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An outbreak of a possibly new *Salmonella enterica* subspecies *enterica* serovar with the antigenic formula 11:z41:e,n,z15, Greece, March to May 2016: preliminary results

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Eleven *Salmonella* spp. isolates with the antigenic type 11:z41:e,n,z15 - not referred to in the 9th edition of the White-Kauffman–Le Minor Scheme - were identified at the National Reference Laboratory for *Salmonella* in Greece. Their pulsed-field gel electrophoresis profiles were indistinguishable. No apparent epidemiological link has yet been identified; the results of a case–case study are pending.

Between 24 March and 27 May 2016, eleven *Salmonella* spp. isolates with an unusual antigenic type were identified by the National Reference Laboratory for *Salmonella* and *Shigella* (NRLSS) in Greece.

The antigenic type of the eleven isolates was 11:z_{41}:e,n,z_{15}, which is not referred to in the 9th edition of the White-Kauffman–Le Minor Scheme [1]. The isolates were cultured from stool and collected from ten patients with diarrhoea; for one asymptomatic case, the sample was obtained during a routine test for acquiring a certificate for occupational use. However, the latter case reported having had gastroenteritis symptoms some weeks before. None of the isolates fermented malonate but all fermented dulcitol, indicating that they belong to *Salmonella enterica* subspecies *enterica* [1]. All were susceptible to the laboratory routine panel of antimicrobial agents, including third generation cephalosporins and fluoroquinolones. Tests were performed using the disk diffusion method and breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were applied [2].The pulsed-field gel electrophoresis (PFGE) profiles, after digestion with *XbaI* according to PulseNet protocol [3], were indistinguishable in 10 of the 11 strains (one result of the last isolated strain is pending) (Figure 1).

According to the database of the NRLSS and of the Veterinary Reference Laboratory for Greece, the antigenic type 11:z_{41}:e,n,z_{15} has never been identified before from animals, animal products or food samples.

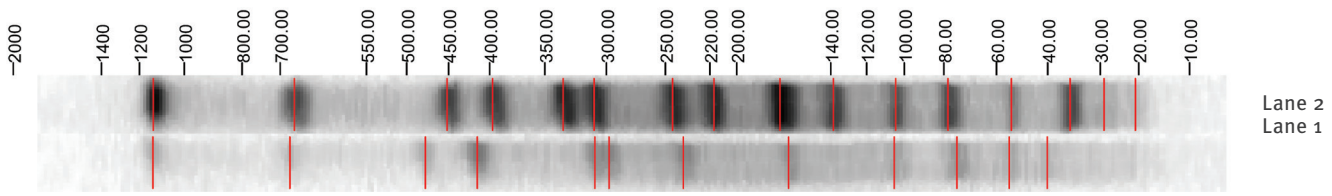
Description of cases and epidemiological curve

All cases, defined as persons with diarrhoea with the new *Salmonella enterica* subsp. *enterica* serovar (n=10), were of Greek nationality (6 male, 4 female). Eight of the cases were children (15 months–3 years old) and two were adults (28–60 years of age). Cases' symptoms included diarrhoea (one case had bloody diarrhoea), vomiting and abdominal cramps, and three of them reported fever (≥38.0°C). Three cases reported relapse of symptoms and all cases will be followed up. Three of the identified cases reported a household contact with similar symptoms (another child in the same family). Investigation of the possible household clusters showed that they were most probably co-infected but none of the household contacts was laboratory-confirmed. In this report, only information for laboratory-confirmed cases is presented.

The majority of the cases (n=9) were scattered in the region of Attica, one case was identified in Kastoria in northern Greece, and another in Korinthos, central Greece. Only one case reported travel abroad to Torino, in Italy, five days before the symptom onset. This

Figure 1

PFGE profile of *Salmonella enterica* subsp. *enterica* isolates with antigenic formula 11:z_{41}:e,n,z_{15}, Greece, April to May 2016 (n=10)



PFGE: pulsed-field gel electrophoresis.

Lane 1: new serovar profile.

Lane 2: Salmonella serotype Braenderup H9812 universal size standard.

PGFE profiles from all cases were indistinguishable.

case stated developing symptoms before returning to Greece. Figure 2 presents the temporal distribution of cases by week of symptom onset.

Actions taken

Communication of findings to other countries

The PFGE profile [4] was uploaded to the European Surveillance System (TESSy) operated by the European Centre for Disease Prevention and Control (ECDC) (ECDC_ID: f5f0517b-f809–4d2b-973f-3f9c520b9d77) and an urgent inquiry (UI) was launched via the ECDC's Epidemic Intelligence Information System (EPIS) (UI-358). According to the ECDC food- and waterborne diseases curators, no isolates with a matching PFGE profile (XbaI.2460) have been reported to TESSy (personal communication, Saara M. Kotila, ECDC, 25 May 2016). Moreover, none of the 15 countries that replied to the UI had identified the new serovar in the past.

Three of the isolates were sent to the World Health Organization (WHO) Collaborating Centre for Reference and Research on *Salmonella* at Pasteur Institute in Paris, France, which is responsible for the validation of new serovars. According to Pasteur Institute, the isolates represent a putative new serotype of *Salmonella enterica* subsp. *enterica* (personal communication, Francois-Xavier Weill, Pasteur Institute, 26 May 2016).

Investigation of cases

Laboratory confirmed cases were interviewed by telephone with a standard trawling questionnaire for investigating salmonellosis cases but no apparent epidemiological link has yet been identified. Cases were geographically scattered, had not travelled inside the country, did not have pets or contact with reptiles, and had not participated in any common activities. Based on the results from the trawling questionnaires, no food item emerged as possible source of the infections.

Thus, it was decided to further investigate this salmonellosis cluster by performing an analytical study. Given the highly selective nature of food-borne case reporting and in order to reduce recall bias, a case–case study for the identification of possible risk factors was designed [5-7]. This study included a comparison group of *Salmonella Enteritidis* cases from the Greek Mandatory Notification System (MNS) matched by age (±1 year), and place of residence. In order to increase the power of the study, the ratio of case–case 1:3 was decided.

A structured web-based trawling questionnaire, containing a long list of possible exposures (food and water consumption, exposures to animals, travel history, activities, etc.) was developed and distributed to all cases (both of unknown *Salmonella* serovar and *SalmonellaEnteritidis*).

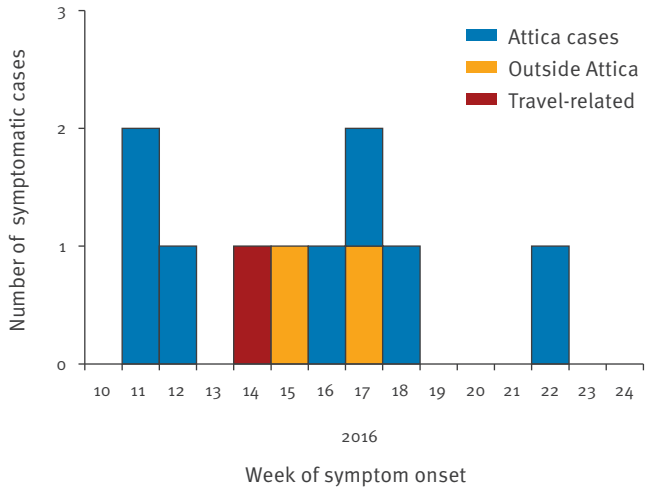
Conclusions

According to some preliminary findings, a new *Salmonella enterica* sub. *enterica* serovar seems to have caused an outbreak in Greece over two months in the first half of 2016, with 10 cases (and one asymptomatic) as of 27 May. Reported cases are mostly children, however this may be influenced by the fact that laboratory tests are performed more frequently in children with gastroenteritis symptoms than in adults with the same symptoms. We cannot be sure about the geographical distribution of cases. The higher number of cases from Attica may be because more isolates are sent to the National Reference Laboratory from this region. Three cases reported relapse of symptoms. Data on the severity of the disease are also gathered and a case–case study is underway. Final results are pending.

We encourage other countries to contact authors in case of identifying isolates of the new serovar of

Figure 2

Distribution of symptomatic *Salmonella enteric* subsp. *enterica* cases of a possibly new serovar with the antigenic formula 11:z_{41}:enz$_{15}$, by week of symptom onset, Greece, April to May 2016 (n=10)



Salmonella enterica susp. *enterica* with the antigenic type 11:z_{41}:e,n,z_{15}.

Acknowledgements

We thank our colleagues from the Veterinary Reference Centre for Salmonella in Chalkis for serotyping some of the isolates for confirmation of the antigenic type. We also thank Saara Kotila at ECDC in Stockholm and Francois-Xavier Weill at Pasteur Institute in Paris, for their support.

Conflict of interest

None declared.

Authors' contributions

Georgia Mandilara: conception and design of the work and laboratory investigation;

Kleon Karadimas: laboratory investigation;

Kassiani Mellou: conception and design of the work and epidemiological investigation;

Leonidas Georgalis: epidemiological investigation;

Michalis Polemis: PFGE profiles analysis and interpretation;

Theano Georgakopoulou: coordination of the project;

Alkiviades Vatopoulos: coordination of the project.

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Active surveillance scheme in three Romanian hospitals reveals a high prevalence and variety of carbapenamase-producing Gram-negative bacteria: a pilot study, December 2014 to May 2015

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We report the findings of an active surveillance scheme for detection of asymptomatic carriers with carbapenemase-producing Gram-negative bacteria (CP-GNB) in Romanian hospitals. During a pilot study from December 2014 to May 2015, faecal cultures were screened in three hospitals (two large, one medium-size) for patients newly admitted to selected wards or inpatients transferred from other wards to an intensive-care unit. The study revealed a high prevalence of CP-GNB detected in 22/27 and 28/38 of the carbapenem non-susceptible isolates from Hospitals 1 and 3, respectively. CP-GNB identified through faecal screening included NDM-1-producing *Serratia marcescens* and *Klebsiella pneumoniae, OXA-48-producing K. pneumoniae* and OXA-23-producing *Acinetobacter baumannii.* The distribution of the CP-GNB varied between the hospitals, with NDM-1-producing *S. marcescens* and *K. pneumoniae* being prevalent in the north-central part of the country and OXA-23/24-producing *A. baumannii,* OXA-48-producing *K.pneumoniae, Morganella morganii* and VIM-2-producing *Escherichia coli/Pseudomonas aeruginosa* detected in the north-east of the country. Conjugation studies showed that carbapenem resistance was transferable and PCR-based replicon typing identified blaNDM-1 on IncFIIs in *S. marcescens* and *K. pneumoniae* from Hospital 1 and blaOXA-48 on IncL plasmids in all *Klebsiella* spp. isolates from Hospitals 1 and 3. Our findings underline the importance of active surveillance for detection of CP-GNB asymptomatic faecal carriers and suggest a likely endemic spread of CP-GNB in Romania.

