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Diffusion and transmission of carbapenem-resistant *Klebsiella pneumoniae* in the medical and surgical wards of a university hospital in Milan, Italy

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Summary Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is emerging as a public health problem worldwide. In Italy, a remarkable increase in CRKP cases has been reported since 2010. In this study, CRKP diffusion, distribution and in-hospital transmission trends were evaluated in a university hospital in Milan, Italy, from January 2012 to December 2013. Isolates from 63 newly detected CRKP-positive patients were genotyped, and possible transmission was determined by combining the molecular results with data concerning the patients' admission and in-hospital transfers. Most of the cases (90.4%) were from general medical and surgery wards, and the remaining 9.6% were from the intensive care unit. Fifteen of the 46 hospital-associated cases (32.6%) were attributable to in-hospital transmission. After the

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Active surveillance;
Active screening

introduction of targeted and hospital-wide control measures, the transmission index significantly decreased from 0.65 to 0.13 ($p = 0.01$). There was also a decrease in the overall nosocomial case incidence, from 0.37 to 0.17 per 1000 person-days ($p = 0.07$). Our findings indicate that the spread of CRKP in Northern Italy hospitals may go far beyond high-risk settings (i.e., intensive care units) and that strict surveillance should be extended to general areas of care.

Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), the resistance of which is largely due to broad-spectrum β-lactamase production (i.e., carbapenemases) [1], are becoming some of the most challenging multidrug-resistant pathogens worldwide [1—3]. Infections that are caused by CRKP are difficult to treat because of the very limited treatment options that are available, which consequently often lead to poor patient outcomes, increased morbidity and mortality, and higher hospital costs [4—6]. Hospitals are particularly important reservoirs of these pathogens because of the combination of seriously ill patients, intensive antibiotic use, and close patient/patient and patient/healthcare worker contact, which encourage the spread of CRKP and infectious outbreaks [7—11].

Bundled interventions consisting of strict hand hygiene, the isolation of infected or colonized patients, and the active surveillance of high-risk wards, such as intensive care units (ICUs), have been recommended as key strategies for preventing CRKP transmission in healthcare facilities [12,13]. However, there is little evidence as to what is the best and most sustainable preventive approach, particularly in contexts in which CRKP is endemic [14,15], which may at least partially explain the disparity in the infection control practices that are used in different hospitals [16,17].

The CRKP infection number has sharply increased in Italy over recent years [18,19], and a series of hospital outbreaks have been described [20—22]. Furthermore, data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) shows that the overall proportion of CRKP isolates from clinical specimens increased from 2.2% in 2009 to 19.4% in 2012 [18]. However, the CRKP infection burden varies widely from hospital to hospital, possibly because of location, case mix, and human and material resource differences [18].

Following an increase in the CRKP infection number at our hospital, we introduced a hospital-wide protocol for implementing a set of control measures in January 2013. The aim of this paper was to describe the trends of newly detected CRKP cases and the relative contribution of patient-to-patient transmission in the year prior to and after its introduction.

Methods

Setting

Luigi Sacco Hospital is a university teaching hospital in Milan, Italy, which admits an average of 20,000 patients per year. It has 506 licensed beds in 27 wards, each of which has its own dedicated medical and nursing staff, including: 339 beds belonging to 19 medical (mainly internal medicine and infectious disease) wards; 159 to eight surgery wards (general surgery, cardiac surgery, orthopedics and urology), and eight to a single ICU. The medical wards have rooms with 2—3 beds, all of the surgery wards have rooms with two beds, and the ICU has eight single cubicles. During the study period, the mean individual patient hospital stay duration was eight days.

Study design and definitions

This study retrospectively analyzed all of the newly identified CRKP cases between January 1, 2012, and December 31, 2013.

A case patient was defined as someone whose clinical or screening samples led to CRKP isolation, and a record was made of each case patient's age, gender, major underlying disease(s), and history of hospitalizations and/or antibiotic treatments in the previous three months; the date of the current hospital admission and the date of the first CRKP detection; the admission ward and any inter-ward transfers; and the discharge or death date.

