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SHORT REPORT
Identification of a hidden outbreak due to the spread of a VIM-3-producing, extensive drug-resistant *Pseudomonas aeruginosa* (XDRPA) clone at a regional hospital in Taiwan

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SUMMARY

A review of the annual prevalence of *Pseudomonas aeruginosa* at a regional hospital in Taiwan revealed a significant increase in the incidence of extensive drug-resistant *P. aeruginosa* (XDRPA) from 2·1% in 2003 to 5·8% in 2007. The first XDRPA isolate was recovered in 2001 from the emergency ward. The widespread dissemination of XDRPA isolates to more than 10 other wards was discovered the following year. Six pulsotypes of 67 XDRPA isolates from 2006 onwards were identified and 91% were a single strain, suggesting the existence of a hidden outbreak. Prior to the recognition of the outbreak, the majority of cases were not considered to be healthcare-associated infections until molecular evidence was provided. A cohort measure was launched by the infection control practitioners that effectively controlled the outbreak. Patients with XDRPA were mostly referred from neighbouring long-term care facilities, which may have been the reservoir of the XDRPA clone.

Key words: Hidden outbreak, VIM-3, XDRPA.

Pseudomonas aeruginosa is one of the most important healthcare-associated pathogens, causing a wide range of mild to severe infections, particularly in immunocompromised patients or patients with cystic fibrosis [1]. The growing multidrug resistance in this organism has limited the treatment options in clinical settings and so the outcome for patients with multidrug-resistant *P. aeruginosa* (MDRPA) infection is generally worse than for individuals infected with relatively more susceptible *P. aeruginosa* [2]. The emergence of extensive drug-resistant *P. aeruginosa* (XDRPA), which is resistant to almost all available antibiotics, through a variety of mutational and horizontally acquired resistance mechanisms has further exacerbated the problem [3].

In Chang Gung Memorial Hospital (CGMH), Keelung, a retrospective analysis of the laboratory reports from the Clinical Microbiology Laboratory (CLM) revealed that the annual numbers (prevalence) of XDRPA cases had increased significantly from 16 (2·1%) in 2003 to 53 (5·8%) in 2007 ($P<0·0005$).

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The present study was conducted to investigate the associated problems.

CGMH is a 1088-bed, regional teaching hospital in northern Taiwan. It is a referral hospital for patients from the local area or residents from neighbouring long-term care facilities. *P. aeruginosa* was isolated and identified by standard methods at the CML of the hospital. The antimicrobial susceptibilities were determined by a standard disk diffusion method and interpreted according to CLSI guidelines [4]. The records from the CML and the healthcare-associated infection (HAI) surveillance system were retrospectively reviewed. For each patient, only the first isolate of *P. aeruginosa* was included for analysis. *P. aeruginosa* isolates with resistance or intermediate resistance to all antimicrobial agents tested (aztreonam, ceftazidime, cefepime, amikacin, gentamicin, ciprofloxacin, piperacillin, piperacillin-tazobactam, meropenem, imipenem) were defined as XDRPA. XDRPA isolates were retrospectively retrieved from the CML collection and subjected to molecular study.

The genetic relatedness of the XDRPA isolates was investigated by pulsed-field gel electrophoresis with *Spe*I digestion. Carbapenem resistance was investigated by PCR and sequencing as described previously [3]. The χ^2 test was used to identify significant differences. A difference was considered statistically significant when $P<0{\cdot}05$.

Between 2001 and 2009, a total of 7140 *P. aeruginosa* clinical isolates were identified. Of these, 217 (3·0%) were XDRPA isolates. The annual distribution of the XDRPA isolates and details of the specimen type and the ward in which they were identified are shown in Figure 1. The first XDRPA isolate was recovered in 2001 from the emergency ward. The widespread dissemination of the isolates to more than 10 other wards was discovered in the subsequent year, followed by an obvious reduction from 2003 to 2004. The number of XDRPA isolates increased again in 2005 and peaked in 2007. Throughout the study period, the XDRPA isolates were distributed widely in 17 of the hospital wards. The majority of isolates were recovered from respiratory tract specimens (51·6%) and urine (35·9%). The XDRPA isolates were most frequently identified from the chest wards (pulmonary care) (37·8%), surgery wards (23·5%), emergency ward and outpatient departments (OPDs) (19·8%). The majority of the patients with XDRPA infection were empirically treated with a colistin-based monotherapy or combination therapy when necessary.

