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Outbreak Report

Social network and genomic analysis of an OXA-48 carbapenemase-producing Enterobacterales hospital ward outbreak in Ireland, 2018–2019

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SUMMARY

Background: Nosocomial transmission and outbreaks of carbapenemase-producing Enterobacterales (CPE) represent a challenge to healthcare systems. In July 2018, a CPE hospital ward outbreak was declared. Our aim was to investigate transmission patterns, using social network analysis and genomics in a nosocomial CPE outbreak.

Methods: A retrospective descriptive analysis of all patients (cases and contacts) admitted to a ward experiencing a CPE outbreak (2018–2019) was undertaken. A case had a negative CPE admission screen, and subsequent positive test. A contact shared a multi-bed area and/or facility with a case (>4 hours). Social networks, including genomics data and ward locations, were constructed. Network metrics were analysed.

Findings: Forty-five cases and 844 contacts were analysed. The median age of cases was 78 years (IQR 67-83), 58% (n=26) were male and 100% had co-morbidities. The median outbreak ward length-of-stay (LOS) was 17 days (IQR 10-34). OXA-48 CPE was confirmed in all cases and from 26 environmental samples. Social networks identified clusters by time, gender and species/sequence type/plasmid. Network metrics indicated potential super-spreading involving a subset of patients with behavioural issues.

Conclusion: Social networks elucidated high resolution transmission patterns involving two related OXA-48 plasmids, multiple species/genotypes and potential super-spreading. Interventions prevented intra-hospital spread. An older patient cohort, extended hospital LOS and frequent intra-ward bed transfers, coupled with suboptimal ward infrastructure, likely prolonged this outbreak. We recommend social network analysis contemporaneously with genomics (on case and environmental samples) for complex nosocomial outbreaks and bespoke care plans for patients with behavioural issues on outbreak wards.

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Introduction

Carbapenems are 'last line' agents used when other antimicrobials are ineffective, particularly to treat infections caused by antimicrobial resistant species of Enterobacterales. Since the early 2000s, there has been a steady global increase in infections with Enterobacterales that produce enzymes called carbapenemases which render the organisms resistant to carbapenems [1]. Carbapenemase-producing Enterobacterales (CPE) infections pose a significant threat to patients and healthcare systems, primarily due to limited treatment options and high mortality. CPE have a high potential to cause nosocomial outbreaks and represents a major public health threat worldwide [2—5].

In Ireland, the number of reported isolates from patients with newly-confirmed CPE increased by almost 15-fold between 2013 and 2018 (from 48 to 707), and has stabilised in recent years (at 965 in 2019 and 916 in 2020) [6]. Indeed, CPE was declared a National Public Health Emergency in Ireland in October 2017 [7,8]. Initial evaluations of the impact of measures taken suggest a positive effect on controlling the incidence of CPE acute hospitals in Ireland [9]. However, despite this positive impact, given the speed at which these organisms have spread globally and their increase in prevalence in Ireland [6,10—12,13], continued reports of hospital outbreaks are very likely.

OXA-48 is the most prevalent carbapenemase in Ireland, accounting for 70% of newly-confirmed cases in 2018 and 67% in 2021 [9,13]. Carbapenemase-encoding genes have shown a distinct ability to spread among several species via many plasmid versions and from many non-human and environmental sources [14]. Detailed characterisation of isolates with whole genome sequencing (WGS) can help clarify the extent of the diversity of spread of these organisms.

Social network analysis (SNA) is a valuable tool in outbreak investigation, used to establish the extent and nature of person-to-person transmission in cases and their contacts. Network analysis can support tailored public health action, outbreak management and control. Network analysis of patient transfer between facilities may even be used to predict which healthcare facilities may experience outbreaks and therefore help target public health resources for prevention [15,16]. Combined with genomics, it can be used to describe outbreak transmission dynamics at a higher resolution [17,18].

This is an outbreak report of an extended OXA-48 CPE hospital ward outbreak in Ireland that occurred between July 2018 and December 2019. In July 2018, three new OXA-48 CPE cases were detected and linked to a tertiary hospital ward. An outbreak was declared and an outbreak control team (OCT) was established. Despite early and ongoing control measures and interventions, the outbreak continued and by March 2019, 31 OXA-48 CPE cases had been detected on the same ward.

