospital stay associated with BSIs caused by MRSA and G3CREC. Hospital expenditure was derived from a publicly available cost model. Trends established by the EARSS determined the trajectories for MRSA and G3CREC prevalence until 2015.

Results

In 2007, 27,711 episodes of MRSA BSIs were associated with 5,503 excess deaths and 255,683 excess hospital days in the participating countries, whereas 15,183 episodes of G3CREC BSIs were associated with 2,712 excess deaths and 120,065 extra hospital days. The total costs attributable to excess hospital stay were 44.0 and 18.1 million euros (63.1 and 29.7 million international dollars), respectively. Based on prevailing trends, the number of BSIs caused by G3CREC is likely to rapidly increase, outnumbering the number of MRSA BSIs in the near future.

Conclusions

Excess mortality associated with BSIs caused by MRSA and G3CREC is significant, and the prolongation of hospital stay imposes a considerable burden on health care systems. A foreseeable shift in the burden of antimicrobial resistance from gram-positive to gram-negative infections will exacerbate this situation and is reason for concern.

Introduction

Managing increasingly limited resources is one of the key challenges in contemporary health care. Although antimicrobial resistance is threatening the success of medical services, the exact societal implications have not been adequately quantified. In order to inform the public health debate in Europe and beyond, reliable estimates about excess mortality, morbidity and costs are imperative. Data about this burden of disease will enable evaluation of antimicrobial resistance against other competing causes of morbidity and mortality. Moreover, medium term trends can shed light on expected health care demands in the near future. Hitherto such information has not been available because of the absence of representative empirical data.
Recently, clinical studies, carried out under the remit of the BURDEN project[1], filled this void. Within the BURDEN framework, we estimated the impact of antimicrobial resistance associated with the two most frequent causes of BSI worldwide – *S. aureus* and *E. coli*.[2] For these pathogens we focused on two of the most clinically relevant resistance phenotypes – methicillin-resistance for *S. aureus* and third-generation cephalosporin resistance for *E. coli*. Both phenotypes are typically associated with resistance to multiple classes of antibiotics and can be regarded as surrogate markers for multi-drug resistance. During these studies the clinical outcome and excess hospital stay for infected patients in 13 different hospitals in as many different European countries were prospectively ascertained.[3,4]
Here we provide estimates on the burden of disease of resistance by combining these results with prevalence data from the EARSS. The EARSS data were collected under the supervision of two of the authors (H.G., M.E.A.D.K.) at RIVM between 1999 and 2009. We report excess mortality, excess hospital stay and the related hospital expenditure associated with MRSA and G3CREC bacteraemias, and provide trend-based trajectories until 2015 for all countries that participated in the EARSS in 2007.

Material and methods

Analyses focused on episodes of MRSA, MSSA, as well as G3CREC and SEC BSIs reported to the EARSS in 2007. In that year, 31 countries participated in the EARSS, consisting of all European Union Member States (excluding Slovakia), the two candidate countries (Croatia and Turkey), two European Free Trade Association (EFTA) countries (Norway and Iceland) and Israel, henceforth referred to as the European region. Susceptibility was determined according to consensus protocols published in the EARSS manual.[5]

Number and incidence of events

Since all diagnostic microbiological laboratories in Estonia, Hungary, Iceland, Ireland, Luxembourg, Malta and Slovenia reported to the EARSS (100% coverage) the total number of BSIs could be directly extracted from the EARSS database for these countries.[6] For the UK, the total number of BSIs caused by *S. aureus* (MRSA and MSSA) was provided by the Health Protection Agency, the Health Protection Scotland, the Welsh Healthcare Associated Infection Programme, and the Public Health Agency Northern Ireland through their mandatory reporting schemes. Data for the UK for *E. coli* (G3CREC and SEC) were extracted from these programs' voluntary reporting schemes. For all other countries, the expected total number of events was based on the number of bacteraemias and hospital beds in the EARSS sample, combined with the total volume of acute care beds per country. National volume data was obtained from the online Eurostat database[7], the Organisation for Economic Cooperation and Development Health Data 2010 database[8], or provided by national institutes for public health (see Table S1 and Acknowledgements). Through the svyglm function in the R package 'survey', the odds of a BSI case per bed, including a CI_{95}, was estimated per BSI type and country. This method fits a GLM with a quasi binomial distribution and logit link function. It accounts for the cluster effect (of sampling within countries) and finite populations (national volume of acute care beds). The model-derived odds, including CI_{95}, were transformed to proportion (*P*) and then multiplied with the national volume of acute care beds to come to country-specific estimates for the total number of bacteraemias (#BSIs). Resulting CI_{95} were smaller for countries with higher national EARSS coverage. Incidence was calculated by dividing these estimates, including the CI_{95}, by population census data taken from the WHO database.[9]

Excess deaths, bed-days and costs

Adjusted risk estimates (*aOR)* for 30-day mortality, mortality proportions for the control group without *S. aureus* or *E. coli* bacteraemia (P_0) and excess LOS in days (*LOSR*) were obtained from the clinical outcome studies described previously (Table S2).[3,4] The excess number of deaths (*D*) and extra bed-days (*B*) associated with BSIs caused by MRSA, MSSA, G3CREC and SEC were then calculated for each country, using equation 1 derived from Bender *et al.*[10] and equation 2, respectively:

Equation 1
$$D = \frac{\#BSIs * P_0 * (aOR - 1) * (1 - P_0)}{aOR * P_0 + (1 - P_0)}$$

Equation 2
$$B = \#BSIs * LOSR$$

To determine CI_{95} for *D* and *B*, we used parametric bootstrapping. We sampled 10,000 simulations from the distribution for the log-odds of *P*, the log-odds of *aOR*, and the log-duration of *LOSR*. Thereafter, *D* and *B* were calculated for these sampled values and CI_{95} could be based on the 2.5% and 97.5% quantiles from the resulting distributions. In this way, the CI_{95} included the uncertainty in the estimated number of bacteraemias as well as the uncertainty in *aOR* and *LOSR*. As a result, CI_{95} were wider for countries with a low EARSS hospital participation ratio, and for burden of disease estimates for G3CREC compared to MRSA, because of wider confidence intervals for the clinical outcome measures for G3CREC (Table S2).

