

## A PLAUSIBLE WORST-CASE SCENARIO OF INCREASING MULTIDRUG RESISTANCE AS A TOOL FOR ASSESSING SOCIETAL RISKS AND CAPABILITIES IN SWEDEN

Roger Roffey, Anna Lindberg, Lena Molin, and Per Wikman-Svahn

A “plausible worst-case scenario” of a gradually increasing level of multidrug-resistant bacteria (carbapenem-resistant *E. coli*) in the human population was developed and used to study how Swedish authorities would manage this situation and to identify preventive measures that could be taken. Key findings include: (1) a scenario in which 5% of the population in southern Sweden become carriers of carbapenem-resistant *E. coli* is possible or even likely in 10 to 15 years; (2) it is not clear when and how the increase of *E. coli* resistant to carbapenems as in the scenario would be detected in the general human population; (3) identified negative consequences of the scenario on society were primarily due to increased demands on the healthcare system and potential consequences for food-producing animals, food safety, and environmental health; and (4) a number of preventive and mitigation measures were suggested, including initiating long-term screening programs for public and animal health as well as for food and water production to monitor increasing levels of carbapenem resistance. Strategies and plans to prevent and handle future increasing prevalence of multidrug-resistant bacteria need to be developed.

**I**NCREASING PREVALENCE OF MULTIDRUG-RESISTANT BACTERIA is an important global challenge, as stressed in recent high-level reports from the World Economic Forum, the European Union (EU), and the United States.<sup>1-3</sup> The effectiveness of antibiotics seems to be in rapid decline,<sup>4,5</sup> and an estimated 25,000 Europeans die every year from drug-resistant bacteria.<sup>6</sup> Unless the rise in multidrug resistance can be reversed or new antibiotics introduced, there will be a substantial rise in incurable infections and fatalities in both developed and developing countries.

A particularly troublesome type of multidrug resistance is carbapenem resistance, because carbapenems are considered the last line of therapy for infections caused by multidrug-resistant Gram-negative bacteria in humans.<sup>7</sup> The preva-

lence of carbapenemase-producing *Enterobacteriaceae* (CPE) in Europe varies from a high in southern Europe to lower in the Nordic countries, and the types of CPE vary among countries.<sup>8-11</sup> The results of a European survey show that CPE are continuously spreading in European hospitals and that the epidemiologic situation for CPE has deteriorated since 2010.<sup>12</sup> The European Centre of Disease Prevention and Control (ECDC) has reported that the overall situation of antimicrobial resistance in Europe is worsening, and particularly the increased prevalence of bacteria that are resistant to carbapenems.<sup>13</sup> CPEs are already endemic in many countries.<sup>11</sup>

Sweden has been fairly successful in fighting multidrug-resistant bacteria over several decades. In 1986 it was the

---

Roger Roffey, MScChemEng, is Deputy Research Director; Anna Lindberg, MScEngBiol, is an Analyst; Lena Molin, PhD, is a Senior Researcher; and Per Wikman-Svahn, PhD, is a Scientist; all at the Swedish Defence Research Agency, FOI, Division of Defence Analysis, Stockholm, Sweden.

first country in the world to ban the use of antibiotics for promoting faster growth in livestock (a similar ban was introduced in the EU in 2006). Political support for and commitment to the work to prevent antibiotic resistance has been strong in Swedish society, and a wide range of stakeholders have been engaged. For example, the Swedish Strategic Program Against Antibiotic Resistance (Strama) was formed in the mid-1990s with local groups in every county and now encompasses both human and veterinary medicine. A government strategy for coordinated work toward the containment of antibiotic resistance and healthcare-related diseases was presented in 2006. As an extension of the strategy, a national cross-sector coordinating mechanism was established in 2012 involving cooperation among 20 authorities active in public health, animal health, food safety, and the environment.<sup>14</sup> All government agencies in Sweden are required to prepare annual risk and vulnerability analyses for their area of responsibility, and several Swedish agencies have addressed antibiotic resistance in these reports.<sup>15-17</sup> Finally, it can be noted that the Swedish government hosted a high-level meeting with 30 nations in Stockholm in December 2014 to promote a Global Anti-Microbial Resistance Collaborative Platform for surveillance of and tracing the spread of multidrug-resistant bacteria.<sup>18</sup>

The changing situation with increasing levels of multidrug-resistant bacteria creates a need to try to anticipate and prepare for future developments. For this reason “foresights” (or “future studies”) have been carried out that cover risks with multidrug-resistant bacteria, for example, in Canada,<sup>19</sup> the Netherlands,<sup>20</sup> and the United Kingdom.<sup>21,22</sup> Also, in Sweden, multidrug-resistant bacteria have previously been identified as a major future threat in foresight studies.<sup>23,24</sup>

The study that we describe here<sup>25</sup> was conducted on behalf of the Swedish Civil Contingencies Agency (MSB) and the Ministry of Defence to provide an input into the annual Swedish National Risk and Capability Assessment, in which risks of national importance are assessed in order to strengthen preparedness and crisis management in Sweden.<sup>26</sup> It was in this context that a “plausible worst-case scenario” of increasing prevalence of multidrug-resistant bacteria was developed and used as a tool for assessing societal consequences and authorities’ preparedness to handle such an event and for discussing preventive measures.

## METHODS

### *Design of the Study*

The objective of the study was to create and analyze a challenging, relevant, and plausible worst-case scenario of increasing prevalence of multidrug-resistant bacteria. Scenarios are typically used to inform, to raise awareness, and to broaden and improve decision making by anticipating

key factors that could influence future developments, thus incorporating perspectives on future developments into current activities and strategies.<sup>27</sup> Plausible scenarios should have a reasonable probability of occurring, as opposed to possible scenarios (which might consider any imaginable scenario, regardless of likelihood) or probable scenarios (which might be more heavily based on extrapolations of the present situation).<sup>28</sup> A plausible worst-case scenario should, therefore, in this article, not be interpreted as the worst imaginable scenario but rather a scenario that serves as a challenging and useful tool for the task at hand.

The requirement was that the scenario should be useful on both the national and regional levels and for different actors in society and that it should be compatible with the National Risk and Capability Assessment framework.<sup>29</sup> The scenario was therefore designed as a cross-sector challenge for the society on a national level. The scenario was devised to depict a situation in which a substantial part of the population was affected by multidrug-resistant bacteria in their everyday life. Finally, the scenario was to include an unexpected and gradual rise in prevalence of multidrug-resistant bacteria, on the basis of the hypothesis that it would create particular challenges.