Because a significant increase in the prevalence of XDRPA was noted from 2·1% in 2003 to 5·8% in 2007 ($P<0{\cdot}0005$), a total of 67 non-repeated XDRPA isolates were retrospectively collected between September 2006 and December 2008 to investigate their genetic relatedness. Six pulsotypes were identified, but the predominant pulsotype was pulsotype 1, which was identified in 61 (91·0%) of the isolates. The other five pulsotypes were found only sporadically in six isolates (Fig. 1). All of the pulsotype 1 isolates also carried the $bla_{\text{VIM-3}}$ gene, while none of the six isolates with other pulsotypes possessed the $bla_{\text{VIM-3}}$ gene. No other carbapenem-resistance genes, including imipenemases and oxacillinases, could be identified in these XDRPA isolates.

As shown in Figure 1, the pulsotype 1/VIM-3 clone of XDRPA appeared to have disseminated to at least 15 wards during an extended period of at least 3 years (2006–2008). The information was quickly forwarded to the infection control practitioners (ICPs). Although the HAI cases of XDRPA did not demonstrate a similar increase (Fig. 1), infection control measures were still implemented to prevent further spread of the pulsotype 1/VIM-3 clone. Cohort care of the patients with XDRPA infection was conducted from the beginning of 2008. The XDRPA prevalence significantly decreased from 5·8% in 2007 to 2·5% in 2008 ($P<0{\cdot}0005$) and remained low in 2009 (Fig. 1).

Outbreaks of HAIs are typically identified by ICPs through established surveillance systems. They may be identified due to a sudden increase in the incidence of infection caused by certain bacteria that are clearly associated with time and place [5]. In the present report, only a few XDRPA cases were reported as HAIs throughout the study period, and therefore, the XDRPA outbreak, caused by the widespread dissemination of the pulsotype 1/VIM-3 clone, was not noted earlier by the ICPs. The problem may be explained by the fact that more than half of the XDRPA isolates were recovered from respiratory specimens. To be categorized as having an HAI, patients with culture evidence from such specimens must also fulfil several clinical criteria [6]. Thus, although many XDRPA isolates had been identified, only a few were subsequently categorized as HAIs. As a result, the ICPs remained unaware of the hidden outbreak until definite molecular evidence was provided by laboratory personnel.

The significant increase in the annual prevalence of XDRPA cases became apparent in the retrospective analysis. However, because the XDRPA cases were

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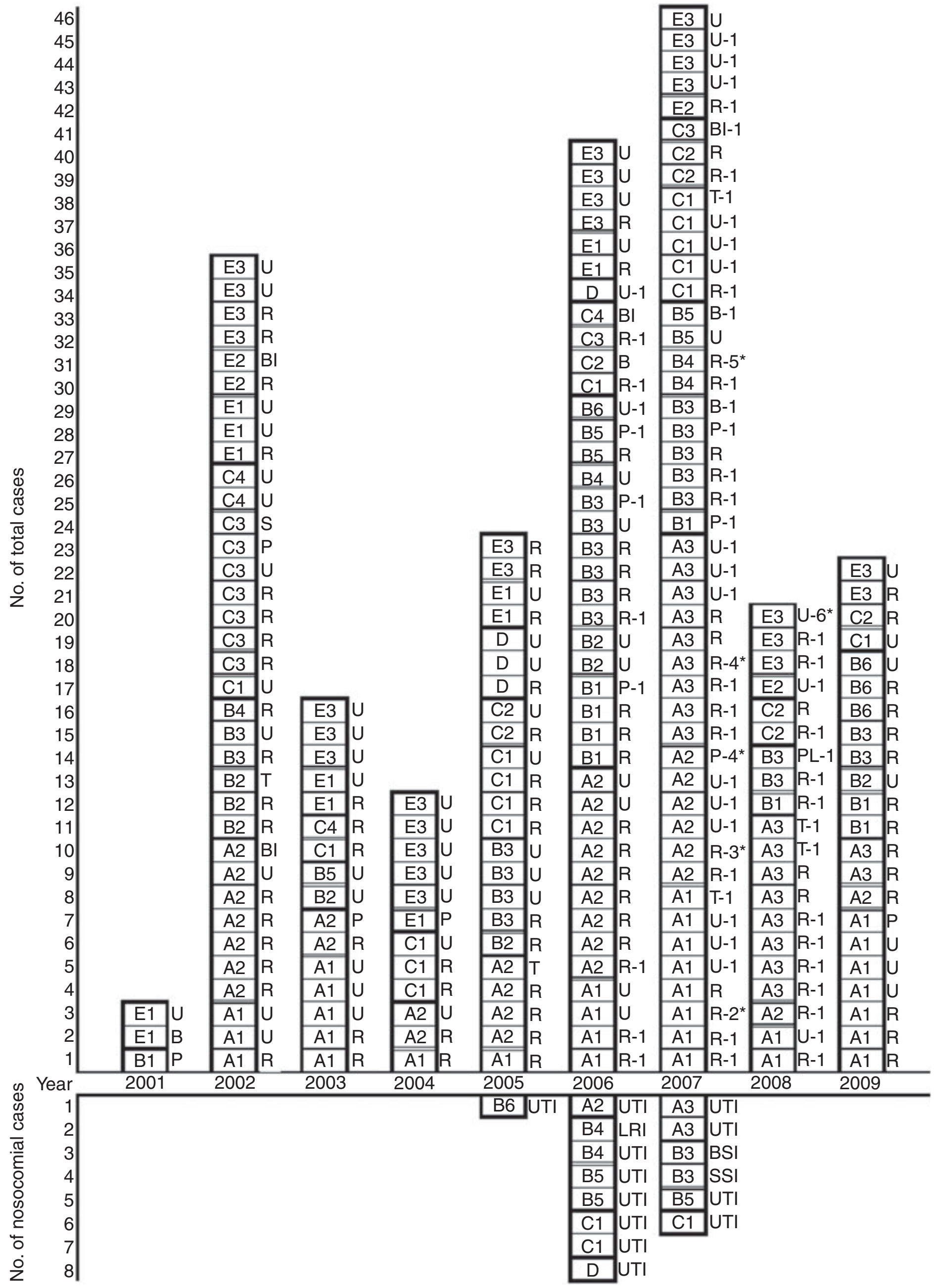