Excess hospital expenditure, including CI_{95}, was based on the product of the excess number of bed-days and country-specific unit costs per hospital day. These hotel costs were derived from the WHO-CHOICE model[11,12], and do not entail extra costs for procedures or treatments associated with antibiotic resistant infections. The model-derived costs in local currency units of 2005 were indexed by country-specific consumer price indices[13-16] to approach costs in 2007. Hereafter these amounts were converted into euros using historical exchange rates[17] and into international dollars using country-specific purchasing power parities for 2007.[12]

Resistance trajectories until 2015

The trajectories for BSIs caused by MRSA and G3CREC in the European region were based on trends in overall incidence of *S. aureus* and *E. coli* BSIs and changes in the relative proportions of MRSA and G3CREC as reported to the EARSS. Data were extracted for all laboratories that consistently reported susceptibility results for *S. aureus* (2001 - 2009) and *E. coli* (2003 - 2009). The final results were generated in a multi-step procedure. First, the secular trends in the absolute number of *E. coli* and *S. aureus* BSIs until 2015 were obtained by linear regression. Second, the rate change in the proportions of methicillin resistance and third-generation cephalosporin resistance was modelled by logistic regression.[18] In both models, year was included as (log)linear independent variable. Higher order terms of time were included on the basis of the F-statistic and the likelihood ratio test ($p<0.05$). Model fit was assessed by the F- and Hosmer-Lemeshow statistic. The product of the two trends provided the crude trajectory for MRSA and G3CREC BSIs until 2015 for the sample of laboratories that consistently reported to the EARSS. Finally, this trajectory was normalised against the reference incidence ascertained for 2007 and scaled to the total number of MRSA and G3CREC BSIs in the European region on the basis of total event estimates for 2007 (#BSIs) described above. All analyses were carried out using R 2.8.1 or SAS 9.2.

The Medical Ethics Committee of the University Medical Centre Utrecht waived ethical clearance for this study.

Results

Burden of resistance

In 2007, 1,293 hospitals from 31 countries reported antimicrobial susceptibility test results for *S. aureus* and *E. coli* causing BSIs to the EARSS database.[6] At the national level, surveillance covered over 47% of all available acute care hospital beds for most countries (IQR, 12%-99%). Altogether, susceptibility results for 18,000 *S. aureus* and 28,024 *E. coli* bloodstream isolates were reported in 2007.

For *S. aureus*, the estimated number of BSIs in the European region totalled 108,434 (CI_{95}, 103,637–112,948), of these, 27,711 (25.6%) were methicillin resistant (range 0% in Iceland and 52% in Malta). *E. coli* caused 163,476 (CI_{95}, 157,891–168,624) BSIs, of which 15,183 (9.3%) were resistant to third-generation cephalosporins (range 2% in Iceland and 40% in Turkey). The incidence of MRSA ranged from zero in Iceland and Norway to 18.7/100,000 (CI_{95}, 17.6–19.9) in Portugal, and for G3CREC from 0.1 (reported number, no confidence interval) in Estonia to 8.1 (CI_{95}, 7.0–9.2) in Israel. (Table 1)

In the same year, an estimated 5,503 (CI_{95}, 3136-8267) excess deaths were associated with BSIs caused by MRSA and 2,712 (CI_{95}, 595-5780) with BSIs caused by G3CREC, based on risk estimates from previous clinical outcome studies (Table S2)[3,4]. In 2007, the UK and France predictably experienced the highest excess mortality associated with BSIs caused by MRSA with 1096 (CI_{95}, 627-1650) and 898 (CI_{95}, 511-1364) fatalities, respectively. For BSIs caused by G3CREC, excess mortality was predicted to be the highest in Turkey (793; CI_{95}, 178-1716) and the UK (504; CI_{95}, 114-1078) and lowest in Iceland (1; CI_{95}, 0-2) and Estonia (0; CI_{95}, 0-1). (Table S3)

At the same time, BSIs caused by MRSA and G3CREC contributed an excess of 255,683 (CI_{95}, 142,934-375,880) and 120,065 (CI_{95}, 52,272-198,338) extra bed-days. This excess LOS accounted for an estimated extra cost of 62.0 million euros (CI_{95}, 31.4-100.0 million), equivalent to 92.8 million international dollars (CI_{95}, 47.0-149.0 million) in 2007. (Table S4)

Trends and future trajectories

For *S. aureus*, 266 laboratories, serving 810 hospitals in 25 countries consistently reported antibiotic susceptibility test results to the EARSS database between 2001 and 2009, totalling 121,469 blood isolates. During the same period, the absolute number of reported *S. aureus* BSIs increased from 10,874 to 15,299. Methicillin resistance increased from 19.1% in 2001 to 22.6% in 2005 and then decreased to 18.0% by 2009. (Figure S1)

For *E. coli*, 281 laboratories, serving 791 hospitals in 28 countries consistently reported antimicrobial susceptibility for 136,217 blood isolates between 2003 and 2009. During this time, the number of *E. coli* BSIs increased from 19,332 to 29,938. Resistance to third-generation cephalosporins increased from 2.7% in 2003 to 8.2% in 2009. (Figure S2)

Figure 1 shows that, based on the relative trends from the EARSS, the number of G3CREC bacteraemias is likely to surpass the number of MRSA bacteraemias in the near future. As a result, the additive burden of G3CREC and MRSA bacteraemias in the European region will increase. If current trends prevail, the trajectories suggest that about 97,000 resistant BSIs and 17,000 associated fatalities could be expected in 2015. Hospital stay and expenditure would likewise increase.

