Chapter 3. Resistance monitoring

National and local monitoring of antibiotic resistance are necessary in order to observe and analyse the development of resistance, to implement countermeasures and to measure the effect of interventions. Purposeful monitoring also forms the basis for the development of recommendations, and for a rational and patient-safe empirical antibiotic treatment of acute infections. Monitoring is also needed to assess the effect of implemented measures. The extent of the sampling for different types of infections, transmission tracing, screening and mapping of outbreaks have great impact on the results when monitoring antibiotic resistance.

Resistance monitoring is largely based on clinical cultures

In Sweden there is a tradition of quite freely taking cultures from patients. Cultures are generally taken from the majority of hospital patients prior to antibiotic treatment. Studies have shown that cultures are taken from around 2 in 3 patients prior to antibiotic treatment in inpatient care, whereas the figure is significantly lower in outpatient care. In primary care, samples are taken from a smaller proportion of patients with infections such as sexually transmitted diseases, complicated urinary tract infections and wound infections. The taking of cultures is not recommended in cases where results are unlikely to influence the choice of treatment (diagnoses such as uncomplicated urinary tract infection in women and upper respiratory tract infections). Resistance monitoring is based on data generated from these clinical cultures and to some extent on cultures from screening, monitoring and tracing the transmission of antibiotic-resistant bacteria monitored according to the Communicable Diseases Act (CDA).

Common breakpoints and a quality-assured methodology

Comparing the prevalence of antibiotic resistance between different laboratories over time requires common breakpoints for the interpretation of results in testing resistance to antibiotics, as well as a quality-assured methodology.

The EUCAST breakpoints for resistance testing have been used in Sweden for many years. EUCAST (European Committee on Antimicrobial Susceptibility Testing) is a European breakpoint committee that establishes SIR-limits for most of the European countries and also functions as the official breakpoint committee for the European Medicines Agency (EMA). Sweden is represented in EUCAST by the Swedish Reference Group for Antibiotics (SRGA). The SRGA is an independent expert group, previously the external reference group of SMI and the Swedish Society of Medicine for antibiotic issues and has worked towards a rational use of antibiotics since 1976. Its tasks include the production and communication of information that is evidence based and manufacturer-independent. The SRGA works to define the sensitivity and resistance of the bacteria to antibiotics (SIR limits), and to analyse the consequences of resistance development on the choice of antibiotics for various patient categories. The SRGA conducts systematic literature reviews and has during 2013 produced a benefit/risk analysis for adults in respect of aminoglycoside treatment of the following
indications: severe sepsis, progressive severe sepsis and septic shock, pyelonephritis and endocarditis.

The SRGA participates in the processes developed by EUCAST and EMA for the determination of breakpoints for new antibiotics, and in the process developed by EUCAST for the revision of breakpoints in respect of pre-existing antibiotics (www.srga.org).

EUCAST describes a standardised disc diffusion method. This is the most common method for testing resistance in Sweden. Over the past few years, however, automated resistance testing has become more common. In spite of their different methodologies, all laboratories use the EUCAST breakpoints, which ensures the comparability of resistance data. The Nordic reference group, Committee on Antimicrobial Susceptibility Testing (NordicAST), provides recommendations that are freely available online on other support methods in resistance testing. This also helps to standardise resistance testing. All clinical microbiological laboratories have been accredited.

Resistance monitoring is mainly done on a voluntary basis and has good geographic coverage

Sweden has four systems of resistance monitoring with national coverage: ResNet, SmiNet, EARS-Net and Svebar. All of the systems except for SmiNet depend on laboratories participating voluntarily and entering their local data into the systems.

3.1 ResNet: To ensure adequate resistance monitoring with comparable data, the methods used for resistance testing by laboratories must be quality-assured continuously. Since 1994, during a set period every year, participating laboratories submit resistance data to the Public Health Agency of Sweden regarding certain combinations of bacterial species and antibiotics via a particular programme. The Public Health Agency of Sweden compiles and feeds back the data through the web-based programme ResNet. The results are used to observe resistance conditions, and by laboratories to continuously assess the quality of their diagnostic methods. The design of ResNet provides country-wide resistance monitoring thanks to the participation of all laboratories.

3.2 EARS-Net: Sweden also takes part in the European monitoring programme EARS-Net which includes invasive isolates (mainly isolates from blood) from seven bacterial species. Data from EARS-Net show the number of resistant isolates in the overall number of isolates in a certain bacterium, for example the proportion of MRSA in all S. aureus taken from blood cultures. The microbiological laboratories report data to the Public Health Agency of Sweden that corresponds to a level of coverage of about 80 percent of the Swedish population. The Public Health Agency of Sweden compiles the results for the European Centre for Disease Prevention and Control ECDC. EARS-Net has an important role in informing about the prevalence and spread of antibiotic resistance in Europe. Only results concerning serious infections, from blood cultures for example, are reported in EARS-Net. This provides a smaller statistical base but the resistance that is reported is important in clinical terms.
3.3 SmiNet. Four types of antibiotic resistance are notifiable in line with the CDA. The notification is made to both The Public Health Agency of Sweden and to the County Medical Officer for communicable diseases. SmiNet is a web-based programme that receives and manages notifications in line with the CDA from treating physicians and from laboratory physicians. An advantage of SmiNet is that resistance is reported sooner and can be monitored continuously, unlike in EARS-Net and ResNet.