In order to create the scenario, initial literature studies of the occurrence and spread of multidrug-resistant bacteria were carried out and followed up with interviews with experts on antibiotic resistance in relevant fields.<sup>30</sup> Relevant aspects of the scenario design were then structured using an established scenario methodology in foresight studies (morphological analysis) and used to construct a scenario narrative.<sup>31</sup> The scenario narrative was sent out to and commented on by a majority of the interviewees, and further scenario-specific discussions were undertaken with the Public Health Agency of Sweden, the National Veterinary Institute, the Swedish Board of Agriculture, the National Food Agency, and the network ReAct. In contrast to most other scenarios used in the Swedish National Risk and Capability Assessment, the present scenario is characterized by a slowly increasing trend over several years, covering a wide geographical area, and resulting in an irreversible situation. A particularly important element in the construction of the scenario was to choose a plausible and relevant type of multidrug resistance and bacteria for the scenario.

The bacteria and multidrug resistance of choice should be characterized by a slow, gradual increase in the occurrence in humans, animals, the food chain, and the environment and should affect more than one sector of the society. Hence, the bacteria that showed near total resistance to antibiotics should affect humans, animals, and the environment so that the situation would have to be handled with a One Health approach.<sup>32-34</sup> Other characteristics to be captured in the scenario were the mode of transmission of the bacteria, which would allow it to spread across sectors and remain undetected in humans and animals during a relatively long period.

The general type of resistance suitable for creating a plausible worst-case scenario was narrowed down to carbapenemase-producing *Enterobacteriaceae*, as both literature and interviewed experts pointed to CPE as an urgent threat internationally and for Sweden.<sup>8,12,13,35-37</sup> CPE also often displays multidrug-resistant phenotypes (resistance to most  $\beta$ -lactam antibiotics and often co-resistance to many others—eg, to fluoroquinolones, aminoglycosides, and trimethoprim), further limiting the therapeutic options and resulting in increased morbidity and mortality.<sup>38</sup>

Today, the most commonly reported type of multidrug resistance in Sweden is ESBL (extended-spectrum  $\beta$ -lactamases)-producing *Enterobacteriaceae* (8,131 cases in 2013).<sup>39-40</sup> ESBL-producing bacteria lead to prolonged hospital stays, increased healthcare costs, and increased morbidity and mortality, even for less serious infections.<sup>41-43</sup> Some people can carry ESBL-producing bacteria from months to a year, and it is difficult to predict who is at the greatest risk.<sup>44-46</sup> Foreign travel to areas where ESBL-producing intestinal bacteria are common increase the risk of becoming a carrier.<sup>47</sup> In a study of carriers conducted among the healthy population in Sweden, the incidence of ESBL-producing *E. coli* was 5% (in some other countries this can exceed 60% of the population).<sup>39,48,49</sup>

The bacterium of choice was *E. coli* because it has the advantage of being common globally in the intestines of humans and animals. To simplify the analysis, no other bacterium was included in the scenario, nor were different levels or mechanisms of resistance or virulence included as this was considered too detailed for the scenario analysis, which was to focus on societal challenges and consequences. In Sweden, CPE are generally referred to as ESBL<sub>CARBA</sub>-producing *Enterobacteriaceae*.<sup>50</sup>

Note was also taken of current surveillance programs for CP *E. coli* and multidrug-resistant bacteria in Sweden. There is no regular monitoring of CP *E. coli* in healthy humans or food-producing animals, although the EU now requires that samples for CPE be taken every 2 years at random from some food-producing animals, including chickens.

The increased prevalence of CPE has significant therapeutic implications: complicated therapy and limited treatment options, predisposing infected patients to higher mortality and longer length of hospital stay, increasing costs for treatment, and serious consequences for health care.<sup>43,44,51</sup>

The first confirmed case of CPE in Sweden was observed in 2005. Since then there have been outbreaks of multidrug-resistant bacteria in hospitals and in other healthcare facilities, but fortunately these have so far been rare.<sup>52</sup> Despite the strict antibiotic policy in Sweden and decreasing antibiotic consumption, CPE is still increasing slowly in samples from both outpatients and hospitals. A total of 95 cases with CPE were reported in Sweden from 2007 to 2013, with 21 new cases in 2012 and 38 new cases in 2013.<sup>35</sup>

In summary, the basis of the scenario was the choice of CP *E. coli*, which was justified because it could potentially cause major cross-sector challenges for public and animal health on national, regional, and local levels. Further details of the scientific basis for the choice of CP *E. coli* and other elements in the scenario are described below, followed by the scenario narrative itself.

After the development and validation of the scenario with experts, the scenario was used as a basis for a workshop with a wider set of invited experts.<sup>30</sup> The workshop was designed to answer the following questions:

1. Could 5% of the population in southern Sweden become carriers of CP *E. coli* in 1 year?
2. How would the events in the scenario be detected and handled by Swedish authorities?
3. What would the consequences be of the scenario on society?
4. What measures should be taken to prevent or manage the situation in the scenario?

Detailed notes were taken at the workshop and then processed into a report that was sent out to all participants for review.<sup>25</sup> The key findings from the workshop are presented below.

### *Scientific Basis for Elements in the Scenario*

The situation depicted in the scenario is based mainly on real events with bacteria with ESBL,<sup>52,53</sup> but made worse by choosing carbapenemase-producing *E. coli* as a particularly challenging multidrug-resistant bacteria. In order to develop the scenario, it was essential to assess the present knowledge concerning how antibiotic resistance is spread between humans, animals, the food chain, and environments, as this aspect is central to the discussion of how realistic or plausible the scenario will be.