Our aim was to describe the outbreak and to investigate transmission patterns using SNA, epidemiological, environmental and genomics data.

Methods

The study design was a retrospective descriptive outbreak analysis, including SNA, combined with genomics of cases, with their patient contacts.

All patients admitted to the ward during the outbreak period (July 2018—December 2019) were included. Hospital staff and visitors to the ward were excluded.

A confirmed CPE case was defined as a patient admitted to the outbreak ward after July 1st 2018 who had a negative admission rectal swab for CPE colonisation (within 24 hours of admission), but who subsequently had a positive microbiological specimen for CPE.

A CPE contact was defined as a patient who was known to have shared a multi-bed area and/or toilet facility with a confirmed CPE case from this outbreak for more than four hours in any hospital inpatient area, other than the Emergency Department (ED).

This outbreak occurred on one ward of a tertiary hospital (with over 800 beds) in Ireland, and an estimated patient catchment population over 295,000 in 2019 [19].

On detection of the outbreak in July 2018, the inpatient population on the ward comprised males and females, the majority were aged ≥65 years and were under the care of a variety of medical specialties. The ward layout had 35 beds, divided into six multi-bed sections and five single rooms (Supplementary Figure S1).

Infection prevention and control (IPC) interventions that were implemented and documented during the course of the outbreak included: screening of patients on admission and weekly thereafter using a rectal swab to detect CPE colonisation; enhanced environmental cleaning and disinfection, followed by hydrogen peroxide vapour (HPV) of single patient rooms on discharge and multi-occupancy bays when vacated; regular HPV decontamination of bathrooms and the sluice room; ward closure and ward decant, followed by enhanced terminal cleaning and HPV decontamination of the entire ward. Depending on the ward capacity, CPE positive patients were isolated or cohorted to reduce exposure to other ward patients.

Confirmation of OXA-48 CPE in clinical and environmental isolates was carried out in the hospital's clinical microbiology laboratory, as previously described [20]. Confirmed CPE isolates were referred to the National CPE Reference Laboratory Service (NCPERLS) for WGS. Environmental sampling of frequently-touched surfaces, sinks and showers in the outbreak ward began in November 2018 and continued to May 2019.

The hospital's outbreak surveillance, patient and laboratory information management systems were used to source the data required for this outbreak report. Environmental sampling data was provided by the OCT. WGS data was obtained from NCPERLS.

The outbreak was described in terms of person, place and time. Analysis was divided into temporal periods, based on the timing of implementation of multiple control measures. Data

validation, coding and descriptive analysis of cases was conducted using STATA15. Patient timelines and locations during the outbreak period were tracked using ClusterTrack. Social networks were constructed of all patients — CPE cases and their patient contacts (using Cytoscape and R version 3.6.1 igraph package), to illustrate interactions between patients and bays/rooms within the outbreak ward over time. Data were collected on all patient bed and ward movements throughout the outbreak period. Social networks of patient cases and their patient contacts were constructed for the whole outbreak period and by temporal clusters. Networks were also constructed by patient characteristics, patient ward location, species, sequence type (ST) and plasmid group.

Social networks were statistically analysed, assessing network metrics to provide insights into case interactions and transmission dynamics. The following metrics were analysed: degree (the number of connections to a case), clustering (a set of densely connected nodes), closeness (a case's centrality based on distance to others in the network), betweenness (the degree to which other cases are connected through a case) and eigencentrality (a measure of the influence of a case in the network). Relative scores were assigned to all cases in the network based on the concept that connections to high-scoring cases contribute more to the score of the case in question than equal connections to low-scoring cases.

Results

Temporal analysis

In late July 2018, a new OXA-48 CPE case was identified, in a clinical sample submitted from primary care to the hospital's microbiology laboratory. On investigation, the patient had been discharged from a ward in the hospital 14 days earlier. Subsequently, two new positive CPE cases linked to the same ward were identified within a week. A CPE outbreak was declared and an OCT established.

Weekly screening of inpatients for CPE carriage was initiated on the ward, followed by closure of the ward three days later, with ward decant and HPV. The OCT recommended that the outbreak ward be closed to new admissions. However, due to competing pressures on the ED and risks of overcrowding there, on four separate occasions during the course of the outbreak, patients were admitted to the outbreak ward. Several IPC interventions were implemented during the course of the outbreak (Supplementary Table SI).

