

A microsimulation model projecting the health care costs for resistance to antibacterial drugs in Sweden

Sofie Larsson^{1,2}, Magdalena Prioux¹, Tobias Fasth¹, Anders Ternhag^{1,3}, Johan Struwe¹, Ulrica Dohnhammar¹, Lisa Brouwers¹

1 Public Health Agency of Sweden, Solna, Sweden

2 Health Metrics unit, Department of Public Health and Community Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

3 Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

Correspondence: Sofie Larsson, Department of Public Health Analysis and Data Management, Folkhalsomyndigheten, 171 82 Solna, Sweden, Tel: +46 10 205 20 91, Fax: +46 8 32 83 30, e-mail: sofie.larsson@folkhalsomyndigheten.se

Background: Previous studies have shown that increasing antibacterial resistance (ABR) globally will cause extensive morbidity, deaths and escalated health care costs. **Methods:** To project economic consequences of resistance to antibacterial drugs for the Swedish health care sector, we used an individual-based microsimulation model, SESIM. Health care consumption was represented as increased numbers of hospital days, outpatient visits and contact tracing for individuals getting clinical infections or becoming asymptomatic carriers. The risk of contracting a resistant bacterium was calculated using the incidence of mandatorily notifiable ABR in Sweden. **Results:** We estimate accumulated additional health care costs attributable to notifiable ABR from 2018 until 2030 to EUR 406 million and EUR 1, 503 million until 2050. Until 2030 the largest proportion, more than EUR 247 million (EUR 958 million until 2050), was due to ESBL, followed by methicillin resistant *Staphylococcus aureus*, carbapenemase-producing Enterobacteriaceae, vancomycin-resistant Enterococci and penicillin non-susceptible Pneumococci which incurred costs of EUR 128 million (EUR 453 million, 2050), EUR 15 million (EUR 58 million, 2050), EUR 13 million (EUR 28 million, 2050) and EUR 2 million (EUR 6 million, 2050), respectively. **Conclusions:** Projections concerning the future costs of ABR can be used to guide priorities and distribution of limited health care resources. Our estimates imply that costs in Sweden will have doubled by 2030 and increased more than 4-fold by 2050 if present trends continue and infection control practices remain unchanged. Still, indirect societal costs and costs for non-notifiable resistance remain to be added.

Introduction

Modern healthcare is dependent on effective antibiotics. As the proportion of resistant bacteria increases, achievements in public health may become at stake and health care procedures which today are perceived as routine will become more risky. Even if resistance levels still are low in Sweden in comparison with other countries, resistance to antibacterial drugs is a global problem and its increase is a major challenge for both Sweden and the rest of the world.¹

In addition to impact on public health, resistance may also have a significant economic impact on society in terms of additional health care consumption and productivity losses. According to the WHO, appropriate studies quantifying the consequences of resistance to antibacterial drugs in terms of health and economic burden are limited.^{2–5} In particular, studies identifying on-top costs, i.e. the additional resource use associated with resistant versus non-resistant bacteria, are scarce.⁶ However, the European Centre for Disease Prevention and Control (ECDC) estimated that antibacterial resistance (ABR) in the EU contributes to 25 000 deaths, and an extra EUR 900 million in hospital costs per year.⁷ Similarly, the Centre for Disease Prevention and Control (CDC), estimated that antibiotic-resistant bacteria (including fungi) results in 23 000 deaths per year in the USA.⁸ In the UK, the O'Neill review estimated that by 2050 antimicrobial resistance (AMR) (resistance in all types of antimicrobial agents) may contribute to about 10 million deaths per year and a significant reduction of the world's Gross Domestic Product (GDP).^{9–11} However, the relevance of some of the estimates used in the O'Neill report have been questioned.¹² World Economic Forum stated in their risk report 2013 that 'arguably the greatest risk of hubris to human health comes in the

form of *antibiotic-resistant bacteria*'.¹³ Finally, it was estimated that the OECD countries together may lose about USD 2.9 trillion in cumulative GDP by 2050 due to AMR.¹⁴