3.4 Svebar: The above monitoring systems are all based on a selection of important bacterial species and resistance mechanisms. Apart from SmiNet, resistance is not continuously reported. Svebar is a national IT system that was developed to expand and improve national and local resistance monitoring. The system is based on all results from cultures being transferred on a daily basis from microbiological laboratories to a system managed by the Public Health Agency of Sweden. Svebar is designed to give an early alert on serious antibiotic resistance or suspected disease transmissions by means of pre-set alert functions. An increasing number of laboratories are joining Svebar and all remaining have communicated their intention to start participating within the next few years.

Epidemiological typing is carried out on all notifiable forms of resistance
Epidemiological typing is required to confirm or dismiss a suspicion of disease transmission of the same bacterial strain between people. In an outbreak, epidemiological typing can also be used to confirm new cases or dismiss suspected chains of transmission.

Epidemiological typing of prioritised bacteria should be carried out continuously to gain knowledge of how the prevalence of virulent or resistant strains varies over time between different geographic areas and populations. Long-term monitoring is also required to evaluate findings of certain strains and in the investigation of outbreaks. Without a baseline of the common types in a population, it may prove difficult to evaluate the results of the epidemiological typing in an outbreak situation.

In Sweden, epidemiological typing is carried out in some form for all types of antibiotic resistance that are notifiable according to the CDA, either in the Public Health Agency of Sweden or in the County Council laboratories. In some cases, continuous typing is carried out and in other cases only point prevalence surveys. In addition, further epidemiological typing of bacteria is done in connection with suspected outbreaks or other suspected epidemiological changes.

Analysis and communication is conducted both nationally and locally
To ensure that resistance monitoring leads to adequate measures it is crucial that the results reach laboratories, physicians, hospital management, decision-makers, authorities and concerned organisations as well as the wider public.

The Public Health Agency of Sweden analyses and compiles national data on antibiotic resistance and the use of antibiotics in human medicine, and publishes them
in the SWEDRES annual report. The report is co-published with SVARM (Swedish Veterinary Antimicrobial Resistance Monitoring) that shows corresponding results in veterinary medicine and is produced by the National Veterinary Institute. Statistics on antibiotic resistance that are notified according to the CDA are also continuously posted on the Public Health Agency of Sweden website. The weekly the Public Health Agency of Sweden newsletter also publishes important news and summaries of scientific articles and events on the subject.

National and local resistance data and data on antibiotic prescription form the pillars of Strama activities at a local level (chapter 2 and section 3.5) and is used in discussions with prescribers in order to demonstrate resistance development and to decide upon the focus of local interventions.

The extent to which laboratories provide detailed local resistance data to Strama groups, disease prevention and control units, infectious disease clinics and pharmaceutical committees varies. In many County Councils it is possible to obtain reports on individual hospitals or follow the development in particularly critical activities such as intensive care or urology. The expansion of Svebar will involve the introduction of automatic feedback of local resistance numbers in standardised formats to laboratories, which can then forward them to other local users.

3.1 ResNet – annual resistance monitoring and quality assurance online

Since 1994, all laboratories in Sweden have participated voluntarily in a national scheme for resistance monitoring and quality assurance which is carried out once a year. The laboratories compile quantitative data (zone diameters) of at least 100 consecutive clinical isolates from a selection of commonly occurring bacteria and commonly used antibiotics. ResNet is an internet-based programme that has been used since 2002 to collect and present this data.

In ResNet it is possible to check the prevalence of resistance in a specific bacterial species to a selection of antibiotics both on national and local level. It also shows the distribution of measurement data (MIC values and zone diameters). This allows laboratories to compare the distribution of their measurement data against the normal distribution and discover potential errors and method shifts. ResNet thus offers laboratories the possibility to continuously assure the quality of their measurement methods.

Implementation

The basis for current resistance monitoring in ResNet was initiated by RAF-M, which was a method group consisting of microbiologists under the authority of SRGA, the reference group for antibiotic issues. The monitoring was later taken over by the Public Health Agency of Sweden.

The bacteria chosen for monitoring has varied over the years depending on signs of increased prevalence of resistance in certain bacterial species. Continuity has
been sought in order to discern tendencies over time. Certain pathogens have almost always been included: *Streptococcus pneumoniae* and *Haemophilus influenzae* from respiratory tracts, *Staphylococcus aureus* from wound cultures and *Escherichia coli* and *Klebsiella pneumoniae* from urine cultures. Species that have been tested more infrequently include *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Enterococcus faecium* and *Enterobacter*. The number of antibiotics that they are tested against varies between two and six and corresponds to common treatment options.

The two criteria that influence the choice of bacterial species for the annual measurement are:

1. clinical relevance
2. commonly occurring bacteria in the routine activities of laboratories so that they quickly can establish a basis.

It is important to adapt the approach of the measurement to the daily activities of the laboratories to avoid unnecessary extra work.

**ResNet has simplified the management of data and reduced the amount of work**

SMI developed the internet-based programme ResNet in 2002 to simplify the submission of data and the feedback of results. Initially, paper forms, and later Excel files, were used but through ResNet the laboratories can submit the results of their resistance testing in a web form (http://resnet.folkhalsomyndigheten.se/ResNet/).

The data is based on cultures included in the laboratories’ routine activities. Some smaller extended analyses may be required. There is also the need for a resource to coordinate ResNet nationally. The work involves going through reports from the individual laboratories to ensure that the data has been submitted correctly. In addition, some time must also be spent on communicating the results (see below).

