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Successful control of the first OXA-48 and/or NDM carbapenemase-producing *Klebsiella pneumoniae* outbreak in Slovenia 2014–2016

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SUMMARY

Background: Carbapenemase-producing Enterobacteriaceae (CPE) occur only sporadically in Slovenia.
Aim: To describe the first Slovenian carbapenemase-producing (CP) *Klebsiella pneumoniae* and *Escherichia coli* outbreak which occurred at the tertiary teaching hospital University Medical Centre Ljubljana from October 2014 to April 2015.
Methods: A CPE-positive case was defined as any patient infected or colonized with CPE. A strict definition of a contact patient was adopted. Measures to prevent cross-transmission included cohorting of all CPE carriers with strict contact precautions and assignment of dedicated healthcare workers, cohorting of all contact patients until obtaining the result of screening cultures, systematic rectal screening of contact patients, and tagging of all CPE-positive cases and their contacts. Educational campaigns on CPEs were implemented. Clinical specimens were processed using standard procedures. Pulsed-field gel electrophoresis (PFGE) was used to determine relatedness. Multi-locus sequence typing was performed on CP *K. pneumoniae* isolates that belonged to different pulsotypes.
Findings: Before the outbreak was brought under control, 40 patients were colonized or infected with OXA-48 and/or New Delhi metallo-β-lactamase (NDM)-producing CPE; in 38 patients OXA-48 and/or NDM-producing *K. pneumoniae* was detected, in seven OXA-48 and/or NDM-producing *E. coli* was found together with *K. pneumoniae*, and in two patients only CP *E. coli* was isolated. The outbreak was oligoclonal with two major CP *K. pneumoniae* clusters belonging to ST437 and ST147 in epidemiologically linked patients.
Conclusion: Initial standard control measures failed to prevent the outbreak. Once the problem had been recognized, strict infection control measures and the education of healthcare workers contributed to the successful control of the outbreak.

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Introduction

Multidrug-resistant Enterobacteriaceae have become a major public health threat [1]. Among these, carbapenemase-producing Enterobacteriaceae (CPE), which are frequently resistant to many other antibiotics, represent an important emerging threat to healthcare systems. The extent of CPE spread differs considerably from country to country with temporal trends showing progressive spread of CPEs and worsening of the epidemiological situation as demonstrated by the EUSCAPE project. For example, rapid spread of OXA-48 and New Delhi metallo-β-lactamase (NDM) carbapenemases was noted [2–4].

According to EUSCAPE data, Slovenia was one of the few European countries where CPEs occurred only sporadically [3]. From 2010, when systematic laboratory surveillance of Enterobacteriaceae with reduced susceptibility to carbapenems began, until 2014, CPEs were rarely detected, and even then mainly in surveillance samples. Most frequently OXA-48- or NDM-producing *Klebsiella pneumoniae* was isolated, followed by VIM-producing *Enterobacter cloacae*. Rarely *Escherichia coli* (mostly with OXA-48 and VIM carbapenemase) and other CPEs were also detected (M. Pirs, unpublished data). The most frequent risk factor for CPE colonization and/or infection was previous hospitalization abroad, with Serbia notably in first place, followed by other Balkan countries, Italy and other CPE-endemic countries. During the last data call for EUSCAPE, Slovenia remained at epidemiological stage 1 even though at the regional level all neighbouring countries reported sporadic hospital outbreaks or regional spread and, in the case of Italy, an endemic situation [3].

In the last week of October 2014, OXA-48-producing *K. pneumoniae* was detected in two patients in two different wards, neither of the two patients had recently been hospitalized in a foreign country; however, their contact turned out to be patient zero who was recently transferred from an intensive care unit (ICU) in Serbia and who was colonized with different CPEs producing OXA-48 and NDM carbapenemase. A CPE outbreak followed with OXA-48 and/or NDM-producing or co-producing *K. pneumoniae*; in some patients OXA-48 or NDM-producing *E. coli* was also detected. We report the investigation of the first hospital outbreak of CPE in Slovenia and the challenges faced in controlling it during the 15 months from October 2014 to February 2016.