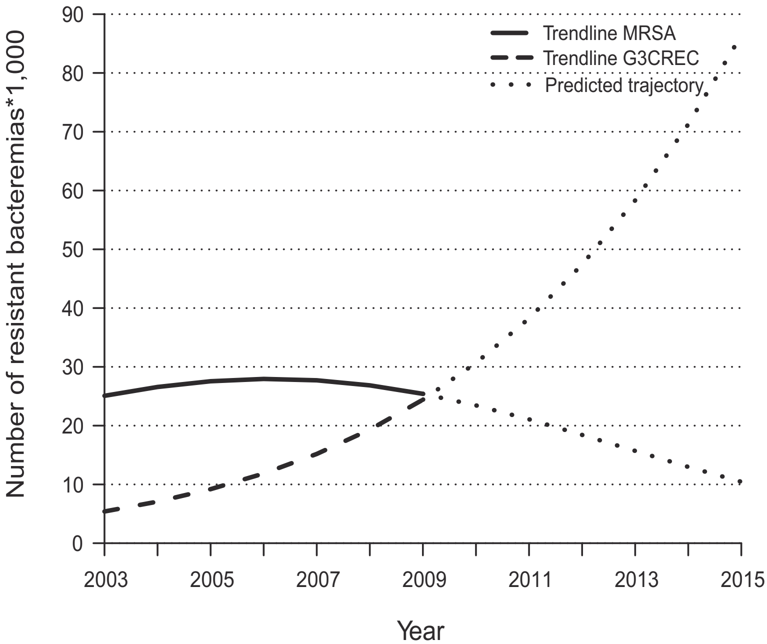

Figure 1. Trends in the estimated number of MRSA and G3CREC bacteraemias in the European region: extrapolated EARSS numbers for 2003-2009, and future trajectories based on regression analysis for 2010-2015.

Table 1. Frequency of *S. aureus* and *E. coli* bacteraemias in 31 European countries in 2007 by resistance phenotype. Estimated absolute numbers and the incidence expressed per 100,000 population of MRSA, MSSA, G3CREC and SEC BSIs. Countries include all European Union Member States (excluding Slovakia), both candidate countries*, two EFTA countries# and Israel.

Country	Number (CI_{95})				Incidence (CI_{95})			
	MRSA	MSSA	G3CREC	SEC	MRSA	MSSA	G3CREC	SEC
Austria	133 (132-134)	1,351 (1,348-1,354)	226 (225-228)	2,285 (2281-2289)	1.6 (1.6-1.6)	16.2 (16.1-16.2)	2.7 (2.7-2.7)	27.3 (27.3-27.4)
Belgium	250 (199-311)	836 (742-941)	84 (56-121)	1,987 (1837-2146)	2.4 (1.9-3)	8.0 (7.1-9.0)	0.8 (0.5-1.2)	19.0 (17.6-20.5)
Bulgaria	68 (41-107)	453 (375-544)	139 (98-192)	453 (374-543)	0.9 (0.5-1.4)	5.9 (4.9-7.1)	1.8 (1.3-2.5)	5.9 (4.9-7.1)
Croatia*	215 (195-236)	351 (325-378)	38 (30-48)	1,228 (1,180-1,276)	4.7 (4.3-5.2)	7.7 (7.1-8.3)	0.8 (0.7-1.0)	27.0 (25.9-28)
Cyprus	87 (70-108)	94 (76-115)	45 (33-61)	187 (162-216)	10.2 (8.2-12.6)	11.0 (8.9-13.5)	5.3 (3.8-7.1)	21.9 (18.9-25.2)
Czech Rep.	254 (241-269)	1,698 (1,662-1,735)	198 (186-210)	2,627 (2,583-2,671)	2.5 (2.4-2.6)	16.7 (16.3-17.0)	1.9 (1.8-2.1)	25.8 (25.4-26.2)
Denmark	21 (6-52)	1,544 (1,384-1,716)	81 (48-129)	2,590 (2,388-2,807)	0.4 (0.1-0.9)	28.4 (25.4-31.5)	1.5 (0.9-2.4)	47.6 (43.9-51.6)
Estonia^	18	188	2	217	1.3	14.1	0.1	16.3
Finland	12 (7-21)	576 (532-622)	32 (23-45)	1,572 (1,502-1,644)	0.2 (0.1-0.4)	10.9 (10.1-11.8)	0.6 (0.4-0.9)	29.8 (28.5-31.2)
France	4,523 (4199-4871)	12,860 (12,305-13,436)	617 (501-752)	30,029 (29,229-30,843)	7.3 (6.8-7.9)	20.9 (20.0-21.8)	1.0 (0.8-1.2)	48.7 (47.4-50)
Germany	2,484 (1,383-4,128)	12,311 (9626-15,417)	1921 (984-3410)	21,632 (18,142-25,628)	3.0 (1.7-5)	14.9 (11.7-18.7)	2.3 (1.2-4.1)	26.2 (22-31)
Greece	1,207 (872-1,611)	1,334 (977-1,764)	110 (31-282)	1270 (929-1,695)	10.8 (7.8-14.5)	12.0 (8.8-15.8)	1.0 (0.3-2.5)	11.4 (8.3-15.2)
Hungary^	279	920	59	1120	2.8	9.2	0.6	11.2
Iceland*#^	0	65	4	101	0.0	21.6	1.3	33.6
Ireland^	507	825	88	1663	11.8	19.2	2.0	38.7
Israel	573 (502-655)	1,168 (1,064-1,281)	558 (486-639)	3,415 (3,250-3,585)	8.3 (7.2-9.5)	16.9 (15.4-18.5)	8.1 (7.0-9.2)	49.3 (46.9-51.7)