In 2013, when the updated Swedish strategy to combat antibiotic resistance was launched,¹⁵ the Swedish Government commissioned the Public Health Agency to estimate the economic impact of ABR. To estimate the potential costs until 2030 and 2050, we developed, tested and validated a simulation model that projected annual incidence of five types of mandatorily notifiable resistance; methicillin resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL) in Enterobacteriaceae, carbapenemase-producing Enterobacteriaceae (CPE), penicillin non-susceptible Pneumococci (PNSP) and vancomycin-resistant Enterococci (VRE). The first part of our study showed a significant increase in the additional resource use due to ABR when duration of treatment for infections and carriage caused by resistant bacteria was compared to similar infections caused by susceptible bacteria.¹⁶

The aim of this study was to project the additional impact of ABR on total health care consumption and associated costs over the period 2018 until 2030 and 2050, respectively, in the Swedish setting, by using a simulation model, as well as the previous calculations of additional resource use.

Method

The microsimulation model

To project the development of ABR in Sweden while taking individual risks of infection into account, we chose a micro approach using the SESIM microsimulation model containing a

representative sample of 300 000 individuals from the 9 million Swedish population. The SESIM model was developed in 1997 at the Swedish Ministry of Finance as a tool to analyse distributional effects of potential policy changes within the Swedish national system of study allowances. Since then, SESIM has been used for various policy studies and has also been updated with new modules, for instance health.¹⁷ In this study, we have used and further developed the health module to project development of ABR.

In a microsimulation model the individuals are each represented separately. The state of the individuals is updated annually according to rules and statistical models taking individual attributes and history into consideration, thereby creating dynamics. For example, a person's health state is updated annually using a statistical model that includes among other factors age, sex, marital status, last year's health care consumption and last year's health state. A major advantage with applying a micro approach in this case is the implementation of a realistic demographic forecast. The risk of acquiring a resistant infection is higher among the elderly than among younger, this aspect of an ageing population is included in our model. Other, more general, advantages with micro-simulations in the health domain is that the individuals' history matters (diseases, health care consumption, smoking habits etc.), individual behaviour (response to policies) can easily be incorporated and finally, the possibility to target policies to specific individuals based on their characteristics and history.^{18,19}

Initial risks of contracting a specified resistant bacterium that we used in the model were based on notified cases of the included types of resistance. Data were collected from the national register SmiNet, held by the Public Health Agency of Sweden,²⁰ to which all cases are reported by laboratories and clinicians along with data on patient age, gender and the specimen type. Both infection and carriage of ESBL, CPE, MRSA, PNSP and VRE are mandatory to report according to the Swedish Communicable Disease Act.²¹ In 2016 altogether almost 15 500 cases of notifiable resistance were reported to SmiNet. To improve representativeness in scarce data we pooled all cases reported from 2012 to 2016 by gender and age into 5-year groups for all resistance types but MRSA where we used data for 2012–14 because of an increase in screening for MRSA in 2015 and 2016. Despite aggregation, some age and gender cohorts had zero cases and the calculated risk would then be zero. To avoid this, a small but non-zero risk was used in the model instead.

Cases were reported to SmiNet based on findings of resistant bacteria in a wide variety of sample sites and types. To facilitate data presentation we grouped cases into the most common clinical infections and carriage, respectively. Specific assumptions of health care consumption and mortality in relation to each category of infection or carriage and type of resistance are presented in the Supplementary table S1. For example, carriage was assumed to be cleared after one year for all but ESBL, and risk for mortality in blood-stream infection was only increased during the first year.

When modelling the development of ABR we used either linear or exponential trends, based on data from 2012 to 2016 (all trends are presented in Supplementary table S2). An exception was made for VRE, for which incidence is associated with outbreaks rather than gradual changes. This was modelled as an annual risk of outbreaks. In case of an outbreak of VRE, it was estimated to cease within four years based on previous national experiences. We also assumed that the development of resistance would not increase the total numbers of infections, but rather that a higher proportion of infections was caused by resistant bacteria, since there has not been a significant increase in infections during the last couple of years.

After implementing risks and trends based on reported data, the simulation model output was an annual number of cases of ABR per type of resistance separated between infections and carriage. Since the model has stochastic elements, we ran the model 30 times to ensure stability of the results. The number of cases generated from

the micro-simulations was then used in a health economic model to calculate the costs caused by resistance.