Introduction

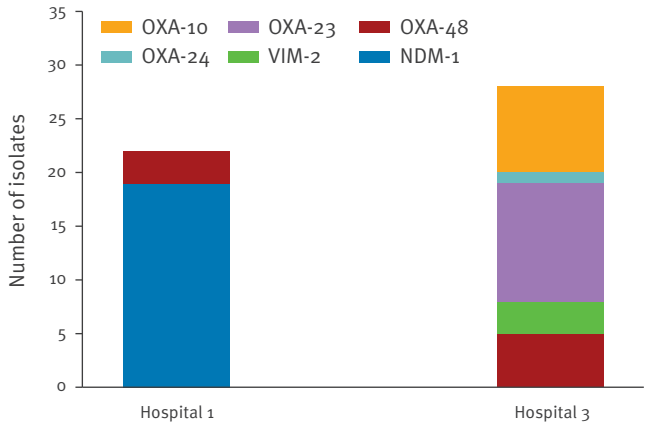
The worldwide emergence of carbapenemase-producing Gram-negative bacteria (CP-GNB) is widely accepted as a major public health threat that has caused international concern. The rapid spread of CP-GNB provides many challenges for healthcare systems, with implications that span from laboratory detection and infection control, to identifying suitable treatment options for organisms that are now starting to exhibit co-resistance to multiple last-resort antimicrobials [1].

The epidemiology of CP-GNB in Europe varies between northern and southern countries. A European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) among national experts from 39 European countries in 2013 showed that carbapenemase-producing *Enterobacteriaceae* (CPE) were continuing to spread in Europe, with *Klebsiella pneumoniae* carbapenemase (KPC)-producing isolates having the widest distribution and the number of OXA-48-producing isolates continuing to rise [2]. In contrast, NDM-1-producing isolates are sporadically reported, mainly from the United Kingdom (UK) [2]. The same report also found that 30 of the 39 European countries had a dedicated surveillance system for CPE and 22 of the countries had national recommendations or specific guidelines for infection control [2]; however, Romania does not have such a surveillance system or CPE infection control guidelines.

Romania contributes to the European Antimicrobial Resistance Surveillance Network (EARS-Net) although only via a small number of laboratories that report only carbapenem-resistant invasive *K. pneumoniae* and

Figure 1

Genes associated with carbapenem resistance (here including bla$_{OXA-10}$) identified in two hospitals, north-central (Hospital 1, 22 isolates) and north-east Romania (Hospital 3, 28 isolates), December 2014–May 2015



Escherichia coli from blood and cerebrospinal fluid. As a result, most European epidemiological reports show that data on CP-GNB from Romania are unknown or uncertain [3]. To get a snap-shot of the epidemiology of CP-GNB in hospitals that do not report to EARS-Net and that were not included in the 2013 EuSCAPE, a pilot CP-GNB surveillance project – introducing faecal screening for carbapenemase-producing bacteria on admission of patients to hospital and following transfer of inpatients from other wards to an intensive-care unit (ICU), as well as screening of clinical isolates – was implemented in three Romanian hospitals during December 2014 to May 2015. Few studies have investigated intestinal colonisation with carbapenemase-producing bacteria at the point of hospital admission: here we report the findings of an active surveillance programme for carbapenemase-producing bacteria in three hospitals in Romania.

Methods

Microbiology laboratories from three Romanian hospitals participated in the study. The hospitals were from two different geographical regions, with two hospitals (Hospitals 1 and 2) from the north-central part of the country, while the third (Hospital 3) was from the north-east of Romania. Hospitals 1 and 2 were large, with 1,299 and 1,892 beds, respectively, while Hospital 3 had a smaller capacity, with 232 beds and about 1,900 patients treated each year (the annual number of patients treated in Hospitals 1 and 2 could not obtained). Ethical approval for the study was obtained from the Hospital Research Ethics Committee at each hospital. Written consent was obtained from all patients for biological sample collection for routine investigation according to the hospitals' protocols.

During the study period (December 2014 to May 2015), surveillance of faecal cultures was introduced in the routine admission procedures as part of infection prevention and control measures. Each hospital analysed faecal cultures within the first 48 hours of hospitalisation for patients newly admitted to selected wards (such as haematology units with transplant recipients, ICUs or cardiac ICUs, nephrology and neonatology, gastroenterology, infectious diseases units and several surgical specialities) and also for inpatients transferred from other wards to an ICU. Screening criteria for newly admitted patients, if applied by the hospital, included previous hospitalisation, previous infections with multidrug-resistant bacteria (if known) or previous antimicrobial treatment.

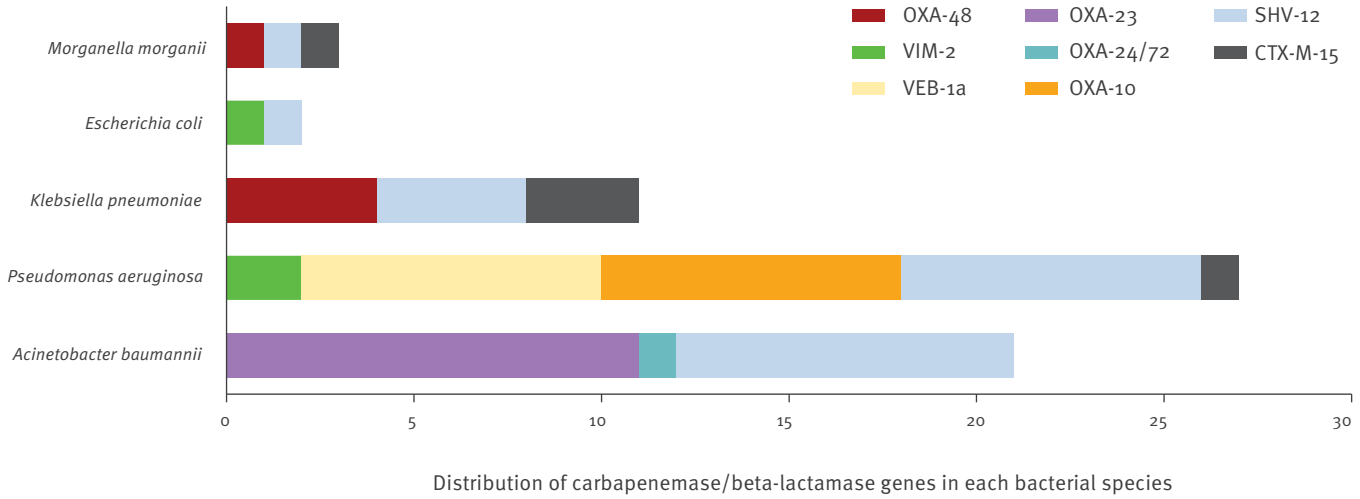
Carbapenem non-susceptible clinical isolates (from blood, urine, tracheal secretions) obtained from patients from the selected wards, were also included in the surveillance and when detected, these patients and their contacts were also checked for faecal colonisation. Suspicion of an ongoing outbreak with a CP-GNB during the study period in Hospital 1 lead to environmental samples being collected, which were also included in the study.

Carbapenemase screening protocols for *Enterobacteriaceae* and non-fermenting Gram-negative organisms were considered and a single protocol was used in the participating hospitals. For screening of faecal samples, a small sample inoculum was placed in 5 mL trypticase soy broth (TSB) containing a meropenem (10 µg) disc and incubated at 37 °C overnight. The following day, 100 µL of TSB was transferred onto a MacConkey agar plate (all discs and media were from Oxoid, Basingstoke, UK) and one disc each of ertapenem (10 µg) and meropenem (10 µg) were placed on different sectors of the inoculum. Clinical breakpoints and screening cut-off values for CPE were according to the European Committee on Antimicrobial Susceptibility (EUCAST) methodology [4]. All carbapenem non-susceptible isolates were identified (VITEK 2 system, Biomerieux, France) and stored at –80 °C for further testing.

Molecular characterisation of isolates was performed at Liverpool University, UK, which consisted of screening for resistance markers by multiplex PCR followed by sequencing. The PCR included screening for extended spectrum beta-lactamases (ESBLs) including *bla*$_{CTX-M}$, *bla*$_{SHV}$, *bla*$_{TEM}$, *bla*$_{OXA}$ and carbapenem-resistance genes (*bla*$_{NDM}$, *bla*$_{KPC}$, *bla*$_{GES}$, *bla*$_{IMP}$, *bla*$_{VIM}$, *bla*$_{SPM}$) as previously described [5-7]. Carbapenem-hydrolysing class D beta-lactamases (CHDLs) corresponding to OXA-23, OXA-24/40, OXA-48, OXA-51, OXA-58 and OXA-148 groups, as well as OXA-10, previously described as narrow-spectrum and recently shown to have CHDL activity in *Acinetobacter* spp. [8,9], were also included. Positive and negative controls were included in all PCR reactions. Minimum inhibitory concentration (MIC) testing for isolates with a unique genotype was performed by

Figure 2

Carbapenemase-producing Gram-negative bacterial species (n =5) and distribution of carbapenemase- and beta-lactamase genes (n = 8) identified in each bacterial species in Hospital 3 (28 isolates), north-east Romania, December 2014–May 2015



Distribution of carbapenemase/beta-lactamase genes in each bacterial species

broth microdilution with Sensititre GNX3F plates (TREK Diagnostic Systems, West Sussex, UK). The results were interpreted according to EUCAST breakpoints for all antimicrobials except for polymyxin B, where Clinical and Laboratory Standard Institute (CLSI) criteria were applied [10,11].

To determine whether the carbapenem-resistance genes were transferable, conjugation was performed by broth mating as previously described [12] and was attempted for all CPE identified in this study. Donor and recipient cells (plasmid-free streptomycin-resistant *E. coli* HB101) were grown to logarithmic phase, mixed in nutrient broth and incubated at 37°C for 18 hours. Transconjugants were selected on nutrient agar (Oxoid, UK) supplemented with streptomycin (50 µg/mL) and cefotaxime (1 µg/mL). To ensure that selected isolates were the recipient *E. coli* and that they contained the transferred resistance gene, PCR was performed for the *uidA* gene [13] as well as carbapenemase-resistance genes. In addition, PCR was performed to identify if ESBL resistance determinants were co-transferred with the carbapenem-resistance. Plasmid DNA was extracted from clinical isolates and transconjugants using a QIAprep spin miniprep kit (QIAGEN, Germany). Plasmid identification using a PCR-based replicon typing (PBRT) scheme [14] was carried out on total DNA from all CPE clinical isolates carrying carbapenem-resistance genes, as well as on plasmid DNA extracted from the clinical isolates and their transconjugants. It was previously observed that PBRT can be inefficient at identifying IncL/M plasmid type, therefore an up-dated method designed to identify and distinguish between IncL and IncM plasmids was used [14,15].

