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PUBLIC HEALTH AGENCY OF SWEDEN

Future costs of antibiotic resistance

Final reporting of Government commission on direct and indirect costs and consequences of antibiotic resistance in Swedish health care



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Article number: 18010

Preface

The resistance of bacteria against antibiotics constitutes a major threat against several parts of modern health care and public health. Therefore, projections on the future development and costs of antibiotic resistance can be used to guide priorities and allocation of the limited resources of health care.

There have been several different estimates on the current and future social costs of the growing problem of antibiotic resistance. They are estimates based on a range of assumptions, a similarity between them. In order to improve the knowledge base, the Swedish Institute for Infectious Disease Control was, in 2013, commissioned by the Government to develop a model to calculate the economic impact of antibiotic resistance. This commission was reported by the Public Health Agency of Sweden in 2014 (1).

The following year the Public Health Agency of Sweden was commissioned to improve the model and perform cost calculations based on different scenarios. In the autumn of 2016 interim reporting of the commission took place (2). The report focused on the direct costs which were identified as a result of the antibiotic resistance which are notifiable according to the Communicable Diseases Act.

This report is the final reporting of the Government commission, where calculations on the development of non-notifiable resistance and indirect costs have been taken into account as far as possible.

The project leaders have been Magdalena Prioux (until 30 June 2017) and Peter Andréasson (from 1 July 2017). The project group comprised of Jakob Bergström, Carin Bergman, Ulrica Dohnhammar, Tobias Fasth, Sofie Larsson, Johan Struwe and Anders Ternhag. Fanny Bergman, Lisa Brouwers and head of unit Malin Grape have also participated actively in the work, as well as head of department Anders Tegnell. A reference group comprising representatives of different competence areas has made useful contributions to the work. Participants of the group are presented at the end of the report.

The Public Health Agency of Sweden

Johan Carlson
Director-General

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Glossary and abbreviations

Carrier	Asymptotic (without signs of symptoms) carrier of, for example, resistant bacteria
CPP	Cost per patient
EARS-Net	European Antimicrobial Resistance Surveillance Network, managed by ECDC
ECDC	European Centre for Disease Prevention and Control
ESBL	The resistance mechanism Extended-spectrum beta-lactamases
ESBL-CARBA	Carbapenemase-producing
GDP	Gross Domestic Product
GLASS	Global Antimicrobial Resistance Surveillance System (managed by WHO)
HAI	Health care-associated infection
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
Notifiable disease	Infectious diseases which should be notified to the County Medical Officer and Public Health Agency of Sweden according to the Communicable Diseases Act and Communicable Diseases Ordinance
PNSP	Penicillin-non-susceptible <i>Streptococcus pneumoniae</i>
Prophylaxis	(In this context:) Measures to prevent infections in connection with medical treatment
RAND	RAND (“Research and Development”) Corporation, American research institute
Resistant bacteria	Bacteria which are insusceptible to antibiotic treatment; bacteria which can no longer be treated with a substance which they were susceptible to originally
ResNet	Internet-based support tool for quality assurance of antimicrobial susceptibility testing and national point prevalence measures of antibiotic resistance
SCAR	Social consequences of antibiotic resistance
SmiNet	Swedish database where notifiable diseases are registered

Susceptible bacteria	Bacteria which react to antibiotic treatment
Svebar	Swedish database for continuous surveillance of antibiotic resistance, through the microbiological laboratories of health care
Swedres	Annual Swedish reporting of antibiotic utilisation and resistance
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

Summary

In this Government commission the Public Health Agency of Sweden has calculated future direct health care costs, indirect costs and other consequences of antibiotic resistance in Sweden. The projections are based on simulations and refer to costs based on two time periods, up until the year 2030 and 2050 respectively. The analysis, which were conducted with a micro-simulation model, refers to notifiable antibiotic resistance and projections are based on actual data from 2012–2016.

In 2016 approximately 15,500 cases of notifiable antibiotic resistance were reported. According to our model, the simulation indicates that this number is estimated to be approximately 32,000 cases in 2030 and approximately 70,000 cases in 2050. Distributed per resistance type, ESBL and MRSA are increasing the most.

We have projected both the direct health care-associated and indirect costs for society. Direct costs are those which arise during treatment of antibiotic-resistant infections within health care and for contact tracing. The calculations are based on the assumption that current procedures for health care have not changed during the modelled time period. Indirect costs refer to those which are not directly linked to care for an individual. It may, for example, refer to higher costs for outbreak with spread of infection, changed treatment strategies or social costs in the form of loss of production during sickness absence.

Our simulation entails that the social costs of antibiotic resistance can be calculated to approximately SEK 4.3 billion up until 2030 and SEK 15.8 billion up until 2050. The cost of the final year 2030 is roughly SEK 400 million and for the year 2050 it is roughly SEK 600 million. The results are based on actual data on direct and indirect costs. We have refrained from performing calculations based on general estimates. Accordingly the report is based on safer data than several regularly cited international studies which were conducted previously. An interesting finding is also that the indirect costs for society, which tend to be cited as the greatest share (3, 4), appear to be significantly lower for Swedish conditions.

These amounts are slightly lower than in the Public Health Agency of Sweden's previous interim report. Which is due to the fact that simulations are based on development trends in two different time periods. In the previous interim report, when we estimated the development based on historical data, a linear trend was the most suitable, but in this report an exponential trend describes the resistance development of recent years in the best manner. For projections of the number of cases up until the year 2050, we have added restrictions in the model so that the final results are not unrealistically high, given what we know about other countries and the national development of the number of cases of resistance.

There are consequences and costs which we have not been able to analyse more in detail. The main reason for this is that there is a shortage of data. Instead we have reasoned about such factors in the report.

In an international perspective, Sweden has a favourable resistance situation, but the analysis shows that the problem is expected to increase significantly unless we face the development with effective countermeasures. The fact that the current situation is relatively good can, to a large degree, probably be attributed to the long term work which is performed in order to reduce the spread of infection within health care and reduce the resistance development through responsible antibiotic usage. The more than fourfold increase in only the notifiable cases which is predicted up until 2050 necessitates changed priorities and greater measures if the level of ambition is to be attained. The experience of other countries also shows that certain resistance types can spread quickly if the countermeasures are delayed.

In order to make better projections and simulate effects of interventions, the data of health care needs to be made more easily accessible. However, we can also state that in certain cases access to data which could provide a more complete view is completely missing.

Finally, this commission and report focus on the costs. Among all the figures and calculations, we cannot forget that infections caused by resistant bacteria almost double the risk of death resulting from the infection if it is serious. Or that patients who suffer from carrier status often feel stigmatised and in some cases are forced to undergo checks for a long time until they are free from the infection.

