Carbapenemase-producing

Carbapenem Resistant *Enterobacteriaceae*

(CRE) in Critical Care Units in Ireland:

A National Pilot Study – June 2011

National Report

September 2011

Table of Contents

1.0 Summary & Recommendations.....3

2.0 Study Working Group Membership.....5

3.0 Background.....6

4.0 Aims.....8

5.0 Methods.....9

6.0 Results.....12

7.0 Discussion.....17

8.0 Conclusions.....19

9.0 Recommendations.....21

10.0 Acknowledgements.....22

11.0 References.....23

Appendix A: Pre-Study Questionnaire.....25

Appendix B: Weekly Denominator Form for Critical Care Unit.....27

Appendix C: Weekly Specimen Form for Microbiology Laboratory..... 28

Appendix D: Enhanced Patient Surveillance form 29

Appendix E: Interim National Recommendations on CRE Screening in Acute Healthcare Facilities in Ireland: July 2011.....32

1.0 Summary & Recommendations

- This first Irish study systematically examined if patients admitted to Irish critical care units in June 2011 were colonised with carbapenemase-producing carbapenem resistant *Enterobacteriaceae*, hereafter termed CRE. CRE is an emerging multi-drug resistant organism for which there are extremely limited antimicrobial treatment options. This study provides an important baseline for CRE epidemiology in Irish critical care units and to our knowledge, it is the first study of its kind conducted in Europe.

- Thirty-five acute hospitals (30 public and five private) representing all regions of Ireland and incorporating 40 critical care units (37 adult and three paediatric) participated in this voluntary four-week pilot study.

- Eighty-four percent of public hospital critical care beds were captured in this study.

- Patients admitted to critical care units were screened weekly for rectal carriage of CRE. There were 839 opportunities to perform weekly rectal swabs for CRE carriage and 760 rectal swabs were taken, reflecting a compliance rate of 91% with the study screening protocol.

- The CRE screening swabs were processed according to a common laboratory protocol at 27 microbiology laboratories. The Health Services Executive approved funding for suspected CRE isolates to undergo confirmatory testing at the Antimicrobial Resistance and Microbial Ecology (ARME) Laboratory at NUI, Galway.

- CRE was not detected in 40 Irish critical care units during this four-week study. Five suspected CRE isolates were referred to ARME and none was confirmed as CRE.

- It is of critical importance that all senior healthcare facility management and healthcare workers ensure that systems are in place to detect and screen patients who are at risk of CRE, in accordance with the national CRE screening guidelines.

- Appropriate antimicrobial prescribing and good infection prevention and control practices by all are essential to prevent the emergence of CRE and other multi-drug resistant organisms. Hospitals should ensure that they have active antimicrobial stewardship programmes in line with national guidelines.

- A national reference laboratory service for confirmation and typing of antimicrobial-resistant Gram-negative bacilli, including CRE, should be established as a matter of urgency. In the interim, it is recommended that a service level agreement with an Irish laboratory is established to ensure that suspected CRE specimens are investigated and reported in a timely fashion.

2.0 Study Working Group Membership

- Dr Karen Burns – Consultant Microbiologist, Health Protection Surveillance Centre (HPSC), Critical Care Programme, HSE & Beaumont Hospital, Dublin.
- Dr Fidelma Fitzpatrick – Consultant Microbiologist, HPSC & Beaumont Hospital & Health Service Executive-Royal College of Physicians in Ireland (HSE–RCPI) Healthcare associated infection (HCAI) Clinical Lead.
- Dr Robert Cunney – Consultant Microbiologist, HPSC & Children's University Hospital, Dublin.
- Mr Stephen Murchan – Surveillance Scientist, HPSC, Dublin.
- Dr Michael Power – Critical Care Programme Clinical Lead, Quality & Safety Directorate, HSE.
- Professor Martin Cormican – Consultant Microbiologist Galway University Hospital, Director National Salmonella Reference Laboratory & Professor of Bacteriology, NUI Galway.
- Dr Dearbhaile Morris – Lecturer in Bacteriology, Antimicrobial Resistance and Microbial Ecology Group, National University of Ireland, Galway.
- Dr Edmond Smyth – Consultant Microbiologist, Beaumont Hospital & President, Irish Society of Clinical Microbiologists (ISCM).
- Dr Kirsten Schaffer – Consultant Microbiologist, St Vincent's University Hospital, Dublin & Chairperson of Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) Subcommittee on Prevention and Control of Multi-Drug Resistant Organisms.
- Dr Cathal Collins – Specialist Registrar Clinical Microbiology, St James's Hospital, Dublin.
- Dr Anne Sheahan – Consultant in Public Health Medicine. HSE-South.

3.0 Background

Carbapenems (meropenem and ertapenem) are broad spectrum intravenous antimicrobials. They have traditionally been reserved for therapy of suspected or confirmed infection in patients who are critically ill and infection in patients known or suspected to be colonised with multi-drug resistant Gram-negative bacilli. In Ireland, the use of carbapenems in hospitals has increased from 1.7 defined daily doses per 100 bed days used (DDD/100 BDU) in 2008 to 2.4 DDD/100 BDU in 2010 (Source: Health Protection Surveillance Centre).

Enterobacteriaceae is the term used to describe groups of Gram-negative bacilli, which are associated with the gastrointestinal tract of humans and animals and related bacteria that occur in the environment. The group includes *Escherichia coli* and *Klebsiella pneumoniae*. In the last decade, there have been an increasing number of reports of patients colonised or infected with carbapenem resistant *Enterobacteriaceae* (CRE). In addition to resistance to carbapenems, these organisms commonly carry genes which confer resistance to almost all classes of antimicrobial agents. Therefore, infection due to CRE is extremely difficult to manage, as there are very limited treatment choices available. Patients who develop CRE infection tend to be critically ill, with severe underlying conditions. The reported mortality from CRE infection has been higher than mortality due to infection caused by carbapenem susceptible bacteria[1].