The patients who were identified as having CRKP within the first 72 h of admission were defined as community-associated cases or imported healthcare-associated cases if they had been

exposed to healthcare settings during the previous three months; those identified by means of a culture that was obtained 72 h after hospital admission were defined as hospital-associated cases.

The patients who had stayed in the same hospital ward during overlapping periods or within a maximum time window of four weeks were defined as being epidemiologically linked [23]. In-hospital transmission was considered to have occurred if genotypically related strains were detected in the epidemiologically linked patients in whom CRKP isolates were first detected more than 72 h after admission. The transmission index was calculated as the number of cases that were attributable to transmission (secondary cases) divided by the number of cases that were not acquired by transmission (primary cases).

The hospital-associated CRKP case incidence was calculated as the number of new cases per 1000 person-days of hospitalization for the semester.

Microbiological testing

Isolates that were obtained from routine microbiological cultures of relevant clinical samples (e.g., urine, wound exudates, bronchial secretions, blood, and peritoneal fluid) were identified at the species level and tested for antimicrobial susceptibility using the automated Vitek 2 system (BioMérieux, Marcy l'Etoile, France). The tested antimicrobials included beta-lactams (ampicillin, amoxicillin-clavulanate, piperacillin-tazobactam, cefoxitin, cefotaxime, ceftazidime, cefepime, imipenem, meropenem, and ertapenem), quinolones (ciprofloxacin), aminoglycosides (amikacin and gentamicin), and trimethoprim/sulfamethoxazole. Susceptibility to colistin and tigecycline was verified with the E-test (BioMérieux, Marcy l'Etoile, France). Interpretation of the susceptibility patterns was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [24].

Rectal swabs, which were collected for epidemiological purposes, were screened for carbapenemase-producing *Enterobacteriaceae* by direct inoculation in selective chromogenic agar, ChromID Carba (BioMérieux Marcy l'Etoile, France). The presumptive carbapenemase-producing *Enterobacteriaceae* colonies were identified by color appearance according to the manufacturer's instructions. Suspected colonies were subcultured onto blood agar plates and were submitted to identification and susceptibility testing with the Vitek 2 automated system.

Phenotype testing

Phenotype testing, which was utilized to differentiate between the β-lactam resistance mechanisms in the CRKP isolates, was performed with a double-disk synergy test (KPC + MBL Confirm ID kit, Rosco Diagnostica A/S, Taastrup, Denmark). The kit consists of four tablets containing meropenem (substrate), meropenem + aminophenylboronic acid (an *K. pneumoniae*-carbapenemase inhibitor), meropenem + dipicolinic acid (an metallo-β-lactamase inhibitor) and meropenem + cloxacillin (an AMPc-β-lactamase inhibitor). Briefly, a pure culture suspension of the isolate that was to be tested was plated on a Muller Hinton agar plate. The four tablets were placed on the inoculated agar plate at a sufficient distance to allow for proper inhibitory zone measurements. After an overnight incubation at +37 °C, the inhibitory zones were measured and compared according to the Manufacturer instructions.

Molecular typing

All of the initial CRKP isolates from each patient were genotyped with automated repetitive extragenic palindromic polymerase chain reaction (rep-PCR) (DiversiLab system, BioMérieux Marcy l'Etoile, France). The band patterns were compared with the Pearson's correlation method with the DiversiLab web-based software. The isolates that had band patterns that were at least 95% similar were considered to be genetically related [25].

Infection control measures during the study period

Hospital-wide policies to prevent nosocomial carbapenem-resistant *Enterobacteriaceae* transmissions were introduced in January 2013 on the basis of an institutional protocol that was developed in accordance with the American Centers for Disease Control and Prevention (CDC) indications [12]. The provisions included the isolation of all CRKP-infected or CRKP-colonized patients in single rooms, hand hygiene enforcement (hydro-alcohol dispensers were placed at the entrance to all patient rooms) and environmental cleaning; the use of dedicated patient care equipment; and the use of disposable gloves and aprons. Rectal swab screening was indicated for all of the patients who were admitted to the ICU, patients with a previous CRKP infection/colonization history upon admission, and roommates of the patients who were diagnosed as having hospital- or community-acquired CRKP infections. The isolation measures were maintained

