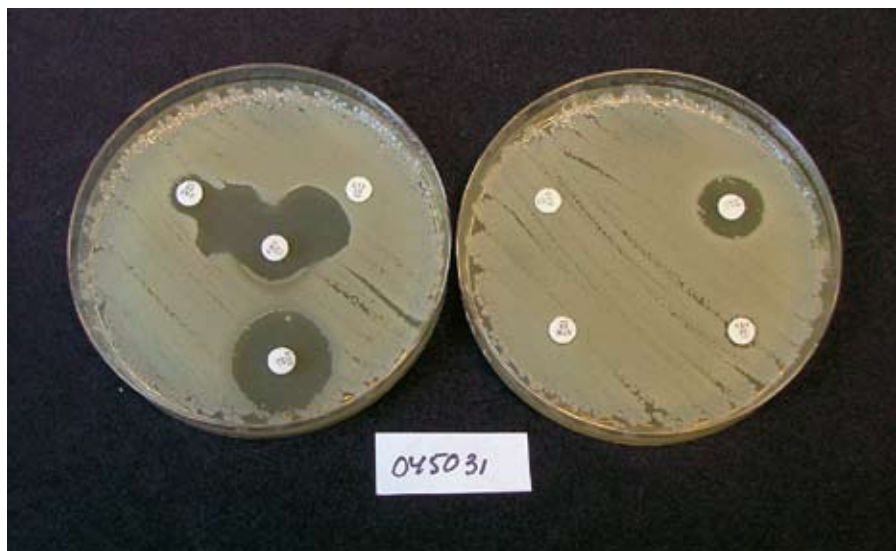


ESBL resistance in enteric bacteria

PROPOSED ACTION PLAN – NOVEMBER 2007



The logo for Strama, featuring a grey curved line above the word 'Strama' in a bold, red, sans-serif font.

Swedish strategic programme
against antibiotic resistance

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Cover photograph: Culture plates with ESBL-producing bacterial strains. The plate on the left shows the synergy between clavulanic acid and cefotaxime/ceftazidime, one of the ways of confirming ESBL-production. The plate on the right shows high-grade resistance to a variety of beta-lactam antibiotics. The photograph was taken at the Department of Clinical Microbiology of Malmö University Hospital by Maria Hylén-Ohlsson.

Strama's remit

Strama's (The Swedish Strategic Programme Against Antibiotic Resistance) remit is to promote multidisciplinary collaboration in the fight against antibiotic resistance. According to its directive, Strama is to initiate measures that primarily affect human health, based on information that includes surveillance reports, and is to work to establish action plans at regional and local level. Strama is of the opinion that the increasing international and national spread of ESBL-producing bacteria requires the creation of national strategy and has therefore taken the initiative in formulating a proposed action plan in order to combat this development. The proposal is evidence-based and draws upon the experience of experts selected by public bodies and other stakeholders (see page 18). The evidence base is available in a separate background document that can be read on <http://en.strama.se/dyn/,84,,.html>.



Summary

Enteric bacteria such as *Escherichia coli*, *Klebsiella pneumoniae* and related species are some of the most important pathogenic bacteria. It is increasingly being reported that they are acquiring a transmissible form of antibiotic resistance – Extended Spectrum Beta-Lactamases or ESBL. This resistance means that some groups of antibiotics (penicillins and cephalosporins), which have been used for many years in the treatment of common infections, including urinary, postoperative and bloodstream infections, are no longer effective. Bacteria with this resistance used to be rare in Sweden, but they are now rapidly increasing. Bacteria with ESBL are often resistant to other antibiotics as well, and this multiresistance makes them particularly difficult to treat. The consequences of this spread of ESBL-producing bacteria are well documented and include increased mortality, prolonged hospital stays, and higher hospital costs.

In Sweden, ESBL-producing bacteria can be found in the community as well as in hospital. Sweden has reported to EARSS, the European surveillance system (<http://www.rivm.nl/earss/>), that in 2006, 1.1 % of all *E. coli* and 0.8 % of all *K. pneumoniae* in blood cultures were ESBL-producing. The number of ESBL isolates has increased rapidly in Sweden within just a few years, and several outbreaks have been reported. Compulsory notification under the Communicable Diseases Act was introduced in February 2007. During the succeeding six months, more than 1 000 cases were reported and every county and region was represented. This means that the number of reported cases of ESBL in Sweden is double that of MRSA (methicillin-resistant *Staphylococcus aureus*).

