A Point Prevalence Study to Determine the Inpatient Rate of Carbapenemase-Producing Organisms at a Large London NHS Trust

J. Henderson[a,b], H. Ciesielczuk[a], S.M. Nelson [b], M. Wilks[a,c], M.N. Cummins[a]

[a] Division of Infection, Royal London Hospital, Barts Health NHS Trust, London, UK

[b] Department of Applied Sciences, University of the West of England, Bristol, Frenchay Campus, Coldharbour Lane, Bristol BS16 1QY

[c] Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London

Running title: Inpatient Point Prevalence Study CPOs

Corresponding author: Jennifer Henderson, Microbiology Department, Royal London Hospital, Pathology & Pharmacy Building, 80 Newark Street, London, E1 2ES, Jennifer.henderson5@nhs.net 0203 4160320

Abbreviations: Barts Health Trust, BHT; Public Health England, PHE; carbapenemase producing organism, CPO; Carbapenemase producing Enterobacterales, CPE; carbapenemase resistant organism, CRO; Carbapenemase resistant Enterobacterales, CRE; amikacin, AMI; meropenem, MER; mecillinam, MEC; piperacillin-tazobactam, TAZ; temocillin, TEM; ertapenem ERT; intermediate, I; resistant, R; sensitive, S; extended spectrum beta-lactamase, ESBL; antimicrobial sensitivity testing, AST; European Committee on Antimicrobial Susceptibility Testing, EUCAST; Intensive care unit, ITU; Matrix assisted laser desorption ionisation time of flight mass spectrometry, MALDI-TOF MS; Newham University Hospital, NUH; Oxacillinase beta-lactamase, OXA-48; Imipenemase metallo-beta- lactamase, IMP; *Klebsiella pneumoniae* carbapenemase, KPC; New Delhi metallo-beta-lactamase, NDM; Verona integron-borne metallo-beta-lactamase, VIM; Not known, NK; Royal London Hospital, RLH; Real-time polymerase chain reaction, RT-PCR; St Barts Hospital, SBH; Whipps Cross University Hospital, WX

Background: There has been an increase in the number of carbapenemase-producing organisms documented across the UK over the past 10 years. From these, the “Big five” carbapenemases (KPC, OXA-48, IMP, VIM and NDM) are the most common types reported in the order Enterobacterales, identified from a variety of reactive screening, outbreak, inpatient surveillance and diagnostic samples.

A point prevalence study to determine the inpatient carriage rate of carbapenemase producing organisms was performed at Barts Health NHS Trust, which encompasses 2.5 million patients across four London boroughs: Tower Hamlets, Newham, Redbridge and Waltham Forest.

Methods: Rectal swabs were collected from consenting inpatients, alongside the ward’s medical speciality, patient’s country of birth, history of foreign travel, length of hospitalisation and history of prior hospitalisation. Swabs were enriched and sub-cultured onto mSuperCARBA selective medium (E&O Laboratories Ltd, UK). All Enterobacterales, *Acinetobacter* and *Pseudomonas* species were identified by MALDI-TOF MS and underwent antibiotic susceptibility testing by disk diffusion, according to EUCAST guidelines. All isolates were screened for the “Big five” carbapenemases using a modified version of a published RT-PCR assay.

Findings: Of the 977 inpatients tested, 35 CPOs were isolated from 30 patients. Of these, NDM was the most frequently detected carbapenemase, followed by OXA-48, with an overall prevalence of 3.1%. Organisms isolated included; *Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis* and *Escherichia coli.*

According to speciality, renal and elderly care patients had the highest prevalence of CPOs, while Intensive Care Unit prevalence was low. Statistical analysis found hospitalisation abroad, any previous hospitalisation, foreign travel and, specifically, travel to India, Pakistan and Bangladesh was associated with increased risk of CPO carriage.

Conclusion: The overall prevalence of CPOs at Barts Health Trust was 3.1%, comprising NDM and OXA-48-type carbapenemases, which is in line with other London-based studies. In our Trust, renal patients and the elderly were associated

with a higher burden of CPOs, while previous hospitalisation and foreign travel was associated with an increased risk of CPO carriage.