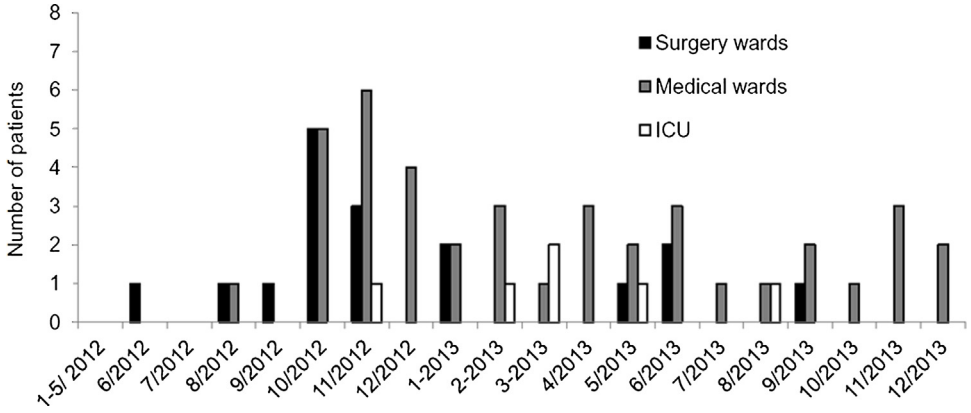

Figure 1 Temporal distribution of newly detected patients who were infected or colonized with carbapenem-resistant *Klebsiella pneumoniae* by hospital ward type (L.Sacco Hospital, Milan, 2012—2013).

until negative results were obtained from at least three clinical and/or screening specimens that were collected at three-day intervals.

The microbiology laboratory activated an automated alert system that sent e-mails to physicians and nurses in charge of the patient's ward and the members of the hospital infection control team (HICT) as soon as a CRKP strain was identified to prompt immediate actions according to the protocol. Two HICT members were responsible for contacting and/or visiting the wards in which new CRKP infection cases were detected to promote full compliance with the recommendations and to verify the presence of all of the equipment and materials.

Statistical analysis

The Chi-squared test was used to assess the transmission index differences in the year prior to and after the control policy introduction.

A Poisson regression was used to compare the new hospital-associated case incidence per semester.

The SPSS statistical software, version 11.0, was used for all of the analyses, and a p value of 0.5 or less was considered to be statistically significant.

Results

Patient data

During the study period, CRKP was detected in 63 patients. No cases were recorded in the first five months of 2012; however, between June and December, 28 patients were found to be infected or colonized, with a peak of 10 cases/month being recorded in October and November. Between January and December 2013, 35 additional cases were identified at an average rate of three cases/month.

Thirty-seven patients (58.7%) were hospitalized in medical wards, 20 (31.8%) were in surgery/post-surgery rehabilitation wards, and six (9.5%) were in the ICU. Overall, 14 of the 27 hospital wards had at least one CRKP-positive patient. Fig. 1 shows the temporal distribution of the newly detected cases by hospital ward type.

Most of the patients were elderly (median age, 75 years, range 22—91) and had debilitating underlying neurocognitive disorders (38%), cancer (33%), diabetes *mellitus* (27%), chronic gastrointestinal diseases (25%), cardiovascular diseases (22%), chronic obstructive pulmonary disease (21%), and/or chronic renal diseases (21%). Clinically severe infections occurred in four patients who were aged <50 years with immunodeficiency disorders (three with HIV infections and one with Crohn's disease).

Fifty-six patients (88%) had been admitted to healthcare facilities in our metropolitan area during the three months preceding the CRKP isolation: 62% to hospitals (19.4% to ICUs) and 38% to long-term care facilities. During the same period, 53 of the 63 CRKP-positive patients (84%) had received broad-spectrum antibiotics (mainly ceftriaxone, ciprofloxacin, or piperacillin-tazobactam).

CRKP was isolated late (after a median of 25 days, range 7—89) during the hospital stays in 46 of the patients (73%); therefore, they were considered to be hospital-associated cases. The remaining 17 cases (27%) were categorized as being imported healthcare-associated cases, and only two of these patients had a previously documented CRKP infection/colonization.