The increasing prevalence of ESBL in the health care system is probably caused by high and/or inappropriate use of antibiotics in combination with the spread of bacteria between patients, and of resistance genes between bacteria. The spread between patients occurs through direct transfer resulting from poor compliance with basic hygiene procedures. Uncritical use of antibiotics selects out the resistant bacteria which proliferate and become more likely to spread

further. Outside the healthcare system, the import of foodstuffs and foreign travel probably contribute, to a hitherto indeterminate extent.

The healthcare system faces some difficult issues in relation to the consequences of the increasing prevalence of ESBL-producing bacteria: Are we on the brink of losing control over the development of antibiotic resistance? How do we need to change our treatment strategies? How will the organisation of the national health service and other forms of care be affected? Can we defuse this new threat by tightening our infection control procedures and use of antibiotics? How do we regain control over this new situation?

The principal healthcare authority is responsible for ensuring that the system has a management structure that ensures safe and secure care (SOSFS 2005:12).

Unit/departmental heads are responsible for establishing procedures that prevent healthcare-related injury and for subjecting these procedures to a continuous process of quality assurance.

Healthcare personnel shall follow basic infection control procedures and other established measures in order to combat the occurrence and spread of ESBL and other communicable diseases.

The aim of Strama's proposed action plan is to limit the proportion of ESBL-producing *E. coli* and *K. pneumoniae* in blood isolates to a maximum of 1 %, and to ensure that the occurrence of ESBL-producing bacteria does not affect current recommendations for the treatment of lower urinary tract infections. Strama believes that the measures outlined in the proposal should be introduced as soon as possible and should be fully in place by the end of 2008 at the latest.

The action plan covers the following areas:

Laboratory methods

- Diagnostic procedures, screening, epidemiological typing and notification under the Communicable Diseases Act.

Health system structure and organisation

- The need for strategic planning, appropriate premises, supply of single rooms, documentation and tracking of patients to simplify contact tracing.

Recommendations for patient care

- Screening investigations.
- Procedures for the care of patients with confirmed or suspected ESBL-producing bacteria.
- Information sharing and contact tracing.

Guidelines for antibiotic use

- Combat further development of resistance.
- The treatment of patients infected with ESBL-producing bacteria.

The development of bacterial resistance is dynamic, and new resistance mechanisms are continuously appearing. Strama's proposed action plan is based on documented principles for the management of patients with ESBL infections, where early case detection and compliance with care procedures and antibiotic recommendations represent key components. Many of the principles ought to be transferable to other resistance mechanisms, which suggests that this programme, at least in part, can serve as a model for other action plans. The rapid development in the field also means that the programme will need to be updated when new information comes to light. Please see the background document at <http://en.strama.se/dyn/,84,,.html> for more detailed information and for the references.

The definition of ESBL

ESBLs are a group of enzymes that break down antibiotics belonging to the penicillin and cephalosporin groups and render them ineffective. ESBL has traditionally been defined as transmissible beta-lactamases that can be inhibited by clavulanic acid, tazobactam or sulbactam, and which are encoded by genes that can be exchanged between bacteria. The currently most common genetic variant of ESBL is CTX-M.

Since the original definition of ESBL was agreed, several new beta-lactamases with equivalent or greater ability to break down beta-lactam antibiotics have appeared. The most clinically relevant of these are the plasmid mediated AmpC beta-lactamases and the metallo-beta-lactamases. The clinical, bacteriological and healthcare hygiene consequences of possessing these enzymes are thought to be the same, irrespective of the type of enzyme.

Strama proposes that

- RAF and RAF-M act internationally to widen the microbiological definition of ESBL to also include other transmissible cephalosporinases and carbapenemases that are not blocked by classical beta-lactamase inhibitors such as clavulanic acid, tazobactam and sulbactam.