Results

A total of 820 clinical, faecal and environmental specimens were analysed: 528 samples were from Hospital 1 (7 clinical, 336 faecal, 185 environmental), 105 from Hospital 2 (all faecal) and 187 from Hospital 3 (23 clinical, 164 faecal). Carbapenem non-susceptible Gram-negative isolates were identified in 27/528 (5%), 12/102 (12%) and 38/187 (20%) of the samples from Hospitals 1, 2 and 3, respectively. Molecular testing identified carriage of at least one gene associated with carbapenem resistance in 22/27 of the carbapenem non-susceptible isolates from Hospital 1, none from Hospital 2 and 28/38 isolates from Hospital 3 (Figure 1).

A total of 19 isolates from Hospital 1 carried $bla_{\text{NDM-1}}$ (17 *Serratia marcescens* and two *K. pneumoniae*) while three isolates (all *K. pneumoniae*) carried $bla_{\text{OXA-48}}$. The NDM-1 positive isolates were from clinical specimens (seven isolates from pharyngeal secretions), faecal screening (nine isolates) and hospital environmental samples (three isolates, from feeding tube, bedside and food jar) while the OXA-48-producing *K. pneumoniae* isolates were all from faecal screening. Of the 19 NDM-1-positive isolates, 15 co-harboured $bla_{\text{CTX-M-15}}$ while two produced LEN-25 beta-lactamases. Moreover, an unexpected variety of species carrying one or sometimes two genes associated with carbapenem resistance were identified in Hospital 3 (Figure 2).

A total of 11 *A. baumannii* isolates from Hospital 3 (nine from clinical samples (blood, tracheal secretions, urine) and two faecal isolates) were found to harbour $bla_{\text{OXA-23}}$ while another clinical isolate carried $bla_{\text{OXA-24/27}}$. The second most prevalent gene associated with carbapenem resistance in this hospital was $bla_{\text{OXA-48}}$, detected in clinical isolates of *K. pneumoniae* (n = 4) and *Morganella morganii* (n = 1). In addition, two *Pseudomonas aeruginosa* clinical isolates carried $bla_{\text{VIM-2}}$ while eight *P. aeruginosa* isolates (six faecal, two clinical) co-harboured $bla_{\text{OXA-10}}$ and $bla_{\text{VEB-1a}}$ beta-lactamase. Futhermore, one patient was found to have faecal colonisation with *E. coli*-producing VIM-2. KPC

Table

Antibiotic susceptibility testing of selected *Klebsiella pneumoniae, Serratia marcescens, Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates, from two hospitals, north-central and north-east Romania, December 2014–May 2015 (n = 18)

Isolate ID (Source)	Species	Genotype	AK	SAM	ATM	FEP	CTX	CAZ	CIP	CST	DOR	DOX	GEN	IMP	LVX	MEM	TZP	PMB	TIM	TGC	TOB	SXT
8TM (F)	*K. pneumoniae*	OXA-48, CTX-M-15, SHV-11	S	R	R	R	R	R	R	S	S	R	R	S	R	S	S	S	R	S	R	S
6TM (F)	*K. pneumoniae*	NDM-1, LEN-25	R	R	I	R	R	R	S	S	R	R	R	R	S	R	R	S	R	S	R	S
5TM (F)	*K. pneumoniae*	NDM-1, CTX-M-15	R	R	R	R	R	R	R	R	R	R	R	R	S	R	R	R	R	S	R	R
4TM (F)	*S. marcescens*	NDM-1, CTX-M-15	R	R	R	R	R	R	R	R	S	S	R	S	S	S	R	R	R	S	R	R
1TM (F)	*S. marcescens*	NDM-1, LEN-25	R	R	S	NT	R	R	S	S	R	R	R	R	S	R	R	S	R	S	R	S
44I (F)	*A. baumannii*	OXA-23, SHV-12	R	R	NT	NT	NT	R	R	S	R	R	R	R	R	R	R	S	R	S	R	S
43I (CL)	*K. pneumoniae*	OXA-48, SHV-11	S	R	R	S	R	R	R	S	S	R	S	S	R	S	R	S	R	S	R	S
42I (CL)	*A. baumannii*	OXA-24/72	R	R	NT	NT	NT	NT	R	S	R	S	R	R	R	R	R	S	R	S	R	R
40I (CL)	*A. baumannii*	OXA-23, SHV-1/28, CTX-M-15	R	R	NT	NT	NT	NT	R	S	R	R	R	R	R	R	R	S	R	S	R	S
73I (CL)	*K. pneumoniae*	OXA-48, CTX-M-15, SHV-1/28	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	S
71 I (CL)	*K. pneumoniae*	OXA-48, CTX-M-15, SHV-1/28	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	S
66 I (CL)	*K. pneumoniae*	OXA-48, CTX-M-15, SHV-1/28	S	R	R	R	R	R	R	S	R	R	R	S	R	S	R	S	R	S	R	R
60 I (CL)	*M. morganii*	OXA-48, CTX-M-15, SHV-12	S	R	R	R	R	R	R	R	S	S	R	R	R	S	R	R	R	R	R	R
51 I (F)	*A. baumannii*	OXA-23, SHV-12	NT	R	NT	NT	NT	NT	R	S	R	R	R	R	R	R	NT	S	R	NT	S	R
48 I (F)	*P. aeruginosa*	OXA-10, VEB-1a, SHV-12	NT	R	R	R	NT	R	R	S	R	R	R	R	R	R	R	S	R	NT	R	NT
45 I (CL)	*A. baumannii*	OXA-23	S	R	NT	NT	NT	NT	S	S	R	S	S	R	R	NT	NT	S	R	NT	S	S
41 I (F)	*P. aeruginosa*	OXA-10, VEB-1a, SHV-12	NT	R	R	R	NT	R	R	S	R	R	R	R	R	R	R	S	R	NT	R	NT
57I (F)	*E. coli*	VIM-2, SHV-12	S	R	R	R	R	R	R	S	R	R	R	R	R	R	R	S	R	R	R	R

AMK: amikacin; ATM: aztreonam; CAZ: ceftazidime; CIP: ciprofloxacin; CL: clinical isolate; CST: colistin; CTX: cefotaxime; DOR: doripenem; DOX: doxycycline; F: faecal isolate; FEP: cefepime; GEN: gentamicin; I: intermediate susceptibility; IPM: imipenem; LVX: levofloxacin; MEM: meropenem; NT: not tested; PMB: polymyxin B; R: resistant; SAM: ampicillin/sulbactam; TGC: tigecycline; TIM: ticarcillin/clavulanic acid; TOB: tobramycin; S: susceptible; SXT: trimethoprim/sulfamethoxazole; TZP: piperacillin/tazobactam.

European Committee on Antimicrobial Susceptibility (EUCAST) breakpoints [4] were used for all antimicrobials except for polymyxin B, for which Clinical and Laboratory Standard Institute (CLSI) interpretative criteria [10,11] were used.

carbapenemases were not identified in any of the hospitals investigated.

Previously unreported species/genes combinations were also identified in Hospital 3. For instance, *A. baumannii* isolates co-harboured bla_{OXA-23} as well as $bla_{SHV-1/28}$, while one *E. coli* isolate obtained from faecal screening co-harboured bla_{VIM-2} and bla_{SHV-12}. All except two isolates from Hospital 3 that carried a gene associated with carbapenem resistance also co-produced CTX-M-15 and/or SHV-12 beta-lactamases.

Overall, of the 50 CP-GNB identified in this study, 27 were from clinical specimens, 23 were obtained through faecal screening and three from environmental samples. Two patients with *A. baumannii* OXA-23-producing infections (pneumonia, bacteraemia) had faecal colonisation with the same CP-GNB. Another patient was found to be colonised with multiple CP-GNBs, where OXA-23-producing *A. baumannii* and OXA-48-producing *K. pneumoniae* were isolated from a wound infection while OXA-10-producing *P. aeruginosa* was detected through faecal screening.

Susceptibility testing showed variable levels of resistance to carbapenems, spanning from NDM-1-producing *S. marcescens* and OXA-48-producing *K. pneumoniae* exhibiting susceptibility to doripenem, imipenem and meropenem through to *P. aeruginosa* co-producing OXA-10, VEB-1a and SHV-12 beta-lactamases, which manifested resistance to all antimicrobials tested except for polymyxin B and colistin (Table). Taken together, these results highlight the difficulties faced by laboratories that only rely on phenotypic methods for detection of carbapenemases.

Due to the multidrug-resistant profiles of many clinical isolates, a suitable recipient for conjugation experiments was identified for only five isolates (one NDM-1-producing *S. marcescens* and two NDM-1-producing *K. pneumoniae* from Hospital 1 and two OXA-48-producing *K. pneumoniae* from Hospital 3); conjugative plasmids were successfully transferred in all five isolates. PBRT showed that bla_{NDM-1} was associated with IncFIIs plasmids in both *K. pneumoniae* and *S. marcescens* from Hospital 1. However, PBRT performed on clinical *Serratia* NDM-1-positive isolates also identified IncM plasmids in five isolates and IncL in three isolates, while no typable plasmids could be found in six clinical isolates carrying bla_{NDM-1}. IncL plasmids were found to be associated with bla_{OXA-48} in *K. pneumoniae* clinical isolates and transconjugants from resistance-transfer studies. In addition, IncL was the only plasmid found in all *K. pneumoniae* clinical isolates that carried bla_{OXA-48} from both hospitals (Hospitals 1 and 3). PCR also showed that no ESBL-resistance determinants had co-transferred with the carbapenem-resistance genes.

Discussion

This pilot study demonstrated a high prevalence of CP-GNB in two of three Romanian hospitals over a six-month period. Furthermore, a variety of carbapenemase-producing species and genes associated with carbapenem resistance were also identified in this study. The distribution of the CP-GNB varied between the two hospitals in which these bacteria were detected: NDM-1-producing *S. marcescens* and *K. pneumoniae* were prevalent in Hospital 1, in the north-central part of the country, but were not identified in Hospital 3, in the north-east. No history of travel abroad could be identified in the patients and the origin of the NDM-1 isolates needs further investigation to understand the epidemiology of NDM-1-producing *Enterobacteriaceae* in eastern Europe [16].