BACKGROUND

Carbapenems are traditionally reserved for the critically ill or patients considered to have an infection caused by a multidrug resistant (MDR) organism. The emergence and expansion of extended spectrum beta-lactamases (ESBLs) over the last two decades has led to increased prescribing of carbapenem antibiotics and the subsequent development of resistance [1]. Carbapenem resistance was first described in 1993 and, since then, a variety of intrinsic and acquired resistance mechanisms have been identified [2]. Inappropriate use of these antimicrobials has also led to an increase in the development of resistance to carbapenems. The dramatic increase in this resistance over the past ten years has now become a significant global cause for concern, with certain regions of the world, including India, Bangladesh, USA, Greece and Turkey, deemed high risk [3], while in other parts of the world, such as Sub-Saharan Africa, the prevalence of carbapenemase-producing organisms (CPO) is still very much unknown [4].

Public Health England (PHE) produced a toolkit to provide advice on the screening and management of CPOs within hospital settings in 2013 [5]. The number of CPO infections and colonisation across the UK is continuing to increase, including outbreaks and clusters reported throughout England, particularly in London and Manchester [6]. A suspected carrier is defined as a patient who, within the last 12 months, has either been an inpatient in the UK, where there are reported cases of CPE, or hospitalised abroad, or a patient who has previously tested positive for a CPE. The toolkit was designed to aid in the management of patients, including;
1) early recognition of patients deemed high risk,
2) early isolation of potential cases,
3) screening,
4) treatment and decolonisation,
5) effective infection prevention and control measures,
6) decontamination and
7) thorough communication.

Barts Health Trust (BHT) infection control and prevention policy states that, upon admission, the patient should be asked if they have previously been hospitalised overseas. All patients with previous carbapenem resistant organism (CRO) carriage or previous admission to a hospital with a known CRO outbreak should be screened. Confirmed cases should be isolated, with strict infection prevention control (IPC) barrier precautions in place. Contact screening should occur if the carrier spent time on an open bay and cohorting of the contacts should be performed until the screening results are available. Isolation and weekly screening should continue for the remainder of the patient's stay (carrier only, not contacts). However, when the timeframe between exposure and positive carriage status is unknown, this period of uncertainty could last anywhere between several days to weeks, until patient status can be determined. It therefore could be beneficial to screen both carriers and contacts weekly throughout the duration of their hospital stay.

BHT has a total of 1,706 acute and general beds, 177 critical care beds and 220 maternity beds across all five sites [7] and covers an area of East London encompassing approximately 2.5 million people. Of this population, 5-36% are of Indian, Bangladeshi or Pakistani origin [8]. This, according to the PHE toolkit, defines them as high risk groups requiring screening upon admission [5].

Currently at BHT no specific patient groups are screened for CPOs. Therefore, it is important to establish which patients need to be investigated based on BHT's patient population, local CPO prevalence and at-risk patient groups, to prevent carriage becoming an infection and to prevent outbreaks.

Point prevalence determines the number of current cases at a defined point in time [9]. Several point prevalence studies (PPS) have taken place across the UK [6,10,11]. These studies provided an insight into the prevalence of CPOs within the UK, as CPO positive cases are typically reported from diagnostic samples, outbreak settings and routine surveillance rather than active screening. This PPS determined the prevalence of CPOs in the inpatient population at BHT, at specific time points, over a 13 month period.

METHODS

Ethics

This study was approved by the Joint Research Management Office (JRMO) at BHT. The Integrated Research Application System (IRAS) application was submitted as a proportionate review, prior to full Health Research Authority (HRA) approval being received (IRAS 219422).

Patients

All 1883 inpatients ≥18 years old, excluding maternity (considered outpatients), were eligible for this study and approached by nursing staff assigned to each ward. Rectal swabs were collected from all able and consenting inpatients at BHT, at specific time points, between September 2017 and October 2018 (Figure 1). Alongside sample collection, the following information was collated by the nursing staff on a risk factor study sheet: the ward's medical speciality, patient's country of birth, history of foreign travel, length of hospitalisation and history of prior hospitalisation. Excluded groups were those unable to consent, such as patients suffering from dementia, those on ventilation devices and paediatrics.