During the outbreak period, three temporal clusters were evident (Figure 1): cluster 1 (n=31; July 2018—February 2019); cluster 2 (n=11; April 2019—May 2019); cluster 3 (n=3; July 2019—August 2019). Between cluster 1 and 2, there were six weeks with no new cases identified and between cluster 2 and 3 there were nine weeks with no new cases identified. Between July 2018 and December 2019, 45 new OXA-48 CPE cases were linked to the outbreak, 22 (49%) of whom were admitted to the ward while the outbreak was ongoing, due to competing risks of ED overcrowding. (Supplementary Figures S2, S3 and S4). Patients were informed prior to admission to the outbreak ward.

The last case linked to the outbreak was identified on 12th August 2019. The outbreak was declared over 90 days following detection of the last case.

Descriptive analysis

Of the 45 OXA-48 CPE cases linked to the outbreak ward, the median age was 78 years (interquartile range IQR 67-83) and

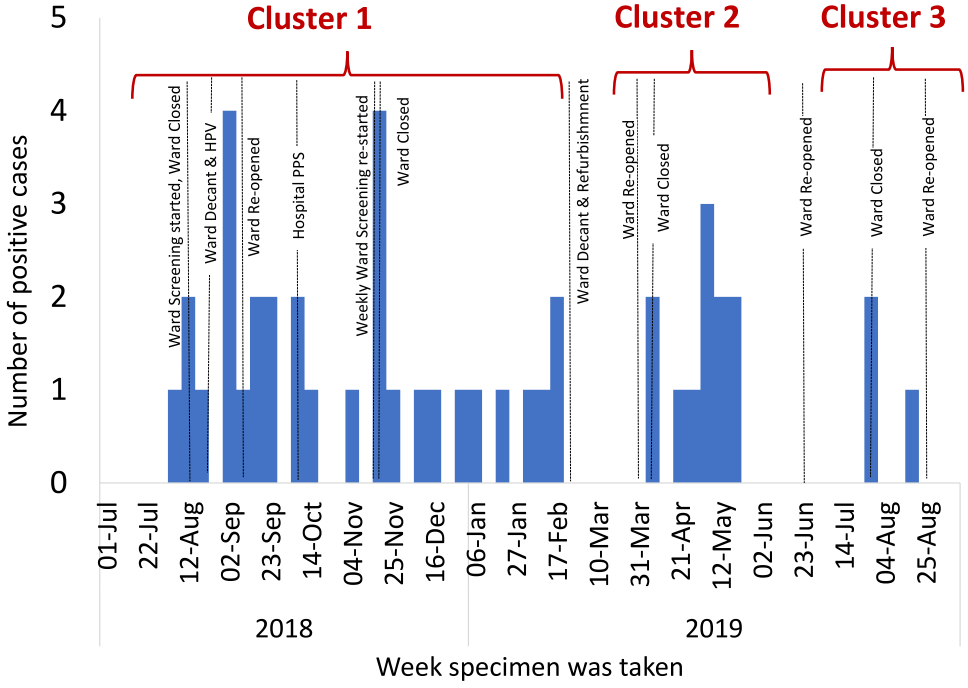

Figure 1. Epi-curve of confirmed CPE outbreak cases by week specimen was taken (n=45) and timeline of IPC measures, 2018-2019. Three temporal clusters are indicated on the graph.

58% (n=26) were male (Table I). All cases had multiple complex co-morbidities. Seven patients ultimately died, although cause of death data was not available during this study.

Microbiological results

WGS analysis identified the bla_{OXA-48} carbapenemase producing gene in all sequenced isolates (n=56 clinical isolates, from 45 cases). Seven different Enterobacterales species were identified. *Enterobacter hormaechei* was the most frequently identified species (69%; 31 cases), followed by *Escherichia coli* (18%; 8 cases). The 12 *E. coli* isolate genomes comprised 12 different sequence types (STs) and the *E. hormaechei* isolates comprised five STs (ST78, ST108, ST1126, ST135 and ST66), of which ST78 was the most common. There were two major OXA-48 plasmid types (denoted as groups 1 and 2) identified among the cases. There were 13 (29%) cases harbouring species with plasmid group 1 and 32 (71%) cases harbouring species with plasmid group 2.