Introduction

This report is the final report of a Government commission in which the Public Health Agency of Sweden was requested to develop a model for projections of future costs of antibiotic resistance. The commission also includes calculating the direct and indirect costs resulting from antibiotic resistance.

The report focuses on the antibiotic resistance which is notifiable according to the Communicable Diseases Act, namely Enterobacteriaceae (intestinal bacteria) with the resistance mechanism Extended-spectrum beta-lactamases (ESBL) including carbapenemase-producing Enterobacteriaceae (ESBL-CARBA), Methicillin-resistant *Staphylococcus aureus* (MRSA), Penicillin-non-susceptible *Streptococcus pneumoniae* (PNSP) as well as Vancomycin-resistant enterococci (VRE).

The Public Health Agency of Sweden has previously published reports (1, 2) on the direct costs of health care for notifiable antibiotic resistance. Direct costs refers to higher health care costs resulting from care of patients with infection or carrier status of antibiotic-resistant bacteria within outpatient and inpatient care as well as for contact tracing when this is prescribed according to the Communicable Diseases Act. Indirect costs refer to those which are not directly linked to care of an individual. It may, for example, refer to higher costs for outbreak (spread of infection), changed treatment strategies or social costs in the form of loss of production during sickness absence.

The previous report (2), which was published in November 2016 and which was an interim report on the Government commission, projected the number of cases and the direct health care costs based on different scenarios up until 2024. Then we considered how much extra antibiotic resistance would cost health care if the Swedish situation were to develop to the level of 2014 in four different EU countries: Germany, Great Britain, Hungary and Italy. The modelling illustrated significant differences in future costs if in 2024 we have a resistance situation corresponding to that of Italy in 2014, compared to the slower development we observe in Sweden.

Similar to previous reports, we have taken into account the number of cases of infection and carrier status with the notifiable bacteria. Thereafter we used a micro-simulation model to make projections of the number of future cases. In the projections we have assumed that greater resistance does not drive the development of infections, that is, that there will not be more infections because a larger share of the bacteria which causes them are resistant. On the other hand, we have taken into account the changed demography; higher population results in more infections in total. We have then calculated the additional cost of care of a patient with carrier status and clinical infection of each resistance type, compared to the corresponding infection caused by a susceptible bacteria. Finally, we have multiplied the different costs with the number of projected cases to obtain calculations of the future costs resulting from resistance. In the model we have used two different time horizons: up until the year 2030 and 2050 respectively.

There are several international reports which have estimated the costs of antimicrobial resistance. The latest was published by the World Bank in 2017 (5). It describes scenarios up until 2050 in the form of low and high level of resistance. They estimate that by 2050 the costs may comprise as much as 1.1–3.8 per cent of GDP. Previous reports with global efforts include, for example, the international accounting firm KPMG's report and the American research institute RAND's reports from 2014 (6, 7). They both make trend projections for 2050 and calculate the same amount of costs for the global economy as the World Bank (KPMG 1.66–6.8 per cent of GDP and RAND 0.06–3.06 per cent of GDP). Both these reports also form the basis of the British O'Neill report (8). In a report from 2015, the OECD estimated the cost of antibiotic resistance as USD 2.9 billion in 2050, which according to them corresponds to 0.16 per cent of GDP (9). In several international reports the calculations have included resistance against HIV, malaria and tuberculosis medicines, which in many parts of the world entails a very large burden on the health and medical care system. This means that they cover more than just antibiotic resistance.

The difference between this report and the reports by KPMG, RAND, O'Neill and OECD is that we have access to actual data, primarily on the notifiable resistance (number of diagnosed cases) here in Sweden. As far as possible we have also based the calculations on actual direct costs of health care and indirect costs for society. Therefore, we find that the estimates of future Swedish costs of notifiable resistance are based on safer data than the global reports above.

This main report is supplemented by a total of seven appendices in Swedish which present data, methods and results in more detailed levels:

1. Simulation method
2. Cost calculations of notifiable antibiotic resistance
3. Health effects of antibiotic resistance
4. Costs of changing antibiotic prophylaxis
5. Outbreak with antibiotic-resistant bacteria
6. Compensation from patient injury insurance
7. Existence of “non-notifiable” antibiotic resistance

Projection for development of notifiable antibiotic resistance

Agenda 2030 specifies the work against antibiotic resistance as a prioritised area and can be seen as a condition for fulfilling many sustainability goals (10).

Therefore, within the framework of this commission, we have chosen to make a projection for 2030 in order to provide a view of how the situation in Sweden will develop if the trend of recent years continues. We have also selected 2050 as the final year as several future scenarios for antibiotic resistance which were published over recent years have focused on this year specifically.

Number of cases of notifiable antibiotic resistance

In order to project the future development of antibiotic resistance in Sweden, we have used cases of notifiable resistance reported to the database SmiNet as a basis.

SmiNet data has been obtained for five years, 2012–2016, with the exception of data on MRSA, where we instead obtained data up until 2014. The reason for this is that between 2015–2016 we had a disproportionately large number of reports of MRSA cases in SmiNet, as a result of higher sampling among migrants to Sweden during these two years. The trend returned to the previous level from 2017. For more details on the method in Swedish, see appendix 1, “Simulation method”.

In 2016 approximately 15,500 cases of notifiable antibiotic resistance were reported in total. According to the simulation, this is estimated to amount to approximately 32,000 cases in 2030 and approximately 70,000 cases in 2050 (provided that the current trends continue). Distributed per resistance type, ESBL and MRSA are the most common and are increasing the most. As the number of cases of the different resistance types differs significantly, we have chosen to present them in different figures, see Figure 1 and Figure 2. Appendix 1 presents the results per resistance type and infection.