The economic model

In the economic model we used actual data from national registers and information on resource use for patient care and contact tracing, to quantify the on-top consumption of health care and antibiotics due to resistance. Identification of consumption associated with each case of resistance was feasible due to the widespread use of the social security number in Sweden, making it possible to link registers by the individual. Consumption of prescribed antibiotics and health care (days in hospital care, outpatient visits and primary care visits) was identified for reported cases during the 30 days following sampling date. Cost of prescribed antibiotics was collected from the Prescribed Drug Register, and data on health care consumption from the National Patient Register.^{22,23}

To identify the on-top consumption due to resistance we subtracted the health care consumption due to infections caused by susceptible bacteria, which was estimated as average health care consumption for all infections where data were available (blood-stream infections and pneumonia).²⁴ For diagnoses where this information was unavailable (urinary tract infections and skin and soft tissue infections) clinical experts were consulted to provide a best estimate. For all cases, except ESBL, all family members were assumed to be contact traced, as requested by law. If the case was a child between 1 and 5 years of age an additional 15 individuals representing peers and teachers in a nursery group were contact traced as well. For VRE, which was assumed to only transmit in hospital environment, an additional 10 individuals were contact traced, representing other patients cared for at the same hospital ward.

Costs for primary care visits were collected from a public pricelist from the southern care region.²⁵ Costs for hospital days and outpatient visits were derived from the Case Costing Database of the Swedish Association of Local Authorities and Regions (SALAR).²⁴ Data on extra staff hours associated with contact tracing were provided by Värmland and Stockholm counties, and transformed to costs using standardized salary costs for relevant professional groups. Laboratory costs for contact tracing were collected from the Region Skåne clinical microbiology laboratory price list.²⁶ Identified health care consumption and costs are presented in the Supplementary tables S3 and S4. All costs were discounted by 3% to calculate the present value, according to Swedish guidelines.²⁷

The economic model combines the output of the microsimulation model (number of ABR cases) with additional resource use and health care costs, depending on resistance type and infection type. This means that we have only calculated the additional cost from resistance and not the total cost of treating infections.

The study was approved by the Ethical Review Board in Stockholm (dnr. 2013/1840-31/2).

Results

Our simulation suggests that there will be about 32 000 and 71 000 annual cases of ABR in Sweden in 2030 and 2050, respectively. Annual cases of ESBL, which is currently the most frequently reported type of resistance in Sweden (about 70% of all notified cases), is expected to almost double (1.97 times) until 2030 and more than 4-fold (4.52 times) until 2050. The resistance with the greatest increase is CPE with a change factor of 3.44 until 2030 and 8.14 until 2050, as shown in table 1. None of the included types of resistance are projected to decrease over the modelled period. Projections of cases are based on historical trends during the years 2012–16 for each type of resistance over the modelled period.

The microsimulation model generated a total number of cases for each type of resistance, consisting of individuals with either a clinical

Table 1 Projection of number of cases and change factor per resistance type

Year	ESBL	CPE	MRSA	PNSP	VRE	Total
2018	11 303	140	3281	127	278	15 129
2019	12 071	174	3765	138	226	16 374
2020	12 929	197	4112	137	309	17 684
2021	13 857	248	4493	130	281	19 009
2022	14 838	231	5043	153	276	20 541
2023	15 389	286	5561	178	320	21 734
2024	16 415	325	5770	190	393	23 093
2025	17 464	324	6294	172	323	24 577
2026	18 371	330	6685	190	289	25 865
2027	19 290	382	7072	187	294	27 225
2028	20 293	435	7616	186	297	28 827
2029	21 168	435	7809	196	302	29 910
2030	22 261	481	8584	222	348	31 896
–	–	–	–	–	–	–
2050	51 130	1139	17 794	583	308	70 954
Change factor						
2030	1.97	3.44	2.62	1.75	1.25	2.11
2050	4.52	8.14	5.42	4.59	1.11	4.69

Table 2 Number, and percentage, of cases in 2030 and 2050, divided into infection site and resistance type