Between November 2018 and May 2019, a total of 394 environmental specimens from the outbreak ward were tested, with 26 (6.6%) positive for OXA-48 CPE identified in the following areas: ward treatment room, ward sections C, E, and F and singles rooms 1-5 [20].'

The detailed molecular epidemiology of this outbreak has been previously described [20].

Social network analysis

Of the 45 outbreak cases, 844 patient contacts were identified. The median number of contacts per case was 11 (IQR 7-20). Of the 844 contacts, 33 (4%) were either found to be cases or went onto become cases.

SNA revealed that just one outbreak case (patient number 41) was identified as having no identifiable contact with other outbreak cases or contacts. Clustering of cases by gender was observed in social networks, with a clear division between male and female cases (Figure 2). One male and one female case who were accommodated in the same multi-bed area, were later identified as being positive for CPE OXA-48 plasmid group 1 in early September 2018.

Social networks illustrated changes in predominance of species, ST and plasmid group over time. A mix of cases with OXA-48 plasmid group 1 (35%) and plasmid group 2 (65%) positive isolates was identified within the first cluster of outbreak cases (July 2018—February 2019). Thereafter, only two cases (both males) with OXA-48 plasmid group 1 positive isolates were identified (one in April 2019 and one in August 2019). The remaining cases had positive isolates for OXA-48 plasmid group 2 (Figure 3). Temporal social networks illustrated a persistence of *E. hormaechei* over time. *E. hormaechei* ST108, ST1126 and ST78 were identified during the first cluster of the outbreak July 2018—February 2019, along with a mix of other STs. As time progressed, ST78 predominated, isolated from 16% (5/31) of cases in July 2018—February 2019, 55% (6/11) in April—May 2019 and all three (100%) cases in July and August 2019 (Figure 4; Supplementary Figure S4).

SNA indicated locations with possible increased transmission/potential hotspots during the outbreak i.e. a predominance of cases associated with two multi-bed bays on the ward (Supplementary Figure S5). The final cluster of outbreak cases occurred between July and August 2019, with three new CPE cases identified. All three were male, with chronic wounds, admitted to the same six-bedded section and all had OXA-48 *E. hormaechei* ST78 detected (Figure 4).

Social network centrality metrics were used to identify cases who may have been influential in the transmission dynamics of CPE in this outbreak (i.e. a case connected to a high number of other cases), (Supplementary Tables SII and SIII). Compared to all other outbreak cases, case number 12 had higher eigencentrality and centrality metrics (degree, closeness and betweenness) and case number six ranked second in eigencentrality (Table II, Figure 5).

Table I
Baseline characteristics of CPE outbreak cases, 2018-2019 (n=45)

Characteristics	Number of cases (%)
Total number CPE	45
Sex - male	26 (58%)
Age in years (median, IQR)	78 (67—83)
Ward LOS in days (median, IQR)	17 (10—34)
Hospital LOS in days (median, IQR)	35 (18—82)
Admission from other hospital	2 (4%)
Admission from long term care facility	3 (7%)
Admitted to HDU/ICU during study period	11 (24%)
Case fatality ratio (CFR)	7 (16%)
Number identified through screening	43 (96%)
Number identified from clinical sample	2 (4%)

Discussion

This lengthy single-ward outbreak led to 45 cases of OXA-48 CPE and exemplifies the complexity and difficulty in the control of CPE, particularly in the context of an already busy acute hospital, with high bed occupancy. The first case was identified in late July 2018, with the final case, over one year later in mid-August 2019. Three distinct temporal clusters were identified, with intervals without new cases between each temporal cluster, six weeks between the first and second cluster and nine weeks between the second and third cluster, coinciding with the implementation of additional IPC measures.

This outbreak involved seven different Enterobacterales species, multiple clones within each species and two OXA-48 plasmid groups. The *E. hormaechei* species persisted throughout the outbreak and increased in predominance over time. Similarly, the clonal group ST78 persisted throughout the outbreak and was the only clonal group identified from the final cluster of cases in July/August 2019 [20]. CPE hospital outbreaks involving *E. hormaechei* with possible environmental sources can be extended over time and difficult to control [21].