**Results**

ResNet is a point prevalence measurement and as such, is only representative of the time period in which the measurements were carried out. Since the measurements are repeated annually, it is however possible to see tendencies over time. The design of ResNet gives the resistance monitoring country-wide geographic coverage thanks to the participation of all the laboratories. The basis for the measurements (normally more than 3,000 items of measurement data per species and antibiotic per year) is larger than in most international studies.

The programme uses a map of Sweden for the geographic representation of resistance frequency.
Figure 3.1 a and b Map generated from ResNet of resistance levels for *E. coli* against a) nitrofurantoin and b) mecillinam for 2012.

Numbers in black represent unchanged resistance frequencies compared to previous year, blue decreased and red increased numbers. Based on data from ResNet, the Public Health Agency of Sweden presents the national average for resistance for a specific bacterial species against selected individual antibiotics. These diagrams are available on the Public Health Agency of Sweden website and in the annual report SWEDRES.

Resistance to nitrofurantoin remains low whilst resistance to mecillinam has increased slightly in recent years (figure 2.9). Both nitrofurantoin and mecillinam are first choice treatments in national treatment recommendations for lower urinary tract infections in women in outpatient care. By continuously following the development of resistance in ResNet it is possible to see the effects of antibiotics that are suggested in the national treatment recommendations for outpatient care. For increased user-friendliness on a local level, each laboratory/County Council may also have their results summarised in a table.

Conclusions and lessons learned
Since the laboratories contribute measurement data to ResNet every year, they are now able to continuously ensure the quality of their measurement methods. From this perspective, it has been particularly useful for them to generate their own measurement data. (An alternative would have been to send cultures to a national organisation that would generate measurement data for all laboratories.)
ResNet has given laboratories, decision-makers, authorities, Strama groups and other concerned organisations access to resistance data for clinically important bacteria and enabled them to see tendencies over time. The total amount of data from all cultures is large enough to draw conclusions about changes over time on a national level. Data on a local level must, however, be interpreted with caution since the basis may be too small for drawing reliable conclusions about change.

One of the limitations of ResNet is that the software receives and presents aggregated data per laboratory, bacterial species and antibiotic. This means that it is not possible to see the prevalence of multi-resistant strains in the material, information that is sometimes desirable when developing or following up on local treatment guidelines. So far, such information has had to be retrieved directly from the computer system of the local laboratory, but it will now also be made available in Svebar (section 3.4).

In addition to the collection of resistance data, a central and important aspect of ResNet is that it enables quality-assurance of data. Good national cooperation between the local laboratories, the national/Nordic method group and the Public Health Agency of Sweden has made this possible. Another precondition for the design of ResNet is that cultures are taken from patients quite frequently in Sweden, making it possible for laboratories to carry out resistance testing and provide the healthcare sector with information.

Anyone who wishes to develop a similar programme should begin by establishing good cooperation within a laboratory network. A resource is also required on a national level to coordinate the cooperation and to collate the data and provide feedback.

3.2 EARS-Net – European resistance monitoring of invasive infections

EARS-Net (the European Antimicrobial Resistance Surveillance Network) is a European network of national monitoring systems, which is led by the European Centre for Disease Prevention and Control, ECDC. EARS-Net plays an important role in documenting the prevalence and development of antibiotic resistance in Europe.

The monitoring includes seven bacterial species from invasive infections: *S. aureus*, *S. pneumoniae*, *E. faecalis*, *E. faecium*, *E. coli*, *K pneumoniae* and *P. aeruginosa* as well as Acinetobacter species which have been included since 2012.

**Implementation**

EARS-Net is the largest publicly funded monitoring system for antibiotic resistance in the European region. EARS-Net has achieved a status and a commitment from the participating countries which has enabled the monitoring to continue for almost 15 years.

The current EARS-Net originated from a European collaboration led by the Dutch National Institute for Public Health and the Environment, RIVM, which was insti-
gated in 1998. From the start it was agreed that each country’s results from the resistance testing of invasive infections (mainly from blood) should represent at least 20 percent of the country’s population.

Initially there was a focus on *S. aureus* which would reflect hospital-related infections and *S. pneumoniae* which would represent society-related infections. Later on, the programme was broadened to include more pathogens and more countries joined. ECDC took over the coordinated efforts in 2010 and the programme changed its name from EARSS to EARS-Net. The work is supported by a steering group in which experts from a number of participating countries rotate.

There are currently 27 EU countries as well as Norway and Iceland participating in EARS-Net. More than 900 laboratories serving over 1,400 hospitals provide EARS-Net with data. The participating hospitals and laboratories provide services for an estimated population of 100 million European citizens.

Each country is responsible for gathering and collating their data and reporting it to a central database at ECDC once a year. The data that is reported is the total number of blood cultures for the seven bacteria included and the prevalence of resistance to two or more antibiotics, which are defined by species. Details regarding the laboratory taking the sample, sample date, age of the patient and which hospital and unit the sample comes from are also included.

In Sweden, the reporting is coordinated by the Public Health Agency of Sweden. The Swedish laboratories were very interested in joining EARS-Net right from the start. Three quarters of the laboratories in the country currently participate, which corresponds to a level of coverage of about 80 percent of the Swedish population. Extensive work is required to validate data and to supplement and format the reports. The WHO’s Whonet software is a valuable tool and is available free of charge. Depending on the IT system of the local laboratory, their need for manual work will vary. Some can automatically generate a file including all isolates for a particular year, whilst others continuously enter their data in a report file (often in a format that is compatible with Excel).