Methods

Setting

The University Medical Centre Ljubljana (UMCL) is a tertiary teaching hospital with approximately 2200 beds and 100 ICU beds. The outbreak involved several medical wards – different internal medicine, infectious diseases and surgical departments. Three major ICUs (one medical, two surgical) were primarily affected. Among the activities of the dedicated infection control unit (InfCU) are laying down hospital guidelines for infection control, outbreak control management, organizing educational activities for healthcare workers (HCWs) and tracking carriers of multidrug-resistant (MDR) bacteria and their contacts during current hospitalizations and readmissions.

Definition of cases and outbreak period

A CPE-positive case was defined as any patient infected or colonized with CPE regardless of the epidemiological data. In the first phase of the outbreak a very strict definition of a contact patient was adopted – all patients who were hospitalized in the affected ward were tagged as a contact patient. When the outbreak was coming under control at the end of the first phase, contact patients were defined less strictly as those who shared a room with a CPE-positive case and/or who shared HCWs with a CPE-positive case during their current hospitalization; strict definition remained only for ICU patients (if a CPE-positive case was hospitalized in ICU, all ICU patients underwent regular CPE surveillance).

The outbreak period was defined as beginning on October 1st, 2014 (the day of admission of patient zero) and ending on February 9th, 2016 when the last documented transmission occurred. The first phase of the outbreak extended from October 2014 to February 2015; the second phase began in March/April 2015.

Infection control programme

Prior to the outbreak, initial standard control measures tailored to prevent transmission of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae were applied to the control of CPE. These measures included contact precautions with isolation of patients and/or cohorting of patients, including hand hygiene for HCWs, patients and visitors. Dedicated cleaning, disinfection, and tagging of the patients in the hospital information system (HIS) was performed as well as active surveillance for colonized patients according to risk stratification of patients. These measures did not include strict isolation of patients nor cohorting of HCWs.

Measures to prevent cross-transmission included (a) cohorting of all CPE carriers with strict contact precautions and assignment of dedicated HCWs; (b) cohorting of all contact patients until obtaining the result of CPE screening cultures; (c) systematic rectal screening of contact patients – weekly in regular wards, biweekly in ICUs with CPE-positive cases; (d) tagging of all CPE-positive cases and their contacts by InfCU in the HIS, which alerts HCWs that extra procedures must be put into action in accordance with the hospital infection control guidelines; (e) limited transfer of CPE carriers and contact patients to other wards (due to the need for subspecialist care this was not always possible); (f) upon discharging CPE-positive cases, rooms were cleaned and disinfected according to a strict protocol which included terminal aerosol disinfection with hydrogen peroxide. Contact patients with three consecutive negative rectal CPE surveillance cultures were released from the contact cohort, but they remained tagged in the HIS. Rapid communication between microbiological laboratories and InfCU was established to ensure early warning and timely sharing of any pertinent epidemiological information; access to online results of microbiological testing was already routinely available.

If a CPE-positive case was transferred to another hospital or long-term care facility, the institution was notified in advance, and if a contact patient was transferred, the receiving institution was notified in advance and asked to perform follow-up rectal screening. Readmission of a CPE-positive case or contact patient was automatically detected during registration due to

tagging in HIS. Hospital management and department heads were apprised of the situation and kept up-to-date with the development of the outbreak. InfCU also notified other hospitals in Slovenia as well as the Public Health institute and the National Infection Control Committee at the Ministry of Health of the Republic of Slovenia.

Educational campaigns on CPEs and the reinforcement of infection control practices (notably hand hygiene as well as equipment and environmental cleaning, injection safety, and standard and isolation precautions) were implemented by the InfCU for HCWs in affected wards.