The diagnosis of ESBL

Currently agreed Swedish and European breakpoints detect all clinically relevant ESBL using cefotaxime and ceftazidime, i.e. at least one of these would be categorised as I or R. Previously, all bacterial isolates with demonstrated ESBL have been reported as resistant to all beta-lactam antibiotics apart from carbapenems. The new recommendation from the Swedish Reference Group for Antibiotics' methodology subcommittee (SRGA-M) now offers the possibility of reporting the isolate, following MIC determination, according to the SIR category as defined by the new breakpoints. Genotype characterisation of ESBL is only carried out in Sweden these days by laboratories with a special interest in ESBL. These methods can complement other epidemiological typing methods and may be of value in e.g. the investigation of outbreaks. Simple PCR-based methods that can be carried out by most Swedish laboratories, at least at regional level, are now available. With multiplex-PCR it is possible to classify CTX-M positive isolates into 4 subgroups, while further characterisation requires DNA sequencing or pyrosequencing. The classification of TEM- and SHV-derived ESBL still requires DNA sequencing.

Strama proposes that

Microbiology laboratories

- identify the species of all clinically relevant *Enterobacteriaceae*.
- investigate all *E. coli* and *K. pneumoniae* for the presence of ESBL in accordance with SRGA's recommendations. Laboratories should in addition consider the general investigation of other Enterobacteriaceae for the presence of ESBL, especially multiresistant isolates¹.
- establish standard operating procedures for the rapid communication of information to healthcare hygiene and communicable disease leads when bacteria with ESBL and/or multiresistance¹ have been detected in hospitals or in homes for the elderly.
- establish methods for the genotyping of commonly occurring ESBL-producing bacteria or, alternatively, establish a collaboration with another laboratory with this capability in order to be able to establish or exclude associations in the context of investigating suspected outbreaks.
- report the results of completed genotyping via SmiNet2.

SRGA's subcommittee on methodology

- formulates recommendations for how laboratories should detect other enzymes (e.g. cephalosporinases and carbapenemases) that fall outside the current definition of ESBL.

The Swedish Institute for Infectious Disease Control

- establishes methods for the characterisation of isolates with unusual genotypes, so that the findings can be accepted for more detailed characterisation/confirmation.

¹Multiresistance in *Enterobacteriaceae* is defined as resistance to three or more of the following classes of antibiotics: cephalosporins, carbapenems, quinolones, aminoglycosides and trimethoprim/co-trimoxazole.

Notification under the Communicable Diseases Act

ESBL-producing *Enterobacteriaceae* have been notifiable under the Communicable Diseases Act since 1st February 2007. The Board of Health and Welfare's ordinance places a duty on microbiology laboratories to notify cases of ESBL-producing bacteria, but a clinical notification need not be made.

1 021 cases were notified during the first six months. *E. coli* was the most commonly reported bacterial species, followed by *K. pneumoniae*. The species was not stated in 15 % of notified laboratory reports. 70 % of laboratory reports were urine cultures, and 5 % were invasive isolates. The resistance patterns were incompletely stated in the notifications, so the prevalence of multiresistance in the notified cases cannot be determined.

Strama proposes that

Laboratories report

- bacterial species.
- the bacterium's susceptibility to cefotaxime and ceftazidime, imipenem and meropenem, a quinolone, trimethoprim (or co-trimoxazole) and an aminoglycoside.

The Swedish Institute for Infectious Disease Control

- clarifies the criteria for reporting via SmiNet2.
- adapts the relevant lists for reporting antibiotic resistance via SmiNet2.
- makes it possible to specify genotype of ESBL-producing bacteria via SmiNet2.

Epidemiological typing of bacteria with ESBL

Epidemiological typing of bacteria is mainly done for two reasons: to monitor local spread and control outbreaks, and in order to obtain a national epidemiological picture. At regional/local level, laboratories need to implement a method of typing that enables the typing of all identified ESBL producers and the early detection of epidemiological clustering of bacterial isolates. Smaller laboratories may possibly be able to collaborate when skills or equipment are lacking.

Strama proposes that

- reference methodology for the typing of ESBL-producing bacteria is made available at the Swedish Institute for Infectious Disease Control and at the regional laboratories.
- tests from ongoing outbreak investigations are reported within 14 days of the receipt of the isolate.