**Results**

ECDC collates the data and publishes an annual report with an analysis of developments in Europe. Statistics by country are illustrated with maps, diagrams or tables and are available in a database on the ECDC website. Statistics have often been made available for the European Antibiotic Awareness Day on 18 November and have thus helped the participating countries to raise awareness in the media or in activities organised on the day. Sweden and the other Scandinavian countries have comparatively good resistance conditions. Sweden is one of the few countries where less than 1 percent of all *S. aureus* are cases of MRSA. However, Sweden also has a notable prevalence of *Enterobacteriaceae* with ESBL or other resistance in gram-negative bacteria. A few cases of invasive infections with carbapenem resistant *Enterobacte-
riaceae have been discovered so far in Sweden. The Public Health Agency of Sweden is responsible for ensuring that data from Sweden is reported to EARS-Net and it also publishes the Swedish results in the annual report SWEDRES.

**Figure 3.2** Total yearly numbers of bloodstream infections by seven pathogens reported to EARS-Net from Sweden (20 laboratories, covering approximately 80 percent of the population). Source SWEDRES 2012.

The numbers of isolates of *E. coli* and *S. aureus* in bloodstream infections were much greater than the other pathogens, and they also showed increasing trends over the years, whereas the numbers of the other five pathogens were stable. Still, the percentages of resistant strains in bloodstream infections were relatively low (SWEDRES 2012).

An increase in the number of carbapenem-resistant *Enterobacteriaceae* has been noted in a growing number of European countries over the past years. In the light of this serious threat, ECDC and CDC in the USA have published risk assessments and recommendations to control and prevent the development (36, 37).

On the other hand, the proportion of MRSA bacteraemia has decreased or stabilised in most EU countries (38). Targeted interventions in several European countries may have had an effect on this development. In England for example, several radical reforms were introduced, which in 2011 had led to an 84 percent reduction in cases of MRSA bacteraemia compared to 2002 (39). However, many EU countries still have a high incidence of MRSA which shows that it remains a serious problem.

**Conclusions and lessons learned**

Although data from EARS-Net only includes resistance in invasive infections, and thus is likely to reveal only the tip of the iceberg, it still provides information that shows tendencies over time. Comparisons of resistance in EU countries must be interpreted with caution since varying sampling procedures may affect the results. Some countries take blood cultures more frequently from patients whilst others only focus on complicated cases, which may give a distorted image of the resistance situation.
For quality assurance purposes, all countries participate in external quality mailing lists organised by UK-NEQAS, an organisation that provides service for external quality control. The introduction of the EUCAST system and its breakpoints in a growing number of countries in Europe (and outside Europe) makes the comparison of data between countries more reliable.

There is significant interest in participation in EARS-Net and, thanks to the participating countries, monitoring has continued successfully for almost 15 years. In compilations produced by the RIVM in the Netherlands and the ECDC, all countries have been able to see their own data in relation to other countries. Every year the participating countries meet to exchange experiences and discuss possible expansions of the programme.

In Sweden, statistics from EARS-Net have proven a valuable tool, used both nationally and by local Strama groups, to demonstrate the increasing importance of the rational use of antibiotics and disease prevention as resistance is becoming more prevalent.

### 3.3 SmiNet – continuous monitoring of resistance in accordance with the Communicable Diseases Act

SmiNet is a system for national and local monitoring of diseases in accordance with the Communicable Diseases Act. The system was developed by the Swedish Institute for Communicable Disease Control, now the Public Health Agency of Sweden, and the County Medical Officers for communicable diseases.

Some forms of antibiotic resistance are notifiable in accordance with the CDA. This applies to *Enterobacteriaceae* (intestinal bacteria) with the ESBL resistance mechanism, methicillin-resistant *S. aureus* (MRSA), penicillin-resistant pneumococci (PNSP) and vancomycin-resistant *E. faecalis* and *E. faecium* (VRE). SmiNet reports cases both in real time and continuously, where appropriate. Reporting is done both by the clinically treating physician and by the laboratory. For ESBLA/M only laboratory reporting is required.

#### Implementation

The Swedish Communicable Diseases Act aims to prevent and stop the transmission of disease. Approximately 60 diseases are notifiable according to the CDA. This means that physicians are obliged to notify each diagnosed case of such a disease to the County Medical Officer for communicable diseases and to the Public Health Agency of Sweden. The County Medical Officers for communicable diseases constitute an independent authority, coordinating disease prevention and control in their respective County Council and providing information on how different cases should be handled.

Some of the notifiable diseases are deemed to be particularly serious and also oblige the physician to trace the transmission. The treating physician shall also inform the patient/carrier of particular rules of conduct in order to avoid further transmission of the disease. The laboratories are also obliged to report the discovery of a notifiable
The double notification by physicians and laboratories greatly increases the sensitivity of the monitoring.

SmiNet is a web-based programme that receives and manages notifications in line with the CDA from treating physicians and from laboratory physicians. Over the course of a year, SmiNet receives about 75,000–80,000 notifications for the roughly 60 diseases that fall under the CDA. The system is designed to collect the information needed to continuously monitor the prevalence of the diseases locally and nationally, in order to prevent and stop disease transmission, in accordance with the CDA.

Since 1969, Sweden has had a notification system which at first only involved notifications on paper. Today, notifications are made electronically by treating physicians and by laboratories (it is still possible to send a paper form). Some laboratories also have automatic transfers from their IT systems to SmiNet.

The local communicable diseases units can see and supplement information on cases in SmiNet in their own County Councils. Authorised persons within the Public Health Agency of Sweden can access the information logged in the shared databases from all the County Councils, and thereby gain a national overview.