Figure 1. Projected number of cases of ESBL and MRSA

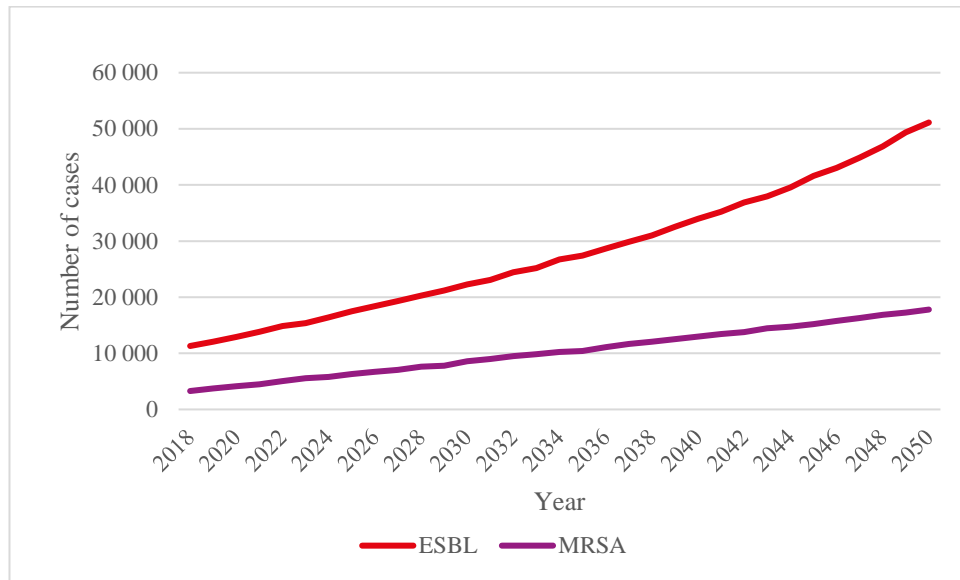
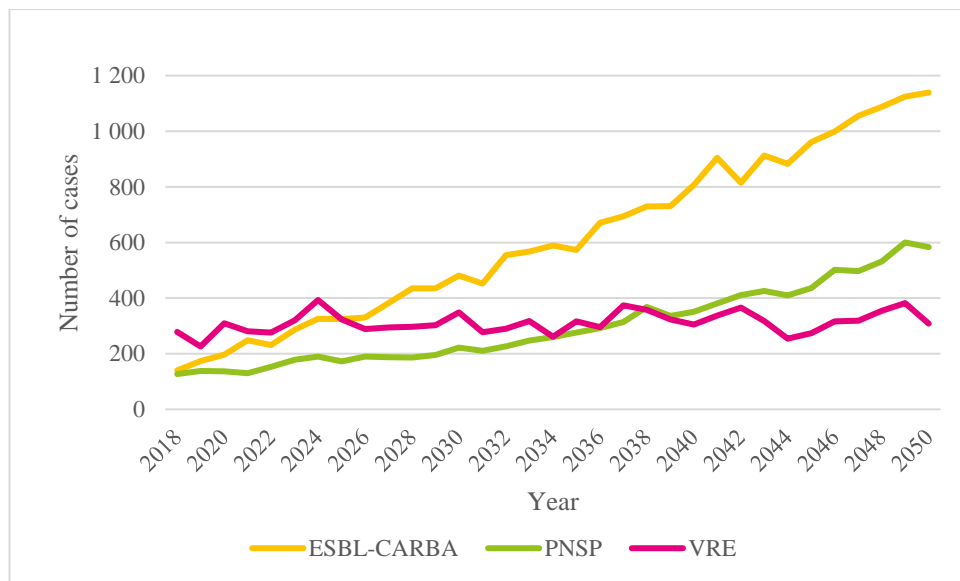


Figure 2. Projected number of cases of ESBL-CARBA, PNSP and VRE



Discussion

Based on the cases reported to SmiNet, it is clear that MRSA and ESBL are the dominating resistance problems among those notifiable according to the Communicable Diseases Act. For MRSA it entails both sick persons and carriers without symptoms. The number of cases of the most severe resistance form ESBL-CARBA are still low from an international perspective, but are increasing quickly.

The development of clinical infection caused by PNSP is declining during the projected period. However, as the number of carriers of PNSP is increasing, the total development of PNSP is still growing.

We have modelled the development of notifiable antibiotic resistance in Sweden by basing the projection on individual risks of suffering from an infection or from

being a carrier based on the reported cases. Thereafter we have applied these in a micro-simulation model. Thus, the model is based on actual risks and trends based on reported data in SmiNet. For certain age groups there are none or very few cases during the period on which the trend is based, which entails more uncertain outcomes for these groups.

The number of cases in 2030 is lower than the estimate we did for 2024 in the previous report (2), despite both projections being based on observed trends. The reason is that the trends in this commission are based on data from 2012–2016, that is, an update from the period 2008–2012 which was used in the previous analysis. Due to the difference between the results, we have validated the trends used in this report against care data from the National Board of Health and Welfare in order to assess the reasonableness of the levels in the future. In practice this entailed that the projections on the number of cases has decreased. The previous report overestimated the number of cases slightly in the short and medium term, which also resulted in an overestimation of the cost calculations. For more details, see appendix 1, “Simulation method” (in Swedish).

Methods for calculation of costs for notifiable antibiotic resistance

The analyses of costs for notifiable antibiotic resistance are calculated based on the number of estimated cases of resistance in the previous section. We focus on the additional cost caused by the resistance compared to the infection being caused by correspondingly susceptible bacteria. Thus, we do not take into account the cost of the infection but only the higher cost as a resistant bacteria caused the infection. The costs of carriers are also included in the analysis.

Direct costs

Health care costs

In the first reporting of this Government commission, (1) we estimated the resource demand within health care for inpatient, outpatient and primary care, antibiotic usage and contact tracing. We have used the same resource demand as a basis in this report, but have updated the costs to the price levels of 2016.

All patients with an infection caused by resistant bacteria are deemed to be treated with other antibiotics than common treatment options. We use the same assumptions as the report “Economic impact of antimicrobial resistance” (1). The costs of health care resources are presented in Table 1.

Table 1. Costs of health care resources

Health care resources	Cost SEK	Source
Per inpatient care day	8,310	(11)
Extra cost per day for inpatient care of ESBL-CARBA for invasive infection	1,160	(1)
Per outpatient care visits	3,665	(11)
Per primary care visits	1,539	(12)
Contact tracing		
Fixed cost for inpatient care	7,500	(1)
Variable cost for:		(13)
• ESBL-CARBA	206	
• MRSA	149	
• PNSP	119	
• VRE	189	

For contact tracing of patients who are not treated within inpatient care, there is an additional cost for primary care visits for each patient (1).

The technical development of medicines, technology and methods entails new treatment opportunities and in order to take them into account we have assumed an annual cost increase of 0.8 per cent (14). The costs which have been applied to the

simulated future care consumption have been discounted¹ by 3 per cent annually, in accordance with the recommendations of the Dental and Pharmaceutical Benefits Agency (TLV) in its general advice on economic evaluation, TLVAR 2017:1 (15).

We have also conducted a literature search to examine whether there are new published research results on direct costs of notifiable and non-notifiable resistance. We can state that only few such studies of good quality have been published, and that it is not possible to draw any conclusions or add supplementary data on additional costs caused by antibiotic resistance. See further information in appendix 2 “Cost calculations of notifiable antibiotic resistance” (in Swedish).