Information about CPEs was also provided to CPE-positive patients and contact patients as well as their families/visitors in a leaflet.

Microbiological methods

Clinical specimens were processed using standard procedures [5]. Screening for CPE carriage was performed by plating surveillance samples (mainly rectal swabs) on to chromogenic agar chromID Carba Smart (bioMérieux, Marcy l'Etoile, France) and tryptic soy enrichment broth supplemented with 50 mg/L vancomycin which was subcultivated on to chromID Carba Smart following overnight incubation at 37°C. Bacterial colonies were identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility was determined using the disc diffusion method and interpreted according to current EUCAST criteria (www.eucast.org). Susceptibility to colistin and tigecycline was determined using gradient diffusion strips (Biomérieux). To analyse cumulative susceptibility of CPE isolates, the antimicrobial susceptibilities of the first isolates by species per patient and by carbapenemase were analysed. Screening for carbapenemase production was performed for all Enterobacteriaceae with reduced susceptibility to carbapenems according to the current EUCAST guidelines [6].

Carbapenemase characterization

LightMix modular carbapenemase kits (manufactured by TIB Molbiol, distributed by Roche Diagnostics, Berlin, Germany) were used to identify blaKPC, blaNDM, blaVIM, blaIMP and blaOXA-48-like carbapenem resistance genes (additional information in Supplementary Appendix A).

Pulsed-field gel electrophoresis (PFGE) was used to determine relatedness among carbapenemase-producing (CP) *K. pneumoniae* and *E. coli* isolates using *Xba*I restriction endonuclease (additional information in Supplementary Appendix A).

Multi-locus sequence typing (MLST) was performed on CP *K. pneumoniae* isolates that belonged to different pulsotypes according to Diancourt (http://bigsdb.pasteur.fr/klebsiella/) (additional information in Supplementary Appendix A).

Results

Epidemiological investigation of the outbreak

During the last week of October 2014, OXA-48-producing *K. pneumoniae* was detected in two patients in two different UMCL wards. Neither had a history of hospitalization in a foreign country. The InfCU investigation found that during hospitalization in the main surgical ICU, both were in contact with a patient who had been transferred from a hospital in Serbia three weeks before and who tested negative for CPE colonization upon admission (the patient did test positive for meticillin-resistant *Staphylococcus aureus* and carbapenem-resistant *Acinetobacter baumannii* carriage). At the same time as the two index patients were detected, this patient was transferred to another ICU and surveillance cultures upon admission showed that the patient was colonized with OXA-48-producing *K. pneumoniae*, OXA-48-producing *E. coli*, NDM-producing *E. coli*, and NDM-producing *Proteus mirabilis* (four months later NDM-producing *Providencia stuartii* was also detected). Based on the epidemiological data, namely the hospitalization in Serbia, this patient was determined to be patient zero; no other potential source was found as CPEs are only sporadic in Slovenia. Following negative initial CPE rectal surveillance cultures, no further screening was performed until the patient was transferred to the second ICU. Further investigation showed that the patient who had been hospitalized in a Serbian hospital following severe trauma with tetraparesis for a total of three days was transferred to UMCL on the fourth day when MDR surveillance samples were immediately taken.

As this was now considered an outbreak, local epidemiologists and the Public Health Institute were notified. From the time of admission of patient zero to detection of index patients, more than 200 contact patients had already been discharged. With the help of epidemiologists, most of those patients were screened for CPE colonization. At the affected wards new CPE-colonized patients were detected, eight in November and four in December (Figure 1). Some of them were in direct contact with patient zero in the ICU, whereas others came into contact with ICU contacts of patient zero who were subsequently transferred to regular wards. In a few new CPE-positive cases there was no direct contact with colonized patients; however, they were in adjacent rooms and were cared for by the same HCWs (Figure 1; Supplementary Appendix B, Figure B1). This led to a stricter screening policy which was later adopted into national guidelines. All CPE carriers were cohorted and, where possible, dedicated HCWs were assigned.