Animals may act as reservoirs of resistant bacteria, and transmission of CPE strains and/or multidrug resistance genes to humans through the food production chain is considered likely.<sup>54-59</sup> Examples of transmission of an *E. coli* multidrug resistance plasmid between chickens and from chickens to people in contact with the animals has been documented.<sup>60-62</sup> In Sweden CP *E. coli* or CPE has not been found in farmed animals,<sup>39</sup> but in other European countries some studies have reported the occurrence of CPE in food-producing animals.<sup>63-65</sup> ESBL-producing *Enterobacteriaceae* have been detected in cattle, chickens, pigs, raw milk, and lettuce.<sup>61,63,66,67</sup> The transmission of multidrug resistance from soil to clinic or vice versa is a real possibility.<sup>68</sup>

There is already a high and increasing occurrence of ESBL-producing *E. coli* with resistance to broad-spectrum cephalosporins in Swedish and European broiler populations, which is of concern.<sup>69,70</sup> Furthermore, transmission

of ESBL-producing *E. coli* to humans through the food chain is considered likely if strains spread more widely in food-producing animals.<sup>71</sup>

*E. coli*-producing ESBL has been frequently found on Swedish chicken meat, regardless of origin, but has also occurred to a lesser extent on imported pork, beef, vegetables, and farmed fish foodstuffs.<sup>39</sup> In a Swedish study, it was found that there were 3 separate populations of ESBL-producing *E. coli* in Sweden: (1) food and food-producing animals, (2) imported food, and (3) humans and the environment. This means that people and their activities are important sources of the ESBL-producing bacteria found in sewage and the environment.<sup>39,61,71,72</sup> Samples of ESBL-producing *E. coli* have been reported in water samples from rivers and lakes in Sweden.<sup>73</sup>

There are examples of exchange of antibiotic resistance genes between environmental bacteria and clinical pathogens, although the frequencies of transmission are not clear.<sup>69,74-77</sup> Bacterial communities from water environments, including hospital and wastewater sewage, have been reported to contribute to the dissemination of carbapenemase-encoding genes of clinical relevance.<sup>78-81</sup> Analysis of bacteria isolated from sewage can provide useful information on how antibiotic resistance is developing for a specific area from a community or a hospital.<sup>82</sup> Contamination of vegetables, other crops, or soil using polluted irrigation water is a poorly documented route of spread of multidrug resistance that needs further examination.<sup>5,83</sup>

### Summary of Scenario Narrative

The scenario narrative presented at the workshop is provided in a shortened version here. For the complete scenario with all details, see the scenario report.<sup>25</sup>

The scenario involves CP *E. coli* (ESBL<sub>CARBA</sub>) prevalence that increases rapidly to 5% in the normal human population over 5 years in southern Sweden. The region affected has chicken producers, feed manufacturers, dairy producers, and rearing of beef calves and beef cattle. A major chicken production plant and chicken feed manufacturer in a flood-affected area becomes contaminated. The chickens do not become ill but are carriers; thus, the contamination is not detected, but it remains on the chicken carcasses and reaches consumers when the chicken meat is distributed in stores. There is no regular sampling for *E. coli* in the feed supplied to these kinds of plants. Barbecued chicken and beef burgers are the summer trend. When the EU investigates the occurrence of CP *E. coli* in chickens, which is done every second year, they find, after a year, a high incidence at the chicken production plant.

The summer was very warm, and the area is often affected by flooding because of extremely heavy rainfalls. Local sewage treatment plants cannot cope with excess polluted water, which has to be released untreated into lakes and overflows onto unused land as well as farmland pastures where cattle are released. There are also cases of CP

*E. coli* in clinical samples from animals. The water used for irrigation contaminates huge fields of vegetables and strawberries. Two years after the hot summer, a study of water samples shows that almost 6% of *E. coli* downstream from a sewage treatment plant was CP *E. coli*. The resulting contamination is not severe enough to cause illness among consumers, so it is not detected. Taken together, this increases the spread and prevalence of multidrug-resistant bacteria, including CP *E. coli* in humans and food-producing animals and as a contaminant in food and in the environment.

People continue to travel on holiday to areas for sun and warmth, where they risk becoming carriers of CP *E. coli*. During this period, the proportion of surgery abroad increases, and food and animal feed imports increase from regions with high prevalence of CP *E. coli*. In the public health sector, there are several outbreaks with CP *E. coli* affecting hospitals and several other healthcare facilities in the region. No regional health authority sees the overall pattern that is developing. Preliminary data of a screening study showed that 5% of the population in southern Sweden are carriers of CP *E. coli*.

## RESULTS

In general, we found that the scenario worked very well in that it established a common ground for discussions at the workshop among a wide range of authorities with different responsibilities related to carbapenem resistance in various sectors of Swedish society. Some of the most interesting findings are presented below.

All respondents who answered an evaluation form agreed that the workshop fulfilled its purpose. Most respondents thought that the consequences of the scenario were identified and felt that the scenario was useful for them.

### Key Findings

The key findings, structured from the 4 workshop questions, are as follows:

#### 1. Could 5% of the population in southern Sweden become carriers of CP *E. coli* in 1 year?

The participants thought that the scenario was something out of the ordinary and challenging but not unexpected, at least in the long term. They estimated that a situation in which 5% of the population in southern Sweden becomes carriers of CP *E. coli* was *unlikely* within the next 5 years, but possible or even *likely* in 10 to 15 years. In contrast to the scenario narrative, the participants thought that the main cause of this development would be because of travel and the inflow of other global activities, rather than from outbreaks and spread of resistant bacteria within Sweden.

#### 2. How would the events in the scenario be detected and handled by Swedish authorities?

It is difficult for authorities within each sector to create an overall picture and to follow the development of increasing levels of carbapenem resistance. The spread of CP *E. coli*

would be detected in humans and animals when samples are taken, but it was not clear if, or when, the trend of increasing prevalence of CP *E. coli* would be noticed in the population. Coordination between many authorities would therefore be important in a situation like the one in the scenario and information would have to be retrieved early and disseminated to those who would handle the situation. In humans, responsible authorities may only detect a tip of the iceberg by monitoring clinical samples (eg, samples from clinical cases and cases from contact tracing and sampling upon suspicion of carriage).

The healthcare sector would be challenged in handling the situation, as its capacity could be insufficient to meet the demand in accordance with best practice procedures today. The key to success in preventing the establishment of CP *E. coli* is limiting the use of antibiotics, early detection through good diagnostic practices, and containment of spread through patient and contact screening as well as infection prevention and control measures.

In animal husbandry, the situation would be handled, but it was not clear if all animals that were carriers were to be put down because they could be asymptomatic carriers. To what extent this would prove to be an option would depend on the type of food-producing animal and the percentage of multidrug resistance carriers and decisions taken on economic compensation for producers. There were no plans or routines at the time of the workshop to handle such a situation. As for the environment, detection would occur only if specific studies were performed, and the way this was to be handled was not clear.