Information can be supplemented gradually

All people who have registered residence in Sweden are given a civic registration number as a form of identification. This makes it possible to link up different notifications regarding the same case in SmiNet. Each notification must include a diagnosis, some details about the patient and the treating physician. The laboratories have case criteria that define necessary components for the case to be classified as a discovery of ESBL or MRSA. Notifications from laboratories must include the species, data regarding the patient and the laboratory physician in charge.

To facilitate speedy reporting, the number of mandatory fields to be filled in by a laboratory or physician must be kept to a minimum. To obtain the details necessary for subsequent measures, additional information may be added gradually; this includes the likely source of transmission, the channel of transmission and details regarding resistance. Most of the fields in SmiNet are drop-down menus with multiple choice options in order to facilitate searches and statistical summaries.

Most of the notifiable forms of resistance are notified by both the physician and the laboratory. *Enterobacteriaceae* with ESBL$_A$ and ESBL$_M$ are the exception, as they are only notifiable for the laboratory, which in these cases makes the epidemiological information limited. All notifiable forms of antibiotic resistance involve the obligation to trace the transmission, except for ESBL$_A$ and ESBL$_M$. In SmiNet, the notifications from laboratories and clinical units are linked up, thus gathering all information on a particular case in one place. This also applies if there are many notifications from clinical units or laboratories concerning the same case. As such, epidemiological summaries of antibiotic resistance may avoid double notifications and can be based on unique cases alone.
To gain an overview of the epidemiological situation and understand the transmission of disease, epidemiological typing of isolates in the notifiable bacteria is conducted, either at the Public Health Agency of Sweden or in the laboratories. For some species, only point prevalence measurements are conducted and for others, epidemiological typing of all isolates is carried out. This information is also submitted in SmiNet and is added to the case in question.

The communicable diseases units act locally and the Public Health Agency of Sweden acts nationally

The local units for communicable disease control work on all cases within the County Council according to the CDA, to prevent further transmission of disease. They support the treating physician in tracing disease transmission. They also supplement the notifications in SmiNet as more information on each case becomes available and monitor the local development. They monitor the local development and assure local actions are taken, by for example healthcare givers.

The Public Health Agency of Sweden carries out national monitoring and communicate the information on its website and in annual reports. An important task is to identify possible sources of transmission across County Council borders, carry out an epidemiological typing, and provide information and support to the communicable disease units. The freely available CASE software, which was developed by the agency, is used to make statistical analyses. CASE uses different algorithms to calculate whether the number of notifications deviates from the expected level, over time and by area. Deviations are automatically reported to the administrator in charge at the agency.

Before issuing annual reports, units for communicable disease control go through the notified cases and add missing information. The units also contribute information regarding ongoing disease transmissions or experiences from their handling of outbreaks in the electronic newsletter produced by the Public Health Agency of Sweden which has country-wide coverage. There are also networks concerning specific agents through which people from all County Councils and from the agency meet and exchange information and experiences.

Results

A country-wide spread of VRE is a clear example of a quickly arising problem. In 2008, 618 cases were reported, which is nearly 12 times as many as the previous year. An epidemiological typing showed that the main strain being spread in several counties was *E. faecium* with the resistant gene *vanB*. Screening and comprehensive local disease prevention measures and controls in the affected counties led to a decrease in the spread in 2009-2010. Since then, the Public Health Agency of Sweden has developed a knowledge base about VRE with suggested measures to prevent transmission. Monitoring of MRSA has clearly shown how paths of transmission can change. As in many other parts of the world, MRSA in Sweden is no longer mainly transmitted
in healthcare settings but out in society at large. In 2012, 2,097 cases of MRSA were reported. Of all the cases contracted in Sweden, 68 percent were community-acquired and the afflicted were younger than those acquiring MRSA in healthcare. Changes in epidemiology present new challenges in preventing community-acquired MRSA and preventing further transmission to hospitals and other healthcare environments.

The most serious threat is posed by the significant increase in Enterobacteriaceae with ESBL in Sweden and other countries. ESBL leads to increased mortality, prolonged care periods and increased costs for the hospitals. Swedish healthcare has seen several ESBL outbreaks, such as those in neonatal units, where they have caused deaths. Enterobacteriaceae with ESBL is the most common notifiable resistant bacteria in Sweden. In 2012, 7,225 new cases were reported. The number of cases has increased by 14–33 percent every year since they became notifiable for the laboratories in 2007. ESBL\textsubscript{CARBA} cases are, so far, rare in Sweden and the majority of discovered cases have been among patients who have previously received healthcare abroad. In the light of the rapid spread in many countries, an obligation to notify and trace the transmission was introduced for treating physicians regarding Enterobacteriaceae with ESBL\textsubscript{CARBA} (carbapenemase-producing Enterobacteriaceae – CPE) in March 2012. The measure helps to identify cases of Enterobacteriaceae with ESBL\textsubscript{CARBA}, to limit disease transmission in Swedish healthcare, and to follow developments in order to implement adequate countermeasures.

Conclusions and lessons learned

SmiNet has enabled communicable disease units and the Public Health Agency of Sweden to continuously monitor notifiable forms of antibiotic resistance. The extensive data facilitates good monitoring of these bacteria both nationally and locally. SmiNet makes it possible to discover and map outbreaks and transmissions and to study the epidemiology for different patient groups. Data from SmiNet is also important for the work on the rational use of antibiotics (see the example in section 3.5). However, SmiNet only includes positive culture findings and no denominator data. It is therefore not possible to find out through SmiNet whether a change in resistance conditions is due to changes in sampling procedures since the system does not show if the overall number of cultures has increased or decreased.