Two closely-related yet distinct pOXA-48 plasmid types were identified in this outbreak. From February 2019 onwards, plasmid group 2 was identified in all cases, with the exception of two male cases [20]. Both plasmid groups have been found across Ireland in recent years [22].

SNA identified links between 44 (of the 45) outbreak cases and their patient contacts. There was only one case with no identifiable links to the outbreak network of cases and contacts. All outbreak ward sections and rooms were linked to cases.

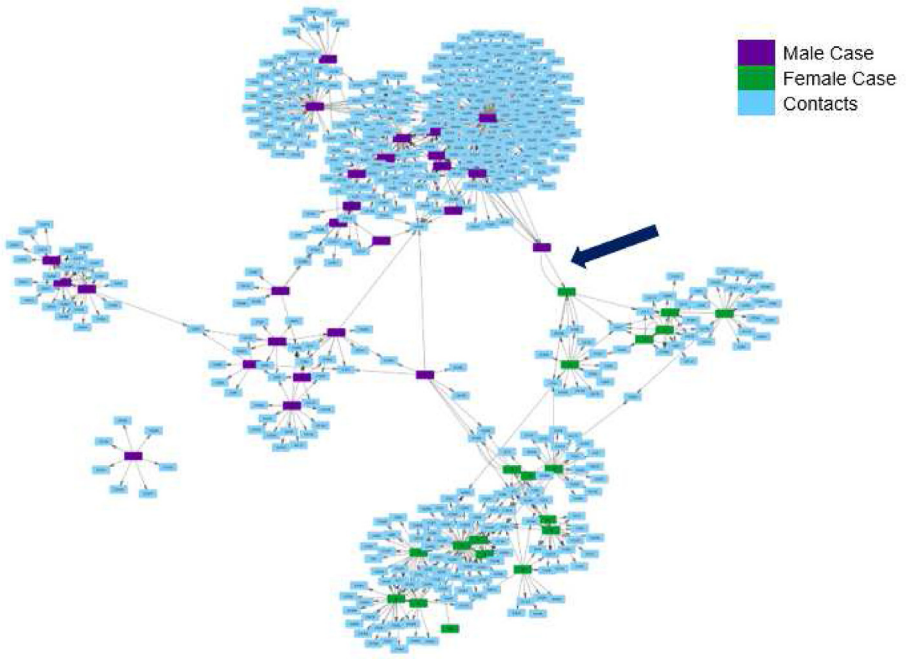

Figure 2. Social network of all CPE outbreak cases (N=45) by gender and their patient contacts (blue) (N=844), 2018-2019. The blue arrow indicates a transmission event/contact between male (purple) and female (green) cases.

Transmission dynamics in temporal clusters was illustrated with clear clustering of male and female cases, as expected, as the ward sections are generally not mixed gender. One male and one female case had shared a multi-bed section, with CPE OXA-48 plasmid group 1 identified from both. There is no evidence to suggest that this possible transmission event led to onward transmission to other female patients. Temporal social networks identified persistence and clustering of *E. hormaechei* species, with changing predominance of ST clonal groups and plasmid groups over time.