Two main mechanisms of carbapenem resistance have been described:

1) **CRE due to impermeability**: Multi-drug resistant *Enterobacteriaceae* develop reduced permeability to carbapenems – the antimicrobial cannot enter the bacterial cell in effective quantities and thus becomes ineffective. This type of resistance tends to arise when patients have been exposed to carbapenems, such as during lengthy courses of antimicrobial treatment of complex infection. This type of resistance is not transferrable between bacteria. However, the resistant bacteria can be transferred from one patient to another. This is more likely if infection prevention and control precautions are not consistently adhered to in the healthcare setting.

2) **Carbapenemase-producing CRE**: *Enterobacteriaceae* may acquire resistance genes from other *Enterobacteriaceae*. This genetic material provides the information required to manufacture enzymes, known as carbapenemases. Carbapenemases destroy carbapenems, rendering them ineffective. The genes that encode carbapenemase production in *Enterobacteriaceae* are generally mobile and easily transferred between bacteria. Carbapenemase production has spread worldwide in the past 15 years and is now a prominent resistance mechanism reported in many countries including, Greece, Eastern USA, parts of China and Israel and more recently, India and Pakistan. The predominant genetic mechanisms of carbapenemase production differ from country to country. KPC, VIM, OXA-48 and NDM-1 are the most commonly reported carbapenemases.

Prior to 2010, only one case of carbapenemase-producing CRE had been reported in Ireland. During late 2010 and early 2011, the Health Protection Surveillance Centre (HPSC) began to receive several new reports of patients with CRE, including CRE outbreaks from around the country. The detection of carbapenemase-producing CRE, hereafter known as CRE, from a patient became notifiable to the relevant Department of Public Health in March 2011. Between January and May 2011, CRE had been reported from ten patients in three hospitals. When CRE outbreaks were reported, they tended to have links to critical care units. In response to the emergence of CRE in Ireland, interim CRE screening guidelines were issued in February 2011 and updated in April 2011.[2]

In April 2011, a multi-disciplinary working group was convened to plan a pilot study to screen patients for CRE. The target population for this pilot study was patients admitted to critical care units. This patient group was selected for the following reasons:

1) Defined patient population.
2) Patients admitted to critical care units have many of the reported risk factors for acquisition of CRE colonisation or infection – critical illness, immunosuppression, exposure to broad spectrum antimicrobials, presence of invasive medical devices, organ failure.

3) Reported CRE cases in Ireland have involved patients admitted to critical care units.

The Health Services Executive provided funding for reference laboratory costs associated with the project.

4.0 Aims

1. To raise awareness of CRE in acute hospitals in Ireland.
2. To establish if patients in Irish critical care units were colonised with CRE in order to inform national CRE screening guidelines.
3. To determine current CRE screening practices in Irish critical care units.
4. To determine current microbiology laboratory practices with regard to detection of carbapenem resistance.
5. To ensure that all microbiology laboratories were capable of undertaking CRE screening.
6. To raise awareness of the interim national guidelines for CRE screening.

5.0 Methods

In April 2011, Irish critical care units and microbiology laboratories in public and private hospitals were invited to participate in a voluntary four-week collaborative pilot study due to commence in June 2011.

A pre-study questionnaire (Appendix A) was developed and issued with the study invitation. Hospitals were requested to complete the questionnaire, indicating if they would participate and providing contact information for a nominated critical care unit contact and microbiology laboratory contact.

- Inclusion criteria: All patients admitted to a participating adult or paediatric critical care unit during the four-week study period. Neonates admitted to paediatric critical care units were included.
- Exclusion criteria: Infants admitted to neonatal intensive care units (NICU) were excluded from this study.

In collaboration with the microbiology laboratory, each participating critical care unit was requested to agree the CRE screening schedule. Rectal screening swabs were performed on the same day each week over the study period. Compliance with the study protocol for each unit was measured as the number of weekly screening swabs taken as a proportion of the number of patients present in the unit on the day of weekly screening. Admission CRE screening swabs were not counted in the calculation of compliance. Any possible carbapenemase-producing organism isolated from any screening swab (admission or weekly) or from any clinical specimen was to be included in the study. The completed critical care denominator form was returned by each participating unit at the end of the study (Appendix B).

The microbiology laboratory was asked to complete a weekly microbiology laboratory specimen form recording the number of screening swabs received in the laboratory, the number of suspected carbapenemase producers detected and referred for confirmatory testing and the number of confirmed carbapenemase producers detected (Appendix C).

Participating microbiology laboratories were provided with a laboratory protocol for CRE screening, which incorporated use of positive and negative controls. The CRE screening protocol was adapted from that recommended by the US Centers for Disease Control and Prevention (CDC). http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_Ecoli.pdf

Participating microbiology laboratories were also requested to record if suspected CRE isolates had been detected from clinical specimens (non-screening specimens), such as urine, blood, wound swabs, obtained from any critical care patient during the course of the study.

The national enhanced patient surveillance form for CRE was adapted for the purposes of the study. Participants were requested to complete an enhanced patient surveillance form if carbapenemase-producing CRE was confirmed during the study period (Appendix D). Participants were reminded of their obligation to notify the relevant Department of Public Health in the event of detection of CRE from a patient.

All completed study documentation was returned for collation at the HPSC and all suspected CRE were referred to the laboratory of the Antimicrobial Resistance and Microbial Ecology (ARME), National University of Ireland (NUI), Galway, for confirmatory testing.

Confirmation of carbapenemase production

Upon receipt at the ARME laboratory, suspect carbapenemase-producing CRE isolates were:

1) Screened for susceptibility to meropenem and ertapenem by Etest® in accordance with the manufacturer's instructions.

2) Examined by the modified Hodge test using the Clinical and Laboratory Standards Institute (CLSI) methodology.

3) Examined for *Klebsiella pneumoniae* carbapenemase (KPC), metallo-beta-lactamase, AmpC cephalosporinase plus porin loss activity by a commercial synergy test (Rosco Diagnostica, Taastrup, Denmark).