Italy	2,679 (2,336-3,068)	5177 (4687-5706)	1,149 (928-1,415)	9,264 (8,609-9,944)	4.6 (4.0-5.2)	8.8 (8.0-9.7)	2.0 (1.6-2.4)	15.7 (14.6-16.9)
Latvia	29 (19-41)	311 (279-347)	23 (15-34)	131 (110-155)	1.3 (0.9-1.8)	13.7 (12.2-15.2)	1.0 (0.6-1.5)	5.7 (4.8-6.8)
Lithuania	35 (25-47)	351 (317-387)	27 (19-38)	351 (317-388)	1.0 (0.7-1.4)	10.4 (9.4-11.4)	0.8 (0.6-1.1)	10.4 (9.4-11.4)
Luxem-bourg^	24	91	11	264	5.1	19.5	2.4	56.5
Malta^	55	50	15	102	13.5	12.3	3.7	25.1
Nether-lands	36 (11-92)	2,985 (2,672-3,319)	205 (131-309)	4,734 (4,345-5,141)	0.2 (0.1-0.6)	18.2 (16.3-20.2)	1.2 (0.8-1.9)	28.8 (26.5-31.3)
Norway[#]	0	1,280 (1,176-1,391)	59 (38-86)	2,814 (2,671-2,961)	0.0	27.3 (25.0-29.6)	1.3 (0.8-1.8)	59.9 (56.8-63)
Poland	322 (220-449)	1,777 (1,520-2,058)	64 (25-133)	2,775 (2,452-3,122)	0.8 (0.6-1.2)	4.7 (4.0-5.4)	0.2 (0.1-0.3)	7.3 (6.4-8.2)
Portugal	1,989 (1,870-2,113)	2,159 (2,037-2,287)	431 (376-492)	3,866 (3,707-4,030)	18.7 (17.6-19.9)	20.3 (19.2-21.5)	4.1 (3.5-4.6)	36.4 (34.9-37.9)
Romania	139 (76-233)	382 (268-529)	225 (141-344)	551 (413-720)	0.6 (0.4-1.1)	1.8 (1.3-2.5)	1.0 (0.7-1.6)	2.6 (1.9-3.4)
Slovenia^	36	394	35	832	1.8 (1.7-1.9)	19.7 (19.4-19.9)	1.7 (1.7-1.8)	41.5 (41.2-41.9)
Spain	2,223 (1,979-2,484)	6,663 (6,244-7,110)	1,385 (1,195-1,595)	18,405 (17,725-19,096)	5.0 (4.5-5.6)	15.0 (14.1-16.1)	3.1 (2.7-3.6)	41.6 (40-43.1)
Sweden	25 (20-31)	2,533 (2,482-2,585)	90 (80-101)	4,382 (4,316-4,446)	0.3 (0.2-0.3)	27.8 (27.2-28.3)	1.0 (0.9-1.1)	48.1 (47.3-48.8)
Turkey*	3,968 (3,599-4,349)	7,677 (7,178-8,202)	4,440 (4,051-4,849)	6,666 (6,187-7,163)	5.3 (4.8-5.8)	10.3 (9.6-11.0)	5.9 (5.4-6.5)	8.9 (8.3-9.6)
UK^	5520	11,021	2,821	20,779	9.1	20.3	4.6	34.2
Total[1]/ Mean[2]	27,711[1] (26,042-29,103)	80,723[1] (77,595-83,846)	15,183[1] (13,852-16,353)	148,292[1] (144,039-152,271)	4.8[2] (4.5-5.0)	13.9[2] (13.4-14.5)	2.6[2] (2.4-2.8)	25.6[2] (24.9-26.3)

^Total number and incidence of bacteraemias as reported to the EARSS or by national health authorities (UK), no confidence intervals provided; Rep. = Republic

Discussion

By combining representative data on clinical outcome with population-based incidence figures, we estimated that more than 8,000 deaths and 62 million euros in excess costs were associated with MRSA and G3CREC BSIs in the European region in 2007. To our knowledge, this is the first quantification of the burden of disease for antimicrobial resistance in this region based on empirical data.

As early as 1998, the European Union conference titled '*The Microbial Threat*' in Visby, Denmark, emphasized that the most important questions regarding increasing resistance concern the potential rise in morbidity, mortality and costs.[19] Although more insight into the prevalence of antimicrobial resistance has been gained[20-23], its overall effect on human health and societies remained to be defined. With some notable exceptions such as TB, HIV, malaria and gonorrhea, most of the disease burden attributable to antimicrobial resistance is caused by hospital associated infections due to opportunistic bacterial pathogens. These often cause life threatening or difficult to manage conditions such as deep tissue, wound or bone infections, infections of the lower respiratory tract, central nervous system, or the bloodstream. We chose to investigate the burden of disease associated with antimicrobial resistance in BSIs. This decision was guided by the clinical importance of BSIs and the fact that prevalence data are available from one of the largest international surveillance systems (EARSS), recording antimicrobial resistance for more than 1,400 European hospitals.

This study took advantage of recently published observational studies.[3,4] These were purposely designed to provide an objective measure about excess mortality and LOS associated with MRSA and G3CREC BSIs for Europe. In addition, these studies took into account that MRSA and G3CREC bacteraemias add to, rather than replace, the burden of disease caused by their susceptible counterparts.[24-28] To this effect, clinical outcome measures of patients with resistant as well as susceptible BSIs were compared to those of uninfected controls.

However, three potential threats to the validity of our estimates need to be considered. First, a potential source of bias is inherent to the surveillance data from the EARSS. Second, bias may have been introduced through the clinical outcome measures from the BURDEN studies. Finally, effect modification due to varying levels of appropriate empirical treatment could have influenced our results.

The incidence of resistant BSIs reported by EARSS hospitals may differ from the national average, because of the size, different standards of care and/or different local epidemiology of EARSS hospitals.[29,30] This limitation in representativeness, however, only applies to a minority of countries. In 2007, ten of the EARSS national networks collected complete data for all acute care hospitals in these countries, a further 11 networks had coverage above 50%.[6] Incidence data from alternative sources, such as the BMR-Raisin network in France[31], and nationwide registration of *S. aureus* BSIs in Denmark[32], underline the representativeness of our estimates for these countries. However, for Germany, Italy, and Greece, where EARSS population coverage was below 20%, the estimated incidence may be less reliable. The direction of this potential bias is not easily predictable. In the case of Germany, where mandatory reporting for MRSA bacteraemia started in 2009, data indicate that our model may have underestimated the true burden.[33]

Compared to the clinical outcome studies that provided the baseline for the current investigation[3,4], other, recent, well designed studies came to more conservative estimates for the clinical impact of MRSA.[34,35] However, differences in study design and outcome measures make direct comparisons difficult; presented HRs[34,35] cannot be directly compared with ORs.[3,4] Moreover, Wolkewitz *et al.*[34] focused on a single centre, while Lambert *et al.*[35] observed outcomes of patients during their stay in ICUs. Estimates used in the present study were based on 30-day follow-up in multiple centres from different European countries. This provided better comprehensiveness and consequently bears more relevance to the burden of disease estimates for acute care for Europe as a whole.