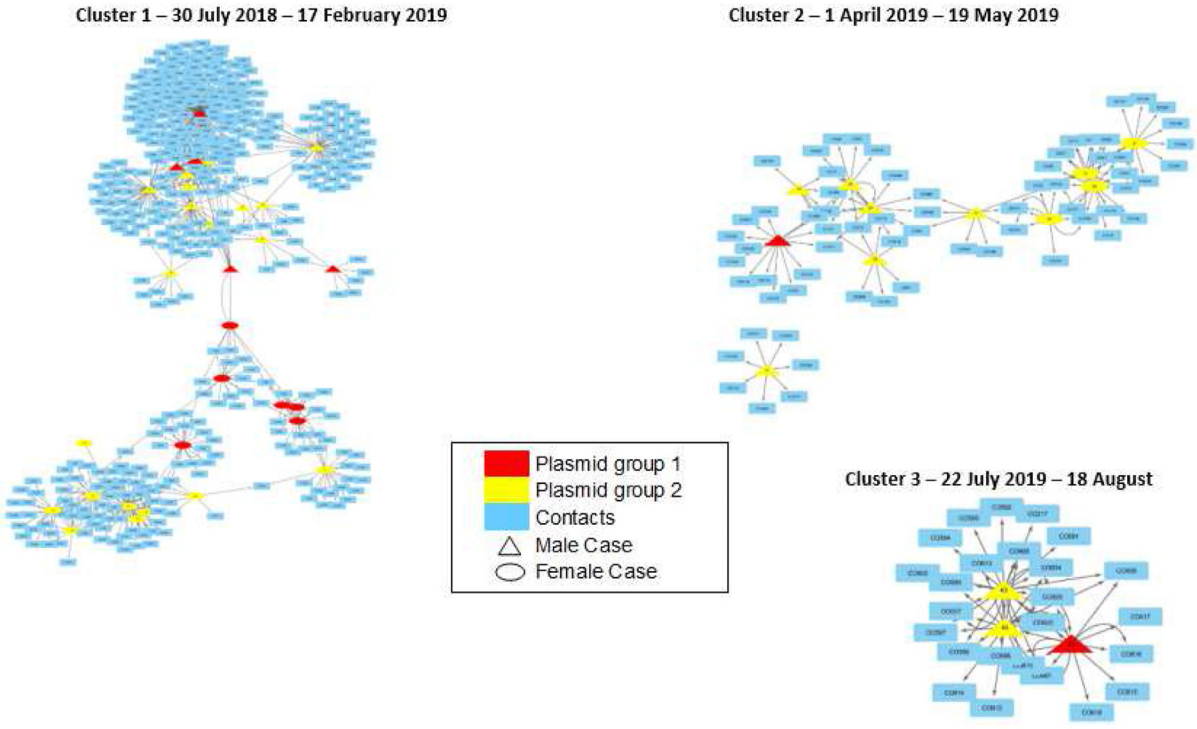

Figure 3. Social network of CPE outbreak cases (N=45) and their patient contacts (N=844), by temporal cluster, CPE OXA-48 plasmid group and gender. Cases are colour coded by plasmid group (1 and 2); male cases are indicated by triangles and females by ovals.

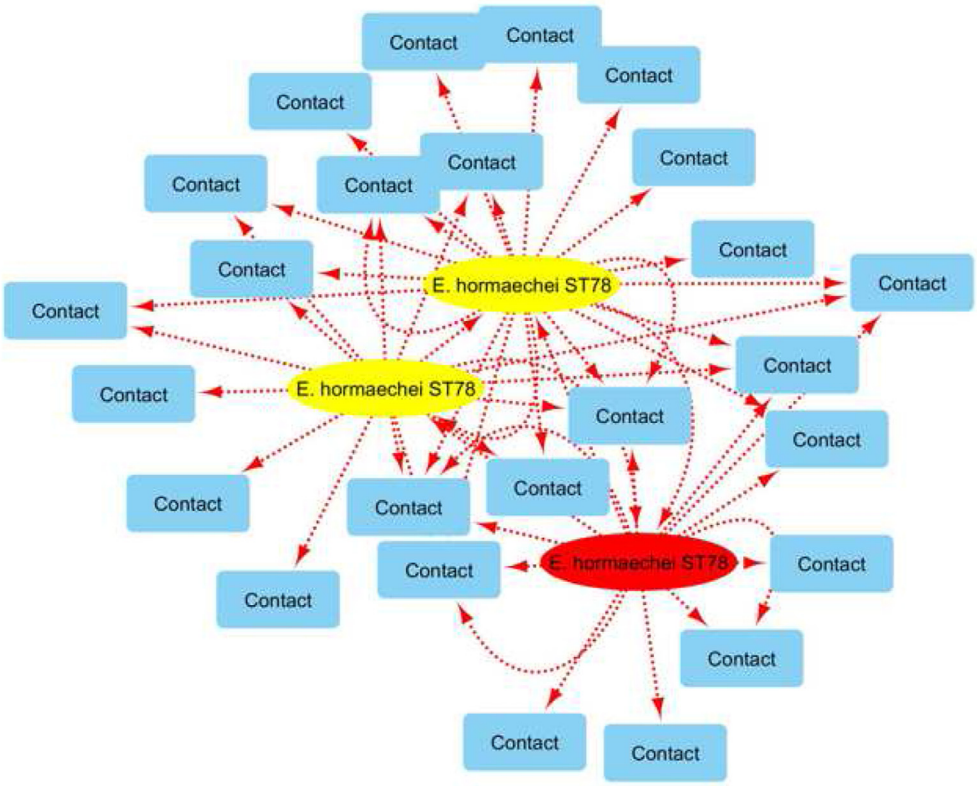

Figure 4. Social network of CPE outbreak cases and their patient contacts from Cluster 3 (July—August 2019), by OXA-48 plasmid group (group 1 is red and group 2 is yellow), species and sequence type (ST).