During the first phase of the outbreak, a total of 17 patients with OXA-48 or NDM-producing *K. pneumoniae* (in some cases CP *E. coli* was also isolated) were found in five different UMCL wards (including two ICUs), all with an epidemiological connection to the outbreak. In January 2015, *K. pneumoniae* co-producing OXA-48 and NDM was detected in two newly CPE-colonized patients with clear epidemiological connection to the outbreak. With all precautions in place, the outbreak began to wane in February 2015 with only one newly colonized patient and no additional spread in the most affected ward where patient zero remained in ICU (Figure 1; Supplementary Appendix B, Figure B1). As the outbreak was now largely under control, a less strict screening policy was implemented in regular wards; in ICUs a biweekly screening policy remained in place.

In March/April 2015, new momentum built up with the spread of CP *K. pneumoniae* in a third major ICU with nine newly discovered cases (Figure 1). The most probable breach of infection control measures occurred in the ICU where patient zero was again hospitalized. Even though dedicated ICU HCWs were assigned, they assisted in an emergency resuscitation in

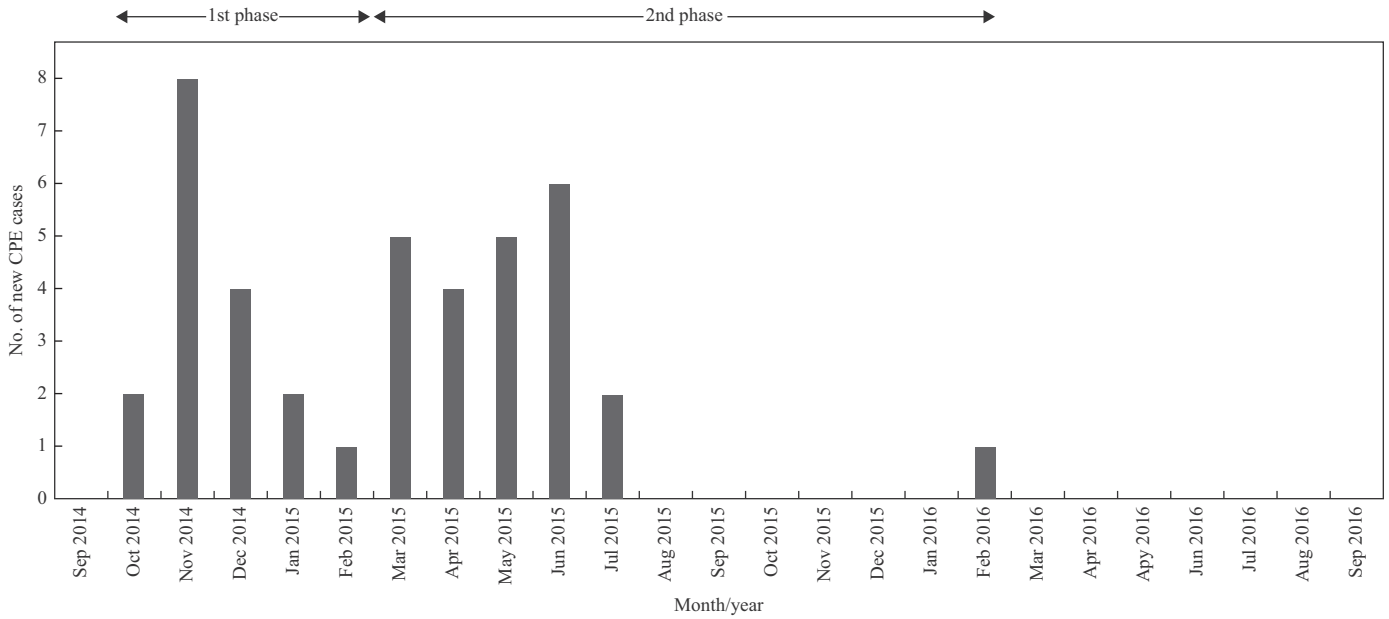

Figure 1. Timeline of newly discovered carbapenem-resistant Enterobacteriaceae (CPE)-positive cases during the outbreak.