Indirect costs

Indirect costs refers to such additional costs which are not directly linked to care contacts of an individual with antibiotic resistance but are overall costs for society. In this report these are measured through lost production. There are also other indirect costs of antibiotic resistance, for example, higher costs of processing of outbreak with spread of infection or changed treatment guidelines in health care. However, these are not included in the simulation as neither outbreak nor the demand of new treatment guidelines can be identified in the model. Indirect costs which are not production-related are discussed in the section “Other consequences of antibiotic resistance.”

Production loss

Costs of production loss arise when an individual cannot work due to ill-health (16). In this report we take into account production loss due to ill-health, that is, during sickness absence. Production loss is calculated for individuals aged 0–64 years. For individuals aged 0–14 years the cost of temporary parental allowance (care of a sick child, VAB) is calculated for guardians, and for individuals aged 15–64 years production loss is calculated based on sickness absence or sick leave.

We have analysed register data of notifiable resistance from the Public Health Agency of Sweden, outpatient and inpatient care data from the National Board of Health and Welfare, primary care data from Stockholm County Council and Region Västra Götaland as well as data on long term sick leave and VAB from *Försäkringskassan* (Swedish Social Insurance Agency). This aims to calculate the difference in duration for sickness absence for infection caused by resistant bacteria in comparison to infection caused by susceptible bacteria. In the analysis we have used the following infections: invasive infection (infection in blood or cerebrospinal fluid), infection in skin and soft tissue, urinary infection and pneumonia. Appendix 2 “Cost calculations of notifiable antibiotic resistance” presents methods and analysis in more detail (in Swedish).

¹ A method for taking into account that future costs are valued less than their current level of valuation.

The cost of production loss per day (SEK 1,417²) is calculated based on average salary of the population, including employer's contributions:

- Average monthly salary: SEK 32,800 (17)
- Social security contributions: 31.42 per cent (18)

Results

For long term sick leave the analysis does not show that persons infected with resistant bacteria have longer sick leave than persons infected with susceptible bacteria. The analysis was conducted with respect to age, gender, infection type and resistance type. Therefore, we have chosen to calculate the cost of production loss as a result of greater care need for resistance, for example, a higher number of days in inpatient care or a higher number of visits in outpatient or primary care. This means that we are using the same care duration in this context as when we calculate the direct health care costs.

Discussion

The assumption on resource demand (see figures 2 and 3 in the report "Economic impact of antimicrobial resistance" (1)), which forms the basis of the calculations of both health care resources and production loss, are based on current procedures for health care. This means that uncertainty in the results over time increases as we cannot predict changes in procedures linked to care or contact tracing of individuals with infection caused by resistant bacteria. In addition, data sources of infection differ for resistant and susceptible bacteria which further impedes the interpretation of the results.

The analysis of register data does not show an increase in long term sick leave as a result of antibiotic resistance. This may be due to the fact that the groups differ in terms of other sickness and thereby the reason for sick leave which is registered with *Försäkringskassan*. *Försäkringskassan*'s register only registers the first reason for sick leave, which entails that infections which arise during other sick leave are not specifically registered but remain a subset of the first cause of sick leave. Therefore, it is not possible to distinguish the share of sick leave attributable to infection. In this analysis we have not taken into account co-morbidity, which may be significant for the risk of becoming ill with a resistant bacteria and the severity of the disease. This can impact the duration and thereby the cost of sick leave.

It is also not possible to capture differences in short term absence through analysis of collected data, as *Försäkringskassan* starts to pay sickness benefit only after 14 days. This means that the differences we see in the demand of health care resources cannot therefore be seen in the analysis of register data of sick leave. Several

² 32,800 x 1.3142 x 12 months / 365.25 days per year = SEK 1,417 per day.

studies present the effect of resistance development on GDP, but few studies have presented the magnitude of costs resulting from health care costs and costs resulting from production loss. ECDC estimates that approximately 10 per cent of the total costs derive from production loss resulting from disease (19), which is in line with our results.

According to a systematic review by WHO, there are a few studies by high-income countries which show that infections caused by bacteria with certain resistance entail longer total care duration in hospitals (20).

There are not any studies which compare how antibiotic resistance affects the total sickness duration or the course (sick leave) after discharge from hospital.

According to the assessments made by Lof (*Landstingens Ömsesidiga Försäkringsbolag*) 2014–2015, medical disability of up to 5 per cent was deemed to exist after 3–6 months depending on which bacteria was concerned and whether there were remaining symptoms (see appendix 6, “Compensation from patient injury insurance” (in Swedish)). This indicates that individuals with an infection caused by resistant bacteria have impaired health for a longer duration than for infection caused by susceptible bacteria. This would also entail a greater impact on the production, which we cannot show through analysis of data for long term sick leave.

For temporary parental allowance from *Försäkringskassan* only the month of payment is registered and therefore it is difficult to link this information to specific infection cases. This has impeded our analysis of production loss resulting from care of a sick child.

Production loss resulting from premature death has not been included, according to practice for similar calculations in Sweden. Consequently our analysis differs from the international analyses which calculate production loss for all individuals who die before reaching pensionable age. As a result of this, the costs of production loss in this report are lower than in several international reports.

Projected cost calculations

In this section cost projections are presented based on reports in the two previous sections: the number of cases per resistance type and the costs related to each infection type.

The analysis shows that the total direct costs of health care are calculated as amounting to SEK 390 million and SEK 740 million for the years 2030 and 2050, while production loss is approximately SEK 26 million and roughly SEK 36 million for the same year. All in all this means approximately SEK 410 million and SEK 780 million for health care and production loss. According to these results, production loss corresponds to approximately 6–7 per cent of the total costs. This is slightly below the 10 per cent for production loss resulting from disease presented in the analysis of ECDC (19).

Total costs accumulated are approximately SEK 4.3 billion by 2030 and SEK 15.8 billion by 2050, see Table 2. Figure 3 and Figure 4 show the development of costs divided by resistance type up until 2050.