Finally, the current analysis did not consider the impact of a delay in appropriate therapy. This may have had a negative effect on clinical outcome. However, considering that ineffective empirical therapy is often a direct consequence of antimicrobial resistance, we did not separate this effect from our analysis as we regard it as an integral part of the burden caused by resistance.

Using empirical data improved the validity of our estimates of the impact of antimicrobial resistance in the European region. However, limiting our study to BSIs caused by two, albeit important, pathogens ignores the consequences of antimicrobial resistance due to infections of other causes and at other anatomical sites. More work is therefore required to fathom the total magnitude of antimicrobial resistance as a public health issue. A recent report from the European Centre for Disease prevention and Control (ECDC) also estimated the human and economic burden of disease of antimicrobial resistance in Europe.[36] This report included six of the bacterial pathogens under surveillance by the EARSS and, in addition to BSIs, included four other types of infections: pneumonia, and abdominal, urinary tract, and soft tissue infections. It should be noted that these estimates must be used with caution for several reasons. Country-specific incidence estimates for

BSIs were extrapolated from self-reported national catchment populations, an approach which frequently overestimates EARSS coverage.[6] In addition, burden of disease estimates were mainly based on risk data from small, single centre studies. At the same time, questionable assumptions were necessary to estimate the incidence and burden of disease for infections at other anatomical sites based on estimates for BSIs.

Even when considering these restrictions our results suggest that mortality attributed to antimicrobial resistance is considerable, but not excessive when compared to other causes. For high income countries in Europe, including 21 of 31 participating in the EARSS, WHO reports that the highest number of deaths is associated with cardiovascular disorders (373 deaths per 100,000).[37] Among communicable diseases, lower respiratory tract infections (29.5 per 100,000) rank highest.[37] For G3REC and MRSA BSIs, the estimated mortality (1.5 per 100,000 in the high income countries) is *on par* with rates for HIV/AIDS (1.5 per 100,000) or tuberculosis (1.0 per 100,000).[37]

How will this change in the near future? Here, we project that the combined burden of resistance of MRSA and G3CREC will be growing, leading to a predicted incidence of 3.3 associated deaths per 100,000 inhabitants in 2015. The burden of resistance will thereby likely surpass the current estimates for casualties associated with, for example, cervical cancer (2.7 per 100,000).[37] Although these presented forecasts emphasize the increasing importance of resistance, especially for third-generation cephalosporin resistance in *E. coli* BSIs, these predictions should be interpreted with caution. The presented trajectories were based on a continuation of current trends, reflecting the unlikely scenario that saturation effects of present control efforts[38] or expansion of newly emerging clones or resistance mechanisms[39,40] will not take place. Since these events are highly unpredictable they may thwart attempts towards reliable trend analysis.

We conclude that excess mortality associated with MRSA and G3CREC is high, even though it represents only a fraction of the total burden of disease associated with antimicrobial resistance. Forecasts about changes in the coming years are disturbing; despite anticipated gains in the control of MRSA, the persistently increasing number of infections caused by third-generation cephalosporin-resistant gram-negative pathogens is likely to outweigh this achievement soon.

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Supporting information

Table S1. Number of acute care beds for 2007: beds per 10 000 population.

Country	Number of hospital beds (per 10,000 inhabitants)*
Austria	56.8
Belgium	43.0
Bulgaria	49.1
Croatia	34.0
Cyprus	34.8
Czech Republic	51.5
Denmark	30.8
Estonia	38.0
Finland	20.5
France	35.4
Germany	56.9
Greece	39.6
Hungary	41.4
Iceland	40.7
Ireland	26.7
Israel	21.1
Italy	31.4
Latvia	52.4
Lithuania	51.1
Luxembourg	44.4
Malta	26.9
Netherlands	28.9
Norway	27.6
Poland	46.2
Portugal	27.9
Romania	44.8
Slovenia	37.8
Spain	25.6
Sweden	23.2
Turkey	23.7
United Kingdom	27.3

* All data were provided by Eurostat[7], except for Finland, National Institute for Health and Welfare; Iceland, Ministry of Health Iceland; Israel, Ministry of Health Israel; and Sweden, Swedish Institute for Infectious Disease Control.

Table S2. Parameter estimates: aORs for 30-day mortality and excess LOS in days associated with MRSA, MSSA, G3CREC and SEC bacteraemias, and the derived Number Needed to be Exposed for one excess death (NNE).[3,4]

Bacteremias	aORs for 30-day mortality (CI_{95})	NNE (CI_{95})	Excess LOS in days (CI_{95})
MRSA	4.4 (2.8-7.0)	4.9 (3.4-9.2)	9.2 (5.2-13.5)
MSSA	2.4 (1.7-3.3)	11.2 (7.4-20.0)	8.6 (6.8-10.4)
G3CREC	4.6 (1.7-12.3)	6.3 (2.6-25.2)	7.9 (3.5-13.0)
SEC	1.9 (1.4-2.5)	18.9 (11.1-35.7)	2.9 (1.7-4.0)

Table S3. Estimated number of excess deaths associated with MSSA, MRSA, G3CREC and SEC bacteraemias in 2007. Countries include all European Union Member States (excluding Slovakia), both candidate countries*, two EFTA countries# and Israel.