an adjacent regular ward. One of the new contacts was transferred to the third ICU where the second phase of the outbreak began. In May/June, 11 new cases were detected. Strict infection control measures were implemented, and so the outbreak waned again and essentially stopped in July 2015 (Figure 1). During the second phase, five additional UMCL wards were affected. Unfortunately, as several CPE carriers were patients with a prolonged hospital stay and prolonged colonization, another spread occurred in February 2016 in a fourth ICU (Figure 1; Supplementary Appendix B, Figure B1).

A total of 40 patients were affected. The majority (90.0%, 36/40) had positive rectal surveillance cultures and more than half (52.5%, 21/40) of the patients were only colonized. In three patients CPEs were isolated from blood cultures — in two cases OXA-48-producing *K. pneumoniae* and in patient zero NDM-producing *P. mirabilis*. In 10 (25.0%) patients CPEs were isolated from urine, in eight (20.0%) from the lower respiratory tract, in five (12.5%) from wounds/tissue samples, and in two patients (5.0%) also from the abdominal or thoracic cavity.

At least five patients were transferred to other hospitals in various Slovenian regions where no further spread was documented; in all cases hospitals were forewarned. At least two patients were hospitalized in non-acute wards and four elderly patients returned to their long-term care facilities. At least two patients were transferred to spas for the rehabilitation of trauma patients and patient zero was transiently admitted to a central Slovenian rehabilitation facility. At least 14 patients have since died, most of them from unrelated causes as the patients were all polymorbid and mostly elderly; CPE infection contributed to the deaths of one patient with positive CPE blood cultures and of another elderly patient.

During the outbreak period, eight additional patients with recent hospitalization in foreign countries were detected at admission with positive CPE surveillance cultures. They were systematically placed under contact precautions isolation. No secondary CPE-positive patients were detected in their wards, none had any contact with outbreak patients, genotyping showed distinct pulsotypes, and they were thus excluded as a potential source of that part of the outbreak.

Duration of CPE colonization

Sufficiently detailed data were available only for six patients as the rectal surveillance cultures of CPE-positive cases were only repeated when indicated, i.e. upon readmission. Colonization with CP *K. pneumoniae* lasted at least five months (median: 18.8 months). The longest colonization was documented for two patients who were colonized for more than two years until their deaths. One important observation was that one patient was transiently negative two months after initial colonization and again positive after six months. In one patient, surveillance cultures from a stool sample performed on outpatient basis were positive. When the patient was readmitted a week later, rectal swab surveillance cultures were negative.

Microbiological investigation of the outbreak

Microbiological investigation of the outbreak was complicated from the outset as patient zero was colonized with four different CPEs producing OXA-48 or NDM carbapenemase, namely *K. pneumoniae*, *E. coli*, *P. mirabilis*, and *P. stuartii*.

In total, CPEs were found in 40 patients, 31 had only *K. pneumoniae*, seven had both *K. pneumoniae* and *E. coli*, and in two only *E. coli* was detected. CP *K. pneumoniae* was isolated from 38 patients. When carbapenemase genes were taken into account, there were 42 different isolates, as some of the patients had multiple strains with different carbapenemase genes (Table I). The majority of the CP *K. pneumoniae* were susceptible to colistin (92.5%) and tigecycline (71.1%). CP *E. coli* was isolated from nine patients (Table I). All isolates were susceptible to colistin and tigecycline. In two patients NDM-producing *P. mirabilis* was isolated and NDM-producing *P. stuartii* was detected in one.