Table 2. Results for additional costs due to antibiotic resistance, SEK million

Costs	2030	Accumulated by 2030	2050	Accumulated by 2050
Health care costs	388	4,033	742	14,949
Production loss	26	289	36	900
Total costs	414	4,321	778	15,849

Figure 3. Projection of total costs of ESBL and MRSA

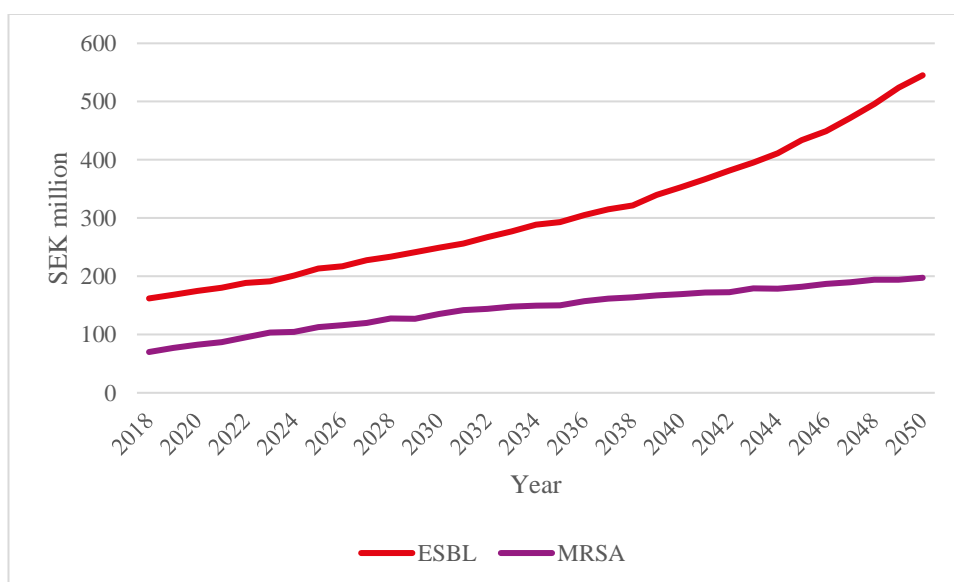
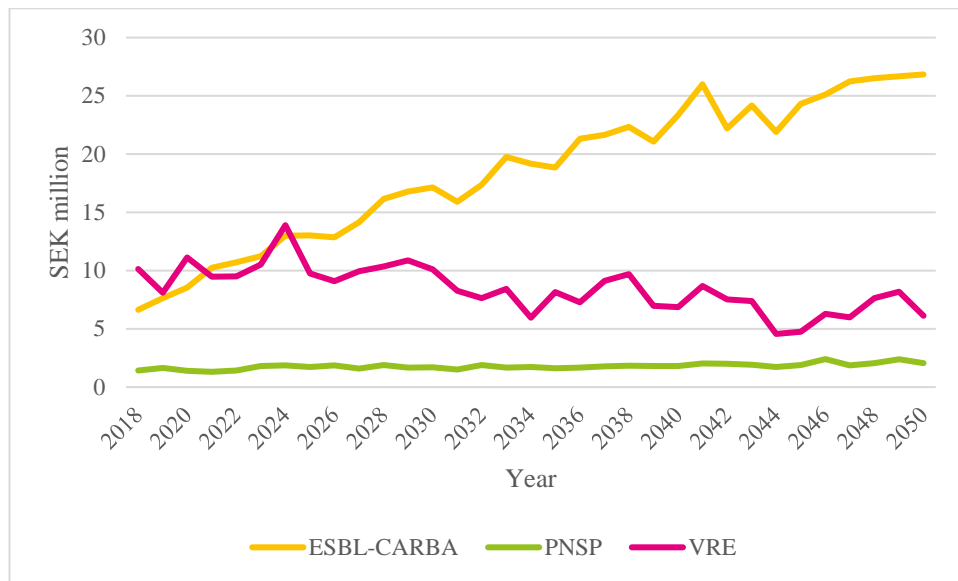


Figure 4. Projection of total costs of ESBL-CARBA, PNSP and VRE (observe difference in scale on the y-axis compared to figure 3)



Discussion

The costs of the notifiable resistance are expected to increase significantly by 2030 and 2050. According to calculations, the total costs for a year, 2030 and 2050, amount to SEK 414 million and SEK 778 million respectively. This can be compared to the total health care budget which was SEK 290 billion in 2015. The accumulated cost is estimated as approximately SEK 4.3 billion and SEK 15.8 billion by 2030 and 2050.

The analysis is based on that current health care structures on treatment and contact tracing in connection with antibiotic resistance have not changed over time. This is probably a conservative assumption as the structures will probably change if the resistance levels increase. As we cannot predict when such a change will take place or how it will affect health care, we can neither include this in the analysis. The section “Changed procedures for antibiotic prophylaxis for operations” presents a detailed discussion on the impact of the choice of prophylaxis for different surgical operations.

The costs of production loss due to premature death are reported in several international reports (6-8), which means that the costs will be high. Our analyses only take into account production loss resulting from sickness absence. The results for this are in line with the costs of production loss reported by ECDC (19).

Other consequences of antibiotic resistance

Within the commission we have also highlighted some other aspects of increasing antibiotic resistance which may entail consequences for health care and society but which cannot be included in the modelling. These are

- impact on quality of life
- any risk of higher mortality
- changed procedures and costs of how antibiotics are used for treatment and prevention within health care
- the demand of resources for handling outbreak with resistant bacteria in hospitals
- payment of compensation from the patient insurance resulting from infection with antibiotic-resistant bacteria.

Quality of life

Health economics models often calculate both costs and health effects. Health impact can be measured through disease-specific outcomes, for example, fractures or heart attacks, or through general measures of quality of life. Sweden often uses quality-adjusted life years (QALY) to measure quality of life, which is a combined measure of quality of life and life expectancy. Using quality of life as a measure of effectiveness enables comparisons between therapy areas and provides a more comprehensive picture of the health effects of a treatment.

We have studied the impact on quality of life for the clinical infections invasive, urinary, skin and soft tissue infection as well as pneumonia. Published literature has been reviewed both with respect to effect of resistant compared to susceptible bacteria (independent of infection type) and only with respect to infection type. No studies have been able to show a difference in quality of life based on whether the infection was caused by resistant or susceptible bacteria. For detailed analysis, see appendix 3 “Health effects of antibiotic resistance” (in Swedish). Therefore, we have used impact on quality of life based on infection type, irrespective of whether it was caused by a resistant or susceptible bacteria. Invasive infections and pneumonia have the greatest impact on quality of life (21).

The individuals who are carriers of a resistant bacteria are generally not deemed to have impaired quality of life as they lack clinical symptoms. Studies have been published which suggest that several individuals still have an impact on quality of life due to anxiety and perceived stigmatisation. The assessments performed by Lof 2014–2015 also show that remaining carrier status after 3–6 months was deemed to entail 1–2 per cent medical disability. More about this in the section “Compensation from patient insurance” and appendix 7 (in Swedish). However, as we have not identified any studies which can quantify this impact, such impact is not included at this stage of the analysis.

Risk of higher mortality

In order to estimate any excess mortality in the patient group infected by resistant bacteria, it should be compared to a patient group with corresponding infection caused by fully susceptible bacteria. In addition, patient populations need to be similar to each other in several other respects such as being equally sick when they seek care, having the same age structure and gender distribution. Therefore, based on data in SmiNet and the mortality register you cannot determine who passed away directly or indirectly due to a resistant bacteria. You can neither determine what the resistance property entails for the risk of death, compared to if a person were to fall ill with the same bacterial infection but without respective resistance.