Analysis of social network metrics signalled two cases who may have been influential in the outbreak transmission dynamics and identified potential super-spreading events. Although SNA was done retrospectively, it revealed that these two patients had multiple complex epidemiological links to other outbreak cases early during the outbreak. One case who was linked to seven other cases was a patient with ongoing behavioural disturbance who was moved ten times during a lengthy admission to the outbreak ward. Another patient with behavioural disturbance was linked to five other cases and moved 15 times during a lengthy admission to the outbreak ward. Risk factors associated with CPE colonisation or infection include prolonged LOS [23,24]. Dementia has been reported as a risk factor associated with 14-day mortality for patients with bacteraemia due to OXA-48 carbapenemase-producing *K. pneumoniae* [25]. Increased risk of CPE colonisation or infection in psychiatric patients or patients with behavioural disturbance is not well documented. SNA combined with WGS have been used as innovative tools to elucidate transmission patterns amongst risk groups/communities at risk for TB and COVID-19 [17,26].

While the OCT recommended that the outbreak ward be closed to new admissions, patients were admitted to the closed ward on four occasions, due to competing risks of ED overcrowding and high bed occupancy elsewhere across the hospital. Those patients were informed prior to transfer that they were being admitted to a ward with an active CPE outbreak and over time, 22 went onto acquire CPE on the ward.

While the aim of performing SNA and molecular epidemiology in this outbreak was to gain a better understanding of the dynamics, in the context of a protracted outbreak, the main limitation was with regard to the timing of the analysis. This study commenced during the latter stages of the outbreak. These tools are potentially more powerful when undertaken in the earlier stages of an outbreak to ascertain early transmission dynamics and therefore break the chains of transmission.

In spite of the complexity of this OXA-48 CPE hospital ward outbreak, SNA combined with genomics provided insights into the outbreak transmission dynamics, which most likely involved both person-to-person transmission and exposure to environmental sources in the ward. SNA elucidated transmission patterns between ST types and plasmid groups over time, highlighting the persistence of *E. hormaechei* ST78 and OXA-48 plasmid group 2 as the outbreak progressed, despite IPC measures, possibly due to nosocomial adaptation. Genomics combined with SNA revealed interspecies gene transmission and helped to clarify epidemiological links between cases. This CPE outbreak involved two OXA-48 plasmids, multiple species and genotypes, highlighting the importance of IPC measures to prevent colonisation by multiple species and opportunities for such occurrences. As yet there is no proven method for decolonisation of patients carrying CPE. Therefore, stringent IPC measures to reduce transmission and prevent invasive infection must be adhered to.

In this study, we elucidated outbreak transmission patterns in an acute hospital setting at high resolution in a novel

Table II
Key characteristics of two outbreak cases identified through centrality metrics as potentially influential in the outbreak transmission dynamics

Key characteristics	Case number 12	Case number 6
First CPE positive isolate	September 2018	August 2018
Genomic typing	CPE OXA-48; *E. coli* ST59; plasmid group 1	CPE OXA-48; *E. hormaechei* ST1126; plasmid group 1
Diagnosis	Chronic psychiatric diagnosis and behavioural issues	Chronic psychiatric diagnosis
Hospital LOS	>400 days	>500 days
Outbreak ward LOS	>300 days	>300 days
Complex movements	Moved on 10 occasions within the outbreak ward	Moved on 15 occasions with the outbreak ward
OXA-48 CPE positive environmental samples	Positive samples identified from three ward sections/rooms (section F, rooms 2 and 3) that case was accommodated in	Positive samples identified from four ward sections/rooms (section F, rooms 3, 4 and 5) that case was accommodated in
Number of patient contacts	176	37
Number (%) of patient contacts that were confirmed cases	7 (4%)	5 (13.5%)