### 3. What would be the consequences of the scenario on society?

The primary negative consequences of the scenario on society are attributable to increased demands on the healthcare system. The healthcare system will have to find different ways of handling and treating patients when a high percentage might be carriers of CP *E. coli*. For example, hospitals will be required to have more single rooms for patients, prepare for longer stays and more complicated treatments, and implement more strict hygiene routines and infection control measures. People will become sick or die from diseases previously not considered serious, which will increase the burden on the healthcare system and the health insurance system. The participants stated that the cost for human healthcare will likely increase greatly due to the rising levels of carbapenem resistance. Any real or perceived reduced capability in healthcare services may diminish peoples' trust in authorities.

Other potential negative effects are related to animal health, food safety, and releases of multidrug-resistant bacteria into the environment. Participants suggested that consumers might demand active measures or the food-producing industry will be negatively affected. This could affect international trade in animals and food products, if national restrictions are imposed, depending on decisions taken on how to prevent CPE transfers to Sweden. The

presence and continued release of CP *E. coli* or CPE from sewage treatment plants or from hospitals and farms into surface waters was acknowledged as a problem, but present knowledge was lacking among workshop participants on how resistance genes are further spread in the environment and how this might in the long term affect human health or society as a whole.

### 4. What measures should be taken to prevent or manage the scenario?

The problem of timely detection of increased levels of CP *E. coli* as in the scenario suggests a need for long-term CPE screening programs for human and animal healthcare systems as well as for food and water production. Better plans should be developed to handle the trend of increasing levels of CPE in humans, animals, feeds, and food products and in the environment. Hygienic and cleaning routines have to be improved and enforced for healthcare facilities and many other facilities such as nursing homes for the elderly and kindergartens and daycare centers.

Increasing levels of multidrug-resistant bacteria including CPE is a global problem, and participants suggested that we need a systems approach that would look more toward the future rather than just focusing on the present situation. Economic assessments of increasing levels of multidrug-resistant bacteria were seen as necessary to draw attention to the problems (analogous to the *Stern Review on the Economics of Climate Change*<sup>84</sup>).

Improved methods for water purification for wastewater treatment systems were suggested, as well as regularly taking samples from surface waters and the outflow from sewage treatment plants, hospitals, and pharmaceutical plants to elucidate the prevalence of multidrug-resistant bacteria. A sample from a specific sewage plant can give an indication of the types of antibiotic-resistant bacteria and resistance genes for a population that the plant serves.

## DISCUSSION AND CONCLUSIONS

Having a cross-sector plausible worst-case scenario as a base for the workshop led to a recognition among participants of the future problems society could face and a discussion on possible preventive and mitigating measures that need to be implemented. The workshop resulted in interesting answers to the 4 questions posed.

The first question we wanted to answer was when such a plausible worst-case scenario could occur. Perhaps the most remarkable finding from the workshop was that a situation in which 5% of the population in southern Sweden becomes carriers of CP *E. coli* was deemed likely by the experts within 10 to 15 years. The spread of CP *E. coli* and CPE is facilitated by interspecies gene transmission, use of antibiotics in human or animal healthcare, poor sanitation and hygiene in communities and hospitals, and the increasing frequency of global travel and trade, allowing multidrug-resistant bacteria to be transmitted into Sweden

and spread to other countries. The latter mechanisms were seen as a major reason for the long-term likely increase of CP *E. coli* or CPE in Sweden. Workshop participants agreed that in spite of current plans and all measures taken over a long period in Sweden, they were not convinced that these were sufficient to prevent a future situation as envisioned in the scenario. Such a projected substantial increase in the prevalence of CPE in a country that is in the forefront in the fight against multidrug-resistant bacteria is very worrying.

The second question was how the events in the scenario would be detected and handled by Swedish authorities. It was clear that current surveillance programs for multidrug-resistant bacteria in Sweden could not ensure timely detection of the increased levels of CP *E. coli* in animal or human populations. The occurrence of CPE might already be underestimated both in animals and in healthy humans. In Sweden, most detected cases are found in hospitals, and there is therefore a risk that only the tip of the iceberg is seen. There is a need to better follow the occurrence and spread of CP *E. coli* or CPE and multidrug resistance in general in the human and animal populations, as well as the spread of CP *E. coli* or CPE and antibiotic resistance genes between humans, animals, the food chain, and the environment. To initiate regular programs for the surveillance of the human population for CPE is, however, not a simple matter, as ethical aspects must also be taken into account. A first screening study was carried out in Sweden in 2014.<sup>39</sup>

The third question had to do with what the wider consequences of the scenario could be on society. The overall costs for a society in the EU for healthcare due to a subset of drug-resistant bacteria is estimated to be around €1.5 billion annually.<sup>2,6</sup> It has also been estimated that the cost of multidrug-resistant bacteria in humans could cost the Swedish society about 160 million Swedish crowns per year, with the largest cost consisting of inpatient treatment and contact tracing (the total cost for health care in Sweden is 250 billion Swedish crowns).<sup>85</sup> However, it has been suggested that estimates of the cost of multidrug resistance are underestimated, because they are mainly based on the incremental cost related to the extra treatment of patients.<sup>86</sup> Also, the cost of more and extended sick leave, deaths, and suffering in general will affect society.

The fourth question was, what measures should be taken to prevent or manage the consequences of the scenario? Several measures were identified at the scenario workshop. Here we discuss some of these together with other measures that could be the basis for further consideration by EU member states and relevant authorities and actors.

On the international level, actions are urgently needed for surveillance monitoring and information exchange on measures that have been shown to prevent or limit the rapid spread of multidrug-resistant bacteria. The Global Anti-Microbial Resistance Collaborative Platform initiative is welcome and should be supported.

More knowledge is needed on how multidrug-resistant bacteria and antibiotic resistance genes are spread between

humans, animals, the food chain, healthcare institutions, water treatment plants, and in the environment, as knowledge was found to be too limited even among the experts. Increased research efforts are needed to determine pathways for spread of multidrug resistance in general and specifically for CPE and to see that actions are initiated based on this knowledge. In addition, the development of (and ensuring access to) new antibiotics and therapies should be promoted.

On the national level, collaboration among authorities responsible for public health, animal health, food and water production, and environmental protection should be a priority and should be further developed building on present cross-sector cooperative frameworks. The work on prevention of antibiotic resistance should continue along the lines of One Health, as a cross-sector activity engaging many authorities and actors. One way to raise awareness and exchange information is to initiate dedicated forums and regular seminars where CPE and antibiotic resistance issues are discussed among a wider group of authorities, NGOs, and the general public, to avoid limiting the discussion to experts.