As we have not been able to calculate differences in mortality based on the available data, we have used data from ECDC (9) as well as WHO (20) on mortality resulting from antibiotic resistance, see Table 3. If we apply these risks to Swedish cases with invasive infection, this means that 33,000–42,000 persons may die in Sweden due to antibiotic resistance by 2050.

Table 3. Accumulated number of deaths by 2030 and 2050

	ECDC			WHO		
	Risks	2030	2050	Risks	2030	2050
ESBL	30%	3,933	40,568	23.6%	3,094	31,914
ESBL-CARBA	30%	18	99	27.0%	16	89
MRSA	10%	75	590	26.3%	200	1,583
VRE*	9%	50	125	NA	–	–
		4,076	41,383		3,311	33,586

* VRE is represented by cases of clinical disease, which are primarily urinary or wound infections. Therefore, we use the risk of urinary infection from ECDC's report (9).

Discussion

Few studies have examined the difference in quality of life based on whether the infection was caused by resistant or susceptible bacteria. As there is no data concerning this difference, we have instead used impact on quality of life resulting from infection. This means that the duration of the disease is the decisive factor. For individuals who received inpatient care, we used the number of days in hospital. On the other hand for individuals who have been in contact with outpatient or primary care, their sickness duration is uncertain and therefore there are not any major differences in the impact on quality of life, caused by the resistance.

In addition to the direct impact on quality of life due to infection, antibiotic resistance may also have an indirect impact on health as the resistance of an individual, or outbreak at hospital, may entail that operations are postponed or cancelled. We have not taken this type of impact into account as there are not any studies which address how the quality of life is impacted.

All in all, the analyses on quality of life and mortality resulting from antibiotic resistance are uncertain. Good studies are lacking, many times register data is inadequate as the diagnosis codes (ICD10) for the causation bacterial species, or if the bacteria has a specific resistance type, are not used during the care encounter or on the death certificate. This would be facilitated if the IT system of health care supported basic transfer of this information (which is available in the laboratories) to medical record systems.

Changed procedures resulting from antibiotic resistance

Another possible consequence of higher antibiotic resistance is changed procedures for which antibiotics are used to treat or prevent infections.

A subproject of this Government commission has been to examine any costs resulting from the need to change procedures for antibiotic treatment and prophylaxis. We report both an estimate of the cost for updating the national treatment recommendations produced by the Medical Products Agency, and a review of changed procedures for antibiotic prophylaxis for operations where infection with staphylococcus (*Staphylococcus aureus*) needs to be avoided.

Changed infection treatment

If the resistance levels increase, the costs increase in different steps. In the first step you can change treatment to other similar options where the administration method does not change. That is, tablet treatment is replaced with another treatment or an injection treatment is replaced with another treatment, but the patient can be treated in outpatient or inpatient care in the same manner as before. This change primarily entails a higher cost of drugs.

Additional increases in the resistance levels mainly entail a risk of there no longer being any tablet treatment and that the patient must instead receive injection treatment. For patients who have already been hospitalised, this still entails a risk of limited additional costs in the form of more expensive substances and longer care durations (as changing to tablet treatment is not applicable). For patients who would normally receive tablet treatment in outpatient care, this instead entails one of the following options:

1. Home care of the patient to administer the injection.
2. The patient goes to an out-patient clinic at a hospital or medical centre and receives the injection.
3. The patient is hospitalised and receives the treatment.

All three options entail higher health care costs and also indirect costs due to the patient's travel costs, any lost working hours, etc.

A concrete example of when this occurred is gonorrhoea, where the tablet treatment used previously with ciprofloxacin is replaced by injection treatment with cephalosporin. Clinics also report that it is increasingly common for patients

with uncomplicated urinary infections to be treated with injections as the causation bacteria has ESBL resistance which cannot be treated with tablets. It has not been feasible to try to estimate the cost of all different diagnoses within the framework of the project where the causation bacteria has a notifiable resistance.

Update to national treatment recommendation

We contacted the Medical Products Agency with a question on the resource consumption for updating a national treatment recommendation (22). The process includes work in an internal project group with investigators, project managers, administrators and internal experts, as well as work meetings with external experts, for example, representatives of other agencies and the profession.

Naturally the cost of the update depends on the scope of the work which is performed. The average cost of update of a national treatment recommendation is estimated (according to e-mail -correspondence with Peter Rosenberg, the Medical Products Agency, 5 June 2017) as approximately SEK 930,000 divided among:

- internal work (just below annual working hours, approximately 1,300 hours), payroll expenses SEK 534,000 (18, 23)
- external experts (approximately 80 hours in total), direct costs approximately SEK 400,000 (including accommodation, travel and working hours).

Changed procedures for antibiotic prophylaxis for operations

Antibiotics are used for prevention purposes during surgery when they are shown to reduce the infection frequency. The substances and dosage depend on the location and expected duration of the operation as well as the prevailing resistance situation. For many planned, so-called 'clean' operations, prophylaxis is used to protect against *Staphylococcus aureus*, which may exist on the skin. For other types of operations, for example, operation of the abdomen, where there is a risk of bacteria spreading from the intestine, other antibiotics are used, often several kinds. Accordingly the costs of different types of prophylaxis differ, as the cost, administration method and duration of medicines vary.

If all patients who underwent hip and knee joint prosthesis operations, surgeries within the aorta as well as coronary vessel and valve operations in 2015 (approximately 43,000 surgeries according to the National Board of Health and Welfare's statistical database) would have received prophylaxis against MRSA instead of against susceptible *Staphylococcus aureus*, a conservative estimate shows that this would entail a cost increase of SEK 1.1 million. This corresponds to an increase of 13 per cent (appendix 4 "Costs of changing antibiotic prophylaxis" (in Swedish)).

If for other (not studied) surgeries where peroral prophylaxis was used, you had to change to intravenous prophylaxis, the cost would increase significantly.

The investigation also showed that all clinics do not comply with the evidence presented in a report on surgical prophylaxis from SBU (24). Previous studies (25) also show that compliance among individual doctors is inadequate and that therefore the actual costs ought to be significantly higher.

The parties who are involved when procedures for antibiotic prophylaxis are developed, implemented and updated locally, varies across the country. By means of a survey we chose to ask 24 heads of operations at surgical clinics at what MRSA level they would like to change prophylaxis. Of the ten received answers, the individual answers for thorax surgical procedures (operations of the coronary vessel, cardiac valve and aorta) are distributed among 0–2 to 30 per cent, for vessel surgical procedures (aorta, peripheral artery and carotid surgery) from 0–2 to 20 per cent and for orthopaedic surgery (hip and knee prosthetic surgery) from 10 to 20 per cent.