4) Total genomic DNA was extracted from all isolates received using the QiaAmp® DNA Mini kit (Qiagen, Crawley, U.K.), and screened for the presence of bla_{VIM}, bla_{IMP}, bla_{GIM}, bla_{SIM},

bla$_{SPM}$, *bla*$_{KPC}$, *bla*$_{OXA\text{-}51\text{-}like}$, *bla*$_{OXA\text{-}23\text{-}like}$, *bla*$_{OXA\text{-}40\text{-}like}$, *bla*$_{OXA\text{-}58\text{-}like}$, *bla*$_{NDM}$, *bla*$_{OXA\text{-}48}$, and *bla*$_{GES}$ by PCR using specific primers and protocols as previously described.[3,4,5,6]

6.0 Results

6.1 Demographics of participating critical care units

Completed questionnaires were received from 37 acute hospitals incorporating 44 critical care units. Thirty-five hospitals (30 public and five private), incorporating 40 critical care units (37 adult and 3 paediatric) agreed to participate in the study (*Table 1*). All regions of Ireland were represented in this study (*Figure 1*).

Table 1. Participating hospitals classified by hospital type

Hospital Type	Number of participating hospitals
Public (HSE) Hospital	**30**
▪ Tertiary Referral Hospital	5
▪ Regional Hospital	7
▪ General Hospital	16
▪ Paediatric Hospital	2
Private Hospital	**5**
TOTAL	**35**

Figure 1. Map illustrating location of participating hospitals

Participating critical care units were further classified based on the 2009 UK Intensive Care Society Levels of Critical Care for Adult Patients (*Table 2*). The classification of critical care beds in Irish critical care units was obtained from the national critical care bed stock survey of acute public hospitals conducted by the Health Service Executive Critical Care Programme in 2010.

Table 2. Classification of participating critical care units

LEVEL OF CARE	NUMBER OF PARTICIPATING CRITICAL CARE UNITS	DEFINITION
LEVEL 2 ONLY **High Dependency Unit**	3	Patients needing pre-operative optimisation Patients needing extended post-operative care Patients stepping down to Level 2 care from Level 3 Patients receiving basic respiratory support Patients receiving basic cardiovascular support Patients receiving advanced cardiovascular support Patients receiving renal/neurological/dermatological support
LEVEL 3 ONLY **Intensive Care Unit**	24	Patients receiving advanced respiratory support **OR** Patients receiving a minimum of two organs supported
MIX OF LEVEL 2 & LEVEL 3 CARE PROVIDED WITHIN UNIT	13	
TOTAL	**40**	

6.2 Pre-study questionnaire findings

Participation in this voluntary pilot study was high, at 84% of public hospital critical care unit beds. *Table 3* summarises results from the pre-study questionnaire.

Table 3. Summary of pre-study questionnaire results

Result	Number	Further Information
Hospitals (critical care units) returning completed questionnaires	37 (44)	
Participating hospitals (critical care units)	35 (40)	
Total critical care beds surveyed	299 Average 6.7 beds per unit (Range 2-16 beds)	257 in public hospitals 42 in private hospitals
Total critical care beds participating	258	216 in public hospitals 42 in private hospitals
Microbiology laboratories completing pre-study questionnaire	31	
Participating microbiology laboratories	27	

6.2.1 Critical care screening practices

Fifteen hospitals (41%) reported routinely screening patients admitted to their critical care unit(s) for rectal carriage of vancomycin resistant enterococci (VRE).

- Thirteen performed VRE screening on admission to the unit and of these, two performed no further screening and 11 repeated VRE screening on a weekly basis.
- Two hospitals did not perform VRE screening on admission to the unit, but performed VRE screening on a weekly basis.

Eight hospitals (22%) reported routinely screening patients admitted to critical care units for rectal carriage of CRE. All eight performed admission CRE screening and six repeated CRE screening weekly thereafter. Of the eight hospitals performing routine CRE screening in critical care units, six had reported patients with confirmed CRE in the twelve months prior to completing the questionnaire.

6.2.2 Microbiology laboratory testing practices

Thirty-one microbiology laboratories serving 37 acute hospitals completed the pre-study questionnaire. Three of the microbiology laboratories also provided services to a second hospital and one laboratory also provided services to three additional hospitals. Of the 31 respondents, 24 (77%) reported having carried out testing for CRE at some point. Seven of the laboratories (23%) had not yet undertaken any testing for CRE.

Twenty microbiology laboratories (65%) reported that they routinely identified *Enterobacteriaceae* isolated from clinical specimens of critical care unit patients. Eighty-four percent of microbiology laboratories routinely included a carbapenem when performing antimicrobial susceptibility testing on *Enterobacteriaceae*. However, three microbiology laboratories (10%) did not. Two laboratories reported that carbapenem susceptibility testing was performed on urinary isolates, in the event of resistance to the first-line antimicrobial agents.

Due to microbiology laboratory staffing shortages in three hospitals, the study screening swabs were sent elsewhere for processing. Therefore, a total of 27 microbiology laboratories participated in this study and processed CRE screening swabs for 40 critical care units.

6.3 Study findings

All 27 participating microbiology laboratories adhered to the recommended laboratory protocol for processing CRE screening swabs.

Rectal swabs were taken from patients in 34 of 35 participating hospitals. One of the paediatric hospitals was already routinely performing CRE screening on faeces specimens. This practice continued throughout the study.

Of the eight hospitals where admission CRE screening was already routine practice, this practice continued and all eight hospitals were requested to also perform weekly CRE screening thereafter.

A total of 839 admitted patients were documented as having been present in the 40 critical care units over the study period. As the length of stay for each patient was not recorded, it is important to note that this does not imply that 839 patients were screened, rather that there were 839 opportunities to perform CRE screening. One patient may have been present for only one of the weekly screens and another patient may have been screened on four consecutive weeks. Of the 839 opportunities to perform CRE screening, 760 CRE screening swabs were taken, reflecting 91% overall compliance with the study protocol. Compliance with the study protocol for individual hospitals ranged from 55 to 100%. On average, 28 CRE screening swabs (range 6-126) were processed by participating microbiology laboratories over the four-week study period.

Carbapenemase-producing CRE was not detected in any of the 40 participating critical care units during this four week pilot study. Five suspected CRE isolates (all *Enterobacter sp.*) taken from four patients in four geographically distinct hospitals were referred to the ARME reference laboratory at NUI Galway for confirmatory testing.