Fig. 1. The curve of the outbreak of extensive drug-resistant *P. aeruginosa* (XDRPA) infections. Each cell represents an XDRPA-infected patient. The wards from which the isolates were identified are indicated as A–E within the cells with the adjacent numbers indicating different wards (A, chest; B, surgery; C, internal medicine; D, paediatrics; E, emergency ward/outpatient department). The specimen types are indicated on the right side of each cell (R, respiratory specimens; U, urine; P, wound pus; T, tips; BI, bile; B, blood; PL, pleural effusion; S, stool). The pulsotypes are shown behind the recovery sites for the available samples. The majority of the isolates harboured the bla_{VIM-3} gene, except for those indicated with an asterisk (*). Cases of healthcare-associated infections are shown on the bottom of the figure, and the infection types are indicated (UTI, urinary tract infection; BSI, bloodstream infection; LRI, lower respiratory tract infection; SSI, surgical site infection).

widely distributed in 17 different wards, no significant increase was noted in the respective wards. Even in 2007, when the number of XDRPA cases peaked, the average number of XDRPA cases per month was <4. This number was too small to attract attention. Furthermore, although a rapid increase in the number of XDRPA isolates was observed in 2002, the subsequent decrease in the number of isolates over the following 2 years, most likely due to the occurrence of the severe acute respiratory syndrome (SARS)

outbreak in Taiwan, may have hindered the early discovery of the XDRPA problem [7, 8]. Although XDRPA incidence increased in 2005, the problem remained unidentified until 2006 when this study was initiated. Once it was discovered, with the implementation of only a simple but stringent cohort policy, the XDRPA prevalence soon reduced by half in the following years. The early identification of a hidden outbreak is one of the most important steps in hospital infection control [9].

In 2008, when XDRPA prevalence was reduced, the pulsotype-1/VIM-3 XDRPA clone still persisted. CGMH is a referral hospital in a region where many long-term care facilities are situated in neighbouring communities. Residents in long-term care facilities often suffer from many clinical situations, and antibiotics may often be prescribed unnecessarily [10]. If the pulsotype-1/VIM-3 XDRPA clone had already been widespread in these long-term care facilities, this clone is most likely to have been imported into the hospital with the admission of such patients. The hypothesis is supported by the substantial number of XDRPA cases identified in the emergency ward or OPD every year. With the implementation of the cohort policy in 2008–2009, these patients would then have received special care and hence, the avoidable spread of XDRPA would have been efficiently prevented.

In summary, an extended, hidden outbreak of XDRPA infection was identified by laboratory molecular investigation and was effectively controlled by cohort treatment measures. Communication between the referral hospitals and the neighbouring alternative healthcare facilities should be improved to reduce the possibility of such outbreaks.

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DECLARATION OF INTEREST

None.

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