Table I
Carbapenemase-producing Enterobacteriaceae and carbapenemase genes among 40 outbreak patients

Isolate	No. of patients	Carbapenemase genes	No. of patients with specific carbapenemase genes
Klebsiella pneumoniae	38	OXA-48	22
		OXA-48 and NDM	18
		NDM	2
Escherichia coli	9	OXA-48	8
		OXA-48 and NDM	2
		NDM	1
Proteus mirabilis	2	NDM	2
Providencia stuartii	1	NDM	1

Pulsed-field gel electrophoresis analysis of CP *K. pneumoniae* revealed one major cluster belonging to ST147; all isolates were OXA-48 producers. The other two major clusters were related; both belonged to ST437 and included isolates that produced OXA-48, NDM, or that co-produced OXA-48 and NDM carbapenemase. Some of the patients had different strains producing different carbapenemases that were found in both major related clusters belonging to ST437. Additionally, two unrelated CP *K. pneumoniae* pulsotypes were found belonging to two different STs (Figure 2). We have also demonstrated the presence of different STs over a longer period of time (in patient zero). All CP *E. coli* available for typing belonged to different pulsotypes (in patient zero, one *E. coli* was an NDM-producer and the other OXA-48); no clusters were found (Figure 2).

Discussion

We report the investigation of the first hospital outbreak of CPE in Slovenia. The epidemiological investigation has shown that the two index patients had been in contact with a patient who had recently been transferred from an ICU in Serbia and who was colonized with four different CPEs producing OXA-48 and NDM carbapenemases. Unfortunately, initial screening using CPE surveillance rectal cultures was negative, and there was no follow-up screening until the patient was transferred to another ICU. The reason why the initial screening failed to detect CPE colonization may be that the time from the colonization with CPEs in the Serbian ICU to rectal sampling in UMCL was too short, which is why our guidelines generally recommend taking two consecutive surveillance samples, preferably one week apart, in patients with critical epidemiological risk factors for CPE carriage such as hospitalization in foreign hospitals [7]. It is possible that the colonization would have been detected during the initial screening if the patient had had polymerase chain reaction (PCR)-based CPE screening. Even though the laboratory capacity exists, this is rarely performed and only when indicated by InfCU.

Initial infection control measures mirroring those for ESBL outbreaks failed to stop the spread, and strict screening policy as part of a multi-modal infection control strategy, which was later adopted into national guidelines, was implemented [8,9]. Cohorting of patients and the assignment of dedicated HCWs proved to be crucial [10]. However, during weekends and holidays strict cohorting of staff was not always possible. There was also a breach of cohorting while performing resuscitation on the ward. The majority of the affected patients were ICU patients, most of whom required antibiotic treatment contributing to the increased colonization pressure [11]. In UMCL, antimicrobial stewardship is well established at hospital and ward levels. No additional measures for antimicrobial prescribing were identified that could have helped to control the outbreak. Several of the CPE-positive cases remained hospitalized, and no additional transmissions occurred in those wards. The second phase of the outbreak probably resulted from a lapse in infection control measures due to HCW crossover, namely, dedicated ICU HCWs assisted in an emergency resuscitation in an adjacent regular ward. The last transmission, more than six months later, occurred at the fourth ICU where CP *K. pneumoniae* from a long-term carrier was transmitted to a contact patient. A multi-modal infection control strategy seems to be most effective. The involvement of public health authorities, hospital management, HCWs in affected wards, CPE carriers and their families is needed to control the CPE outbreak, as documented in various outbreak situations [8,9,12—14].