7.0 Discussion

The emergence and rapid dissemination of carbapenemase-producing CRE worldwide is a cause for concern. Treatment options for infection due to these multi-drug resistant organisms are extremely limited and effective therapy may be delayed whilst microbiology laboratory confirmatory results are awaited. Therefore, infection due to CRE is more likely to result in the death of a patient compared with infection due to carbapenem susceptible *Enterobacteriaceae*.[1] The multi-drug resistant nature of these bacteria coupled with stagnation in production of novel antimicrobial agents with potential activity against CRE mandates that all practical steps are taken to delay or prevent CRE becoming endemic in Ireland. There has been a change in the epidemiology of CRE in Ireland since the latter half of 2010. As of September 2011, all of the major mechanisms of carbapenemase production have now been reported in Ireland (KPC, VIM, OXA-48 and NDM-1).[7,8,9] In addition, there have been significant CRE outbreaks in two large Irish hospitals (KPC & OXA-48) in distinct geographical regions.[9]

This voluntary pilot study aimed to assess current CRE screening practices in Irish critical care units, current CRE detection practices in Irish microbiology laboratories and to systematically conduct screening for CRE in a defined high-risk patient population. The study also raised awareness of CRE and the current interim national CRE guidelines and ensured that almost all microbiology laboratories gained experience in processing CRE screening swabs.

There was an excellent response to the study invitation from Irish critical care units and microbiology laboratories. This study captured 84% of the public hospital critical care beds in 35 critical care units. Five critical care units in private hospitals also participated.

One tertiary referral hospital indicated that it was not in a position to participate in the study citing critical care staff shortages as a barrier to participation. A second tertiary referral hospital indicated that it was not in a position to participate in the study owing to microbiology laboratory staff shortages. A further three microbiology laboratories also cited staff shortages as a barrier to participation in the study.

The CRE screening results of the latter three hospitals were transported for processing by the Microbiology Laboratory in Galway University Hospital, thus facilitating participation of their critical care units in the study.

Routine CRE screening was already carried out in the critical care units of eight hospitals (22%) prior to this study. Six of the eight hospitals had already reported detecting patients with carbapenemase-producing CRE in the 12 months prior to the study and in four of the six, CRE had been associated with patients admitted to a critical care unit.

The interim national guidelines regarding CRE screening in Ireland were first issued in February 2011. The guidelines recommended that CRE screening be carried out on any patient with a history of hospitalisation for more than 48 hours in a healthcare facility outside Ireland in the previous year. Shortly afterwards, an outbreak of KPC CRE with documented inter-hospital transmission outside of the region was reported from the Mid-West of Ireland and the interim guidelines were updated in April 2011 to include a recommendation to perform CRE screening on any patient transferred from an acute hospital in the Mid-West or with a history of admission to an acute hospital in the Mid-West in the past year. It was recommended that all acute hospitals in Ireland put in place robust measures to ensure prompt identification and screening of 'at-risk' patients. Of the 31 microbiology laboratories responding to the pre-study questionnaire, 77% had prior experience of performing CRE screening. All participating microbiology laboratories processed CRE screening swabs in accordance with the study laboratory protocol and processed an average of 28 screening swabs over the duration of the study. There were 839 opportunities to perform CRE screening during the four weeks of the study and there was a high level of compliance with the screening protocol (91%) in the participating units. Carbapenemase-producing CRE were not detected in any of the 40 participating critical care units during this four week pilot study.

8.0 Conclusions

This pilot study establishes an important baseline with regard to current CRE screening and microbiology laboratory diagnostic practices in Ireland. To our knowledge, this is the first study to systematically screen for CRE at a national level in a high risk population. Based on the findings of this short pilot study, CRE was not detected in 40 Irish critical care units. It is important to note, that cases of CRE affecting patients admitted to critical care units have been notified before this study commenced and since this study concluded. Therefore, it is of critical importance that vigilance for CRE is maintained throughout Ireland and that all practical measures are taken by all healthcare professionals to identify and screen patients, who may be at-risk of CRE carriage. CRE has become a predominant resistance mechanism reported with increasing frequency from several countries, including Greece and Israel. The experience of these countries has demonstrated that CRE can emerge and become endemic in a country within a short period of time.

Prompt recognition of CRE carriers will minimise the risk of CRE spreading in Irish hospitals and protect vulnerable patients (such as those admitted to critical care units) from the potentially devastating effect of CRE infection.

The interim national guidelines on CRE screening in acute healthcare facilities in Ireland were updated again in July 2011, taking into account the findings of this study and a second significant CRE outbreak (OXA-48) reported from a tertiary referral hospital in Dublin (Appendix E). The latest CRE screening recommendations are maintained on the HPSC website.http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/StrategyforthecontrolofAntimicrobialResistanceinIrelandSARI/CarbapenemResistantEnterobacteriaceaeCRE/ScreeningforCREinIreland

Systematic CRE screening of patients admitted to critical care units is not currently recommended, unless the patient falls into an 'at-risk' category:

- Transferred from or with a history of admission to any healthcare facility abroad for more than 48 hours in the past 12 months
- Transferred from or with a history of admission to a named healthcare facility in Ireland (for more than 48 hours) reporting a CRE outbreak.

However, based on the experience of individual hospitals, the local infection prevention and control team may advise CRE screening in patients admitted to critical care units.

This pilot voluntary study demonstrated the feasibility of performing CRE screening in critical care units. The provision of funding from the HSE allowed for suspect isolates to be referred to and tested in an Irish laboratory. There is currently no designated reference laboratory for confirmation of carbapenemase production in Ireland. At present, suspected CRE isolates are referred to references laboratories abroad with ensuing significant delays in confirmation.

Patients suspected of having CRE are isolated with Contact Precautions. Therefore, delay in confirmation of CRE translates into isolation rooms being occupied for lengthy periods pending reference laboratory confirmation. Rapid confirmation of CRE has a role to play in ensuring appropriate use of limited isolation room facilities.

9.0 Recommendations

- This study should be repeated periodically (at a minimum of every 1-2 years) to monitor the epidemiology of CRE in Irish critical care units.