Authorities need to develop strategies for handling or preventing a future situation like the one in the scenario, when multidrug-resistant bacteria, including CP *E. coli*, become more widespread in society. This strategy should include developing lists of concrete measures for public and animal health, food safety, and environmental protection that can be implemented on a national or regional level. For example, in a case of widespread prevalence of CPE, there should be guidelines and procedures for handling animals that are carriers but not ill, as CP bacteria could be transmitted through the food chain. Measures implemented in Sweden have to some degree been successful and have slowed the trend of increasing levels of CPE and multidrug-resistant bacteria, but still the levels are continuing to increase. This raises the question how much the increasing levels of CPE can be affected by domestic measures when the levels to some degree depend on external inflows, such as animal and food imports, increased travel abroad, and immigration.

If, as in the scenario, the trend of increasing levels of CPE continues, there could be very significant costs to health care, human health, and society more generally. CPE cannot be “eradicated”—rather, it is something we have to manage if we are to continue to benefit from antibiotic therapies. For CPE there is a clear danger that waiting for the burden to become significant before taking action may mean waiting until it is too late to stop an unwanted future scenario. One final suggestion for raising the awareness among EU’s member states could be to organize a foresight study, in which this problem with rising levels of CPE and other multidrug-resistant bacteria could be worked on and assessed in more detail—for example, by an initiative by the European Commission to be led by the ECDC.

This study has shown that the use of a plausible worst-case scenario can be a useful tool to engage responsible authorities in an informal discussion and exchange of views between sectors on how to best meet the future threat of increasing levels of multidrug-resistant bacteria in society.

## ACKNOWLEDGMENTS

This work was financially supported by the Swedish Civil Contingencies Agency (MSB). We would like to thank all representatives from Swedish authorities, ECDC, and other experts who were interviewed and for their participation in the scenario workshop. In addition, we thank the 2 reviewers for helpful suggestions to improve the article. No conflicts of interest are declared.

## REFERENCES

- World Economic Forum. *Global Risks 2013*. Insight Report. 8th ed. Geneva: World Economic Forum; June 2013.
- Communication from the Commission to the European Parliament and the Council. *Action Plan Against the Rising Threats from Antimicrobial Resistance*. COM (2011) 748. Brussels: European Commission; 2011. [http://ec.europa.eu/dgs/health\\_food-safety/docs/communication\\_amr\\_2011\\_748\\_en.pdf](http://ec.europa.eu/dgs/health_food-safety/docs/communication_amr_2011_748_en.pdf). Accessed March 26, 2015.
- The White House. *National Strategy for Combating Antibiotic-Resistant Bacteria*. Washington, DC: The White House; September 2014. [https://www.whitehouse.gov/sites/default/files/docs/carb\\_national\\_strategy.pdf](https://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf). Accessed March 26, 2015.
- Nathan C, Cars O. Antibiotic resistance—problems, progress, and prospects. *N Engl J Med* 2014;371(19):1761-1763.
- Wellington EM, Boxall AB, Cross P, et al. The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. *Lancet Infect Dis* 2013;13(2):155-165.
- ECDC/EMA. *The Bacterial Challenge: Time to React*. Technical Report. Stockholm: European Centre for Disease Prevention and Control; European Medicines Agency; 2009. [http://ecdc.europa.eu/en/publications/Publications/0909\\_TER\\_The\\_Bacterial\\_Challenge\\_Time\\_to\\_React.pdf](http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf). Accessed March 26, 2015.
- Magiorakos AP, Struelens M, Jasir A. *Risk Assessment on the Spread of Carbapenemase-Producing Enterobacteriaceae (CPE) Through Patient Transfer Between Healthcare Facilities, with Special Emphasis on Cross-Border Transfer*. ECDC Technical Report. Stockholm: European Centre for Disease Prevention and Control (ECDC); September 2011. [http://ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/risk\\_assessment\\_CPE.aspx](http://ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/risk_assessment_CPE.aspx). Accessed March 26, 2015.
- Cantón R, Akóva M, Carmeli Y, et al; European Network on Carbapenemases. Rapid evolution and spread of carbapenemases among *Enterobacteriaceae* in Europe. *Clin Microbiol Infect* 2012;18(5):413-431.
- Patel G, Bonomo RA. “Stormy waters ahead”: global emergence of carbapenemases. *Front Microbiol* 2013;4:48.
- Nordmann P, Naas T, Poirel L. Global spread of Carbapenemase-producing *Enterobacteriaceae*. *Emerg Infect Dis* 2011; 17(10):1791-1798.
- Magiorakos AP, Suetens C, Monnet DL, Gagliotti C, Heuer OE; EARS-Net Coordination Group and EARS-Net participants. The rise of carbapenem resistance in Europe: just the tip of the iceberg? *Antimicrob Resist Infect Control* 2013; 14:2(1):6.
- ECDC. Technical Report. *Carbapenemase-Producing Bacteria in Europe: Interim Results from the European Survey on Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Project 2013*. Stockholm: European Centre for Disease Prevention and Control; 2013. <http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-carbapenemase-producing-bacteria-europe.pdf>. Accessed March 26, 2015.
- ECDC. *Annual Epidemiological Report 2013*. Reporting on 2011 Surveillance Data and 2012 Epidemic Intelligence Data. Stockholm: European Centre for Disease Prevention and Control; 2013. <http://ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf>. Accessed March 26, 2015.
- FHM. *Svenskt arbete mot antibiotikaresistens: Verktyg, arbetsätt och erfarenheter [Swedish Work on Antibiotic Resistance: Tools, Methods and Experiences]* [in Swedish]. Solna: Public Health Agency of Sweden (Folkhälsomyndigheten, FHM); 2014.
- SoS. *Socialstyrelsens risk- och sårbarhetsanalys 2013 [Risk and Vulnerability Assessment 2013 from the Board for Public Health and Welfare]* No. 2013-11-20 [in Swedish]. Stockholm: SoS, Board for Public Health and Welfare; 2013.
- SMI. *Smittskyddsinstitutets risk- och sårbarhetsanalys 2012 [SMI Risk and Vulnerability Assessment 2012]*, No. 2012-19-5 [in Swedish]. Solna: SMI, Swedish Institute for Communicable Disease Control; 2012.
- SVA. *SVA:s Risk- och sårbarhetsanalys 2013 [SVA Risk and Vulnerability Assessment 2013]* [in Swedish]. Uppsala: SVA National Veterinary Institute; 2012.
- Swedish Ministry of Health and Social Affairs. International collaboration to build global AMR surveillance, 2-3 December 2014, the Swedish Ministry of Health and Social Affairs and the Public Health Agency of Sweden. (To collect, analyze, compare and validate AMR data, share information for decision making, support capacity building; provide guidance to address gaps, overview of available technical and human resources, and facilitate networking across sectors nationally, internationally). Stockholm: Ministry of Health and Social Affairs. <http://www.folkhalsomyndigheten.se/amr-stockholm-2014/programme-and-presentations/>. Accessed March 26, 2015.
- NCCID. *Foresight Exercise on Infectious Diseases in Canada: Future Trends and Emerging Issues*. A Program of the International Centre for Infectious Diseases Inc. Winnipeg, Manitoba: National Collaborating Centre for Infectious Diseases; December 2005. [https://cdn.metricmarketing.ca/www.nccid.ca/files/Foresight\\_Final\\_Report.pdf](https://cdn.metricmarketing.ca/www.nccid.ca/files/Foresight_Final_Report.pdf). Accessed March 26, 2015.
- National Security Analysts Network (ANV). *Thematische verdieping AMR en nationale veiligheid [AMR and National Security]* [in Dutch]. ANV on commission by the Ministry of Security and Justice, on behalf of the Steering Committee for National Security (SNV), Netherlands; October 2014.