The median hospital stay duration was 40 days (range 5—201). Eleven patients (17.4%) died during their hospitalization: two were colonized by CRKP and nine had severe diseases that were caused by CRKP, including sepsis ($n = 2$), hospital-acquired pneumonia ($n = 2$), chronic wound infections ($n = 2$), peritonitis ($n = 2$), and pyelonephritis ($n = 1$).

CRKP isolates

In most cases, CRKP was isolated from clinical samples: urine ($n = 26$, 41.3%), surgical exudates ($n = 9$, 14.3%) or chronic wounds ($n = 6$, 9.5%), bronchial secretions ($n = 8$, 12.7%), blood ($n = 3$, 4.8%), and peritoneal fluid ($n = 2$, 3.2%). Nine patients had CRKP that was detected from rectal swabs: five were roommates of patients with a CRKP infection and four were patients who were screened upon admission to the ICU.

All of the CRKP isolates were resistant to β-lactams and ciprofloxacin; however, most were intermediately susceptible to gentamicin and tigecycline, all but three were susceptible to colistin, and only one was sensitive to trimethoprim/sulfamethoxazole (Fig. 2). Forty isolates (63.5%) were fully sensitive to only colistin, one was sensitive to only tigecycline (1.6%), and two (3.1%) were resistant to all of the tested antibiotics, including colistin. All of the isolates were phenotypically confirmed as carbapenemase producers.

Genotyping revealed six distinct cluster patterns and eight singletons. Twenty-seven isolates were defined as clone A, 11 as clone B, 10 as clone C, three as clone D, two as clone E, and two as clone F (Fig. 2). There were no significant variations in the antimicrobial susceptibility of the different clones. Amongst the major clones, A, B and C, 6/27 (22.2%), 2/11 (18.2%) and 2/10 (20%) of the isolates were resistant to gentamicin, and 10/27 (37%), 25/11 (18,2%) and 4/10 (40%) were resistant to tigecycline, respectively. Two of the three isolates that were resistant to colistin belonged to major clones A and B, and one was a singleton. There was no specific association between the clinical severity of the CRKP infections (as defined by fatal outcomes) and isolate genotypes (pattern A = 2 cases; patterns B, C and F = 1 case each; and singletons = 4 cases).

Genotypic relatedness of the isolates that were recovered from epidemiologically linked patients

Table 1 summarizes the epidemiological characteristics of the cases and the genotype profiles of the isolates. The isolates of most of the hospital-associated (93.5%) and imported (70.5%) cases belonged to one of the six cluster groups, with a clear prevalence of clone A (45.6% and 35.2%, respectively). A comparison of the genotype patterns of the isolates that were obtained from the 31 patients who were epidemiologically linked to other CRKP-positive patients made it possible to estimate that a transmission event occurred in 15 of the 46 hospital-associated cases (32.6%). Fig. 2 shows the transmission indices before and after the introduction of the control protocol. Most of the cases that were attributable to transmission ($n = 11$) occurred in 2012, before the control measures had been implemented. Six of these occurred in one general surgery ward and five occurred in the medical wards (four in the internal medicine wards and one in an infectious disease ward) to which two CRKP-infected surgical patients had been transferred. The four transmission episodes in 2013 (each including one index case and only one possible secondary case) occurred in three internal medicine wards and one infectious disease ward.

Fig. 3 shows that the transmission index significantly decreased from 0.65 (95%CI: 0.41—0.83) in the period between June and December 2012 to 0.13 (95%CI: 0.05—0.28) in the period between January and December 2013 ($p = 0.01$).

The hospital-associated case incidence

There was also a trend toward a decrease in the overall hospital-associated CRKP case incidence from a peak of 18 per 72,888 person-days in the last six months of 2012 (incidence 0.37 per 1000 person-days; 95%CI: 0.23—0.51) to 10 per 75,185 person-days in the last six months of 2013 (incidence 0.17 per 1000 person-days; 95%CI: 0.08—0.27) ($p = 0.07$) (Fig. 4).

Discussion

Carbapenem-resistant *K. pneumoniae* poses a number of challenges in terms of infection control and treatment, particularly in countries such as Italy where it has rapidly become endemic and there is a considerable likelihood of infectious outbreaks [20—22].