- Every microbiology laboratory should be able to undertake CRE screening, as per national guidelines. A local standard operating procedure should be devised by every microbiology laboratory for processing and reporting CRE screening results.

- Every microbiology laboratory should be resourced with adequate staff to conduct and maintain CRE screening as per national guidelines and most importantly in the event of a CRE outbreak.

- A designated national reference laboratory service for the characterisation of antimicrobial resistant Gram-negative bacilli, including CRE and tracking the molecular epidemiology of such pathogens in Ireland should be resourced as a matter of urgency. Such a laboratory service would also have an important role to play with regard to monitoring of epidemiology of pathogens, such as CRE, in Europe. In the interim, it is recommended that a service level agreement with an Irish laboratory is established to ensure that suspected CRE specimens are investigated and reported in a timely fashion.

- Appropriate antimicrobial prescribing and good infection prevention and control practices are essential to prevent the emergence of CRE and other multi-drug resistant organisms in all healthcare settings, including critical care units. Standard Precautions (which include hand hygiene) should be used by all staff at all times. Hospitals should ensure that they have active antimicrobial stewardship programmes, in line with national guidelines. This should include restriction of carbapenem use. Carbapenems should only be prescribed following consultation with a clinical microbiologist or infectious diseases physician. Hospitals should conduct regular audits of carbapenem use and feedback of antimicrobial consumption data to prescribers.

10.0 Acknowledgements

The members of the study working group wish to sincerely thank and acknowledge the staff of the critical care units, microbiology laboratories, infection prevention and control teams, the staff at the ARME laboratory for their enthusiastic participation and the Intensive Care Society of Ireland (ICSI) for its endorsement of this study.

11.0 References

1. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of Carbapenem-Resistant *Klebsiella pneumoniae* Infection and the Impact of Antimicrobial and Adjunctive Therapies. *Infect Control Hosp Epidemiol* 2008;29:1099-1106.

2. Burns K, Schaffer K. CRE update issued on laboratory detection and infection control measures. May 2011. Epi Insight - volume 12 issue 5 - CRE - update issued on laboratory detection and infection control measures

3. Woodford N et al. Outbreak of *Klebsiella pneumoniae* Producing a New Carbapenem-hydrolysing Class A β lactamase, KPC-3, in a New York Medical Center. *Antimicrob Agents Chemother* 2004;48:4793-99.

4. Dallenne C, Da Costa A, Cecre D, Favier C, Arlet G. Development of a set of multiplex PCR assays for the detection of genes encoding important β lactamases in *Enterobacteriaceae*. *J Antimicrob Chemother* 2010;65:490-95.

5. Woodford N. 2010. Rapid characterisation of beta-lactamases by multiplex PCR. Chapter 14, In: Stephen H. Gillespie and Timothy D. McHugh (eds.), Antibiotic Resistance Protocols; Second Edition, Methods in Molecular Microbiology, vol 642.

6. Nordmann P, Poirel L, Carrer A, Toleman M, Walsh TR. How to Detect NDM-1 Producers. *J Clin Microbiol* 2011;49:718-21.

7. Roche C, Cotter M, O'Connell N, Crowley B. First Identification of Class A Carbapenemase-Producing *Klebsiella pneumoniae* in the Republic of Ireland. *Eurosurveill* 2009;14(13);4-5.

8. Prior AR, Roche C, Lynch M, Kelly S, O'Rourke K, Crowley B. First identified case of VIM-producing carbapenem resistant *Klebsiella pneumoniae* in the Republic of Ireland associated with fatal outcome. *Eurosurveill* 2010;15(50):25.

9. O'Brien DJ, Wrenn C, Roche C, Rose L, Fenelon C, Flynn A, Murphy V, Fitzgerald SF, Fenelon LE, Crowley B, Schaffer K. First isolation and outbreak of OXA-48-producing

Klebsiella pneumoniae in an Irish hospital, March to June 2011. *Eurosurveill* 2011;16(29):4-6.

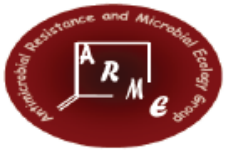
Appendix A- Pre-Study Questionnaire

NATIONAL PILOT STUDY OF CARBAPENEMASE-PRODUCING CRE IN CRITICAL CARE UNITS – PRE-STUDY QUESTIONNAIRE

Name of your hospital	
Number of critical care units in your hospital	
Number of critical care beds open in your hospital	
Is rectal screening for VRE routinely performed in your critical care unit(s)? If yes, tick appropriate box:	Yes ☐ No ☐ On admission to unit ☐ Weekly screen ☐
Is rectal screening for Carbapenem-resistant *Enterobacteriaceae* (CRE) routinely performed in your critical care unit(s)? If yes, tick appropriate box:	Yes ☐ No ☐ On admission to unit ☐ Weekly screen ☐
To date, has the microbiology laboratory undertaken CRE screening on any patient sample from any clinical location in the hospital?	Yes ☐ No ☐

Does the microbiology laboratory routinely perform full identification and susceptibility testing on all *Enterobacteriaceae* isolated from patients admitted to the critical care unit?	Yes ☐ No /only on request ☐
Does the microbiology laboratory routinely test susceptibility to a carbapenem (meropenem, imipenem or ertapenem) for all *Enterobacteriaceae* undergoing antimicrobial susceptibility testing	Yes ☐ No ☐
Following local consultation between critical care unit(s) and microbiology laboratory, does your hospital agree to participate in the national 4 week pilot CRE screening in ICU project? If no, please provide reason why the hospital is not in a position to participate	Yes ☐ No ☐
If yes, please provide contact details (name, work e-mail address and work telephone number [direct extension]) of two nominated local contacts for the study	**1.Critical care unit contact** Name: E-mail: Tel: **2: Microbiology laboratory contact** Name: E-mail: Tel:

Appendix B – Weekly Denominator Form for Critical Care Unit



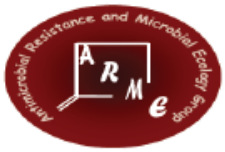
NATIONAL PILOT STUDY OF CARBAPENEMASE-PRODUCING CRE IN CRITICAL CARE UNITS: WEEKLY DENOMINATOR FORM FOR CRITICAL CARE