CPO detection

Swab diluent (approximately 200 µL) was transferred to 3 mL nutrient broth (Thermo Fisher Scientific, UK) as a means of non-selective enrichment and incubated overnight at 37°C. The broth was sub-cultured onto mSuperCARBA (E&O Laboratories Ltd, UK) selective medium and incubated again overnight at 37°C. All colonies were identified by MALDI-TOF mass spectrometry (Bruker Daltonics, Germany). Antibiotic susceptibility testing (AST) was performed on all

Enterobacterales, *Acinetobacter* and *Pseudomonas* species by disk diffusion against meropenem, ertapenem, fosfomycin, mecillinam, amikacin, temocillin and piperacillin-tazobactam, according to EUCAST guidelines [12]. All isolates were screened for the possession of a carbapenemase gene, using a PCR described previously [13].

Statistical analysis

For each of the risk factors recorded in this study, the relative risk with 95% confidence intervals was calculated, to determine the association with CPO carriage.

RESULTS

Of the 1883 acute inpatient beds, and assuming an average 90% occupancy (n = 1694) [7], just 977 of the 1694 (58%) consented and participated in this study. For each of the participating wards, the risk factor study sheet was partially or totally incomplete due to resistance and time constraints of the nursing staff. Of the 977 patients tested, 557 (57%) returned the study sheets. Therefore, the data collected for each risk factor is lower than desired.

In total, 35 CPOs from 30 patients were identified, providing an overall prevalence of 3.1%. A breakdown of prevalence at each BHT site is detailed in table 1. Whipps Cross University Hospital (WX) had the highest CPO prevalence at 4.5%, compared to the lowest at Newham University Hospital (NUH) of 1.04%.

The most prevalent carbapenemase was NDM, with 21 (60%) detected and 14 (40%) OXA-48 enzymes. No IMP, VIM or KPC enzymes were detected. Of the positive samples, 14 (40%) were *Klebsiella pneumoniae*, 6 (17.1%) *Enterobacter cloacae,* 11 (31.4%) *Escherichia coli,* 1 (2.9%) *Pseudomonas oryzihabitans*, 2 (5.7%) *Proteus mirabilis* and 1 (2.9%) *Citrobacter freundii* (Table 2). Five patients' samples tested positive for two carbapenemase genes (PPS19, 27, 28, 29 and 30; Table 2). These were distinguished by colonial appearance on chromogenic media, antibiogram and confirmed by MALDI-TOF MS identification.

The risk factors associated with CPO carriage (Table 3) were tabulated for all inpatients participating in the study, based on the completed study forms. However, patient information was incomplete in a large number of cases, therefore the quality of this data varies.

Country of birth and foreign travel are documented in figure 2.

One hundred and twenty seven (22.8%) patients reported previous hospitalisation within the last 12 months, of which 22.1% were UK-based, 0.72% abroad and 77.18% did not report the location.

Where recorded (57%), length of hospitalisation ranged from <1 day to 12 weeks, with a mean of 6 days.

The relative risk for each of the risk factors that were documented as part of this study are detailed in table 3. Despite the highest burden of CPO carriage being observed in our renal and elderly patients, hospitalisation within the last 12 months, whether in the UK or abroad, was the largest risk factor associated with CPO carriage. This was closely followed by foreign travel within the last 12 months, specifically to India, Pakistan or Bangladesh. Country of birth outside of the UK and Republic of Ireland carried the lowest risk.

For comparison with the CPO prevalence calculated as part of this PPS, we determined our CPO infection rate for the same time period. This figure was obtained by calculating the number of infections caused by CPOs from the total number of clinical samples received, minus those unlikely to yield CPOs (e.g. *Legionella* urinary antigen, mycobacteria detection). It was approximated that the number of infections caused by CPOs was 0.05% (94 out of 193,702), the majority of which were recovered from urine specimens.