Country	Estimated excess mortality (CI_{95})			
	MRSA	MSSA	G3CREC	SEC
Austria	26 (15-40)	122 (67-182)	40 (9-87)	129 (64-205)
Belgium	50 (27-78)	75 (41-115)	15 (3-34)	112 (56-180)
Bulgaria	13 (6-25)	41 (22-63)	25 (5-56)	26 (12-41)
Croatia	43 (24-64)	32 (17-48)	7 (1-15)	69 (34-110)
Cyprus	17 (9-27)	8 (5-13)	8 (2-18)	11 (5-17)
Czech Rep.	51 (29-76)	153 (85-229)	35 (8-76)	148 (74-235)
Denmark	4 (1-11)	139 (77-210)	14 (3-35)	146 (72-233)
Estonia[a]	4 (2-5)	17 (9-25)	0 (0-1)	12 (6-19)
Finland	2 (1-5)	52 (28-78)	6 (1-13)	89 (44-141)
France	898 (511-1,364)	1,157 (641-1,746)	110 (24-241)	1,696 (840-2,695)
Germany	493 (220-924)	1,107 (581-1,765)	343 (65-860)	1,222 (588-1,979)
Greece	240 (126-397)	120 (61-197)	20 (3-63)	72 (33-125)
Hungary[a]	55 (32-83)	83 (46-124)	11 (2-23)	63 (31-100)
Iceland[a]	0	6 (3-9)	1 (0-2)	6 (3-9)
Ireland[a]	101 (58-152)	74 (41-111)	16 (4-34)	94 (47-149)
Israel	114 (64-175)	105 (58-159)	100 (22-215)	193 (95-307)
Italy	532 (299-817)	466 (257-710)	205 (45-450)	523 (260-841)
Latvia	6 (3-10)	28 (15-43)	4 (1-9)	7 (4-12)
Lithuania	7 (4-11)	32 (18-48)	5 (1-11)	20 (10-32)
Luxembourg[a]	5 (3-7)	8 (5-12)	2 (0-4)	15 (7-24)
Malta[a]	11 (6-16)	4 (2-7)	3 (1-6)	6 (3-9)
Netherlands	7 (2-20)	269 (148-409)	37 (8-85)	267 (132-428)
Norway	0	115 (64-175)	10 (2-24)	159 (79-253)
Poland	64 (33-107)	160 (87-247)	11 (2-32)	157 (77-254)
Portugal	395 (225-595)	194 (108-294)	77 (17-166)	218 (109-347)
Romania	28 (12-53)	34 (17-57)	40 (8-95)	31 (15-53)
Slovenia[a]	7 (4-11)	35 (20-53)	6 (1-13)	47 (23-75)
Spain	442 (250-672)	599 (332-905)	247 (54-534)	1,040 (513-1,657)
Sweden	5 (3-8)	228 (127-342)	16 (4-35)	248 (123-394)
Turkey	788 (445-1,194)	690 (384-1,046)	793 (178-1,716)	377 (185-599)
UK[a]	1096 (627-1,650)	1108 (615-1,664)	504 (114-1,078)	1174 (583-1,863)
Total	5,503 (3,136-8,276)	7,261 (4,021-10,910)	2,712 (595-5,780)	8,377 (4,148-13,296)

Countries include all European Union member states (excluding Slovakia), both candidate countries (Croatia and Turkey), two EFTA countries (Iceland and Norway), and Israel.
[a] Total number as reported to the EARSS or by national health authorities (UK), CI solely based on CI of NNE from the clinical outcome studies; Rep. = Republic

Table S4. Estimated excess number of bed-days and costs associated with MRSA, MSSA, G3CREC and SEC bacteraemias in 2007.

Country	Excess number of bed-days in thousands (CI_{95})				Excess costs in thousand euros (CI_{95})			
	MRSA	MSSA	G3CREC	SEC	MRSA	MSSA	G3CREC	SEC
Austria	1.2 (0.7-1.8)	11.6 (9.2-14.1)	1.8 (0.8-3.0)	6.6 (4.0-9.2)	279 (157-413)	2,630 (2,092-3,192)	407 (180-674)	1,492 (909-2,083)
Belgium	2.3 (1.2-3.6)	7.2 (5.5-8.9)	0.7 (0.3-1.2)	5.7 (3.5-8.0)	506 (273-787)	1,575 (1,218-1,967)	147 (59-269)	1,255 (762-1,764)
Bulgaria	0.6 (0.3-1.1)	3.9 (2.9-5.1)	1.1 (0.5-2.0)	1.3 (0.8-1.9)	20 (9-37)	127 (94-165)	36 (15-65)	42 (25-62)
Croatia	2.0 (1.1-3.0)	3.0 (2.4-3.7)	0.3 (0.1-0.5)	3.5 (2.2-4.9)	136 (76-204)	207 (163-254)	21 (9-36)	243 (148-340)
Cyprus	0.8 (0.4-1.3)	0.8 (0.6-1.1)	0.4 (0.1-0.6)	0.5 (0.3-0.8)	119 (64-185)	118 (87-156)	52 (22-94)	79 (47-115)
Czech Rep.	2.3 (1.3-3.5)	14.5 (11.6-17.6)	1.6 (0.7-2.6)	7.5 (4.6-10.5)	214 (120-319)	1,329 (1,060-1,612)	143 (63-237)	690 (420-963)
Denmark	0.2 (0.1-0.5)	13.2 (10.3-16.4)	0.6 (0.2-1.3)	7.4 (4.5-10.5)	55 (15-143)	3,745 (2,906-4,642)	182 (69-354)	2,108 (1,283-2,978)
Estonia[a]	0.2 (0.1-0.2)	1.6 (1.3-2.0)	0.0	0.6 (0.4-0.9)	13 (8-20)	130 (103-158)	1 (1-2)	50 (31-70)
Finland	0.1 (0.0-0.2)	4.9 (3.9-6.1)	0.3 (0.1-0.5)	4.5 (2.8-6.3)	27 (12-50)	1,144 (901-1,407)	59 (24-107)	1,048 (643-1,470)
France	41.7 (23.3-62)	110.2 (87.6-134.0)	4.9 (2.1-8.3)	86.3 (52.6-120.3)	8,941 (4,999-13,281)	23,600 (18,757-28,711)	1,045 (450-1,788)	18,489 (11,269-25,776)
Germany	22.9 (10.1-42.6)	105.4 (75.6-141.7)	15.2 (5.3-32.4)	62.2 (36.8-90.8)	4,878 (2,144-9,077)	22,447 (16,093-30,167)	3,239 (1,118-6,890)	13,238 (7,840-19,337)
Greece	11.1 (5.8-18.0)	11.4 (7.7-16.1)	0.9 (0.2-2.5)	3.6 (2.0-5.7)	1,850 (967-2,998)	1,900(1,287-2,679)	145 (32-422)	606 (340-940)
Hungary[a]	2.6 (1.5-3.8)	7.9 (6.3-9.6)	0.5 (0.2-0.8)	3.2 (2.0-4.5)	218 (123-322)	666 (530-809)	39 (17-65)	272 (166-380)
Iceland[a]	0.0	0.6 (0.4-0.7)	0.0 (0.0-0.1)	0.3 (0.2-0.4)	0	164 (131-199)	9 (4-15)	86 (52-120)
Ireland[a]	4.7 (2.6-6.9)	7.1 (5.6-8.6)	0.7 (0.3-1.2)	4.8 (2.9-6.7)	1,367 (770-2,023)	2,065 (1,642-2,507)	203 (90-337)	1,397 (851-1,949)
Israel	5.3 (2.9-7.9)	10.0 (7.8-12.3)	4.4 (1.9-7.4)	9.8 (6.0-13.8)	662 (367-991)	1,252 (977-1,545)	553 (240-930)	1,228 (751-1,721)
Italy	24.7 (13.7-37.2)	44.4 (34.5-55.0)	9.1 (3.9-15.6)	26.6 (16.1-37.5)	4,811 (2,670-7,252)	8,635 (6,718-10,711)	1,770 (758-3,046)	5,183 (3,132-7,310)
Latvia	0.3 (0.1-0.4)	2.7 (2.1-3.3)	0.2 (0.1-0.3)	0.4 (0.2-0.5)	16 (8-27)	162 (127-203)	11 (4-21)	23 (14-33)
Lithuania	0.3 (0.2-0.5)	3 (2.4-3.7)	0.2 (0.1-0.4)	1.0 (0.6-1.4)	19 (10-32)	180 (141-224)	13 (5-24)	61 (37-86)
Luxembourg[a]	0.2 (0.1-0.3)	0.8 (0.6-0.9)	0.1 (0.0-0.1)	0.8 (0.5-1.1)	93 (52-138)	328 (261-398)	37 (16-61)	319 (194-445)