The Swedish Institute for Infectious Disease Control

- draws up recommendations for the typing of bacteria with ESBL, drives the development of methodology in the field and establishes the capacity to confirm suspected outbreaks.
- makes available a method for plasmid typing.

Microbiology laboratories

- establish a strategy for the epidemiological typing of ESBL-producing bacteria using one of the methods proposed in the background document. Regional collaboration would be reasonable.
- Send selected bacterial isolates with a suspected epidemiological association to the Swedish Institute for Infectious Disease Control for further characterisation in order to obtain a national overview of the most important ESBL clones.

The consequences of ESBL

Meta-analyses have demonstrated an association between ESBL bacteraemia and increased mortality. Six studies have shown that infection and colonisation with ESBL-producing bacteria is associated with prolonged hospital stay, and three studies have demonstrated increased financial costs. Despite these substantial consequences, reported in international studies, it is not possible, using current Swedish healthcare documentation, to measure the effects of ESBL-producing bacteria on mortality, hospital stays, and increased costs. Contact tracing and identification of patients that may have been exposed and who may need testing must be done manually and with great difficulty, as it is difficult to identify which patients have been cared for at any particular place at a particular time.

Strama proposes that

- accurate ICD-10 additional codes² for antibiotic resistance, U80.0 (ESBL)
- and aetiological agent
 - B96.1 *Klebsiella pneumoniae*
 - B96.2 *Escherichia coli*
- are registered when patients with ESBL-producing bacteria are being cared for (in addition to disease diagnosis codes).
- care providers develop and make available tools for tracing patients (including bed identifiers) throughout the healthcare chain.

²<http://www.who.int/classifications/apps/icd/icd10online/>

Strategies to combat the continuing growth of the ESBL problem

The consistent application of basic infection control procedures (proper hand hygiene and the use of gloves and protective clothing in all hands-on patient care), cleaning of the patient's immediate environment and the placement of patients that are carriers of ESBL-producing bacteria in single rooms have been shown to limit the prevalence and spread of ESBL.

The use of cephalosporins and quinolones are risk factors for the appearance of ESBL in both community and hospital care. Reducing the use of cephalosporins has been shown to reduce the prevalence and spread of ESBL, but the long-term effects of changing antibiotic strategies have only been studied to a limited extent.

The experience gained from ESBL outbreaks in Sweden suggests that overcrowding in hospitals, and multi-bedded rooms with common hygiene facilities increase the risks of contagion. A combination of comprehensive screening and a review of hygiene and antibiotic policies have been put in place in order to combat outbreaks. It is still too early to say whether the measures introduced have had the desired effect, or to predict the long-term outcomes.

Strama proposes that

- healthcare providers draw up a strategic plan to combat the spread of ESBL. The plan should include
 - an executive committee with a clear remit and mandate which can be summoned at short notice when outbreaks occur.
 - healthcare hygiene guidelines, antibiotic strategies and advice on the mobilisation of single rooms in association with an outbreak.

Recommendations for the care of patients with ESBL-producing bacteria

In those counties where guidelines for the care of patients with ESBL-producing bacteria have been drawn up, their contents vary somewhat. Over and above the consistent application of basic hygiene procedures it is generally agreed that the following factors put patients at high risk of spreading ESBL-producing bacteria: abdominal drainage/stoma, tracheostoma, large wounds that need dressing, indwelling urinary catheters/intermittent clean catheterisation, urinary or faecal incontinence and diarrhoea. It is unclear how long the risk of contagion posed by intestinal carrier status persists. In an outbreak, local adaptation of the following recommendations may be needed, e.g. to ensure dissemination of information.

Strama's proposal

Screening of patients on hospital admission

- Patients that have been hospitalised abroad (during the preceding six months) or have had contact with healthcare during an outbreak should undergo screening with cultures. Tests should be taken from the rectum/faeces and, where appropriate, from urinary catheters, wounds and abdominal drains or equivalent.
- Staff need not be screened with cultures.

Standard operating procedures in healthcare

- Patients and visitors should be informed about the importance of good hand hygiene.
- Patients with diarrhoea or urinary/faecal incontinence should be

nursed in single rooms with their own hygiene facilities, have all their food served in their room and should keep out of communal areas of the main ward.