FORM COMPLETED BY:

WORK E-MAIL ADDRESS:

HOSPITAL NAME:		**UNIT NAME:**		
WEEK OF STUDY	**DATE WEEKLY CRE SCREENING SWABS TAKEN**	**DAY OF WEEK WHEN THE WEEKLY CRE SCREENING SWABS TAKEN**	**NUMBER OF PATIENTS ADMITTED TO THE UNIT AT THE TIME CRE SCREENING SWABS TAKEN**	**NUMBER OF CRE SCREENING SWABS TAKEN**
WEEK 1				
WEEK 2				
WEEK 3				
WEEK 4				
TOTAL				

Appendix C – Weekly Specimen Form for Microbiology Laboratory

NATIONAL PILOT STUDY OF CARBAPENEMASE-PRODUCING CRE IN CRITICAL CARE UNITS: WEEKLY MICROBIOLOGY LABORATORY SPECIMEN FORM

FORM COMPLETED BY:

WORK E-MAIL ADDRESS:

HOSPITAL LABORATORY NAME:		**NAMES OF CRITICAL CARE UNITS SERVED BY THIS MICROBIOLOGY LABORATORY:**		
WEEK OF STUDY	**TOTAL CRE SCREENING SWABS RECEIVED IN LABORATORY (WEEKLY SCREENS +/- ADMISSION SCREENS)***	**NUMBER OF QUERY CARBAPENEMASE CRE ISOLATES FROM SCREENING SWABS**	**NUMBER OF QUERY CARBAPENEMASE CRE ISOLATES FROM CLINICAL SAMPLES**	**NUMBER OF CONFIRMED CARBAPENEMASE PRODUCERS CONFIRMED BY REFERENCE LABORATORY**
WEEK 1				
WEEK 2				
WEEK 3				
WEEK 4				
TOTAL				

Appendix D – Enhanced Patient Surveillance Form

55791

National Pilot Study of Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae (CRE) in ICU
Enhanced Surveillance Form, v1.5 (June 2011)

hpsc

Please complete as fully and legibly as possible

HSE Feidhmeannacht na Seirbhíse Sláinte Health Service Executive

CONTACT DETAILS IN CASE FURTHER DISCUSSIONS OF THIS CASE ARE REQUIRED:

Name:

Telephone Number: **Email:**

Section 1: Demographic information:

Hospital code: **Patient ID (MRN or Chart No.):** **Sex:** M F Unk

Age: **If <1 year, please state if age in days (D) or months (M):** D M

Date of hospital admission: / / 20 **Date of ICU admission:** / / 20

Admitted to this healthcare facility (HCF) from:

Home Other Hospital Long-term care facility Nursing Home Other

Section 2: Clinical Information:

At the time of CRE detection was the patient already colonised or infected with another HCAI pathogen?

Yes No

If YES, please indicate organism(s):

MRSA

VRE

ESBL-producing Enterobacteriaceae

Other / multi-drug resistant organism → Please state:

Was this patient transferred to this HCF from a hospital abroad? Yes No

If YES to hospitalisation abroad, please state country:

Did the patient travel abroad in the 12 months prior to hospitalisation? Yes No Unk

If YES to travel abroad, please state country/ies:

If YES to travel abroad, please state reason(s) for travel:

Holiday Visiting friends and relatives

Work Other → Please state:

Medical Unk

Risk Factors for CRE:

Hospitalisation in last 12 months

ICU admission in last 12 months

Surgery in last 6 months

Immunocompromised

Diabetes mellitus

End-stage renal disease or renal replacement therapy

Chronic lung disease

Chronic liver disease

Recurrent urological problems

None of the above

Unk

Isolation of CRE from this patient represents: Infection **or** Colonisation

55791

Patient ID (MRN or Chart No.):

Please repeat Patient ID above to allow adequate form matching

If YES to infection, the likely source is:

- ☐ Bacteraemia without obvious focus
- ☐ Central nervous system
- ☐ Respiratory tract
- ☐ Urinary tract
- ☐ Intra-abdominal
- ☐ Genital tract
- ☐ Skin / soft tissue
- ☐ Surgical wound
- ☐ Infection of prosthetic material
- ☐ Other → Please state:

Outcome:

- ☐ Survived and remains an inpatient in ICU
- ☐ Survived and discharged from ICU → Date of discharge: ☐☐ / ☐☐ / 20☐☐
- ☐ Died → Date of death: ☐☐ / ☐☐ / 20☐☐

SECTION 3: ANTIMICROBIAL INFORMATION

Antimicrobials administered during this admission PRIOR to CRE isolation:

- ☐ Beta-Lactam + beta-lactamase inhibitor
- ☐ Cephalosporin
- ☐ Meropenem
- ☐ Ertapenem
- ☐ Aztreonam
- ☐ Fluoroquinolone
- ☐ Gentamicin
- ☐ Tobramycin
- ☐ Amikacin
- ☐ Tigecycline
- ☐ Colistin
- ☐ Chloramphenicol
- ☐ Co-trimoxazole

If this represents CRE infection, please state the agents used to treat this infection:

	Number of days given:
☐ Meropenem	☐☐ days
☐ Ertapenem	☐☐ days
☐ Aztreonam	☐☐ days
☐ Fluoroquinolone	☐☐ days
☐ Gentamicin	☐☐ days
☐ Tobramycin	☐☐ days
☐ Amikacin	☐☐ days
☐ Tigecycline	☐☐ days
☐ Colistin	☐☐ days
☐ Chloramphenicol	☐☐ days
☐ Co-trimoxazole	☐☐ days

Did initial choice of empiric antimicrobial therapy cover the CRE isolated? ☐ Yes ☐ No

If NO, how many days elapsed between date of culture and date of initiation of appropriate antimicrobial therapy?