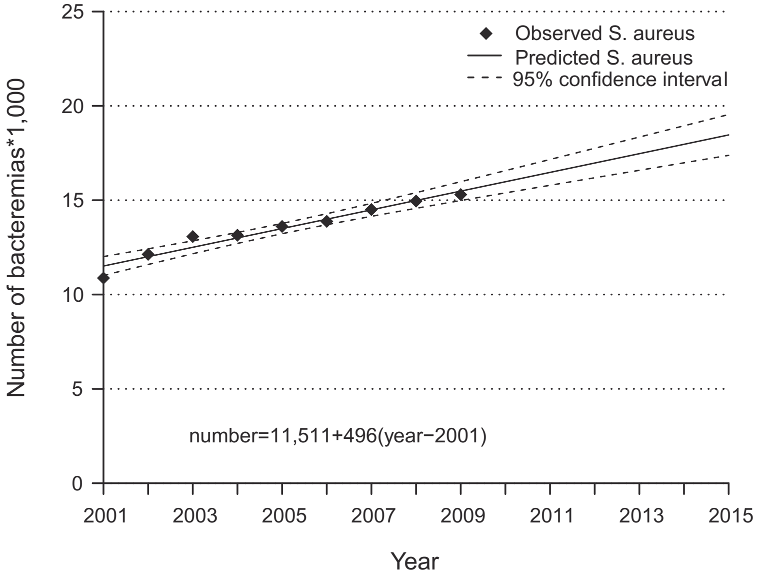
Table S4. Continued

Country	Excess number of bed-days in thousands (CI_{95})				Excess costs in thousand euros (CI_{95})			
	MRSA	MSSA	G3CREC	SEC	MRSA	MSSA	G3CREC	SEC
Malta[a]	0.5 (0.3-0.8)	0.4 (0.3-0.5)	0.1 (0.1-0.2)	0.3 (0.2-0.4)	51 (29-76)	43 (34-53)	12 (5-20)	30 (18-41)
Netherlands	0.3 (0.1-0.9)	25.6 (20.0-31.6)	1.6 (0.6-3.0)	13.6 (8.2-19.1)	78 (21-208)	5,971 (4,662-7,390)	378 (150-711)	3,177 (1,923-4,467)
Norway	0	11.0 (8.6-13.5)	0.5 (0.2-0.9)	8.1 (4.9-11.3)	0	3,865 (3,033-4,758)	164 (65-306)	2,850 (1,736-3,996)
Poland	3.0 (1.5-4.9)	15.2 (11.6-19.5)	0.5 (0.1-1.2)	8 (4.8-11.4)	195 (98-322)	998 (758-1,277)	33 (9-81)	523 (317-747)
Portugal	18.4 (10.3-27.3)	18.5 (14.6-22.6)	3.4 (1.5-5.7)	11.1 (6.7-15.5)	2,276 (1,277-3,383)	2,294 (1,812-2,803)	423 (186-712)	1,378 (837-1,922)
Romania	1.3 (0.6-2.5)	3.3 (2.1-4.8)	1.8 (0.7-3.4)	1.6 (0.9-2.4)	57 (25-110)	146 (96-213)	79 (30-151)	71 (40-107)
Slovenia[a]	0.3 (0.2-0.5)	3.4 (2.7-4.1)	0.3 (0.1-0.5)	2.4 (1.5-3.3)	31 (17-46)	319 (254-387)	26 (12-43)	226 (138-315)
Spain	20.5 (11.4-30.8)	57.1 (45.1-70.0)	10.9 (4.8-18.5)	52.9 (32.3-73.9)	3,529 (1,964-5,299)	9,816 (7,749-12,030)	1,882 (825-3,186)	9,097 (5,553-12,704)
Sweden	0.2 (0.1-0.4)	21.7 (17.3-26.3)	0.7 (0.3-1.2)	12.6 (7.7-17.6)	58 (32-90)	5,432 (4,323-6,588)	178 (79-297)	3,152 (1,923-4,398)
Turkey	36.6 (20.5-55)	65.8 (52.0-80.5)	35.1 (15.4-59.0)	19.2 (11.6-27.0)	1,705 (956-2,560)	3,061 (2,420-3,748)	1,634 (719-2,747)	892 (540-1,259)
UK[a]	50.9 (28.7-75.4)	105.5 (83.9-128.1)	22.3 (9.9-36.9)	59.7 (36.4-83.3)	11,755 (6,622-17,393)	24,350 (19,362-29,557)	5,147 (2,279-8,525)	13,782 (8,398-19,233)
Total	255.7 (142.9-375.9)	691.4 (548.5-840)	120.1 (52.3-198.3)	426.2 (259.6-594.9)	43,961 (23,885-67,786)	128,701 (99,791-160,510)	18,068 (7,535-32,216)	83,087 (50,337-117,131)

Countries include all European Union member states (excluding Slovakia), both candidate countries (Croatia and Turkey), two EFTA countries (Iceland and Norway), and Israel.