Most of the 63 CRKP-positive cases that were identified in our study over an 18-month period predominately involved elderly patients with debilitating clinical conditions who were hospitalized in general surgery and medical wards. These findings are in line with those of recent studies showing that the spread of CRKP in Italy is becoming a matter of concern in areas of care that were

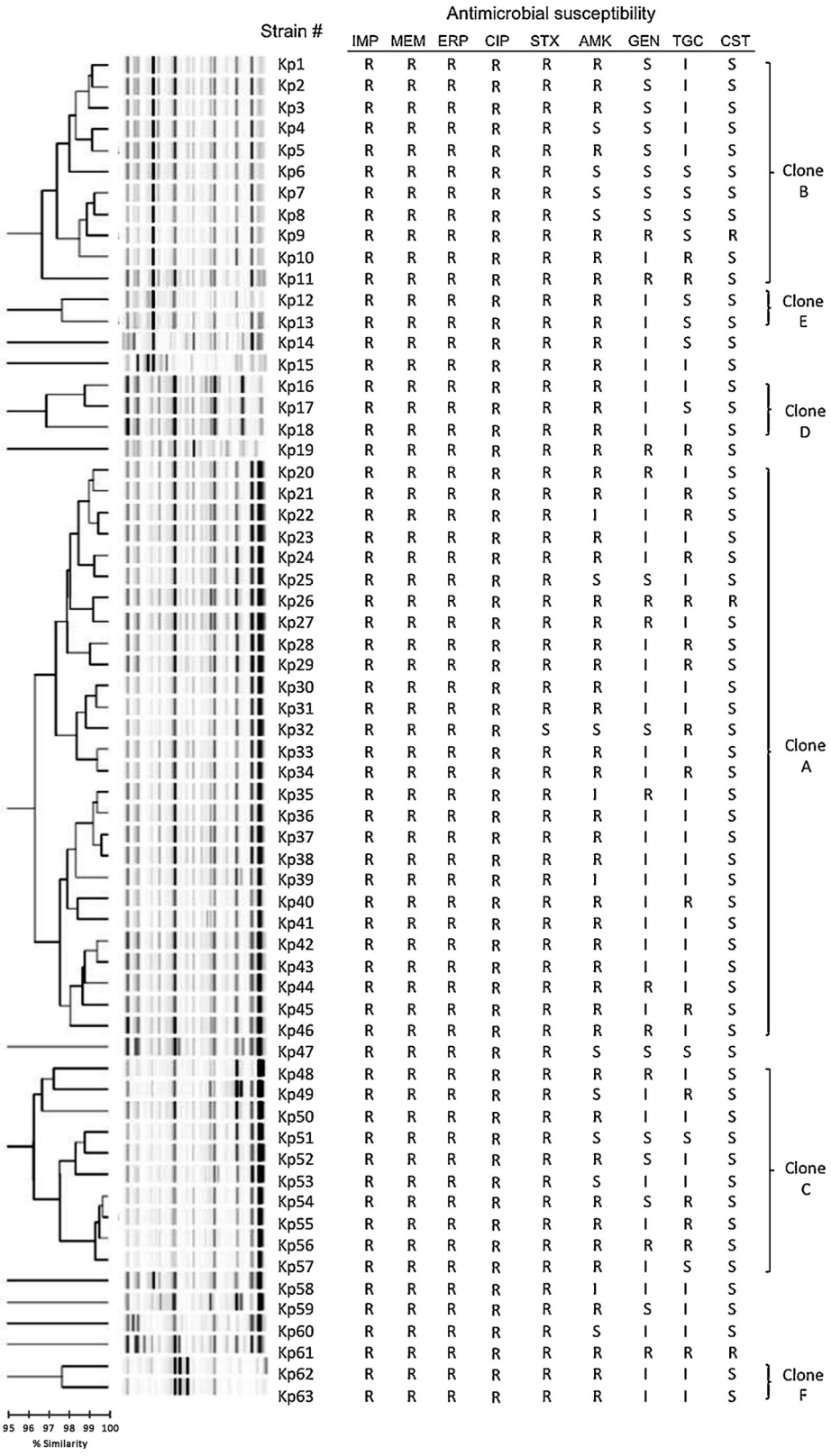

Figure 2 Dendrogram of repetitive sequence-based polymerase chain reaction patterns and the antimicrobial susceptibility of the observed carbapenem-resistant *Klebsiella pneumoniae* isolates. IMP = imipenem, MEM = meropenem, ETP = ertapenem, CIP = ciprofloxacin, STX = trimethoprim-sulfamethoxazole, AMK = amikacin, GEN = gentamicin, TGC= tigecycline, CST = colistin. S = sensitive, I = intermediate, R = resistant.