An organisation is needed to work actively with the system both in terms of technology and content. The Public Health Agency of Sweden has a project group comprised of County Council representatives that continuously develops SmiNet. They work on adapting the notification forms for the clinical notifications and making the optional questions more specific for each agent in order to shorten forms. An important issue to resolve when developing a similar system is to define what type of information is needed in order to make the monitoring relevant and sufficient to take measures. This should be weighed against the work involved for the person who files the report and supplements it with further information.
3.4 Svebar – an IT system for early alerts and continuous resistance monitoring

An increase in the development of resistance and outbreaks of resistant bacteria in Swedish healthcare has shown that the current systems are too limited and slow and require manual management. Svebar is an IT system that the Public Health Agency of Sweden is developing with representatives of microbiological laboratories in order to improve local and national resistance monitoring. The aim is that all culture findings from the country’s laboratories will be automatically transferred to Svebar on a daily basis. Svebar gives an early alert about findings of very serious antibiotics resistance or other undesired changes in resistance conditions. The large amount of data also allows for a continuous and more extensive resistance monitoring locally and nationally.

Svebar should satisfy the increased need for local statistics with aggregated resistance data. Many laboratories currently have difficulties compiling such statistics without manual resource-intensive work, since IT systems are mainly designed to handle individual patient samples. Svebar is designed so that statistic reports can be easily generated for national and local use.

The laboratories’ participation in Svebar is voluntary. The aim is for all of the laboratories to be connected by 2015.

Implementation

The Public Health Agency of Sweden is responsible for running Svebar. There is an initial cost to the laboratories, in the form of time and money to develop the file that is to be introduced into the system. After that, reporting is automatic.

Every night each connected laboratories automatically send a file with the culture findings from the past 14 days to the system, and the file is saved in a short-term storage. The pre-set alerting algorithms search through the storage and issue an alert when there is a hit. An alert is generated when there is a finding of a bacterial species that is resistant to one or more antibiotics, for example for findings of *E. coli* resistant to carbapenems. There will also be an alert if the system discovers a trend, for example if more than 30 percent of *E. coli* in a laboratory is resistant to ampicillin.

National alerts are sent by e-mail to the contact person at the local laboratory and to administrators at the Public Health Agency of Sweden and if needed they can discuss the alert. Local alerts only reach the contact person in the local laboratory.

Since Svebar receives data continuously, the system can react to findings that may come to change since they have not yet been fully analysed by the laboratory. For this reason, Svebar has been divided into a short-term storage that can react quickly and a long-term storage that receives more processed data. Every night, the short-term storage receives data from the past 14 days, which means that there is one day’s shift compared to the previous day and an overlap of 13 days. The long-term storage saves the oldest day from the previous night’s report. This means that culture findings are
kept in short-term storage for 13 days before being transferred to long-term storage. This creates a good margin for the culture finding to be fully analysed in the laboratories before it is stored permanently in Svebar.

Data reported by the laboratories to the short-term storage includes:

• Sampling year
• Sex and age of the patient (year and month of birth)
• Laboratory number (the ID number of the referral)
• Type of test (Test material)
• Analysis (i.e. urine culture, blood culture, etc)
• Sample-taking laboratory
• Microorganism (or the reporting of a negative finding in a culture)
• Resistance pattern (SIR and MIC)

Details about the laboratory number enable the laboratories to go back and follow up on a patient sample that has generated an alert in Svebar. According to Swedish rules on storing data, those details are erased before the results are stored in the long-term storage since it would otherwise be possible, nationally, by linking local registers, to connect a finding to a specific person. In other words, data in long-term storage is anonymous.

There are definitions for how data is reported to Svebar. When a laboratory is connecting to Svebar, there is a need for a mutual standardisation of the nomenclature and file format that will be sent to the system every night.

**Results**

Svebar facilitates early discovery and a short response time to outbreaks through its alert function. This may help put a quick stop to the transmission of disease, which in turn saves money for the healthcare system and reduces the number of patients afflicted. The system requires the Public Health Agency of Sweden or the local laboratory to define in advance what findings should generate an alert. By continuously following the development of resistance it is possible to discover changes at an early stage, changes which may motivate altering the settings of the alert system.

The large amount of data from all the culture findings provides a good statistical basis for national and local resistance monitoring. The fact that reporting is done automatically saves time and resources and the system is designed to produce statistical reports quickly. As such, Svebar will improve access to local aggregated resistance data required for the development of treatment recommendations and to facilitate local work on the rational use of antibiotics. The possibility to follow development of multi-resistance in Svebar is also essential for the designing and revision of treatment recommendations.
All laboratories have access to their local data and to aggregated national data. The Public Health Agency of Sweden is responsible for regularly feeding back national and local resistance data in reports to the laboratories. Together with the laboratories, it makes suggestions on particularly important matters to follow and compile in the standard reports. In addition to this, Svebar makes it possible to individually analyse aetiology and the prevalence of resistance for a certain patient group, locally or nationally. An example of a question that the system can answer is: How many cases of bacteraemia were discovered during a year in children, which bacterial species were the most common and what proportion of these bacteria were resistant to one or more antibiotics?