For more details about the design and results of the survey, see appendix 4 “Costs of changing antibiotic prophylaxis” (in Swedish).

Discussion

The impact of efficient antibiotic prophylaxis must be compared to several other infection-inhibiting factors and measures, everything from the patient’s physical condition to the competence of the surgeon and the operating environment. In the ideal case the prophylaxis regime is changed in close collaboration with infection doctors, clinical microbiologists and health care hygienists based on infection registration and the local resistance situation. Therefore, simply asking the surgeons when the prophylaxis should be changed may provide a misleading view, but it still provides an indication of their risk assessment. There is also a risk that other possible strategies, for example, pre-operative MRSA screening (which is however much more expensive) are discussed in the context.

Outbreak

Outbreak entails spread of contagion with antibiotic-resistant bacteria within health care. Major changes to resources-use may be required for the clinics which are affected in order to rectify the problem. For example, it may entail that patients are moved to another bed within the ward, to another ward or, in the worst case, to another hospital. It may also entail closed locations of beds, greater sampling of co-patients, personnel and the environment as well as changed cleaning procedures, which entails cost increases for health care.

In this part we have examined how costs and resource consumption during outbreak are generally structured within Swedish health care. This was conducted based on national data reported in the database of communicable diseases, SmiNet, by a survey for infection control and health care hygiene departments on occurred outbreak and related resource demand as well as through a summary of identified cost items. For detailed information on the method, refer to appendix 5 “Outbreak with antibiotic-resistant bacteria” (in Swedish).

Results

The following cost driver activities were identified in the survey as common during an average outbreak:

Activities		
Sampling (patient, personnel, close relative)	Extra administration for health care hygiene	Education/information effort
Environmental test	Relocation of patient	Outbreak handling group
Care in a single room	Renovation	Stop of intake (days)
Hygiene round	Extra cleaning efforts	

Based on the data of county councils and regions, an average cost of approximately SEK 73,000 (SEK 14,000–137,000³) per case in an outbreak was estimated.

Items in the cost calculations of county councils		
Cleaning and laundry	Purchased care	Administration
Sampling/screening (patients, personnel, close relative)	Reduction of beds	Personnel costs
Environmental sampling	Long care duration	Information/training

The activities identified in the survey generally conform to the items of the county councils and regions in their cost calculations.

Together with departments of communicable disease control and prevention as well as health care hygiene departments in county councils and regions, the Public Health Agency of Sweden has estimated how many outbreaks with antibiotic-resistant bacteria were detected in Sweden. According to the estimates, it entails approximately 30–40 outbreaks per year 2013–2015, with 8–14 cases per outbreak on average. This roughly entails a cost of outbreak in Sweden of approximately SEK 29 million per year, based on the average cost per case.

The cost of outbreak has not been included in the simulation model as it does not include the number of outbreaks but only the total number of cases of respective resistance type. Therefore, we cannot make a projection on the number of outbreaks based on this data.

³ The analyses were performed by Gävleborg, Halland, Västernorrland, Västmanland and Örebro.

Discussion

The estimates for the cost of outbreak are uncertain. This is mainly due to the fact that it is difficult to quantify activities and cost items which are directly related to a given outbreak. It is also the case that outbreaks are handled differently at different clinics or within different county councils depending on the size of the outbreak and resistance types.

Outbreaks may also entail that planned care, for example, operations must be postponed. This per se does not entail higher costs but impacts the quality and efficiency of health care, which in the long term may entail indirect costs. Thus, outbreaks do not appear to entail more than marginally higher costs for health care.

Compensation from patient insurance

The Swedish Patient Injury Insurance Act (1996:799) regulates that all health care providers in Sweden must have insurance to cover the damages that are covered by the law (so-called patient injuries).

Löf's (*Landstingens Ömsesidiga Försäkringsbolag*) mission is to investigate and provide compensation to patients who suffer from unavoidable injuries in conjunction with care and treatment in Sweden. As well as to contribute to the work of decreasing such injuries.

The Patient Injury Insurance Act do not take into account what bacteria that caused the infection or if the bacteria is resistant or not, but rather that transmission and injury has occurred in connection with health care.

The size of the compensation depends on the Liability Act. This means that it is an individual assessment of every injury to decide the extent of the compensation. Levels of compensation can therefore change over time. Previously assessments of, for example, MRSA, ESBL and VRE was made with respect to the patient's obligation to self-report the injury, this is, however, not the case anymore.

If the patient do not have any symptoms of the infection and the bacteria itself has not caused any inconvenience, it is not considered as a medical disability. The only compensation that the patient can receive then is for the presumed suffering that the patient may be considered to have had.

During the period 2014–2015 Löf paid compensation due to MRSA of SEK 1,623,600, ESBL SEK 263,000 and VRE SEK 76,300. In total almost two million Swedish krona, distributed over almost 40 patients.

Thus, it appears that only a small share of the roughly 800 patients who according to the SmiNet report were infected with notifiable antibiotic-resistant bacteria in Sweden 2014–2015 reported this to the patient insurance. The reason for this is not known. This means that the cost of these requirements may increase if more people apply for compensation in the future.

See appendix 6, "Compensation from patient injury insurance" (in Swedish).

Other antibiotic resistance

In addition to the notifiable antibiotic resistance which the majority of this report focuses on, there are also other types of antimicrobial resistance that can have consequences for health care and society. These include combinations of bacteria and resistance patterns which are not covered by the Communicable Diseases Act as well as multidrug-resistant tuberculosis and gonorrhoea.

Antibiotic resistance not covered by the Communicable Diseases Act

Even though the most severe forms of antibiotic resistance are notifiable in accordance with the Communicable Diseases Act, there are a range of other variants which also have clinical significance and can cause problems during treatment (appendix 7, “Existence of ‘non-notifiable’ antibiotic resistance” (in Swedish)).

The resistance levels for several common combinations of bacteria and treatment options are roughly 10 per cent. This means that thousands of patients have infections with bacteria which are resistant to one of the primary, or remaining, treatment options. One example is antibiotic resistance of *E. coli* and *K. pneumoniae* in urine cultures, where 15–20 per cent of the isolates are resistant to trimethoprim and 4–9 per cent to mecillinam. This has impacted the national treatment recommendations for uncomplicated urinary infection among women so that trimethoprim is no longer the first choice.