☐☐ days

SECTION 4: OTHER RELEVANT CLINICAL INFORMATION:

Page 2 of 3

55791

NATIONAL PILOT STUDY OF CARBAPENEMASE-PRODUCING CRE IN ICU
Enhanced Surveillance Form, v1.5 (June 2011)

LABORATORY CONTACT DETAILS IN CASE FURTHER DISCUSSIONS OF THIS ISOLATE ARE REQUIRED:

Name:

Telephone Number: **Email:**

SECTION 5: LABORATORY INFORMATION:

Laboratory code: **Hospital code:** **Patient ID (MRN or Chart No.):**

Date of birth: / / **Sex:** M F Unk

Specimen number: **Specimen date:** / / 20

Specimen Type:

- Rectal screen
- Other sterile site → Please state:
- Blood
- Other non-sterile site → Please state:
- CSF

Organism: *E. coli* *K. pneumoniae* *Other - please state:*

Antimicrobial susceptibility testing (AST) method used: EUCAST CLSI BSAC

AST results:

Meropenem	R	I	S	Meropenem MIC, if I/R:	mg/L			
Imipenem	R	I	S	Imipenem MIC, if I/R:	mg/L			
Ertapenem	R	I	S	Ertapenem MIC, if I/R:	mg/L			
3rd-Generation Cephalosporin	R	I	S	**Fluoroquinolone**	R	I	S	
Aztreonam	R	I	S	**Tigecycline**	R	I	S	
Gentamicin	R	I	S	**Colistin**	R	I	S	
Tobramycin	R	I	S	**Chloramphenicol**	R	I	S	
Amikacin	R	I	S	**Co-trimoxazole**	R	I	S	

Is this case part of a suspected outbreak? Yes No

Was this isolate referred to the Reference Laboratory (NUI Galway) for confirmation of the CRE? Yes No

The case classification of this carbapenemase-producing CRE is: Confirmed Probable

If CONFIRMED, please state resistance gene: VIM IMP KPC OXA NDM Other → Please state:

SECTION 6: OTHER RELEVANT LABORATORY INFORMATION:

Please return the ORIGINAL form to HPSC, 25-27 Middle Gardiner Street, Dublin 1 and a COPY to your local Dept of Public Health

Appendix E – Interim National Recommendations on CRE screening in Acute Healthcare Facilities in Ireland – July 2011

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

hpsc

Updated Interim National Recommendations on Carbapenem Resistant Enterobacteriaceae (CRE) screening in Acute Healthcare Facilities in Ireland, July 6th 2011

These updated national recommendations provide interim guidance for healthcare professionals on the following issues:

- Which patient groups should be screened for CRE carriage
- When to pre-emptively isolate a patient with contact precautions in an acute healthcare facility, pending CRE screening results
- Infection prevention and control precautions for known CRE colonised or infected patients.
- Communication of CRE status
- Prevention of CRE transmission
- Recommended laboratory protocol for processing CRE screening specimens

A multidisciplinary expert group is currently preparing national guidelines for prevention and control of multi-drug resistant organisms, including CRE. The draft version of the guidelines for consultation is expected in Autumn 2011.

Up-to-date information regarding CRE, including the current recommendations for patient screening when a history of admission to a named healthcare facility has been reported, is maintained on the website of the Health Protection Surveillance Centre here http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/StrategyforthecontrolofAntimicrobialResistanceinIrelandSARI/CarbapenemResistantEnterobacteriaceaeCRE

Detection of carbapenemase-producing CRE is notifiable to your local Medical Officer of Health

"Carbapenem resistant enterobacteriaceae (CRE) are multi-drug resistant bacteria for which there are extremely limited available antimicrobial treatment options. Invasive infection due to CRE has been associated with increased morbidity, mortality, length of hospitalisation and increased healthcare costs. Prevention of spread of CRE within Irish healthcare facilities is of the utmost importance. In March 2011, the isolation of carbapenemase-producing CRE from a patient, whether

colonisation or infection, became notifiable to the Medical Officer of Health. An enhanced patient surveillance form should be completed for every notified case of confirmed carbapenemase-producing CRE. The enhanced surveillance form can be accessed here http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/StrategyforthecontrolofAntimicrobialResistanceinIrelandSARI/CarbapenemResistantEnterobacteriaceaeCRE/SurveillanceForms

Which patient groups should be screened for CRE carriage and what infection prevention and control precautions should be applied?

All acute healthcare facilities must have systems in place to identify and perform screening for CRE carriage on the following categories of patients:

1. **Any patient transferred/repatriated from a healthcare facility in any foreign country:**
   - The patient should be isolated on admission with transmission-based (contact) precautions.
   - A rectal swab should be taken for CRE carriage.
   - Screening swabs for CRE carriage should also be taken from any draining wounds, broken skin, indwelling device sites (urinary catheters, drains, intravascular catheters, endotracheal tubes etc.).
   - Screening for carriage of other multi-drug resistant organisms, such as MRSA, VRE and ESBL-producing enterobacteriaceae is also highly recommended.

2. Any patient being admitted to an acute healthcare facility in Ireland (emergency or elective) should be specifically questioned regarding a **history of admission to a healthcare facility abroad in the past 12 months. If that patient has been an inpatient in a healthcare facility abroad for more than 48 hours**:
   - The patient should be screened for rectal carriage of CRE.
   - A risk assessment should be performed in conjunction with the local infection prevention and control team regarding the need for pre-emptive isolation of the patient pending results of CRE screening swabs. Isolation is recommended for patients with:
     i. Diarrhoea
     ii. Draining wounds
     iii. Productive cough
     iv. Indwelling devices (e.g., tracheostomy, urinary catheter, drains).

If the patient attended the foreign healthcare facility for less than 48 hours or as a day patient (e.g., holiday dialysis):

- The decision to perform CRE screening should be made locally based on risk assessment and discussion with the local infection prevention and control team.