Svebar contains denominator data, i.e. the number of both negative and positive cultures. It can also show if differences in the prevalence of resistance, during a period or between laboratories, can be attributed to a difference in the sampling frequency. In other words, it forms a better basis for clarifying whether there is an actual increase or decrease.

One of Svebar’s current limitations is that resistance reported to the long-term storage reflects the whole catchment area of the laboratory, which includes different types of care activities for which resistance conditions may vary. For legal reasons of personal integrity there is currently no opportunity to go more in-depth and analyse the prevalence of resistance in health centres, in individual hospitals or surgical and haematological units, which is important for the development of more targeted treatment recommendations and in order to direct the empirical treatment. It is likely that the risk of contracting a urinary tract infection caused by resistant bacteria differs between an otherwise healthy woman visiting a health centre and a woman suffering from cancer in a haematological unit who has previously undergone several antibiotic therapies. Svebar has, however, been developed to receive resistance data on a health centre, hospital or unit level (referred to as HSA ID or originator information). In the long term, it should therefore be possible to extract such information provided that the storing procedure conforms to Swedish rules on data storage. Another condition is that laboratory reporting of originator information becomes standardised and follows the same format. A national project is currently in place to promote such standardisation.

Conclusions and lessons learned

By means of Svebar, Sweden has improved its capacity to stem the development of resistance and to prevent disease transmission, capacities that benefit the entire population.

It was important to invite all of the laboratories early on in the process in order to inform them about Svebar and to reach a joint agreement on how data from Svebar would be used. The system relies on the voluntary participation of the laboratories. To avoid using data on a national level without the consent of the local laboratories that have submitted the data, there is a mutual agreement on use between the Public Health Agency of Sweden and the laboratories.
Anyone aiming to develop a similar monitoring system should keep in mind the value of reaching a common agreement on standardised nomenclature for test material, names for analyses and antibiotics, and the reporting format. If the laboratories lack IT systems, it is beneficial to introduce the same system in all the laboratories participating in the monitoring programme.

3.5 Examples of how resistance data is used as a tool to change prescription in hospitals

Over the course of a few years, the number of ESBL findings rapidly increased in Sweden and several outbreaks were reported. In February 2007, compulsory reporting of ESBL was introduced in accordance with the Communicable Diseases Act, in order to gain a good national overview. This worrying development was noted across the country and efforts were made to handle the problem.

In Skåne, the southernmost county of Sweden, the local Strama group (Strama Skåne) summoned all hospital physicians to meetings in 2007. By using local resistance data from urine and blood cultures together with national and European data from SmiNet and EARS-Net, the group was able to clearly illustrate the threat and suggest necessary measures. Below follows a description of this initiative, based on an interview with Eva Melander, the chief physician for disease prevention and control, and chairman of Strama in Skåne.

Implementation

Strama Skåne initially met with all of the chief physicians for the hospitals in Skåne and received their support, which made it easier to subsequently reach the clinical directors and the physicians in the hospitals. The chief physicians ordered all physicians to attend one of the meetings held by Strama Skåne at each hospital.

Resistance statistics were presented at the meetings, demonstrating the increasing prevalence of ESBL in Skåne and Sweden. Maps showed that the development had accelerated further in other parts of Europe. Strama informed the physicians about the few existing treatment options in case of serious infection with ESBL-producing bacteria. Besides breaking down beta-lactam antibiotics, they often carry resistance to other groups of antibiotics such as quinolones and aminoglycosides. The fact that ESBL threatened to lead to increased mortality and morbidity made many agree that vigorous efforts were required to counteract this development.

Strama Skåne had also compiled data on the prescription of antibiotics in hospitals which showed a high and unbalanced use of cephalosporins and quinolones. It indicated that these substances were strongly associated with the development of ESBL. A proposal was then presented to change the empirical treatment by reducing the use of cephalosporins and quinolones and increasing the use of penicillin.
Some of the main messages from Strama Skåne to the physicians were:

- Reduce the general use of cephalosporins and quinolones
- Do not use quinolones for lower urinary tract infections in women
- Use benzylpenicillin for respiratory tract infections
- Contact an infection consultant when a patient with ESBL requires antibiotic treatment

Resistance data was also used to emphasise the importance of applying basic procedures for infection control (chapter 1) to prevent disease transmission. Strama Skåne also informed the physicians about routines for screening and care of patients with ESBL. Initially the bar was set high and it was recommended that all patients with ESBL were to be cared for in single rooms. Since ESBL has unfortunately become increasingly common, this requirement has gradually had to be dropped in the local guidelines for disease prevention. Meanwhile, compliance with procedures for infection control has become all the more important.

Eight staff from Strama Skåne spread these messages in the 10 hospitals in Skåne during 2007. In each hospital a number of meetings were arranged, ensuring that all physicians would have the opportunity to attend. At the meeting, Strama Skåne distributed a reference manual on the empirical antibiotic treatment of patients with community-acquired infections. The recommendations were developed by representatives of infectious disease clinics in the hospitals involved in the Strama work. Many physicians also received e-mails with the same information and a link to the local recommendations.

**Results**

Strama Skåne felt that the meetings elicited great support from the physicians. The serious threat and the rapid development of resistance made it easier for many to take the messages on board. The prescription of antibiotics changed drastically. The use of parenteral cephalosporins measured in DDD fell by 45 percent and the use of PceG rose by a corresponding 45 percent in hospitals in Skåne between 2006 and 2008. The use of piperacillin/tazobactam rose by nearly 50 percent whereas the use of carbapenems remained relatively unchanged. The use of quinolones fell by 25 percent.