In our study, bla_{NDM-1} was identified in 17 isolates of *S. marcescens* across clinical, environmental and faecal isolates, all of which were obtained from the same neonatal unit, suggesting the likelihood of an outbreak, which will be further investigated. This is the largest number of NDM-1-producing *S. marcescens* detected in one hospital in Europe, with only one previous report of a clinical isolate in Germany [17], highlighting the spread of bla_{NDM-1} into another *Enterobacteriaceae* species. Although an opportunistic pathogen, *S. marcescens* has emerged in the past decades as an important source of hospital acquired-infections and outbreaks in both adult and paediatric intensive-care patients [18,19]. Hospital 1, where the NDM-1-producing *S. marcescens* and *K. pneumoniae* were isolated, had previous *Serratia* spp. outbreaks during 2010–12 in the same neonatal unit with *Serratia* spp. isolates that did not produce carbapenemase (data not shown). Our conjugation studies identified bla_{NDM-1} to be associated with conjugative IncFIIs plasmids in both *K. pneumoniae* and *S. marcescens*, which could suggest interspecies transfer of bla_{NDM-1} via mobile genetic elements. Whole genome sequencing will be carried out of the NDM-1-negative and NDM-1-producing *Serratia* and *Klebsiella* isolates obtained in this study, as well isolates from previous outbreaks in this neonatal unit, to understand the molecular epidemiology of NDM-1-producing *S. marcescens* in this hospital and in surrounding areas in eastern Europe.

In contrast, NDM-1 was not found in Hospital 3, whereas OXA-23- and OXA-24-producing *A. baumannii*, OXA-48-producing *K.pneumoniae* and *M. morganii*, as well as OXA-10-producing *P. aeruginosa*, were the most prevalent in this hospital. Interestingly, the bla_{OXA-10}-carrying *P. aeruginosa* isolates exhibited resistance to all tested carbapenems, which could imply that OXA-10 beta-lactamases in *Pseudomonas* spp. may have catalytic activity against carbapenems, as has been demonstrated for *Acinetobacter* spp. [9]. Further research is necessary, however, to establish the ability of OXA-10 beta-lactamases to compromise therapeutic effectiveness of carbapenems in *Pseudomonas* spp. OXA-48-producing *K. pneumoniae* was the most common CPE in Hospital 3 and conjugation studies identified bla_{OXA-48} to be associated with IncL plasmids. Previous studies have shown that plasmids carrying bla_{OXA-48} share similar features, in that they have an IncL/M backbone and are very similar in size (about 60–70 kb) suggesting their wide dissemination in different countries through an epidemic plasmid [20]. A recent study specifically assigned bla_{OXA-48}-carrying plasmids to the IncL group [15]; in our study, we demonstrated the association of bla_{OXA-48} with IncL plasmids in all carbapenemase-producing *K. pneumoniae* isolates from two hospitals in different geographical regions in Romania.

Previously unreported species/genes combinations, or bacteria co-harbouring more than one carbapenemse-encoding gene, were also identified in Hospital 3. Detection of a patient colonised with *E. coli*-producing VIM-2 is the first known report of *E. coli* harbouring bla_{VIM-2} in a hospital patient in Romania, following previous detection of this genotype in patients from Germany between September 2009 and May 2013 [21]. Our study also detected *M. morganii*-producing OXA-48, a CP-GNB that has not been previously reported in Europe, but has been described in clinical isolates from Lebanon and Kuwait [22,23].

A. baumannii is known to be an agent of nosocomial infections associated with ICUs [24]. It is widely recognised that this bacterium is very well adapted to withstand dry environmental conditions and disinfectants, being able to survive for a long time (several months) on hospital surfaces [24]. Previous molecular analyses of *A. baumannii* isolates from Hospital 3's cardiac ICU obtained in 2011–12, identified widespread infections with OXA-23-producing *A. baumannii* belonging to European clones I and II (data not shown). Such findings should trigger appropriate infection control measures, however, previous studies have shown that very often routine infection control measures are insufficient to control *A. baumannii* and enhanced measures, such as using closed tracheal suction systems, patient isolation or sometimes ward closure, are necessary to control this resilient opportunistic pathogen [24].

There are only a few previous reports on the isolation and/or characterisation of CP-GNB from Romanian hospitals, which described NDM-1-producing *E. cloacae*, OXA-48-producing *K. pneumoniae*, OXA-23-producing *A. baumannii* and VIM-2-producing *P. aeruginosa* clinical isolates [25-29]. In one study, Deshpande et al. analysed clinical isolates from three Romanian hospitals in 2011 and found 3% of isolates from two hospitals with reduced susceptibility to carbapenems, two of which were NDM-1-producing *E. cloacae*, the other being OXA-48-producing *K. pneumoniae* [25]. Only a few years later, our study demonstrates a high prevalence of carbapenem non-susceptible Gram-negative isolates, ranging from 5% to 20%, as well as a great diversity of bacterial species and genes associated with carbapenem resistance. Detection of CP-GNB through the implementation of a patient screening programme demonstrated the presence of these bacteria in clinical and faecal samples of newly admitted hospital patients, providing a snapshot of what is likely to be an endemic spread of CP-GNB in this country. Larger, nationwide screening studies are necessary to determine the true prevalence of CP-GNB in Romanian hospitals.

Our study has some limitations. Firstly, the criteria used to select newly admitted patients for screening (previous hospitalisation, previous infection with multidrug-resistant bacteria or previous antimicrobial treatment) were applied in Hospital 3 but could not be applied in Hospitals 1 and 2, where all patients newly admitted to selected wards were screened. Therefore, risk factors for CP-GNB colonisation of newly admitted patients could not be determined. Secondly, clinical data were not available from Hospitals 1 and 2, therefore risk factors for CP-GNB infection could also not be determined.

Despite these limitations, data from Hospital 3, where screening criteria were used for newly admitted patients, showed that two patients selected for faecal screening had multiple hospitalisations in the previous year, one whom was found to have concurrent OXA-23-producing *A. baumannii* faecal and tracheal exudate colonisation. Also, hospital records showed that six patients from whom surveillance cultures yielded faecal carbapenem non-susceptible bacteria had been previously admitted to the same hospital during the past year, during which time they had been treated with imipenem. Of these, one patient had a wound infection with an OXA-48-producing *K. pneumoniae* and also faecal carriage of carbapenem non-susceptible *P. aeruginosa*. Another patient had concurrent faecal and tracheal exudate colonisation, as well as blood cultures containing OXA-23-producing *A. baumannii*. Finally, faecal carriage of VIM-2-producing *E. coli* was found in another patient who had been previously admitted to Hospital 3. These findings highlight the importance of active surveillance of asymptomatic carriers and identification of patients who may have a higher risk of CP-GNB carriage, such as those with previous multiple hospital admissions.

The high prevalence and variety of CP-GNB identified in two of the three hospitals investigated in this study are of concern and suggest the need for a review of the local surveillance and infection control measures. Romania is one of the few European countries that does not currently have a national surveillance system or specific guidelines for the management of CP-GNB infections, nor are hospitals obliged to report such infections to the health authorities [30]. As a consequence, the importance of these infections may be underestimated by hospital authorities. In the hospitals investigated, the ICUs had no facilities for patient isolation and at best, mobile curtains are used to separate beds. Although financial constraints may not allow infrastructure changes that would ensure strict patient isolation, more could be done to educate staff and implement feasible measures to prevent the introduction and spread of CP-GNB. Therefore, reinforcement of measures such as staff education on hand hygiene and contact precautions combined with active faecal culture surveillance are likely to have a direct impact on preventing the spread of CP-GNB and thus reducing the risk of such infections. Introduction of mandatory screening and reporting of CP-GNB by hospitals, as part of a coordinated surveillance programme, should provide an effective framework for the early detection and control of CP-GNB.

In conclusion, our findings emphasise the need for early detection of patients with CP-GNB colonisation or infection, which should lead to the implementation of appropriate infection control measures to prevent the silent spread of these isolates in hospitals. Improvement of surveillance of carbapenemase-producing bacteria in Romania – including introducing guidelines for laboratory detection of intestinal asymptomatic carriers and for infection control and outbreak management – will not only benefit the local patients but will also have an impact at European level, as it is recognised that the spread of carabapenemase-producing organisms is often linked to travel of patients between various countries [16].

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Conflict of interest

None declared.

Authors' contributions

DT coordinated the study, analysed data, wrote the manuscript; CVP and MD assisted in designing the study, organised implementation of surveillance of carbapenemase-producing bacteria in one of the hospitals collected clinical data, read and revised the manuscript; IEM assisted in designing the study, performed molecular testing, analysed data, read and revised manuscript; ADM, AM and FT assisted in designing the study, organised implementation of surveillance of carbapenemase-producing bacteria in two of the hospitals, collected clinical data, read and revised the manuscript.

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Research article

Repeated nationwide point-prevalence surveys of antimicrobial use in Swedish hospitals: data for actions 2003–2010

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This study sought to analyse antimicrobial pressure, indications for treatment, and compliance with treatment recommendations and to identify possible problem areas where inappropriate use could be improved through interventions by the network of the local Swedish Strategic Programme Against Antibiotic Resistance (Strama) groups. Five point-prevalence surveys were performed in between 49 and 72 participating hospitals from 2003 to 2010. Treatments were recorded for 19 predefined diagnosis groups and whether they were for community-acquired infection, hospital-acquired infection, or prophylaxis. Approximately one-third of inpatients were treated with antimicrobials. Compliance with guidelines for treatment of community-acquired pneumonia with narrow-spectrum penicillin was 17.0% during baseline 2003–2004, and significantly improved to 24.2% in 2010. Corresponding figures for quinolone use in uncomplicated cystitis in women were 28.5% in 2003–2004, and significantly improved, decreasing to 15.3% in 2010. The length of surgical prophylaxis improved significantly when data for a single dose and 1 day were combined, from 56.3% in 2003–2004 to 66.6% in 2010. Improved compliance was possibly the effect of active local feedback, repeated surveys, and increasing awareness of antimicrobial resistance. Strama groups are important for successful local implementation of antimicrobial stewardship programs in Sweden.

Introduction

The Swedish Strategic Programme Against Antibiotic Resistance (Strama) was established during the 1990s to promote rational use of antibiotics [1]. At that time in Sweden, data on antimicrobial use in hospitals was limited to statistics on the total amount of deliveries from hospital pharmacies [2]. While such data allow analysis over time and comparison of patterns of antimicrobial use among hospitals and regions, they do not include the indication for therapy and thus do not permit assessment of compliance with recommendations. Knowledge of antimicrobial use in Swedish hospitals was largely restricted to local projects [3] when the national Strama board [1] initiated the nationwide point-prevalence survey (PPS) in 2003. In a PPS, data is registered during one day and gives a cross-sectional figure over, in this case, antibiotic use for different diagnosis groups. Numbers are small when looking only at one hospital but if data are collected for several hospitals, and surveys are repeated, data becomes more reliable.