21. Office of Science and Innovation. *Foresight. Infectious Diseases: Preparing for the Future*. London: Office of Science and Innovation; 2006.
22. Suk JE, Lyall C, Tait J. Mapping the future dynamics of disease transmission: risk analysis in the United Kingdom Foresight Programme on the detection and identification of infectious diseases. *Euro Surveill* 2008;13(44):1-7.
23. MSB. Scenario 5 – Antibiotic-resistant bacteria spread across the world. In: *Five Challenging Future Scenarios for Societal Security*. No. MSB543. Stockholm: MSB, Swedish Civil Contingencies Agency; March 2013. <https://www.msb.se/RibData/Filer/pdf/26562.pdf>. Accessed March 26, 2015.
24. Wahlberg M, Jonsson O, Lindberg A. *Antibiotic Resistance and Societal Security: What Would a More Far-Reaching Antibiotic Resistance Mean for Societal Security?* No. MSB677. Stockholm: MSB, Swedish Civil Contingencies Agency; 2014. <https://www.msb.se/RibData/Filer/pdf/27378.pdf>. Accessed March 26, 2015.
25. Lindberg A, Molin L, Roffey R, Wikman-Svahn P. *Ökad förekomst av antibiotikaresistenta tarmbakterier i samhället—en analys av ESBL<sub>CARBA</sub> inom nationell risk-och förmågebedömning* [Increased incidence of antibiotic resistant intestinal bacteria in society—an analysis of ESBL<sub>CARBA</sub> in National Risk and Capability Assessment] [in Swedish]. FOI Memo report 5108. Stockholm: Swedish Defence Research Agency; 2014.
26. MSB. Nationell risk- och förmågebedömning 2013, Arbetsprocess och nulägesbeskrivning [National Risk and Capability Assessment 2013, Work process and status report] [in Swedish]. Fact sheet MSB-89.5. Stockholm: MSB, Swedish Civil Contingencies Agency; May 2013.
27. Börjesson L, Hojer M, Dreborg KH, Ekvall T, Finnveden G. Scenario types and techniques: towards a user's guide. *Futures* 2006;38(7):723-739.
28. Suk JE, Semenza JC. Future infectious disease threats to Europe. *Am J Public Health* 2011;101(11):2068-2079.
29. MSB. *Risker och förmågor 2012—Redovisning av regeringsuppdrag om nationell riskbedömning respektive bedömning av krisberedskapsförmåga* [Risks and capabilities 2012—Accounting for government commission on national risk assessment and evaluation of emergency preparedness] [in Swedish]. No. MSB545. Stockholm: MSB, Swedish Civil Contingencies Agency; March 2013.
30. In preparation for the workshop, interviews were carried out with experts on multidrug resistance (veterinary science, bacteriology, infectious diseases, epidemiology, public health, hygiene, food safety, environmental protection, environmental pharmacology, and crisis management) from authorities marked with (\*). Invitations to take part in the workshop were sent out and representatives and experts (competence as for interviews) from the following authorities participated: Public Health Agency of Sweden\* (Folkhälso-myndigheten, FHM), National Veterinary Institute\* (Statens veterinärmedicinska anstalt, SVA), National Board of Health and Welfare\* (Socialstyrelsen), Swedish Board of Agriculture\* (Jordbruksverket), National Food Agency\* (Livsmedelsverket), Medical Products Agency (Läkemedelsverket), Swedish Civil Contingencies Agency\* (Myndigheten för samhällsskydd och beredskap, MSB), Swedish Animal Health Service, (Svenska djurhälsovården AB, SvDHV) (interview only), Uppsala University/Akademiska Hospital and the network ReAct,\* Karolinska Institute,\* University of Gothenburg,\* Swedish Environmental Protection Agency\* (Naturvårdsverket), County Council of Västernorrland\* (interview only), County Council of Skåne (Region Skåne), County administrative board of Skåne (Länsstyrelsen Skåne län), the Swedish Association of Local Authorities and Regions\* (Sveriges kommuner och landsting), and European Centre for Disease Prevention and Control\* (ECDC) (interview only).
31. Ritchey T. Morphological analysis. In: Glenn JC, Gordon TJ, eds. *Futures Research Methodology—V3.0*, The Millennium Project; 2009. <http://www.millennium-project.org/millennium/images/FRM-V30.jpg>. Accessed February 2, 2015.
32. One Health recognizes that the health of humans, animals, and ecosystems are interconnected. It involves applying a coordinated, collaborative, multidisciplinary, and cross-sectoral approach to address potential or existing risks that originate at the animal-human-ecosystems interface. One Health Global Network, Webportal.
33. Global 'One-Health' initiative. <http://www.onehealthinitiative.com/index.php>. Accessed March 26, 2015.
34. WHO. *The Evolving Threat of Antimicrobial Resistance. Options for Action*. Geneva: WHO; 2012. <http://www.who.int/patientsafety/implementation/amr/publication/en/>. Accessed March 26, 2015.
35. Swedres/Svarm 2013. *Use of Antimicrobials and Occurrence of Antimicrobial Resistance in Sweden*. Swedish Antibiotic Utilization and Resistance in Human Medicine (SWEDRES) and Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM). Solna: Public Health Agency of Sweden and Uppsala, National Veterinary Institute; 2013.
36. Nordmann P. Carbapenemase-producing *Enterobacteriaceae*: overview of a major public health challenge. *Méd Mal Infect* 2014;44(2):51-56.
37. Johnson AP, Woodford N. Global spread of antibiotic resistance: the example of New Delhi metallo-beta-lactamase (NDM)-mediated carbapenem resistance. *J Med Microbiol* 2013;62(Pt 4):499-513.
38. Brolund A. Overview of ESBL-producing *Enterobacteriaceae* from a Nordic perspective. *Infect Ecol Epidemiol* 2014;4:1-9.
39. Egervärn M, Rosengren Å, Englund S, Börjesson S, Löfmark S, Ny S, Byfors S. *ESBL-bildande E.coli i vår omgivning—livsmedel som spridningsväg till människa*, Slutrapport från ett myndighetsgemensamt projekt antibiotikaresistens [ESBL-producing *E. coli* in our environment—food pathways to humans, Final report of an official joint project on antibiotic resistance] [in Swedish]. National Food Agency, SVA National Veterinary Institute and the Public Health Agency of Sweden; November 13, 2014.
40. Bacteria of *Enterobacteriaceae* with ESBL<sub>CARBA</sub> resistance became notifiable for clinical laboratories in 2007, in general for human medicine in 2012, and for veterinary medicine in 2008 in Sweden, no farm animals are treated with carbapenems.
41. Giske CG, Monnet DL, Cars O, Carmeli Y; ReAct-Action on Antibiotic Resistance. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother* 2008;52(3):813-821.
42. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in *Enterobacteriaceae* bacteraemia: a systematic