Several patients experienced prolonged colonization; the longest colonization was documented for two patients who were colonized for more than two years until they died. Whereas detailed data were available only for six CPE-positive patients who remained hospitalized or were readmitted, five out of six were colonized for more than six months. The duration of CPE colonization is difficult to anticipate and, whereas many patients do experience spontaneous decolonization within six months to a year, a significant proportion of patients can remain colonized for several years [11,14—16]. We have also noted that two CPE carriers transiently tested negative. This could be directly linked to the quality of sampling, but it might also be related to the CPE load in the stool. Such observations where patients' CPE surveillance samples had transiently tested negative have been made before and represent a serious problem upon readmission of known CPE carriers as it is difficult to determine at what point it is safe to declare the patient CPE-free [9,14,16,17]. This experience has led UMCL to the recommendation that, to determine whether spontaneous decolonization of a CPE carrier has occurred, a stool sample (not rectal swab) should be provided for cultivation; ideally PCR screening in combination with cultivation should be used.

The outbreak developed in a relatively straightforward fashion from the epidemiological point of view. The situation was more complex from the microbiological viewpoint, as patient zero was colonized with four different CPEs with either OXA-48 or NDM carbapenemase and some subsequent CPE-positive cases had simultaneously both CP *K. pneumoniae* and CP *E. coli*. Based on molecular typing data of CP *K. pneumoniae*, the outbreak was oligoclonal with two closely related clusters belonging to ST437 and one cluster belonging to ST147. The main spread appears to have occurred via highly successful strains of OXA-48 and/or NDM-producing *K. pneumoniae*. As all OXA-48 or NDM-producing *E. coli* belonged to different pulsotypes, horizontal gene transfer via highly transmissible plasmids from CP *K. pneumoniae* probably occurred. Such horizontal gene transfer may contribute to the