2030												
	Urinary tract infection ^a		Blood-stream infection		Skin and soft tissue infection		Pneumonia		Carriership		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ESBL	10 978	49	1769	8	535	2			8979	40	22 261	100
CPE	22	5	280	58	11	2			168	35	481	100
MRSA			80	1	2469	29			6035	70	8584	100
PNSP			4	2			12	5	206	93	222	100
VRE ^a	47	14							301	86	348	100
2050												
	Urinary tract infection ^a		Blood-stream infection		Skin and soft tissue infection		Pneumonia		Carriership		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ESBL	18 401	36	13 460	26	1466	3			17 803	35	51 130	100
CPE	63	6	665	58	29	3			382	34	1139	100
MRSA			529	3	5043	28			12 222	69	17 794	100
PNSP			1	0			9	2	573	98	583	100
VRE ^a	46	15							262	85	308	100

a: For VRE we only estimated the number of clinical infection, i.e. they are not divided into urinary tract infection, blood-stream infection and so on.

infection (blood-stream infection, urinary tract infection, skin and soft tissue infection or pneumonia) or a carriership. Accumulated results by 2030 and 2050, respectively, which are shown in table 2, shows that the largest proportions of ABR are detected in carriers and that urinary tract infections are the second most common infection type.

The annual additional health care costs due to notifiable ABR was calculated to almost EUR 40 million by year 2030 and 75 million by year 2050. The accumulated cost between 2018 and 2030 added up to more than EUR 400 million and more than 1500 million until 2050. Until 2030 the largest proportion, more than EUR 247 million (EUR 958 million until 2050), was due to ESBL, followed by MRSA, CPE, VRE and PNSP which incurred costs of EUR 128 million (EUR 453 million, 2050), EUR 15 million (EUR 58 million, 2050), EUR 13 million (EUR 28 million, 2050) and EUR 2 million (EUR 6 million, 2050), respectively, as presented in table 3 (exchange rate EUR 1=SEK 9.9448, per 12 February 2018²⁸).

As shown in table 3, the total costs in 2030 were dominated by the cost associated with blood-stream and urinary tract infections caused by ESBL and carriership and skin and soft tissue infection caused by MRSA. Blood-stream infections were in general the most expensive per case, but since urinary tract infections are more frequent, the accumulated costs for them were much higher.

The high costs of MRSA carriers were mainly due to mandatory contact tracing.

Discussion

In our simulation of a future scenario for the development of notifiable ABR in Sweden we found that the accumulated additional health care costs from 2018 until 2030 and 2050, respectively, would reach more than EUR 400 million and EUR 1500 million, even if we manage to maintain the presently low level of resistance and slow pace of its' increase.

To project the future costs we used a microsimulation model, as widely as possible based on actual data. Inputs and variables were based on reported Swedish surveillance data combined with costs derived from healthcare sources. We used the recent years' trend of ABR as a projection of the future development, instead of assuming hypothetical levels. This, in combination with using actual health care costs, adds realism to our results. In contrast, recently published studies have used hypothetical cases based on assumed potential levels of resistance and made calculations of the economic impact from these assumptions.^{8–14} We therefore believe our results will better guide decisions regarding interventions to keep ABR at the same levels as today.

Table 3 Projected accumulated costs until 2030 and 2050, respectively, million Euros

2030						
	Urinary tract infection ^a	Blood-stream infection	Skin and soft tissue infection	Pneumonia	Carriers	Total
ESBL	189	57	1	–	0	247
CPE	13	2	0	–	1	15
MRSA	–	7	50	–	71	128
PNSP	–	0	–	1	1	2
VRE	8	–	–	–	6	13
Total	210	66	51	1	78	406
2050						
	Urinary tract infection ^a	Blood-stream infection	Skin and soft tissue infection	Pneumonia	Carriers	Total
ESBL	539	417	3	–	0	958
CPE	49	7	1	–	2	58
MRSA	–	42	169	–	243	453
PNSP	–	0	–	2	4	6
VRE	16	–	–	–	12	28
Total	603	466	172	2	261	1 503

a: For VRE we only estimated the number of clinical infection, i.e. they are not divided into urinary tract infection, blood-stream infection and so on.

However, the model still has some limitations. The scenarios in the model are based on today's health care structures. The assumption is therefore that patients with resistant bacteria in the future will be treated the same way as today, which would probably not be the case if resistance levels increase significantly. Higher levels of resistance could bring about changes in treatment strategies and infection control strategies, which might affect health care costs due to resistance in the future. In addition, we have not taken the risk of not having last resort antibiotics available as a consequence of changed resistance patterns in the projected period, since development of such resistance (e.g. carbapenem-resistant Enterobacteriaceae), has been comparatively slow thus far. As this may change, it further contributes to our estimate being conservative. Specific conditions, such as environmental factors, medication routines, ongoing outbreaks and endemic situation, affect both the risk of ABR and impact of various interventions, which are not represented in the model.