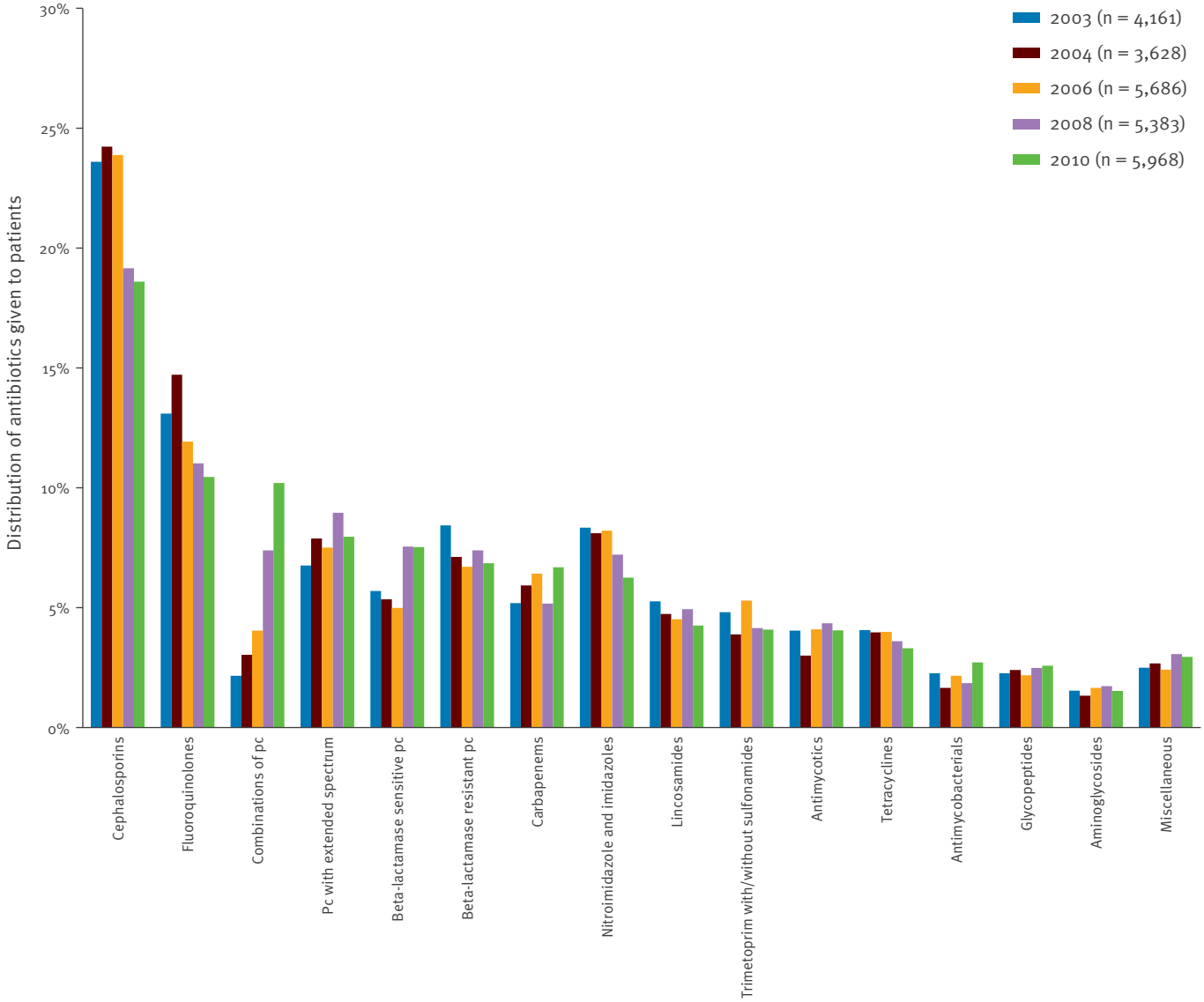
This paper presents an analysis of antimicrobial use related to diagnosis in Swedish hospitals and experiences from interventions based on findings in five PPS from 2003 to 2010.

Methods

Sweden has 21 county councils and ca 80 public acute-care hospitals, all of which were invited to participate in the studies. Participation was optional and between 19 and 21 county councils and 49 and 72 acute-care hospitals (somatic care only, that is, excluding psychiatric care) over the study years. The mean length of stay (LOS) was 5.4 days in 2003, 5.3 days in 2004, 5.1 days in 2006, 5.0 days in 2008, and 4.8 days in 2010 [4].

Figure 1

Distribution of antibiotics given to patients in the nationwide hospital point-prevalence surveys, Sweden, 2003–2010



Excludes antibiotics given as prophylaxis.

The studies were performed as PPS during one day within a two-week period in November 2003, 2004, 2006, 2008, and 2010. Data were collected by infectious-disease specialists at 08:00 from the medical records of all patients receiving systemic antibacterials. The total number of admitted patients was used as the denominator. The survey protocol is available online [5]

Therapy was defined as the conjunction of the drug(s) dispensed, diagnosis and whether the prescription was for community-acquired infection (CAI), hospital-acquired infection (HAI), or prophylaxis [5]. More than one therapy could be registered for one patient, and one therapy could consist of more than one antibiotic.

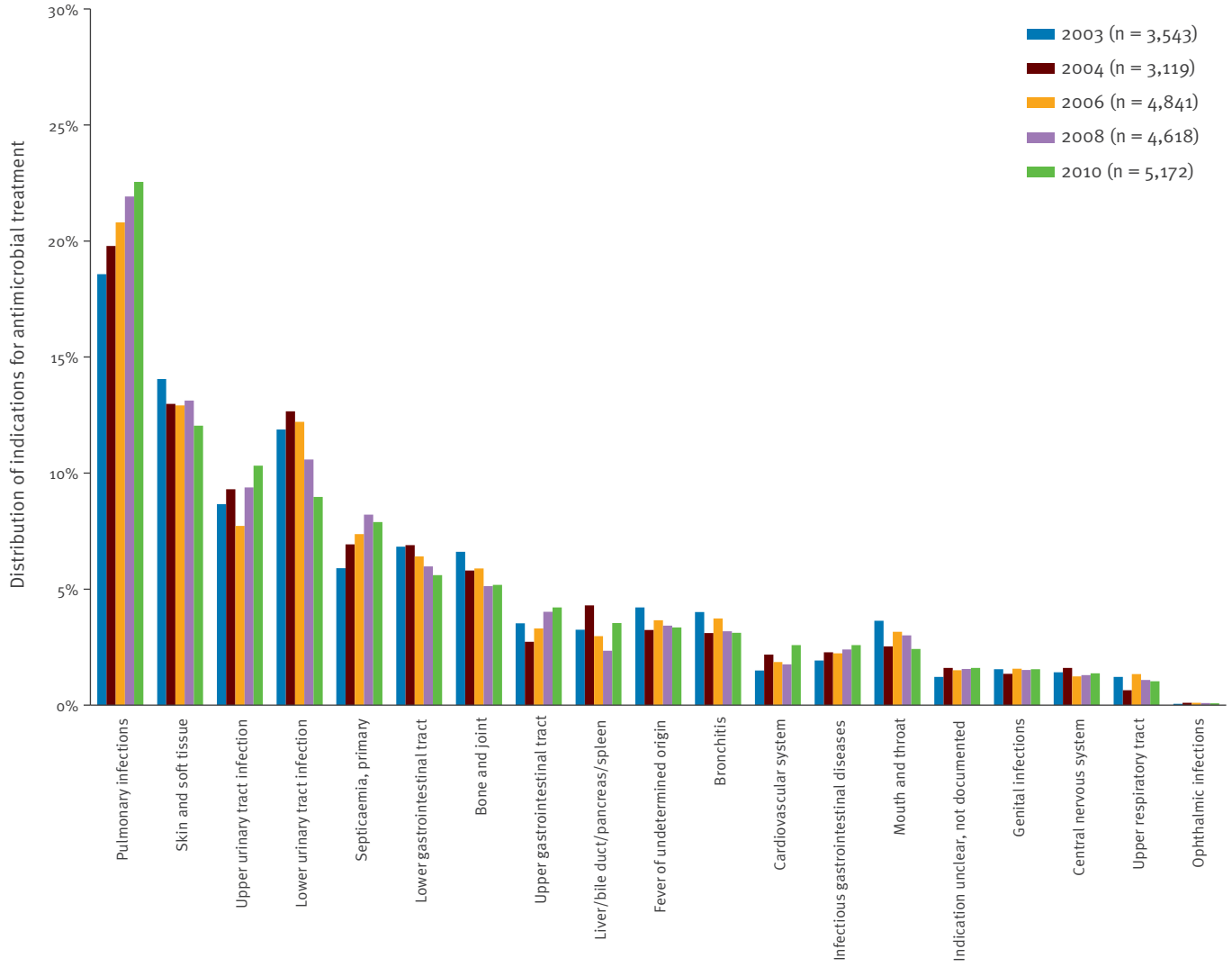
The following patient data were collected: age, sex, prescribed drug(s), dose per administration, number of doses, route of administration, focus of the infection (or for prophylaxis) and significant risk factors for infection such as immunosuppression, presence of foreign material and invasive medical devices.

The assessment also included whether the indication for treatment was documented in the records and whether a relevant culture was done before initiation of treatment. A final assessment of the therapy was made by the surveyors as directed therapy, empirical therapy, or deviating from recommendations.

Duration of surgical prophylaxis was classified as single dose, 1 day, or more than 1 day.

Figure 2

Distribution of indications for antimicrobial treatment according to predefined diagnosis groups, nationwide hospital point-prevalence surveys, Sweden, 2003–2010



Excludes antibiotics given as prophylaxis, includes antimycotics and tuberculostatic treatments.

Antimicrobials were classified according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification System [6]. The defined daily dose (DDD) was used as indicator for antimicrobial pressure and calculated from the amounts of antibiotics given per day according to the WHO definitions, with the exception of oral vancomycin, for which the prescribed daily dose of 500 mg was chosen. DDDs were not registered for children under 16 years. Drugs recorded in this study were: antibiotics (oral vancomycin (A07AA09), terbinafine (D01BA02), oral imidazoles (P01AB) and antibacterials for systemic use (J01), excluding methenamine), antimycotics (J02A) and tuberculostatics (J04A).

Coded patient identity and study data were entered into a web-based interface (Neotide Ltd, Vaasa, Finland) by each local Strama group. A standardised validation was performed, and incongruences were addressed for reassessment by each Strama group.