[a] Total number as reported to the EARSS or by national health authorities (UK), CI solely based on CI of the excess LOS estimate from the clinical outcome studies; Rep. = Republic

A



B

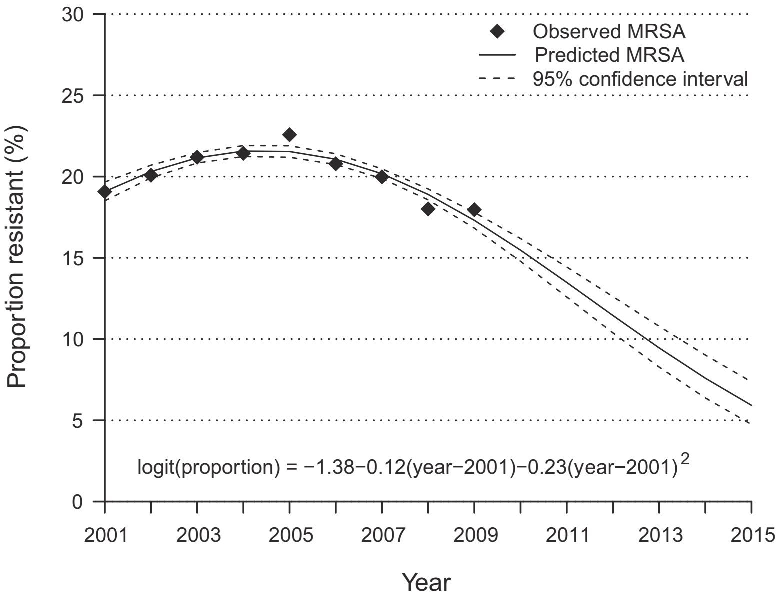
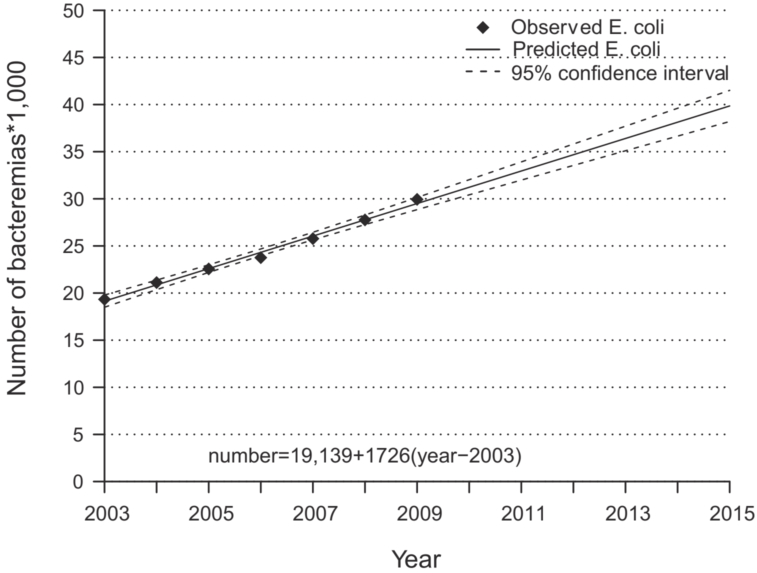


Figure S1. Trends in the number of *S. aureus* BSIs (A) and the proportion of these that were resistant for methicillin (B) for EARSS laboratories consistently reporting from 2001-2009: Diamonds indicate ascertained values and trend line projections are based on regression analysis, regression equations are included.

A



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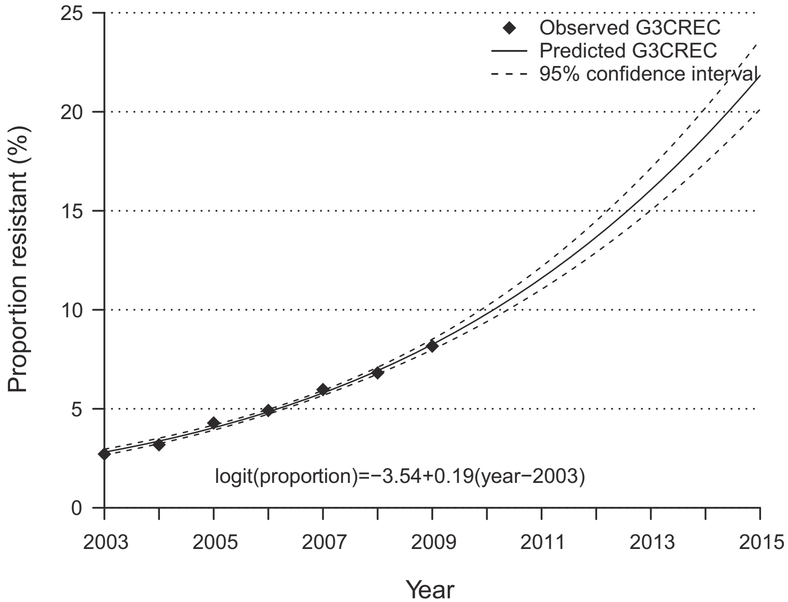

Figure S2. Trends in the number of *E. coli* BSIs (A) and the proportion of these that were resistant for third-generation cephalosporins (B) for EARSS laboratories consistently reporting from 2003-2009: Diamonds indicate ascertained values and trend line projections are based on regression analysis, regression equations are included.