DISCUSSION

The overall CPO prevalence at BHT was 3.1%, across all four sites. This is higher than the 2.2% published by PHE, however, their data was derived from diagnostic samples and targeted routine screening. [14]. For a more accurate comparison, we determined our CPO infection rate for the same time period as the PPS, which was even lower than that reported by PHE (0.05%). Interestingly, this infection rate was also much lower than that reported for neighbouring hospitals and regions, which also derived the data from diagnostic samples: 0.3% Croydon University Hospital, 1.7% Great Ormond Street Hospital (GOSH), 0.9% Homerton University Foundation Trust, 3.8% Imperial College NHS Trust, 0.3% Kingston Hospital NHS Foundation Trust and 0.9% Barking, Havering and Redbridge University Hospitals [14]. The difference in CPO detection between our PPS and the PHE reports demonstrates the need for all large hospital trusts to perform a PPS to determine their true CPO carriage rate and how this compares to their CPO infection rate.

Reported CPE prevalence from the few PPS and large scale screenings performed in the UK ranges from zero cases (Cambridge) to 11% (Manchester), with the majority reporting a prevalence of <0.5% [10,15,16]. This suggests an extremely low burden of CPE across England. However, the majority of studies were localised to London and Manchester, which are not representative of England as a whole. Therefore, more CPO prevalence studies need to be conducted, across the entire UK, to understand the true national CPO picture.

Elsewhere in the world, many point prevalence studies have been performed, [17,18,19] with much higher rates of CPO carriage. Throughout Europe, CPO rates included 64.7% in Greece, 29.7% in Italy, 0% in Norway, 22.5% in Romania and 0% in Luxemburg [20]. This variation in CPO burden highlights the importance of tailored CPO screening and the need to understand the CPO burden across different geographical regions and the world, where risk factors may differ.

The most commonly isolated CPO identified from this study was *K. pneumoniae* (40%), followed closely by *E. coli* (31.4%) and *E. cloacae* (17.1%). These findings were consistent with data from PHE examining suspected CPOs submitted from

other hospital trusts across England [21]. Only two enzyme types were detected, NDM and OXA-48-like carbapenemases, despite our laboratory reports of other carbapenemase enzymes previously (data not shown). In 2017, a UK-wide study was performed over a 6 month period to determine the prevalence of CPE within the UK. This study identified KPC as the most frequently detected carbapenemase (56%), followed by OXA-48-like (28%), NDM (12%) and VIM (4%), with no IMPs detected [22]. This contrasts with the findings from our PPS, as we did not detect any KPC or VIM producers. However, the high rate of KPC detection in this UK study was likely to be due to the documented KPC outbreak in the North West of England [15]. On a par with our PPS, additional studies performed at other London hospitals documented the presence of only OXA-48-like and NDM-producing organisms [10] or NDM producers only [23]. These findings, together with results from other London-focused PPS, suggest that KPC may currently be localised to the North West of England, with OXA-48-like and NDM predominating in and around London. To date, there have been no other published studies detailing the prevalence of CPOs in England other than Manchester, London and Cambridge.

BHT serves an area with a high proportion of residents of Indian, Pakistani and Bangladeshi origin. Patients who have travelled to these countries, which PHE highlights as having a high prevalence of healthcare-associated CPEs, are considered high-risk for carriage of these organisms according to the toolkit. The relative risk of patients born in or travelled to India, Pakistan or Bangladesh was calculated as 1.27 and 4.97, retrospectively. This indicates that travel to these countries is a more relevant risk factor than birth in one of these countries, which had little effect on CPO prevalence here. NDM in particular has been associated with these parts of Asia, with the first patient identified as carrying an NDM-producing organism noting travel to India [24]. In contrast, OXA-48-like carbapenemases have been associated with Europe and the Middle East, in particular Turkey, Spain, France, Belgium and Romania [24].