- review and meta-analysis. *J Antimicrob Chemother* 2007; 60(5):913-920.
43. de Kraker ME, Davey PG, Grundmann H; BURDEN study group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med* 2011;8(10):e1001104.
  44. Alsterlund R, Axelsson C, Olsson-Liljequist B. Long-term carriage of extended-spectrum beta-lactamase-producing *Escherichia coli*. *Scand J Infect Dis* 2012;44(1):51-54.
  45. SMI. *ESBL-producerande tarmbakterier, Kunskapsunderlag med förslag till handläggning för att begränsa spridningen av Enterobacteriaceae med ESBL* [Knowledge base with propositions to limit the spread of *Enterobacteriaceae* with ESBL] [in Swedish]. No. 2012-11-2. Solna: SMI Swedish Institute for Communicable Disease Control; 2013.
  46. Tängden T, Cars O, Melhus A, Löwdin E. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother* 2010;54(9):3564-3568.
  47. Lausch KR, Fuursted K, Larsen CS, Storgaard M. Colonisation with multi-resistant *Enterobacteriaceae* in hospitalised Danish patients with a history of recent travel: a cross-sectional study. *Travel Med Infect Dis* 2013;11(5):320-323.
  48. Chabok A, Tärnberg M, Smedh K, et al. Prevalence of fecal carriage of antibiotic-resistant bacteria in patients with acute surgical abdominal infections. *Scand J Gastroenterol* 2010; 45(10):1203-1210.
  49. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev* 2013;26(4):744-758.
  50. Giske et al. divide ESBL enzymes into 3 main groups: ESBLA, ESBLM and ESBLCARBA. Giske CG, Sundsfjord AS, Kahlmeter G, et al. Redefining extended-spectrum  $\beta$ -lactamases: balancing science and clinical need. *J Antimicrob Chemother* 2009;63(1):1-4.
  51. Aldeyab MA, Harbarth S, Vernaz N, et al. The impact of antibiotic use on the incidence and resistance pattern of extended-spectrum beta-lactamase-producing bacteria in primary and secondary healthcare settings. *Br J Clin Pharmacol* 2012;74(1):171-179.
  52. Giske CG, Kalin M. ESBLCARBA kan bli ett problem i svensk sjukvård [ESBLCARBA can become a problem in Swedish health care] [in Swedish]. *Läkartidningen* 2013; 110:CEFA.
  53. Strömdahl H, Tham J, Melander E, Walder M, Edquist P, Odenholt I. Prevalence of faecal ESBL carriage in the community and in a hospital setting in a county of southern Sweden. *Eur J Clin Microbiol Infect Dis* 2011;30(10):1159-1162.
  54. Agersø Y, Aarestrup FM, Pedersen K, Seyfarth AM, Struve T, Hasman H. Prevalence of extended-spectrum cephalosporinase (ESC)-producing *Escherichia coli* in Danish slaughter pigs and retail meat identified by selective enrichment and association with cephalosporin usage. *J Antimicrob Chemother* 2012;67(3):582-588.
  55. Kluytmans JA, Overvest IT, Willemsen I, et al. Extended spectrum  $\beta$ -lactamase-producing *Escherichia coli* from retail chicken meat and humans: comparison of strains, plasmids, resistance genes, and virulence factors. *Clin Infect Dis* 2013; 56(4):478-487.
  56. European Food Safety Authority. Scientific opinion on the public health risks of bacterial strains producing extended-spectrum beta-lactamases and/or AmpC beta-lactamases in food and food-producing animals. *EFSA J* 2011;9:2322.
  57. Laube H, Friese A, von Salviati C, et al. Longitudinal monitoring of extended-spectrum-beta-lactamase/AmpC-producing *Escherichia coli* at German broiler chicken fattening farms. *Appl Environ Microbiol* 2013;79(16): 4815-4820.
  58. Leistner R, Meyer E, Gastmeier P, et al. Risk factors associated with the community-acquired colonization of extended-spectrum beta-lactamase (ESBL) positive *Escherichia coli*. an exploratory case-control study. *PLoS One* 2013;8(9): e74323.
  59. Woodford N, Wareham DW, Guerra B, Teale C. Carbapenemase-producing *Enterobacteriaceae* and non-*Enterobacteriaceae* from animals and the environment: an emerging public health risk of our own making? *J Antimicrob Chemother* 2014; 69(2):287-291.
  60. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013;13(12):1057-1098.
  61. Nilsson O, Börjesson S, Landén A, Bengtsson B. Vertical transmission of *Escherichia coli* carrying plasmid-mediated AmpC (pAmpC) through the broiler production pyramid. *J Antimicrob Chemother* 2014;69(6):1497-1500.
  62. Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, et al; National ESBL surveillance group. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin Microbiol Infect* 2011;17(6):873-880.
  63. Fischer J, Rodriguez I, Schmoger S, et al. *Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm. *J Antimicrob Chemother* 2012;67(7):1793-1795.
  64. Wang Y, Wu C, Zhang Q, et al. Identification of New Delhi metallo-beta-lactamase 1 in *Acinetobacter lwoffii* of food animal origin. *PLoS One* 2012;7(5):e37152.
  65. Fischer J, Rodriguez I, Schmoger S, et al. *Salmonella enterica* subsp. *enterica* producing VIM-1 carbapenemase isolated from livestock farms. *J Antimicrob Chemother* 2013;68(2): 478-480.
  66. Jakobsen L, Kurbasic A, Skjot-Rasmussen L, et al. *Escherichia coli* isolates from broiler chicken meat, broiler chickens, pork, and pigs share phylogroups and antimicrobial resistance with community-dwelling humans and patients with urinary tract infection. *Foodborne Pathog Dis* 2010;7(5):537-547.
  67. Borck Høg B, Korsgaard H, Agersø Y, et al., eds. *DANMAP 2013—Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark*. DANMAP, The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; Statens Serum Institut; National Veterinary Institute, Technical University of Denmark; and National Food Institute, Technical University of Denmark; 2013. <http://www.danmap.org/~media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202013/DANMAP%202013.aspx>. Accessed March 31, 2015.
  68. Forsberg KJ, Reyes A, Wang B, Selleck EM, Sommer MO, Dantas G. The shared antibiotic resistome of soil bacteria and human pathogens. *Science* 2012;337(6098):1107-1111.