Table 1 The epidemiological characteristics and the genotypic profiles of isolates from the 63 observed patients who were infected or colonized with carbapenem-resistant *Klebsiella pneumoniae* (L.Sacco Hospital, Milan, 2012—2013).

CRKP genotype pattern	Case numbers					
	Overall	Hospital-associated cases	Imported cases	Epidemiologically linked cases	Non-epidemiologically linked cases	Possibly transmitted on the basis of epidemiological linkage and genotyping
Clone A	27	21	6	16	5	14
Clone B	11	7	4	2	5	—
Clone C	10	9	1	6	4	1
Clone D	3	2	1	1	2	—
Clone E	2	2	—	1	1	—
Clone F	2	2	—	1	1	—
Singleton	8	3	5	2	2	—
Total	63	46	17	31	20	15

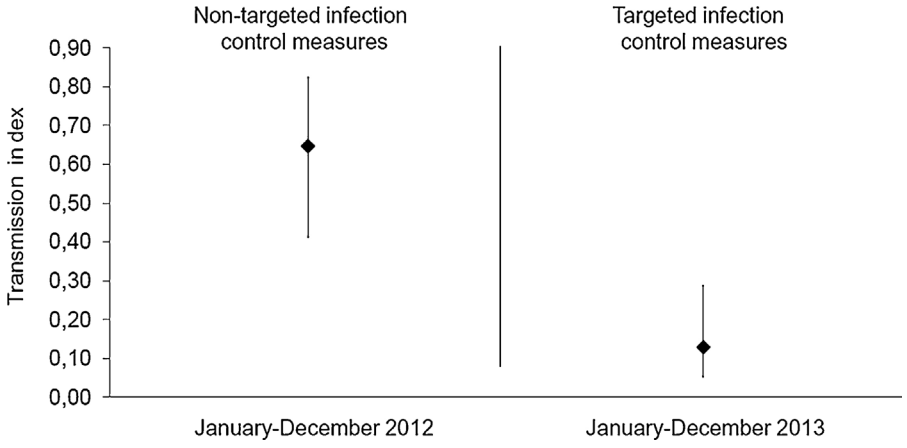

Figure 3 Carbapenem-resistant *Klebsiella pneumoniae* transmission indices before (January—December 2012) and after (January—December 2013) the introduction of a hospital-wide infection control protocol.

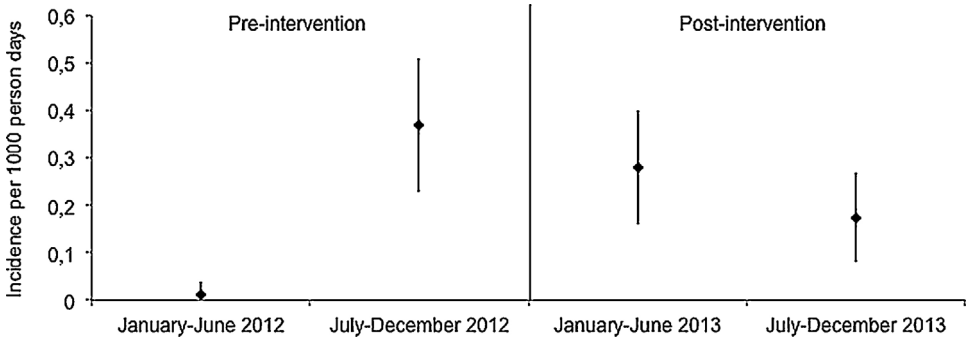

Figure 4 The hospital-associated infection or colonization incidence due to carbapenem-resistant *Klebsiella pneumoniae* before (January—December 2012) and after (January—December 2013) the introduction of a hospital-wide infection control protocol.