In addition to increased consumption of health care, infections with antibiotic-resistant bacteria generate indirect costs, such as production loss from sick leave and disability pension as well as changed routines in the health care sector. In other studies these costs have been assigned a substantial impact from a societal perspective.^{7,9,29} In this study, however, we only include direct health care costs since we lack reliable data for other costs.

There are many other types of ABR than those notifiable under the Communicable Diseases Act. Since we only included notifiable ABR, and only the health care related costs, it is reasonable to assume that cost estimations are quite conservative. However, the model is prepared to include indirect costs and other types of resistance as a next step when data is available.

According to our projections, the total costs of ABR in 1 year, in 2030 and 2050, respectively, will be almost EUR 40 and 75 million. Other studies have estimated that development of ABR will have a large impact on national and global economies.^{7–11,14} The difference between our results and other studies can at least partly be explained by the rather low levels and comparatively slower pace of development of ABR in Sweden today, that our study was limited to notifiable resistance, and also that our study to a greater extent was based on actual data rather than assumptions.

In conclusion, by applying a microsimulation model based on actual data of notified ABR, we found that even in Sweden, which still has comparatively limited resistance levels, the additional health care costs due to ABR may increase 4-fold to a yearly cost of EUR 75 million by 2050 and that the accumulated costs 2018–50 would reach more than EUR 1500 million. To improve forecasts and form a better basis for interventions to tackle ABR at national and

global level, more valid data on human and economic consequences of ABR in different settings need to be collected.

Supplementary data

Supplementary data are available at *EURPUB* online.

Conflicts of interests: None declared.

Key points

- We found that the annual additional health care costs due to ABR may increase 4-fold by 2050 and that the additional accumulated health care costs 2018–50 would reach more than EUR 1500 million, even in Sweden, which still has comparatively low resistance levels.
- Economic analysis of the development of ABR provides important knowledge for informing interventions and strategies to tackle ABR at national and global level.
- Indirect costs and costs for non-notifiable resistance still remain to be studied.

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Choosing Wisely Italy: online survey on opinions and behaviors of 1006 people and 355 volunteers of healthcare advocacy associations

Paola Mosconi¹, Anna Roberto¹, Franca Braga², Lucia Napoli³, Marco Anelli³, Cinzia Colombo¹

1 Laboratory for Medical Research and Consumers Involvement, Department of Public Health, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

2 Department of Public Health, Food and Health Competence Center, Altroconsumo, Milan, Italy

3 Statistical Surveys Department, Altroconsumo, Milan, Italy

Correspondence: Anna Roberto, Biol Sci D, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via G. La Masa 19, 20157 Milan, Italy, Tel: +39 02 39014503, Fax: +39 02 33200231, e-mail: anna.roberto@marionegri.it

Background: In the framework of 'Doing more does not mean doing better - Choosing Wisely Italy' health professionals, general population and healthcare advocacy associations are widely involved. PartecipaSalute-Mario Negri IRCCS and Altroconsumo organized a survey in order to assess the opinions and behaviors of people toward unnecessary tests and drugs.

Methods: An online survey was distributed by Altroconsumo to a voluntary panel of 6304 Italian citizens covering the whole of the country and by PartecipaSalute-Mario Negri IRCCS through the PartecipaSalute website, e-mail lists, website articles, lay journals and Facebook.

Results: In all 1006 people reached by Altroconsumo, and 355 volunteers of healthcare advocacy associations reached by PartecipaSalute responded. Respondents usually decides on their treatment together with the physician, respectively 50% for general population and 64% for volunteers of healthcare advocacy associations. The respondents are aware of the question of over-use of drugs and tests (80%), more often among the volunteers of healthcare advocacy associations (86%). Over-use is considered a problem mostly for economic reasons among the general population, while in the advocacy associations the risks for patients' health is considered more important.

Conclusion: These findings suggest that patients do not always ask for more, especially if they receive an answer to their questions and clarifications about unnecessary treatments. There is a need for further understanding of the factors influencing decision-making aimed at achieving good care. Engaging the public and patients at all levels of healthcare is essential for a valuable use of health resources.

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