The efforts in Skåne coincided with a national effort to call attention to ESBL. Compulsory reporting of ESBL was introduced in accordance with the CDA, which helped to emphasise its importance. National Strama drew up a report suggesting measures (40, 41). National data on use also showed a shift from cephalosporins and quinolones to penicillins.

Strama Skåne has also since continuously organised meetings in hospitals and emphasised rational use of antibiotics. The shift in prescription routines remained constant in Skåne in the following years. However, in the past year, the use of cephalosporins and quinolones has increased somewhat in certain hospitals.
Conclusions and lessons learned

The commitment from the chief physicians was crucial to the work of Strama Skåne. Their support encouraged a greater attendance at the meetings. The serious threat that could be demonstrated with resistance data made many people realise that the revised therapy recommendations were reasonable and important. Some were critical, however, and thought that they would result in an increased number of complications, and in the worst case scenario, deaths. Some perceived the message as an indication that they should stop all use of cephalosporins, which was not the case. The aim was rather to reduce unbalanced use. For this reason, it was vital to emphasise that the recommendations were primarily aimed at the treatment of large patient groups with community-acquired infections, patients who had no underlying diseases. The revised recommendations were thus not aimed at immuno-suppressed cancer patients or seriously ill patients in intensive care units.

As a result of the information campaigns in the hospitals in Skåne, prescription patterns changed dramatically. This may have led to a reduced prevalence of ESBL in hospitals, since the use of cephalosporins and quinolones was reduced. However, it is not possible to prove the extent of such a relationship. As with other preventive measures, it is difficult to know what the situation would be like if prescription had not changed.

The transmission of ESBL in the community and around the world is probably not influenced significantly by the local use of antibiotics in the hospitals. The fact that ESBL is increasing rapidly has posed a certain educational challenge for Strama Skåne, which has to continuously carry the argument that it is important to reduce unnecessary prescription of broad-spectrum antibiotics, since otherwise there is a risk that the situation will worsen.
Interview with Professor Gunnar Kahlmeter

Gunnar Kahlmeter is a Professor of medical microbiology and operations manager of Kronoberg county council. He is president of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and former chairman of the Methodology subgroup of the Swedish Reference Group for Antibiotics (SRGA-M) and of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

“There are no short cuts to success. The reason for Sweden’s relatively low prevalence of resistant bacteria can be found in the structure of our society, our economic wealth and our history”, says Gunnar Kahlmeter, an international authority in the field of antibiotic resistance, including methodology, standardisation and surveillance.

Gunnar Kahlmeter has been part of the ‘antimicrobial scene’ since the 1980s. As former chairman of SRGA-M and EUCAST, Kahlmeter has been a leading advocate of harmonising laboratory methods and antimicrobial susceptibility testing in Sweden and internationally. “We must know our starting point if we are to get anywhere”, he says referring to the need for standardised definitions of susceptibility and resistance.

He has been instrumental in building a completely new system of harmonised breakpoints in Europe, a system countries outside Europe are now adopting. In Sweden, Kahlmeter has been the driving force behind the development of several national surveillance systems, one of which is Svebar, the Swedish system for early warning and surveillance of antimicrobial resistance.

Kahlmeter is rather pessimistic when it comes to the future of antibiotics and efforts to overcome resistance on a national and international level, hence the title of his popular lecture ‘Multi-resistant bacteria – up the creek without a paddle’. He compares the issue of resistant bacteria to the global climate crisis, alluding to the magnitude of the problem and the fundamental changes required to overcome it, not least in terms of political will.

Even so, Kahlmeter believes that lessons learned in Sweden may be useful in a broader context. Countries facing the major public health threat imposed by multi-resistant bacteria can and must work on many levels to reduce this threat. In the long run this involves improving general nutrition and health, health care systems as well as child care and care of the elderly. It also involves investments in public infrastructure, general hygiene, water supplies, management of latrines, sewage and waste and not least education. Kahlmeter concedes that the task may indeed seem overwhelming.

”A good starting point is to set up a national infrastructure consisting of a network of high standard laboratories, using standardised methods and harmonised breakpoints to detect and define resistant bacteria. It is crucial that these national, public health laboratories agree on methods and standards.”
Simultaneously, great efforts must be made to improve general health care and to actively reduce the transmission of bacteria within health care facilities. “This task is far more expensive and time-consuming and even well-to-do Sweden has a long way to go here, not least to improve disease control in homes for the elderly and day care facilities for children”, says Kahlmeter.

From this follows efforts to develop protocols and systems for rational use of antibiotics, such as the work done by Swedish Strama since the mid-1990s.

The war on resistant bacteria is far from won, even in a country like Sweden. Like all experts in the field, Kahlmeter points to the need for international solutions to a problem that knows no borders. As an example, he emphasises the need to develop improved diagnostic procedures. This requires costly investments but will in turn allow doctors to eliminate the unnecessary use of broad spectrum antibiotics in favour of targeted therapy.

Gunnar Kahlmeter describes Sweden as a well-organised, uniform society with comparatively small gaps in income and education. “During the past century we have been able to afford the necessary investments in infrastructure, health services and high quality laboratories with standardised methods. These general developments, not isolated efforts in themselves, can explain why Sweden, as perhaps the only country in the world, has been able to break the trend of increasing antibiotic consumption”.

And yet, it is too early to say what this break actually means and what impact it will have in the long run. “Reduced consumption in Sweden has mainly a symbolic value in a global context. But this should not be underestimated”, Kahlmeter concludes.