69. Börjesson S, Egervärn M, Lindblad M, Englund S. Frequent occurrence of extended-spectrum beta-lactamase- and transferable AmpC beta-lactamase-producing *Escherichia coli* on domestic chicken meat in Sweden. *Appl Environ Microbiol* 2013;79(7):2463-2466.
70. Börjesson S, Bengtsson B, Jernberg C, Englund S. Spread of extended-spectrum beta-lactamase producing *Escherichia coli* isolates in Swedish broilers mediated by an *incI* plasmid carrying *bla*(CTX-M-1). *Acta Vet Scand* 2013;55:3.
71. EFSA. Scientific opinion on the public health risks of bacterial strains producing extended-spectrum  $\beta$ -lactamases and/or AmpC  $\beta$ -lactamases in food and food-producing animals. Panel on Biological Hazards (BIOHAZ). *EFSA J* 2011; 9(8)2322:53-54.
72. Coleman BL, Salvadori MI, McGeer AJ, et al; ARO Water Study Group. The role of drinking water in the transmission of antimicrobial-resistant *E. coli*. *Epidemiol Infect* 2012; 140(4):633-642.
73. Jass J, Olsson PE. Antibiotic resistance in fecal indicator bacteria. Presentation at the Microbiological Spring Meeting in Örebro, Sweden; 10 April 2013.
74. Kristiansson E, Fick J, Janzon A, et al. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. *PLoS One* 2011;6(2): e17038.
75. Wright GD. Antibiotic resistance in the environment: a link to the clinic? *Curr Opin Microbiol* 2010;13(5):589-594.
76. Perry JA, Wright GD. The antibiotic resistance 'mobilome': searching for the link between environment and clinic. *Front Microbiol* 2013 May 30;4(138):1-7.
77. Ashbolt NJ, Amezcua A, Backhaus T, et al. Human Health Risk Assessment (HHRA) for environmental development and transfer of antibiotic resistance. *Environ Health Perspect* 2013;121(9):993-1001.
78. Picão RC, Cardoso JP, Campana EH, et al. The route of antimicrobial resistance from the hospital effluent to the environment: focus on the occurrence of KPC-producing *Aeromonas* spp. and *Enterobacteriaceae* in sewage. *Diagn Microbiol Infect Dis* 2013;76(1):80-85.
79. Zurfluh K, Hachler H, Nuesch-Inderbinen M, Stephan R. Characteristics of extended-spectrum beta-lactamase- and carbapenemase-producing *Enterobacteriaceae* isolates from rivers and lakes in Switzerland. *Appl Environ Microbiol* 2013;79(9):3021-3026.
80. Girlich D, Poirer L, Szczepanowski R, Schluter A, Nordmann P. Carbapenem-hydrolyzing GES-5-encoding gene on different plasmid types recovered from a bacterial community in a sewage treatment plant. *Appl Environ Microbiol* 2012;78(4):1292-1295.
81. Amador PP, Fernandes RM, Prudêncio MC, Barreto MP, Duarte IM. Antibiotic resistance in wastewater: occurrence and fate of *Enterobacteriaceae* producers of class A and class C  $\beta$ -lactamases. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2015;50(1):26-39.
82. Kwak YK, Colque P, Byfors S, Giske CG, Möllby R, Kühn I. Surveillance of antimicrobial resistance among *Escherichia coli* in wastewater in Stockholm during 1 year: does it reflect the resistance trends in the society? *Int J Antimicrob Agents* 2015;45(1):25-32.
83. Söderström A, Österberg P, Lindqvist A, et al. A large *Escherichia coli* O157 outbreak in Sweden associated with locally produced lettuce. *Foodborne Pathog Dis* 2008;5(3): 339-349.
84. Stern N. *Stern Review: The Economics of Climate Change*. London: HM Treasury, Cabinet Office; 2006.
85. FHM. *Sambällsekonomiska konsekvenser av antibiotikaresistens Modellering av anmälningspliktig resistens i Sverige*, slutrapport av regeringsuppdrag till Folkhälsomyndigheten 2013 [Economic Impact of Antimicrobial Resistance] [in Swedish]. Solna: Public Health Agency of Sweden; 2014.
86. Smith R, Coast J. *The Economic Burden of Antimicrobial Resistance: Why It Is More Serious than Current Studies Suggest*. Report 2012. London: London School of Hygiene & Tropical Medicine; 2012. <http://www.lshtm.ac.uk/php/intrafacultyinitiatives/economics/assets/dhamr2012appendix.pdf>. Accessed March 31, 2015.

Manuscript received November 14, 2014;  
accepted for publication February 10, 2015.

Address correspondence to:  
Roger Roffey  
Swedish Defence Research Agency FOI  
Division of Defence Analysis  
SE 16490 Stockholm, Sweden  
E-mail: roger.roffey@foi.se