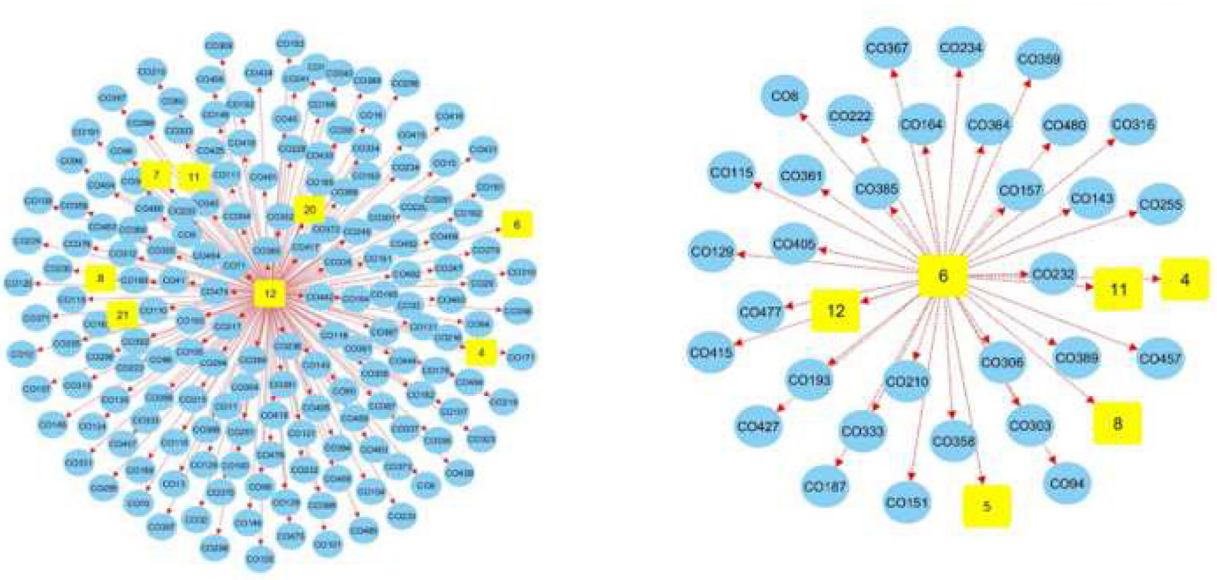

Figure 5. Social networks of CPE outbreak case numbers 12 and 6 and their patient contacts (blue) and contacts who were confirmed cases (yellow).

manner, combining SNA and genomics. SNA illustrates complex epidemiological links that explain transmission patterns (primary and secondary) that may not be identified through classical outbreak investigations and thus provide support and added value to outbreak investigations. We recommend the use of SNA and genomics in combination (to include both case and environmental sampling) early during complex nosocomial outbreaks, in order to identify (and break) transmission chains and potential super-spreading events.

Challenging behaviour due to dementia or other reasons may make it very difficult to apply good IPC practice fully. Based on this study's findings, a CPE-colonised patient with behavioural issues may be considered 'at risk' of onward transmission and should be highlighted in national guidance. In this outbreak, SNA identified possible superspreading events involving patients with psychiatric and behavioural issues and complex bed and ward movements during their hospital stay, highlighting a need for consideration to be given to bespoke care plans for at-risk patients, such as restriction of bed/intra-ward movements during outbreak periods.

Credit author statement

Lisa Domegan: principal investigator, conceptualisation, study design, analysis, manuscript writing, review and edit.

Carina Brehony: co-investigator, study design, analysis, manuscript review and edit.

Fidelma Fitzpatrick: member of OCT, manuscript review and edit.

Karina O'Connell: member of OCT, manuscript review and edit.

Binu Dinesh: member of OCT, manuscript review and edit.

Jacqueline Cafferkey: member of OCT, manuscript review and edit.

Karen Burns: project supervisor, manuscript review and edit.

Ethics and consent

Ethical approval was not required as outbreak investigations are covered under national legislation. Anonymised outbreak data collected as part of the outbreak investigation were used in this study. Informed consent was not gained from patients involved in this outbreak. All patients were treated according to clinical judgement and infection control practices in order to treat them and control the outbreak according to local guidelines. Patients did not undergo randomisation or intervention for the purpose of this report. Data has been analysed and presented anonymously.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.infpip.2023.100282.

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