Travel abroad has been listed consistently as a CPE risk factor in PHE guidelines since 2013. Therefore, information on country of birth and foreign travel was gathered from our study participants. Where this was known, the highest proportion of participants were born in the UK and Republic of Ireland. Perhaps a little surprisingly, the risk for CPO carriage in participants born abroad was very low (0.99), suggesting this risk factor is not as relevant in our patient population. Understandably, however, travel to a foreign country did carry a higher risk (4.53), which would be expected for participants visiting a country where CPOs are endemic or circulate at a higher prevalence than in our Trust and the UK.

A large number of risk factors have been reported in various CPO studies such as, receiving dialysis abroad, patients from renal, haematology [11], vascular and ITU wards, overseas residents, history of overnight hospitalisation abroad and in the UK [6, 23], age in conjunction with antibiotic use [15], the elderly [23], mechanical ventilation, presence of indwelling devices, corticosteroid use [25], immunosuppression , prior antimicrobial use, patient mobility and severity of illness [25]. Renal and elderly care wards were also noted in our study for their higher burden of CPO carriage, however, this was not mirrored with the relative risk (1.27 and 1.39, respectively). It is likely that the increased CPO burden in our elderly patients also explains the high prevalence at WX hospital (4.5%), which serves a significant proportion of the elderly community in this area, including those residing in

nursing homes [26]. Many of our renal patients, most of which are admitted for dialysis, are returning travellers who may or may not have received their dialysis abroad, potentially explaining the increased CPO burden here also. In addition, these patients are rarely isolated in side rooms and the cleaning standards are often challenging, due to the high demand of the dialysis units [27]. This patient group, along with the elderly, are frequently prescribed antibiotics and often referred to other specialities to manage their co-morbidities. Previous hospitalisation both in the UK and, more often, abroad have been frequently associated with increased risk of CPE carriage [5]. In our study, 79.9% of the participants positive for CPE carriage noted previous hospitalisation, with 3.3% hospitalised abroad (Table 2). The RR for all previous hospitalisation was noteworthy at 5.08. Previous hospitalisation in the UK was associated with a much lower RR (2.2) whilst hospitalisation abroad carried the highest RR (17.28). However, it is important to note that this RR had a wide confidence interval, likely a result of the low number of participants with this risk factor. Together this data confirms the relevance of previous hospitalisation in increasing the risk of CPE carriage, as published by PHE. Future work should focus on repeating this study, with a larger proportion of patients hospitalised abroad, to determine the true risk of CPE carriage in patients from our Trust with this history.

Where length of hospital stay was documented, the admission ranged from 5 days to 6 weeks for the CPO-positive cases and between <1 day and 12 weeks for the CPO-negative participants (Table 2). However, the RR (1.34) for patients admitted for longer than 2 weeks suggests that length of stay is not associated with increased risk of CPO carriage, especially as it is not known at what stage these patients acquired the CPO. Another study has determined increased hospital stay to be linked with an increase in MDR organisms, while not specific to CPOs, it could explain the trend observed here [16]. Other studies have identified environmental CPO reservoirs, within the hospital, with the same strain detected among patients and a particular drain system, where the two co-exist [28]. This, together with antibiotic use, could provide the exposure required for CPO acquisition. This may explain the varied CPO carriage observed across our Trust, but it's important not to rule out the community as a source of CPOs.

Limitations

Patient information collected by assigned nursing staff alongside the rectal swabs was generally lacking, due to staff resistance and time constraints. Many wards had not completed the study forms fully and, as a result, missing data ranged from several patients to an entire ward. This had an impact on the risk factor data obtained from this study, which will be biased towards medical specialities where forms were more complete. BHT has a total of 1883 acute beds, however only 977 (58%) of patients were included in this study. Other than staff reasons, patient-focused reasons included inpatients not wanting additional tests which would not aid in their recovery, feeling too unwell, rectal swab thought of as an embarrassing sample type and patients not being included who were unable to consent.

The RLH has a large trauma unit, tertiary referral centre and vascular and neurological departments, while SBH is a specialist centre for predominantly cardiac and oncology services. This could account for the varying prevalence detected amongst the different sites of BHT, as the risk factors for these patient groups will vary. In addition, during the PPS, one ward was subjected to an ongoing OXA-48

outbreak. However, results did not appear skewed by this, as only one NDM producer was detected on the ward during that time.