A systematic approach in feeding back the results to hospitals was achieved by including the local Strama groups in the process. Together with the research team, Strama representatives were involved in formulating three main messages for interventions, based on data from the 2003 and 2004 surveys. These representatives could then present and discuss the study results in their own counties while including relevant local aspects. Interventions also took the form of information leaflets addressing main messages that were sent to all hospital prescribers and displayed in participating hospitals in visible areas such as in lifts and on bulletin boards.

Table 1

Demographics in five nationwide hospital point-prevalence surveys of antimicrobial use, Sweden, 2003–2010

	2003	2004	2006	2008	2010
Number of available beds in Sweden	22,471	22,454	21,628	21,302	21,019
Number of admitted patients in survey					
Tertiary care hospitals	4,808	3,191	6,675	5,269	6,849
Secondary care hospitals	5,977	5,536	7,049	7,189	6,804
Primary care hospitals	2,751	2,621	3,412	3,529	3,429
Specialised geriatric hospitals	NA	NA	NA	331	621
Total (% of available beds)	13,536 (60.2%)	11,348 (50.5%)	17,136 (79.2%)	16,318 (76.6%)	17,703 (84.2%)
Number of patients in survey with antimicrobial treatment (% of admitted patients in survey)	4,178 (30.9%)	3,622 (31.9%)	5,588 (32.6%)	5,339 (32.7%)	5,928 (33.5%)
Age of treated patients in survey (% of treated patients in survey)					
0–16 years	266 (6.4%)	183 (5.1%)	280 (5.0%)	268 (5.0%)	336 (5.7%)
17–60 years	1,102 (26.4%)	913 (25.2%)	1,439 (25.8%)	1,266 (23.7%)	1,453 (24.5%)
61–79 years	1,624 (38.9%)	1,465 (40.4%)	2,187 (39.1%)	2,168 (40.6%)	2,326 (39.2%)
≥ 80 years	1,186 (28.4%)	1,061 (29.3%)	1,682 (30.0%)	1,637 (30.7%)	1,813 (30.6%)
Number of patients in ICUs					
Number of adults in ICUs with antimicrobial treatment (% of all treated adults)	176 (4.5%)	154 (4.5%)	266 (5.0%)	227 (4.5%)	240 (4.3%)
Number of children in ICUs with antimicrobial treatment (% of all treated children)	25 (9.4%)	27 (14.8%)	41 (14.6%)	26 (9.7%)	49 (14.6%)

ICU: intensive care unit; NA: not available.

Statistical calculations of changes over time were performed only for the three intervention areas. The average percentage from the first two surveys were used as baseline measurements and counted as one time period (2003–2004). Changes over time were examined using chi-squared tests. First, a comprehensive test including all study years was performed. If the result of this test showed statistical significance ($p<0.001$), additional chi-squared tests in pairs were performed. Further statistical calculations were not considered appropriate in this descriptive survey because of the high coverage of admitted patients within somatic hospital care.

The survey was assessed by the Regional Ethical Review Board in Lund on 24 September 2003, registration number LU 596-03.

Results

Study demographics are presented in Table 1. The number of admitted patients included varied between 11,348 and 17,703 and the number of patients with antimicrobial treatment varied between 3,622 and 5,928. The proportion of women varied between 48.7% and 49.9%. The median age was 73 years old for women (range: 0–108 years, interquartile range (IQR): 27 years) and 70 years old for men (range: 0-108 years, IQR: 23 years).

The observed prevalence of CAI, HAI, and prophylaxis in different hospital categories is shown in Table 2. Tertiary hospitals and specialised geriatric hospitals had a higher prevalence of treatment for HAI, and tertiary hospitals also had a higher proportion of patients on medical prophylaxis compared with the other hospital categories.

The mean antimicrobial pressure within adult specialties was 40.3 DDD per 100 admitted patients in 2003, 43.1 in 2004, 43.5 in 2006, 45.9 in 2008, and 45.6 in 2010. Antibiotics represented an average of 92.1%, antimycotics, 2.4%, and tuberculostatics, 5.5% of the total DDD per 100 admitted patients, respectively.

The documented indication for antibiotic treatment in medical records varied over the study years between 82.3–85.2%. After oral completion of information from the staff, an indication for treatment could be obtained in 94.9% of patients. The distribution of all given antibiotics used for treatment of infections in adults (prophylaxis excluded) is shown in Figure 1. Cephalosporins and fluoroquinolones were the most frequently used antibiotics, although use decreased over the years of the study. The use of penicillins increased during the study period, especially penicillins in combination with piperacillin.

As shown in Figure 2, pulmonary infections were the most common of the 19 predefined diagnosis groups.

Table 2

Prevalence of community-acquired infection, hospital-acquired infection, and surgical and medical prophylaxis in five nationwide hospital point-prevalence surveys of antimicrobial use, Sweden, 2003–2010

	Number of therapies (% of admitted patients)				
	2003	2004	2006	2008	2010
Community-acquired infection					
Tertiary care hospitals	836 (17.4%)	535 (16.8%)	1,096 (16.4%)	850 (16.1%)	1,112 (16.2%)
Secondary care hospitals	1,022 (17.1%)	1,048 (18.9%)	1,334 (18.9%)	1,294 (18.0%)	1,404 (20.6%)
Primary care hospitals	446 (16.2%)	464 (17.7%)	629 (18.4%)	721 (20.4%)	724 (21.1%)
Specialised geriatric hospitals	NA	NA	NA	52 (15.7%)	65 (10.5%)
Total	2,304 (17.0%)	2,047 (18.0%)	3,059 (17.9%)	2,917 (17.9%)	3,305 (18.7%)
Hospital-acquired infection					
Tertiary care hospitals	510 (10.6%)	365 (11.4%)	841 (12.6%)	690 (13.1%)	901 (13.2%)
Secondary care hospitals	494 (8.3%)	517 (9.3%)	657 (9.3%)	653 (9.1%)	600 (8.8%)
Primary care hospitals	235 (8.5%)	190 (7.2%)	284 (8.3%)	285 (8.1%)	281 (8.2%)
Specialised geriatric hospitals	NA	NA	NA	73 (22.1%)	85 (13.7%)
Total	1,239 (9.2%)	1,072 (9.4%)	1,782 (10.4%)	1,701 (10.4%)	1,867 (10.5%)
Surgical prophylaxis					
Tertiary care hospitals	251 (5.2%)	189 (5.9%)	332 (5.0%)	302 (5.7%)	379 (5.5%)
Secondary care hospitals	263 (4.4%)	195 (3.5%)	306 (4.3%)	294 (4.1%)	261 (3.8%)
Primary care hospitals	111 (4.0%)	125 (4.8%)	158 (4.6%)	171 (4.8%)	120 (3.5%)
Specialised geriatric hospitals	NA	NA	NA	1 (0.3%)	3 (0.5%)
Total	625 (4.6%)	509 (4.5%)	796 (4.6%)	768 (4.7%)	763 (4.3%)
Medical prophylaxis					
Tertiary care hospitals	120 (2.5%)	110 (3.4%)	202 (3.0%)	178 (3.4%)	301 (4.4%)
Secondary care hospitals	95 (1.6%)	84 (1.5%)	72 (1.0%)	97 (1.3%)	90 (1.3%)
Primary care hospitals	13 (0.5%)	19 (0.7%)	22 (0.6%)	22 (0.6%)	28 (0.8%)
Specialised geriatric hospitals	NA	NA	NA	3 (0.9%)	6 (1.0%)
Total	**228 (1.7%)**	**213 (1.9%)**	**296 (1.7%)**	**300 (1.8%)**	**425 (2.4%)**

NA: not available.
All age groups are included.

Table 3 shows the three most common diagnosis groups of CAI and the antibiotic classes used for therapy. Compliance with treatment recommendations for uncomplicated community-acquired pneumonia (CAP) improved because treatment with beta-lactamase-sensitive penicillins increased significantly from 17.0% in 2003–2004 to 24.2% ($p<0.001$) in 2010. Likewise, compliance with treatment recommendations for women with lower urinary tract infections (UTI) improved significantly. In 2003–2004, fluoroquinolones were used in 28.5% for treatment vs 15.3% ($p<0.001$) in 2010. Beta-lactamase-resistant penicillins (isoxazolyl penicillins) were the most commonly used drugs for skin and soft-tissue infections.

Antimicrobials were administered parenterally in 43.0%, 44.4%, 47.3%, 48.2%, and 51.0% of all cases in each study year, respectively. The proportion of treatments with a relevant culture taken before therapy ranged between the study years from 67.7-75.4% for HAI and 62.1–72.6% for CAI. Before parenteral treatment, culture was recorded in a range of 69.4–78.3% of the patients and before oral treatment in 60.3–69.6% of the patients.

The most frequently used antibiotics for surgical prophylaxis over the years were beta-lactamase-resistant penicillins (average 38.4%) and cephalosporins (average 19.4%). Surgical prophylaxis was given as a single dose in 23.7%, 25.5%, 32.4%, 26.4%, and 32.4% of all cases; during one day in 29.3%, 35.0%, 36.8%, 36.3%, and 34.2% of all cases; and for more than one day in 47.0%, 39.5%, 30.8%, 37.2%, and 33.4% of the cases in each study year, respectively. For a single dose, no clear pattern was shown but significant improvement was seen when data for a single dose and one day were combined, from 56.3% in 2003–2004) to 66.6% ($p<0.001$) in 2010. Medical prophylaxis constituted on average 29.7% of all prophylaxis.