generally considered to be at lower risk in which one of the principal targets (and consequently a major reservoir) of CRKP is the geriatric population [26—28]. A possible change in the epidemiology of carbapenem-resistant *Enterobacteriaceae* from traditional high-risk settings (i.e., ICUs) to general care patients is also suggested to be a result of the study findings that were conducted in other countries. Poulou et al. [29] reported that 41% of 73 CRKP infections registered between 2009 and 2011 at a university hospital in Greece were identified in medical wards and 15% in surgical wards. Additionally, during a hospital-wide CRKP infection outbreak in Israel, the neurology and geriatric wards were amongst the most involved wards [11], and a recent state-wide survey of carbapenem-resistant *Enterobacteriacae* in Michigan (USA) found that 49% of the cases were detected in patients who were admitted to the general care ward [30].

Almost all of our patients had a history of hospitalizations and/or stays in long-term care facilities (LTCF) in the Milan metropolitan area, and the fact that CRKP was isolated early during the hospital stay of 27% (within 72 h) of these patients suggests that a substantial proportion of all of the CRKP cases detected in our region may be due to the hospital admission of patients who were previously colonized or infected with CRKP. Patient movements amongst the healthcare facilities belonging to a regional healthcare system can play an important role in the spread of antimicrobial resistance [31], and it was found that the introduction and dissemination of CRKP in acute care hospitals that were affected by recently described outbreaks were related to the transfer of infected or colonized patients from LTCFs [32,33].

To define the CRKP epidemiology in our hospital and to monitor the transmission events rapidly, the CRKP strains were analyzed with a semi-automated rep-PCR system that had a high discriminatory power in detecting clonal relationships during a bacterial outbreak [34]. The molecular results showed that most of the CRKP isolates belonged to three major clusters of genetically related groups, and the data regarding the typical spread of CRKP (i.e., the transmission of identical strains between epidemiologically linked patients) indicated that 32% of the hospital-associated cases were attributable to cross-transmission. However, it is important to note that the mechanisms underlying the spread of carbapenem-resistance in *Enterobacteriaceae* are complex and that epidemics may be due to the horizontal transmission of plasmids rather than clones [35]. Further studies using more sophisticated and costly molecular techniques are therefore needed to clarify the question.

The fact that the number of possible CRKP transmissions was highest in 2012 (transmission index 0.64) probably reflects the inadequacy of the infection control measures in our general surgical and medical wards because the hospital-wide introduction of our early warning alarm system and the implementation of a protocol promoting hand hygiene and ensuring the prompt adoption of precautionary measures (including the isolation of CRKP-positive patients in separate rooms) in January 2013 was followed by a significant reduction in transmission events.

Although no major outbreaks of CRKP occurred after the introduction of the control measures, the overall incidence of hospital-associated CRKP cases did not significantly decrease. This indicated the possible presence of unrecognized transmissions due to a hidden reservoir of asymptomatic carriers. A number of studies in high-risk healthcare settings, such as ICUs, have found that active surveillance that is aimed at identifying patients with asymptomatic gut colonization can be crucial in controlling the spread of CRKP [36,37]. Consequently, in accordance with the CDC guidelines [12], we introduced the active screening of rectal swabs that were taken from patients who were admitted to our ICU and patients with a known history of CRKP colonization/infection at admission as well as from the roommates of newly discovered CRKP-positive patients. However, this probably only provided limited information regarding the real extent of colonization pressure because most of our CRKP cases occurred in non-ICU wards, and many of these were not associated with close contacts between patients.

In conclusion, our findings highlight the importance of hospital protocols for preventing and controlling CRKP transmission and suggest that active CRKP screening in endemic regions should be extended to subsets of at-risk patients who are admitted to general care wards, particularly those transferred from other hospitals or LTCFs; to those with a recent history of broad-spectrum antibiotic treatments; and to older patients with chronic debilitating diseases. Further studies are needed to clarify the risk factors that can better identify candidates for CRKP screening and to define the cost-effectiveness of such a strategy.

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Competing interests

None declared.

Ethical approval

Not required.

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