The true prevalence of CPOs in this PPS may have been underestimated, as the RT-PCR method used only detected the carbapenemase types common to Enterobacterales (VIM, NDM, KPC, OXA-48 and IMP) and not all carbapenemases reported to date. A further limitation was that the rectal swab was not inspected for the presence of faecal matter prior to testing, as stated in the PHE toolkit, for the accurate detection of CPE. It is possible that the enrichment broth method employed in this study partially compensated for this omission, but to what degree it is not possible to calculate.

Since the study did not sample all patients on admission and weekly thereafter, it cannot be determined what proportion of patients were positive for a CPO on admission compared to the proportion becoming positive during their hospital stay. Collating this information would be an obvious benefit to the IPC team and control of CPE transmission within the Trust. When repeating the PPS in the future, care will be taken to distinguish participants who were admitted at that time versus those admitted on a previous day.

In conclusion, a PPS performed across all sites of BHT over a 13 month period revealed a CPO prevalence of 3.1%, with the most frequently detected carbapenemases identified as NDM and OXA-48-like. Risk factors listed in the PHE toolkit, which were also noteworthy in our patient population, were foreign travel and previous hospitalisation, specifically hospitalisation abroad. Though associated with a lower risk, the renal wards and elderly care wards in our Trust were associated with an increased CPE burden.
Performing localised CPO surveillance and/or prevalence studies enables targeted screening that is tailored to the area and local patient population. We recommend that all large acute hospitals perform similar studies to ensure optimal CPO screening, antibiotic stewardship and patient management.

REFERENCES

[1] Gharbi M, Moore L, Gilchrist M, Thomas C, Bamford K, Brannigan E, et al. Forecasting carbapenem resistance from antimicrobial consumption surveillance: Lessons learnt from an OXA-48-producing *Klebsiella pneumoniae* outbreak in a West London renal unit. Int J Antimicrob Agents 2015;46:150-156.

[2] Nordmann P, Nass T, Poirel L. Global spread of carbapenemase- producing Enterobacteriaceae. Emerg Infect Dis 2011;17:1791-1798.

[3] Surveillance of antimicrobial resistance in Europe- Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017. Available from https://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-EARS-Net-2017.pdf [Accessed 8 December 2018].

[4] Codjoe F, Donker, E. Carbapenem Resistance: A review. Med Sci (Basel) 2017;6:1.

[5] Public Health England *Acute trust toolkit for, management and control of carbapenemase-producing Enterobacteriaceae*. London: Health England; 2014. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/329227/Acute_trust_toolkit_for_the_early_detection.pdf [Accessed 3 September 2019].

[6] Wilson HJ, Khokhar F, Enoch DA, Brown NM, Ahluwalia J, Dougan G, et al. Point-prevalence survey of carbapenemase-producing Enterobacteriaceae and vancomycin-resistant enterococci in adult inpatients in a university teaching hospital in the UK. J Hosp Infect 2018;100(1):35-39.

[7] Barts Health NHS Trust Quality Report. Available from https://www.bartshealth.nhs.uk/download.cfm?doc=docm93jijm4n5302.pdf&ver=7777 [Accessed 3 July 2019].

[8] London Datastore. Census Information Scheme. Available from https://data.london.gov.uk/census/. [Accessed 3 July 2019].

[9] Centers for Disease Control and Prevention. Principles of Epidemiology in Public Health Practise, Third Edition, An Introduction to Applied Epidemiology and Biostatistics. Available from (https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson3/section2.html [Accessed 3 July 2019].

[10] Otter JA, Dyakova E, Bisnauthsing KN, Querol-Rubiera A, Patel A, Ahanonu C, et al. Universal hospital admission screening for carbapenemase-producing organisms in a low-prevalence setting. J Antimicrob Chemother 2016;71(12):3556-3561.

[11] Carter Y, Scott J, Pang V. Screening for antibiotic-resistant infection. Nurs Times 2015;11(21):12-14.