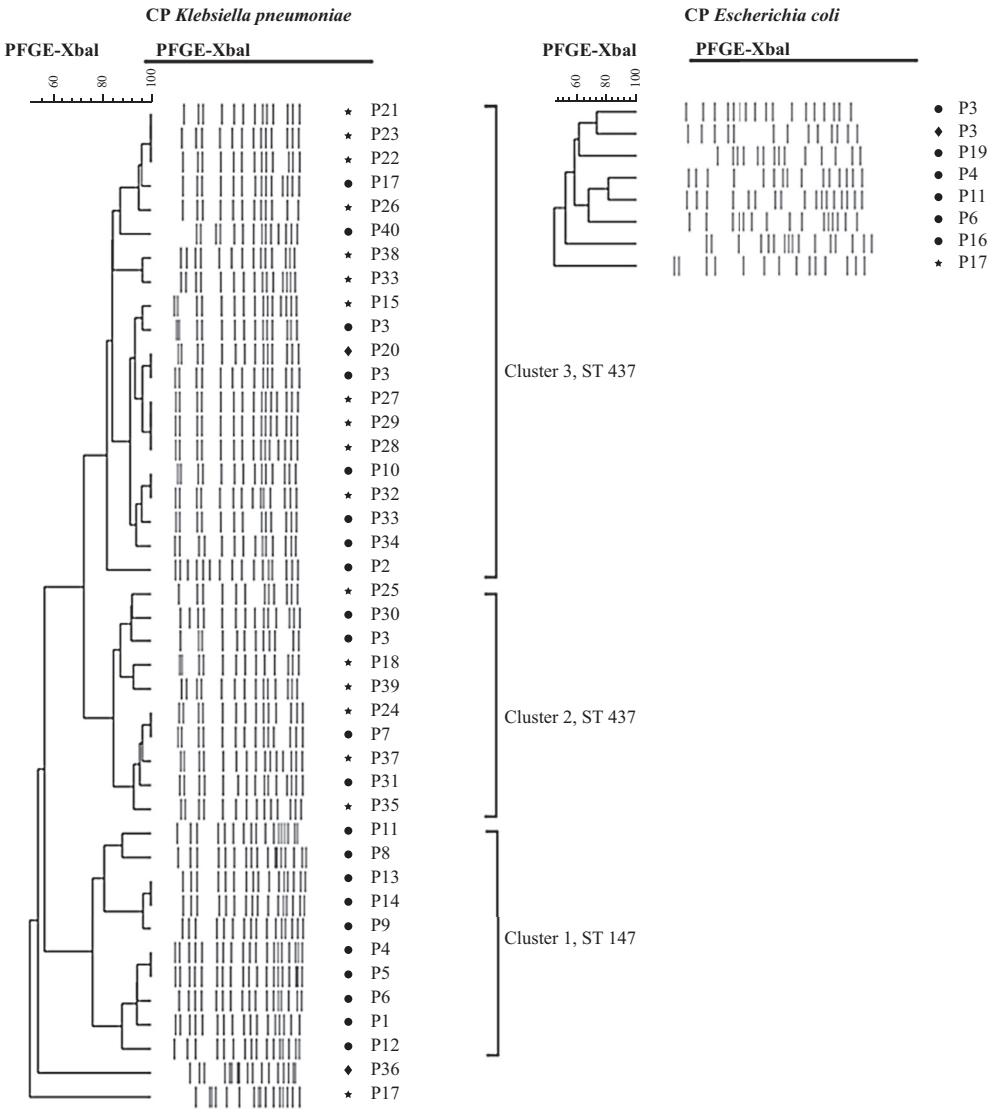

Figure 2. Pulsed-field gel electrophoresis (PFGE) banding patterns after *Xba*I digestion of carbapenemase-producing (CP) *Klebsiella pneumoniae* and *Escherichia coli* isolates. Percentage similarities are shown above the dendrogram; patient numbers and carbapenemase genes are shown on the right.

spread of CPEs [18]. It also complicates the interpretation of genotyping data — the presence of several different clusters can indicate the colonization with multiple strains or multiple simultaneous outbreaks; in such cases the transmission chain can be further elucidated with a detailed epidemiologic investigation, an analysis of plasmids, and the use of more discriminatory genotyping such as whole-genome sequencing [19]. In our case with only sporadic detection of CPEs in UMCL (and in Slovenia in general) detailed epidemiologic investigation showed a connection even in case of different STs without any connection to other CPEs that were introduced into UMCL at the time. Both prevalent sequence types 437 and 147 have so far been rarely described as CP strains [20—22].

Another interesting observation is the detection of OXA-48 and NDM co-producing *K. pneumoniae* early in the outbreak in ST437 clusters. Co-production of carbapenemases of different classes can complicate treatment as next-generation β-lactam/β-lactamase inhibitor combinations currently available are only suitable for serine carbapenemase and are inactive against metallo-β-lactamases. Co-production of OXA-48 and NDM, which can present a serious treatment challenge, has been described in several studies [22—29].

Slovenia was one of the few countries where CPEs occurred only sporadically and until October 2014 it remained at epidemiological stage 1 [3]. In October 2014, the first CPE outbreak occurred and, due to extensive efforts of UMC, HCWs in affected wards, and especially InfCU staff, the outbreak remained limited to UMCL. Slovenia was thus transiently at stage 2a with a single hospital outbreak; however, due to the successful control of the outbreak we are now back to epidemiological stage 1 with sporadic CPE occurrence.

In conclusion, initial control measures mirroring those for ESBL transmission failed to prevent or stop the spread of our first CPE outbreak, mainly due to high transmissibility of the outbreak strain and partly also because of late recognition of patient zero. Genotyping of the CP *K. pneumoniae* and *E. coli*

has demonstrated that outbreak strains of CP *K. pneumoniae* were oligoclonal, whereas other CPEs were most likely affected by the horizontal spread of a highly transmissible plasmid. Strict infection control measures, control of patient movement and limiting patient transfers between wards, a strict screening policy coupled with a comprehensive educational campaign at all levels, and strong management support contributed to the successful control of the outbreak. The greatest hindrances to outbreak control were the high number of transfers between wards (and in certain ICUs) and the fact that the assignment of dedicated HCWs was not always possible. During the outbreak, the UMCL InfCU policy was optimized and has subsequently been adopted as the national InfCU policy for CPE control.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.10.022.

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