Discussion

A major finding in the PPS presented here was that approximately one-third of inpatients in acute-care hospitals in Sweden were treated with antimicrobials. We found that an increasing proportion, from

Table 3

The top six antibiotic classes used to treat the three most common community-acquired infections, nationwide hospital point-prevalence surveys, Sweden, 2003–2010

	Number of antibiotics given (%) per diagnosis				
	2003	2004	2006	2008	2010
Pulmonary infections (n = 3,738)					
Beta-lactamase-sensitive penicillins (J01CE)	98 (17.0)	90 (16.9)	121 (14.3)	208 (25.5)	248 (24.2)
Cephalosporins (J01DB-J01DD)	190 (33.0)	197 (36.9)	287 (33.8)	219 (26.8)	237 (23.1)
Penicillins with extended spectrum (J01CA)	51 (8.9)	50 (9.4)	84 (9.9)	92 (11.3)	92 (9.0)
Tetracyclines (J01AA)	63 (11.0)	67 (12.5)	76 (9.0)	66 (8.1)	86 (8.4)
Fluoroquinolones (J01MA)	28 (4.9)	28 (5.2)	56 (6.6)	54 (6.6)	63 (6.2)
Combinations of penicillins (J01CR)	1 (0.2)	3 (0.6)	22 (2.6)	36 (4.4)	54 (5.3)
Skin and soft-tissue infections (n = 2,064)					
Beta-lactamase-resistant penicillins (J01CF)	109 (29.1)	90 (29.1)	144 (31.8)	140 (31.0)	157 (32.9)
Lincosamides (J01FF)	78 (20.9)	64 (20.7)	90 (19.9)	95 (21.1)	77 (16.1)
Cephalosporins (J01DB-J01DD)	72 (19.3)	45 (14.6)	64 (14.1)	47 (10.4)	60 (12.6)
Beta-lactamase-sensitive penicillins (J01CE)	34 (9.1)	33 (10.7)	41 (9.1)	54 (12.0)	54 (11.3)
Combinations of penicillins (J01CR)	8 (2.1)	5 (1.6)	7 (1.5)	22 (4.9)	33 (6.9)
Fluoroquinolones (J01MA)	27 (7.2)	36 (11.7)	29 (6.4)	31 (6.9)	20 (4.2)
Female lower urinary tract infection (n = 894)					
Penicillins with extended spectrum (J01CA)	54 (35.3)	58 (35.6)	94 (43.3)	101 (56.7)	97 (53.0)
Fluoroquinolones (J01MA)	37 (24.2)	53 (32.5)	41 (18.9)	21 (11.8)	28 (15.3)
Nitrofurantoin (J01XE)	6 (3.9)	8 (4.9)	5 (2.3)	21 (11.8)	19 (10.4)
Trimethoprim (J01EA)	34 (22.2)	31 (19.0)	56 (25.8)	21 (11.8)	17 (9.3)
Cephalosporins (J01DB-DD)	15 (9.8)	12 (7.4)	12 (5.5)	7 (3.9)	14 (7.7)
Trimethoprim with sulphonamides (J01EE)	3 (2.0)	1 (0.6)	7 (3.2)	5 (2.8)	4 (2.2)

Codes in parentheses are classifications from the World Health Organization Anatomical Therapeutic Chemical Classification System [6].

30.9% to 33.5%, of patients received antibiotics on the day of the survey over the study years. For comparison, the European Surveillance of Antimicrobial Consumption (ESAC) surveys, which were based on a protocol similar to ours, showed that an average of 30.1% (range 19–59%) [7] and 29.0% [8] of the patients received antimicrobials in 2006 and 2009, respectively. Standardised PPS methods for reviewing medical information is a reliable tool to describe patterns of antimicrobial use in hospitals [7,9-13]. When data are aggregated, variation is small between the separate studies, despite the expected variation in PPS methodology [14] that was previously noted in smaller studies [10,12].

We found that the prevalence of HAI treated with antimicrobials was of the same order of magnitude as reported for other European countries [15] and comparable to the 8.9–11.3% obtained in the national PPS performed twice a year since 2008 by the Swedish Association of Local Authorities and Regions (data not shown).

In our surveys, the indication for antimicrobial treatment was documented in the medical records in 82.3–85.2% of the cases, which is high compared with other studies [7,8,12]. A documented indication for treatment is important to evaluate compliance with treatment guidelines and rational use of antibiotics [7-9,12].

When we started our surveys, recommendations for antibiotic treatment in hospitalised patients were not as standardised as for some common diagnoses treated in general practice. However, the following had been published: national recommendations for indications and duration of surgical prophylaxis since 1998 [16,17], treatment of mild to moderately severe CAP in 2004 [18], treatment of community-acquired uncomplicated lower UTI in women in 2007 [19], and recommendations for the prevention of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in 2007 [20]. Analyses after the surveys in 2003 and 2004 showed that the proportion of women with community-acquired lower UTI treated with fluoroquinolones (24.2–32.5%), and the overall use of cephalosporins (23.6-24.2% of all antibiotics), particularly in adults with CAP (33.0–36.9%), seemed too high and that the duration of surgical prophylaxis often exceeded one day. Thus, the interventions before the surveys in 2006 and onward were focused on improvement in these areas.

The surveys in 2008 and 2010 suggest that the desired improvements were achieved for UTI and CAP. Also, the proportion of lower UTIs among all treated infections decreased from a maximum of 12.7% in 2004 to 9.0% in

2010, possibly as a result of increased awareness during the feedback process not to treat asymptomatic bacteriuria. Increased use of the combination of penicillins and beta-lactamase inhibitors was probably an effect of the desire to decrease cephalosporin and quinolone use, as recommended in the ESBL-control programme [20]. Increasing awareness of antimicrobial resistance among prescribers in Sweden might also have contributed to the decreased use of cephalosporins and fluoroquinolones. These positive changes are supported by data on hospital consumption based on pharmacy sales [2]. We used an audit and feedback approach as the main intervention. Previously it has been shown that persuasive as well as restrictive approaches may affect antibiotic use [21]. However, the context in which the evidence is to be implemented plays a crucial role in the choice of methodology [22], which we addressed since feedback was given with local data. In modern interventions the role of evidence, context and facilitation is emphasised within the framework Promoting Action on Research Implementation in Health Services (PARIHS), and should be considered for future interventions [23].

It can be argued that the analysis should be restricted only to the subset of hospitals participating in all surveys, but because the coverage was so high, this should only play a minor role.

We found that compliance with evidence-based recommendations for surgical prophylaxis was poor, since the recommendation for most surgeries is only a single dose. This needs further attention, monitoring and intervention. Even if some of the prolonged prophylaxes were misclassified and were actually early treatments, they were not documented as such and were still not in accordance with existing recommendations [16,17]. Interestingly, around one-third of patients receiving prophylaxis in our surveys did so for medical, not surgical, conditions, an observation that has not previously been given much attention. These findings were unexpected and need to be investigated further. Medical prophylaxis might be of particular importance for the development and selection of antibiotic resistance in immunocompromised individuals who often receive long-term prophylaxis in low doses.

Earlier studies in different settings have also pointed to the high antimicrobial pressure in hospitals and frequent inappropriate use and/or poor compliance with guidelines [9,12,24,25]. Several specific areas for improvement suitable for quality assessment and benchmarking have been suggested, such as the high rate of intravenous administration [9,12,25], poor compliance with guidelines [9], lack of culture before treatment [9,10], and prolonged surgical prophylaxis [9,12]. The usefulness of these indicators was further discussed in the ESAC studies [7,8,26].

In our study, parenteral treatments were given in 43.0–51.0% of the cases when excluding prophylaxis. This can be compared with more than 60% parenteral treatment in non-Swedish hospitals in other surveys [8,9,12]. One problem when comparing these figures is that it was not possible to assess the time that elapsed between admission and PPS. Duration of antibiotic treatment at time of PPS is not stated in several studies, including ours. In view of the comparatively short average LOS in Sweden, less than 50% on intravenous treatment is fairly low but can probably be decreased further, as previously shown in targeted interventions [27-29]. Our finding of a slowly increasing proportion of patients receiving intravenous antibiotics was paralleled by a slow increase of the mean antimicrobial pressure of 40.3–45.6 DDD per 100 admitted adult patients and a decrease in the average LOS in Swedish hospitals. The antibiotic pressure in acute care hospitals has continued to increase as measured by sales data [2]. These findings suggest that hospitalised patients in Sweden are more ill and require more intensive treatment than in previous years. When hospitals in the Baltic region were compared with one Swedish hospital, it was suggested that patients in Sweden were more severely ill compared with the other countries [12]. This should be kept in mind when analysing the proportion of intravenous antibiotic treatments as a quality indicator for rational antibiotic use. To improve comparative data analysis in the future, it would be advantageous to document the illness score, for instance with the McCabe score.

Relevant cultures are a prerequisite for rational antibiotic use. In Swedish hospitals, cultures were drawn before treatments in 62.1–75.4% of cases depending on the type of infection. This is more than the 19.7-64.5% reported from university hospitals in five European countries [9] but fewer than the 85% reported from Norway [10]. Cultures before treatment are becoming increasingly important for patient safety, particularly in HAI, because resistance rates are increasing and the time to adequate antibiotic treatment is the most important factor for clinical outcome in severe infections [30]. This suggests that there is room for improvement.

The strength of our PPS method was the nationwide coverage and the fact that local Strama groups were given immediate access to their own data for systematic feedback to prescribers.

Weaknesses in the PPS methodology itself [14] and differences in case mix within clinical specialties and among hospitals mean that benchmarking should be performed with caution and comparisons should be focused on the performance of the same unit over time [8,9,12,24,25,31]. Another disadvantage with the present PPS method is the laborious way that data are collected. Even though data from our surveys are somewhat 'old' they are still relevant for benchmarking and monitoring of compliance and treatment patterns for different diagnoses in Swedish hospitals. In contrast to other publications of PPS surveys we describe

how data have been used for widespread coordinated national feedback and interventions which were later followed up. Furthermore, our surveys informed the ESAC surveys, particularly regarding the survey protocol, and are therefore important for comparing antibiotic stewardship over time in the European Union.

We found that the repeated nationwide PPS were successfully implemented and have contributed knowledge on indications for use of antimicrobials in Swedish hospitals. The compliance with treatment recommendations for treatment of CAP and lower UTI in women has improved after interventions, while the duration of surgical prophylaxis still seems to be too long.

National and local recommendations are a cornerstone of antimicrobial stewardship. Structures like the multidisciplinary local Strama groups are of vital importance for local feedback and implementation of treatment recommendations and for the success and sustainability of antimicrobial stewardship programs. However, the laborious PPS should be replaced by IT-based systems for automatic retrieval of intention-to-treat data from digital records.

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Authors' contributions

Otto Cars: initiated study, designed and planned the study, analysed data and planned interventions. Mats Erntell designed and planned the study, collected data, validated data, analysed data and planned interventions. Johan Struwe, Peter Ulleryd, Inga Odenholt, Mårten Prag and Håkan Hanberger designed and planned the study, collected data, analysed data and planned interventions. Katarina Skärlund and Gunilla Skoog designed and planned the study, validated data, analysed data and planned interventions. Gunilla Skoog, Johan Struwe, Håkan Hanberger and Mats Erntell wrote the manuscript.

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Meeting report: Pre-exposure Human Immunodeficiency Virus Prophylaxis in the EU/EEA: Challenges and Opportunities, Stockholm April 2016

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The ECDC held an expert meeting in Stockholm on 27–28 April 2016 to discuss practical considerations for pre-exposure prophylaxis (PrEP) implementation in Europe. The meeting focused on four key areas: (i) eligibility criteria for PrEP in Europe; (ii) appropriate models of service delivery; (iii) cost-effectiveness of PrEP, and (iv) routine monitoring of people on PrEP.