[12] European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints for bacteria v9.0. Available from http://www.eucast.org/clinical_breakpoints/ [Accessed 4 September 2019].

[13] Henderson J, Ciesielczuk H, Nelson SM, Wilks M. Community prevalence of carbapenemase-producing organisms in East London. J Hosp Infect 2019;103(2):142-146.

[14] Public Health England *Carbapenem (Meropenem or Imipenem) Resistant Organisms (CRO) Monthly Report.* London: Health England; 2017.

[15] Poole K, George R, Decraene V, Shankar K, Cawthorne J, Savage N, et al. Active case finding for carbapenemase-producing Enterobacteriaceae in a teaching

hospital: prevalence and risk factors for colonization. J Hosp Infect 2016; 94(2):125-9.

[16] Mookerjee S, Dyakova E, Davies F, Bamford K, Brannigan ET, Holmes A, et al. Evaluating serial screening cultures to detect carbapenemase-producing Enterobacteriaceae following hospital admission. J Hosp Infect 2018;100(1):15-20.

[17] Ruiz-Garbajosa P, Hernández-García M, Beatobe L, Tato M, Méndez MI, Grandal M, et al. A single-day point-prevalence study of faecal carriers in long-term care hospitals in Madrid (Spain) depicts a complex clonal and polyclonal dissemination of carbapenemase-producing Enterobacteriaceae. J Antimicrob Chemother 2016;71(2):348-352.

[18] National Reference Center for Antibiotic-resistant Gram-negative bacilli, CHU Dinant-Godinne UCL Namur and Hospital Erasme ULB Brussels, Belgium. Multicenter study of the prevalence of carbapenem non-susceptible Enterobacteriaceae (CNSE) and of carbapenemase-producing Enterobaceriaceae (CPE) in Belgium in 2015. Study summary report. Available from http://www.nsih.be/download/MDR/etudepreval2015/2015%20CPE%20Belgium%20prevalence%20study%20report.pdf [Accessed 6 August 2019].

[19] Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and Other Enterobacteriaceae: an Evolving Crisis of Global Dimensions. J Antimicrob Chemother 2012;25(4):682-707.

[20] Surveillance Atlas of Infectious Diseases. Available from https://atlas.ecdc.europa.eu/public/index.aspx. [Accessed 6 August 2019].

[21] Public Health England (2015) *English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) 2010 to 2014*. www.gov.uk/phe [Accessed 8 July 2016].

[22] Trepanier P, Mallard K, Meunier D, Pike R, Brown D, Ashby JP, et al. Carbapenemase-producing Enterobacteriaceae in the UK: a national study (EuSCAPE-UK) on prevalence, incidence, laboratory detection methods and infection control measures. J Antimicrob Chemother 2017;72(2):596-603.

[23] Draz N (2018). An NDM outbreak across three trusts and a stroke unit (presentation). Fifth London CPE Workshop (presented 29/11/2018).

[24] van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence 2017;8:460-469.

[25] Mariappan S, Sekar, Kamalanathan A. Carbapenemase-producing Enterobacteriaceae: Risk factors for infection and impact of resistance on outcomes. Int J Appl Basic Med Res 2017;7(1):32-39.

[26] Legeay C, Hue R, Berton C, Cormier H, Chenouard R, Corvec S, et al. Control strategy for carbapenemase-producing Enterobacteriaceae in nursing homes: perspectives inspired from three outbreaks. J Hosp Infect 2019; 101(2):183-187

[27] Holland M, Gupta I, Abbott G, Bashford S, Hardy K. *Challenges of carbapenemase-producing Enterobacteriaceae (CPE) in Haemodialysis Patients* (Poster). Healthcare Infection Society; 2018.

[28] Hopman J, Meijer C, Kenters N, Coolen J, Ghamati MR, Mehter S, et al. Risk Assessment After a Severe Hospital-Acquired Infection Associated With Carbapenemase-Producing *Pseudomonas aeruginosa*. JAMA Netw Open 2019; 2(2):e187665.