- Patients with other risk factors should be nursed, if at all possible, in single rooms with their own hygiene facilities but may move freely through the ward, provided that any sores/wounds are well-covered. They may eat with other patients but should have all their food and drink served to them.
- Patients without risk factors should be informed about the importance of good hand hygiene.

Dissemination of information

- When patients are transferred within or between healthcare units, the receiving unit should be informed of the patient's carrier status.
- When ESBL-producing bacteria have been demonstrated in a patient, this should be clearly documented in the patient's medical record.

Contact tracing

- When cases cluster, contact tracing should be done under the leadership of infection control specialists. Culture swabs should always be taken from the rectum or faeces in these situations. In appropriate cases cultures should also be taken from catheter urine, wounds and abdominal drains or equivalent.

Antibiotic recommendations

Antibiotic recommendations have two main purposes with regard to ESBL: to combat the selection of ESBL and its associated increase in resistance problems, and to ensure adequate treatment of infections caused by confirmed isolates of ESBL-producing strains. The reduction of cephalosporin use in favour of piperacillin/tazobactam has been shown to be a beneficial antibiotic strategy for reducing the prevalence and spread of ESBL even if the long-term effects of altered antibiotic strategies have only been studied to a limited extent. It is also important to limit the use of carbapenems in order to combat the appearance of other types of resistance.

Evidence for the effect of treating ESBL-producing bacteria with different antibiotic options is incomplete. Please see the background document for examples of suggested empirical treatment whilst awaiting culture results in “normal” and in “outbreak” situations.

Strama's proposal

In order to generally combat the selection of ESBL-producing strains, it is recommended that

- the use of second and third generation cephalosporins is severely reduced. Whenever possible they should be replaced by benzyl-penicillin +/- aminoglycoside, or in serious and/or surgical infections by piperacillin/tazobactam and aminoglycosides.
- quinolones should not be used for the treatment of lower, uncomplicated urinary tract infections in women, either in secondary or primary care.
- quinolones and cephalosporins should not be used for peroperative prophylaxis.

Antibiotic alternatives in the treatment of infections with culture-proven ESBL-producing bacteria:

- Pyelonephritis: piperacillin/tazobactam (at MIC \leq 8 mg/L) can be tried if the patient is clinically stable.
- Pneumonia: piperacillin/tazobactam (at MIC \leq 8 mg/L) or cefepime (at MIC \leq 1 mg/L) can be tried as an alternative to carbapenem.
- Abdominal infection and sepsis: carbapenem.
- Lower urinary tract infection: fosfomycin, pivmecillinam (possibly in combination with co-amoxiclav), nitrofurantoin.

Participating experts

Strama's proposed action plan is evidence-based and draws upon the experience of experts selected by public bodies and other stakeholders:

Rolf Alsterlund, *Department of Infectious Diseases, Kristianstad*

Otto Cars, *Strama*

Hans Fredlund, *Swedish Society for Communicable Disease Prevention and Control*

Christian G Giske, *Swedish Reference Group for Antibiotics (SRGA), SRGA Methodology Subcommittee (SRGA-M)*

Gunnar Kahlmeter, *Swedish Institute for Infectious Disease Control/SRGA/SRGA-M*

Kerstin Mannerquist, *Swedish Institute for Infectious Disease Control*

Eva Melander, *Strama/SRGA-M*

Åsa Melhus, *Uppsala University Hospital/SRGA*

Inga Odenholt, *SRGA*

Barbro Olsson-Liljequist, *Swedish Institute for Infectious Disease Control/SRGA/SRGA-M*

Johan Struwe, *Swedish Institute for Infectious Disease Control/Strama*

Tomas Söderblom, *Swedish Institute for Infectious Disease Control*

Torbjörn Söderström, *Uppsala University Hospital*

Christina Åhrén, *Swedish Association for Infection Control*

Observers from the National Board of Health and Welfare:

Inger Andersson von Rosen

Inger Riesenfelt-Örn

Anders Tegnell

Observer from the National Veterinary Institute:

Christina Greko

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Strama
SE 171 82 Solna
Sweden
Phone +46 8 457 23 67
Fax +46 8 31 36 10
www.strama.se