Multidrug-resistant tuberculosis

Tuberculosis is notifiable in accordance with the Communicable Diseases Act (26). 22 cases of multidrug-resistant tuberculosis (MDR-TB) were reported in 2016. The multidrug-resistant cases comprise 3–4 per cent of all tuberculosis cases. Three of the cases were also XDR-TB, which means that they are extra resistant and thereby complicated to treat and cure (27). The proportion of MDR- and XDR-TB in Sweden is the same as that reported globally (28) and according to a report by WHO from 2014 this level has been relatively stable over recent years (29).

There are not any standardised guidelines for treatment of resistant tuberculosis as this needs to be adapted individually. This means that it is difficult to calculate how much more a case with resistant tuberculosis costs compared to a case caused by susceptible bacteria. Clinical experts have estimated that the duration of treatment can differ up to 18 months and that the cost of treating MDR-TB and XDR-TB may thus be 10–20 and 100 times higher, respectively, than treatment of tuberculosis with susceptible bacteria, depending on where in the world the treatment takes place. In an American survey published in 2014, the average direct health care cost of “normal susceptible” TB was \$17,000, for MDR-TB it was \$134,000 and for XDR-TB it was \$430,000, that is, 25 times higher (30). Long and difficult treatment also entails longer suffering and thus a greater impact on the quality of life of an individual with multidrug-resistant tuberculosis.

Antibiotic-resistant gonorrhoea

In 2016 complete antimicrobial susceptibility testing was conducted of *Neisseria gonorrhoeae* isolate from 601 cases of gonorrhoea, corresponding to 34 per cent of those 1,677 reported in Sweden. High-grade resistance to ciprofloxacin was found among 53 per cent. Approximately one per cent of the strains were resistant to cefixim and three per cent were resistant to azithromycin(31, 32).

The standard treatment for gonorrhoea is injection treatment with cephalosporin which is more expensive than the previously used tablet treatment with ciprofloxacin.

The resistance against cephalosporins ceftriaxone and cefixim has declined over the past three years, which has also been observed in many other countries. This is promising but no major conclusions can be drawn. The resistance to azithromycin which has been approximately 10 per cent since 2010 also declined in 2016 (31).

Due to the prevalence of multidrug-resistant gonococcus strains in Sweden and the surrounding community, antimicrobial susceptibility testing and follow-up sampling after completed treatment are necessary to detect resistance development and ensure that the infection has been cured. Naturally this entails a cost for society.

Conclusions and discussions

The aim of this Government commission has been to, in a transparent manner, present actual and reliable costs and consequences of antibiotic resistance and in different scenarios simulate what will happen if the resistance situation changes. It ought to be a unique circumstance globally that the data for the projections to such a large extent is based on actual data from different sources in health care and among agencies, and that different resistance types have been analysed separately.

Conclusions

According to the projection in the report, the number of detected cases with notifiable resistance types will increase more than fourfold by 2050. This will entail a cost for Swedish society of at least SEK 15.8 billion in current monetary value. Of this amount production loss comprises 5–7 per cent. In addition to this, there will be patient suffering and an unknown number of deaths as prevalent antibiotics are no longer effective.

Based on the risks reported by ECDC and WHO, between 33,000 and 42,000 persons in Sweden may die by 2050 due to invasive infection with MRSA, ESBL, ESBL-CARBA or VRE.

It has not been possible to estimate the consequences (costs and deaths) of non-notifiable antibiotic resistance due to a shortage of data. However, on a yearly basis thousands of people suffer from infections with such bacteria, which ought to generate significant costs, primarily in the form of direct costs of health care through longer care durations or need of a higher level of care.

The difficulty in getting access to and being able to use the data which exists in health care or the systems of agencies has been a recurrent problem and a restrictive factor for performing the commission in the desirable manner.

Discussion

To the best of our knowledge, this is the first attempt to calculate the social costs of antibiotic resistance which are based on an extensive collection of data on actual costs from health care, for sickness absence as well as the number of occurred cases.

The number of cases of antibiotic resistance is increasing, despite the efforts which have already been taken in terms of, for example, hygiene routines in health care or antibiotic usage. Antibiotic resistance results in significant usage of resources within health care due to extended care durations, costs of outbreak and contact tracing. At the same time we can state that we have a better situation in Sweden compared to large parts of the world.

The projection in this report provides an opportunity to assess what a fourfold increase in the number of detected notifiable resistance cases by 2050 may entail for affected patients, for resource use and costs of health care and for the society at

large. It ought to be obvious that it is not possible to handle such a large increase in the number of cases without changed priorities and greater efforts. The fact that control of the resistance development will be lost, as it has in many other countries, may entail risks as well.

Often the indirect costs are specified as being several times greater than the direct costs of health care (3, 4). We have not been able to prove that this is the case in Sweden.

It is, however, possible to impact the development of antibiotic resistance. During the work it has been clear that the data which exists in the systems of health care and agencies cannot be used optimally, is difficult to extract or difficult to access based on legal reasons. For example, diagnosis codes (ICD10) are not used for causation bacterial species, or if the bacteria has a certain resistance type, neither during care encounters or on death certificates. The progress assessment and impact analysis would be facilitated significantly if the IT system of health care supported basic transfer of this information (which is available in the laboratories) to medical record systems. In some cases data is completely lacking, both from health care and the scientific literature. There is great improvement potential here, which is also important for patient safety.

It also entails efforts for better and more developed supervision and access to data, better preventative work within health care, continued investments in health care hygiene and Strama work, continuing professional development for health care personnel, support for more efficient usage of antibiotics and many more aspects. Long term investments and current initiatives are required so that we can curb the trend. There are many positive developments, but there is still a lot more we can do. Therefore, it is also important to continue the work on developing the calculation model.

This final report has utilised and further developed experiences and lessons from the two previous reports. The previous reports mainly focused on identifying different items for direct costs for health care and for making projections on the development of the number of cases (1, 2). Compared to these, some data has also been updated, and efforts have been made to include indirect costs and calculate the total costs for society by and large. Despite the particularly good access to different forms of register data which exists in Sweden compared to other countries, it is very difficult to determine definitive connections or links between antibiotic resistance and social consequences and costs with certainty. Our assessment is that we have captured the main costs but on the other hand the impact on quality of life and number of deaths has been more difficult to determine.

This report does not address the entire social cost of antibiotic resistance but only human medicine. Neither have we addressed estimates or discussions on consequences and costs of antibiotic resistance within veterinary medicine, food production or in the environment.

Participants

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Others who have contributed to the project:

Ann-Louise Johansson and Ann-Cristine Jonsson, both at the Public Health Agency of Sweden, have supported the work with literature reviews

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We would like to thank the AMR-team at WHO Geneva for sharing the search terms on health and economic burden of AMR used in the report “Antimicrobial resistance. Global report on surveillance 2014”.

We would also like to express our gratitude and appreciation to personnel within health care who responded to the surveys we sent.

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