PrEP is the regular use of an antiretroviral medication by people who are uninfected to prevent the acquisition of HIV infection. Currently Emtricitabine/Tenofovir Disoproxil Fumarate (TDF/FTC) or tenofovir alone is used. Since 2010, the efficacy of oral PrEP has been shown in four randomised controlled trials [1-4]. In 2015, the World Health Organization (WHO) recommended that PrEP should be offered as an additional prevention option for people at substantial risk of HIV infection as part of combination prevention approaches [5].

In the European Union/European Economic Area (EU/EEA), men who have sex with men (MSM) are disproportionately affected by human immunodeficiency virus (HIV) and other sexually transmitted infections (STI) [6,7]. Consequently, strengthening efforts to reduce the incidence of HIV and STI among MSM is a priority for the European Centre for Disease Prevention and Control (ECDC), which recently published comprehensive guidance on HIV and STI prevention among MSM [8] and an opinion encouraging countries to consider integrating PrEP into their existing HIV prevention packages for those most at-risk of HIV infection, starting with MSM.

Eligibility criteria for pre-exposure prophylaxis in Europe

Elske Hoornenborg from the AMPrEP project in Amsterdam, the Netherlands, provided an overview of eligibility criteria for PrEP. Review of PrEP studies, demonstration projects and existing guidelines show that eligibility criteria are very similar. WHO guidelines recommend PrEP for population groups with HIV incidence › 3%; United States (US) Centers for Disease Control and Prevention guidelines recommend PrEP for MSM at substantial risk of HIV, and European AIDS Clinical Society (EACS) guidelines recommend PrEP for MSM or transgender people with inconsistent condom use with casual partners or an HIV positive partner not on treatment, with recent STI or use of post-exposure prophylaxis (PEP) [5,9,10].

Key issues emerging from the presentation and following discussion include:

- Eligibility criteria may need to be adapted to reflect the epidemiological context, since population groups at high risk of HIV differ between countries in Europe. MSM at high risk for HIV acquisition are a key group for which PrEP is being considered in many EU/EEA countries.

- The need (i.e. those at high risk of HIV) and demand (i.e. those coming forward for PrEP or accepting if offered) of PrEP should be considered separately when formulating eligibility criteria.

- Eligibility criteria should ensure that PrEP use maximises public health benefit and cost- effectiveness.

- Some country representatives expressed concerns about people who do not meet eligibility criteria but are still obtaining PrEP. However, the evidence to-date suggests that most MSM seeking PrEP self-select, i.e. they are at high risk of HIV.

Appropriate models of service delivery

Sheena McCormack, from University College London (UCL), United Kingdom (UK), presented an overview of options for delivering PrEP, including delivery in clinic-based services, community-based services, by HIV

specialists, primary care physicians, peers and online. She pointed out that whichever model is chosen, consideration must be given to suitable systems for purchasing drugs, additional resource requirements and how best to integrate PrEP into existing services. Integrating PrEP should be relatively straightforward for countries with services offering HIV and STI diagnosis and treatment and PEP, as PrEP is relatively simple to prescribe as there are limited drug choices and few side effects or drug interactions.

Key issues emerging from the presentation and following discussion include:

- Feasible options will depend on the country context and the way in which the health system is organised. In some countries, primary care physicians provide HIV and STI treatment and care and could deliver PrEP, but, in others, HIV care and follow up is provided by HIV or infectious diseases specialists.

- Given differences in country contexts, it is not feasible to make Europe-wide recommendations. Each country will need to consider where HIV/STI testing and treatment are best delivered. However, European guidance on general principles and minimum standards, e.g. for safe prescribing, quality of care and monitoring, and maximising the benefits of PrEP as a prevention tool, would be helpful.

- Encouraging people who are at risk but who are HIV negative to engage with health services is critical, and MSM-friendly services can facilitate this.

- Community-based services should have appropriate referral links and pathways in place to ensure that people on PrEP receive follow-up care and routine monitoring. Specific concerns about online delivery of PrEP include how to promote adherence and provide follow-up care, as well as how to ensure that people are purchasing genuine drugs and reduce the risks associated with stock outs of drugs.

Cost and cost-effectiveness of PrEP

Valentina Cambiano (UCL) and Nigel Field (UCL and Public Health England, UK) presented work on the cost-effectiveness of PrEP among MSM in the UK, using two different models, and the work by Brooke Nichols and colleagues (Erasmus Medical Center, Rotterdam) in the Netherlands.

Available evidence suggests that significant reductions in drug prices will be needed for PrEP to be considered cost-effective (now) if the time horizon under consideration is only short-medium term. However, each infection averted now is averting health service antiretroviral therapy costs for many decades to come and so it is appropriate to consider a long-term time scale (e.g. 80 years). Based on the modelling conducted by Cambiano and colleagues and by Nichols and colleagues, PrEP is likely to prove to be cost effective, although in the Netherlands only if PrEP is taken on demand considering a long time horizon. Presenters pointed out that making the public health case for an intervention such as PrEP, which has a substantial short-term budget impact but potential for substantial longer-term savings in cost and public health benefit, is challenging.

Key issues emerging from the presentation and following discussion include:

- Demonstrating the impact of PrEP on new HIV infections outside of clinical trials will be critical. Positive results from France, where PrEP is currently implemented, and from demonstration projects showing a reduction in new infections will be important evidence to aid decision makers considering PrEP.

- As individual countries might need to conduct their own cost-effectiveness studies, some guidance to standardise these cost-effectiveness studies would be useful. Some participants in the meeting were doubtful whether the cost-effectiveness arguments would be of value in convincing policymakers, as decisions are more strongly influenced by the short-term budget impact.

- The cost of the drugs is the key barrier to free provision of PrEP by public health services. Costs are expected to drop once generic drugs become available in Europe.

Monitoring of people on PrEP

The key points related to routine clinical and public health monitoring of people on PrEP such as adherence, drug resistance and regular STI screening were covered in three presentations.

Pep Coll (Barcelona Checkpoint, Spain) provided an overview of the evidence about adherence to PrEP. Studies have shown that PrEP is efficacious if it is taken as prescribed (in the range of 90%). Ensuring adherence to the dosing regimen is crucial whether PrEP is taken daily or on demand. The barriers to adherence include stigma, lack of community acceptance of PrEP, the need to conceal PrEP use, chemsex, mental health problems, social factors, and mobility.

Robert Grant (University of California, San Francisco, US) discussed the issue of drug resistance in the context of PrEP. Concerns have been raised that generalised or inappropriate PrEP use could result in the development and transmission of drug-resistant strains of HIV. Drug resistance during PrEP use and PrEP trials has been low. A systematic review of drug resistance in PrEP trials found that there were five cases of incident drug resistance in 9,222 people in the active PrEP arms, i.e. the overall risk of resistance was 0.5%. The risk of drug resistance is higher in people with acute HIV infection when they start PrEP, i.e. in the window period, but is low in those who seroconvert while taking PrEP. There

is a case report of oral FTC/TDF PrEP failure to prevent HIV infection despite good adherence. This was a very particular case involving the acquisition of an extensively resistant virus mutated strain. One strategy to mitigate the risk of drug resistance could be the use of more sensitive assays to detect acute HIV infection in the window period.

In her second talk, Sheena McCormack discussed the impact on other STIs following the introduction of PrEP. Both overall European Union/European Economic Area (EU/EEA) and UK data show that bacterial STIs were increasing among MSM before PrEP, particularly among high risk MSM. Data from the UK PROUD study, which was conducted among HIV-negative MSM with a high burden of self-reported STI, show that there was no difference in the proportion with an STI between those on PrEP and those not on PrEP after 12 months, with both groups followed up for HIV and STI every 3 months. The incidence of STIs among MSM is increasing and is likely to continue to increase in Europe with or without PrEP. PrEP can contribute positively to STI control by increasing regular asymptomatic screening, prompt treatment and partner notification, at the same time as providing support to MSM who want to reduce risk behaviour.

Key issues emerging from the presentations and following discussions include:

- Lack of access to PrEP through health services will contribute to adherence problems, because if users are purchasing PrEP online they might not receive quality products, or find it hard to continue to pay or the supplies will not be reliable.

- The rise in practicing condomless sex resulting in greater exposure to STIs by those on PrEP is of concern to some stakeholders. In particular there are concerns that widespread PrEP use could lead to an increase in the incidence of MDR gonorrhoea, although this has not been seen in the US or in France so far. In France, rates of gonorrhoea among PrEP users have actually dropped even though rates of testing have increased in this risk group. In the UK, data from the PROUD study indicates that there is still a good level of condom use in this risk group.

- Clear evidence and messages to various stakeholders (policymakers, public health experts, clinicians, community representatives, etc.) about PrEP and STIs (e.g. that STI rates are already high in those MSM who would benefit most from PrEP, or that rates of STI are increasing with or without PrEP) will be critical. However, an additional increase in STIs is still likely (as was the case historically with similar major developments such as the introduction of oral contraceptives) and the health services need to plan for this eventuality.

- PrEP should be provided as part of a comprehensive package which will also allow for earlier diagnosis and linkage to care of STIs and for other interventions that may reduce the incidence of STIs.

- Surveillance systems should be adapted in order to monitor the use of PrEP, including use outside public health systems, and PrEP failures to ensure suitable measures are carried out to maximise the effectiveness of this prevention strategy.

Conclusions

PrEP should not be considered in isolation but as an additional option for people at substantial risk of HIV infection as one element of a combination prevention approach. There may be several models of service provision that may deliver PrEP effectively to those population groups at highest risk of HIV and the final choice will be determined by the specificities and organisation of countries' health services. The current cost of PrEP remains the main obstacle for implementation in the European setting. The second main obstacle is the potential impact of PrEP on risk behaviour by an already high risk population. However, a well-planned PrEP service will make good use of the need for PrEP users to attend regular check-ups ensuring prompt diagnosis, treatment and the offer of partner notification, while providing specific support to MSM who want to reduce their risk behaviour. Meeting participants identified a number of priority activities that that could be considered to support policy and implementation of PrEP in the EU/EEA, including: updating the current ECDC evidence-based guidance on HIV and STI prevention among MSM to include the new evidence on PrEP implementation; developing a model/tool to support comparable national cost-effectiveness studies; working with Member States to identify minimum standards and principles for service delivery; exploring the possibility of using national surveillance data to estimate the number of people in need of PrEP; identify standard indicators to monitor PrEP and explore the potential to use European HIV cohorts to monitor PrEP use and impact.

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Conflict of interest

None.

Authors' contributions

TN wrote the first draft of the manuscript. AP critically reviewed the paper and gave input to the content, which was incorporated in the report. Both authors read and approved the final manuscript.

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