3. Any patient presenting to an acute healthcare facility in Ireland (includes inter-hospital transfers within Ireland) should be specifically questioned regarding a **history of admission to an Irish healthcare facility reporting an outbreak of CRE in the past 12 months. If that patient has been an inpatient in such an Irish healthcare facility for more than 48 hours**:
    - The patient should be screened for rectal carriage of CRE.
    - A risk assessment should be performed in conjunction with the local infection prevention and control team regarding the need for pre-emptive isolation of the patient pending results of CRE screening swabs. Isolation is recommended for patients with:
        i. Active diarrhoea
        ii. Draining wounds
        iii. Productive cough
        iv. Indwelling devices

    If the patient attended the Irish healthcare facility reporting a CRE outbreak for less than 48 hours or as a day patient:

    - The decision to perform CRE screening should be made locally based on risk assessment and discussion with the local infection prevention and control team.
4. Every Irish healthcare facility must have a system in place of ensuring **rapid identification of a known CRE colonised patient in the event that the patient represents to the healthcare facility or is transferred to another healthcare facility**. Patients with a history of CRE colonisation or infection must be isolated upon presentation to the healthcare facility or transfer to another healthcare facility and screened for rectal carriage of CRE. Screening swabs should also be taken from any draining wounds, broken skin, indwelling device sites (urinary catheters, drains, intravascular catheters, endotracheal tubes etc.)

Jpdated Interim National Recommendations on Carbapenem Resistant Enterobacteriaceae (CRE) screening in Acute Healthcare Facilities n Ireland, July 6th 2011 www.hpsc.ie

Communication

It is the responsibility of the patient's clinical team to **inform the patient** in the event that CRE is detected.

It is the responsibility of the patient's clinical team to **inform the receiving healthcare facility** (whether acute or non-acute) of a patient's CRE status (known or suspected) and the appropriate infection prevention and control precautions necessary. Communication should be clearly documented in all relevant transfer documentation. Further advice should be sought from the local infection prevention and control team, as required.

Infection prevention and control precautions for patients with known CRE colonisation or infection

Patient should be cared for in a single isolation room with *en suite* facility or dedicated commode and in addition to standard precautions, with strict application of transmission-based (contact) precautions. Where contact with the patient is likely, a surgical gown is the preferred personal protective equipment, instead of plastic apron. Further advice should be sought from the local infection prevention and control team, as required. Wherever possible, dedicated staff should be assigned to care only for a CRE positive patient.

Prevention of CRE transmission

Standard precautions

Strict compliance with standard precautions, including hand hygiene, is the cornerstone to prevention of transmission of multi-drug resistant organisms, including CRE. All staff have a responsibility to adhere to standard precautions in caring for all patients at all times.

Antimicrobial stewardship

The prudent and rational use of antimicrobials in all settings (community and acute healthcare facilities) is essential to reduce the risk of emergence of all types of multi-drug resistant bacteria, including CRE. All prescribers have a professional responsibility to use antimicrobials judiciously. The Strategy for Control of Antimicrobial Resistance in Ireland (SARI) published national guidelines on antimicrobial stewardship in Irish hospitals in 2009. All healthcare facilities (acute and non-acute) should review the recommendations of those guidelines as a priority and perform a gap analysis with respect to implementation of the recommendations.

Updated Interim National Recommendations on Carbapenem Resistant Enterobacteriaceae (CRE) screening in Acute Healthcare Facilities in Ireland, July 6th 2011 www.hpsc.ie

Prior exposure to antimicrobials is associated with an increased risk of acquisition of CRE. All healthcare facilities (acute and non-acute) should have systems in place to monitor and restrict the use of the following antimicrobial classes, which have been particularly associated with an increased risk of CRE acquisition:

- Carbapenems (meropenem, ertapenem, imipenem and doripenem)
- Fluoroquinolones (ciprofloxacin, olfloxacin, levofloxacin, moxifloxacin)
- 3rd generation cephalosporins (ceftotaxime, ceftriaxone, ceftazidime)

Laboratory screening methodology

- The laboratory protocol described below is the recommended methodology for detecting CRE on rectal screening swabs or faeces specimens. **ESBL chromogenic media are not recommended for CRE screening**. They will not pick up OXA-48-type CRE, which tend to retain susceptibility to third-generation cephalosporins.

- **In addition to each patient sample to be processed, it is advised that a positive control (NCTC 13438) and a negative control (ATCC 25922) are set up.**

DAY 1

- **Step 1**: Aseptically place a 10µg disc containing ertapenem AND a 5µg disc containing vancomycin into 5ml of trypticase soy broth (TSB).

- **Step 2**: Immediately inoculate the TSB (containing antimicrobial discs) with a rectal screening swab.

- **Step 3**: Incubate aerobically overnight at 35 ±2^{0}C.

DAY 2

- **Step 1**: Vortex the TSB bottle.

- **Step 2**: Subculture 100µl of the incubated TSB culture onto MacConkey agar plate.

- **Step 3**: Streak out the inoculated plates.

- **Step 4**: Aseptically, place a 10µg meropenem disc on the streaked out MacConkey agar plate.

- **Step 5**: Incubate aerobically overnight at 35±2^{0}C.

Updated Interim National Recommendations on Carbapenem Resistant Enterobacteriaceae (CRE) screening in Acute Healthcare Facilities in Ireland, July 6th 2011 www.hpsc.ie

DAY 3

- **Step 1**: Examine MacConkey plate for growth up to the meropenem disc or a reduced zone of inhibition around the meropenem disc. A zone of inhibition of less than 27mm around the meropenem disc should be taken as the cut-off for performing further work on the isolate.
- **Step 2**: Note, if there is more than one colony morphology present, this may represent different species of Enterobacteriaceae. It may be necessary to subculture different colony types to MacConkey plates for purity. If there are no suspect colonies and no reduced zone of inhibition, report swab result as "CRE not isolated" or according to current local laboratory protocol.
- **Step 3**: Select suspect colony for full identification and susceptibility testing using local methodology for organism identification and antimicrobial susceptibility testing.
- **Step 4**: In addition to local methodology for identification and antimicrobial susceptibility testing, set up "E-tests" to both ertapenem and meropenem against suspected colony.
- **Step 5**: Inform clinical microbiologist and infection prevention and control team of the possible isolation of Enterobacteriaceae with reduced susceptibility to carbapenems, pending further results.

DAY 4

- **Step 1**: Read organism identification and susceptibility results in accordance with local laboratory protocol.
- **Step 2**: Read "E-test" MIC results in accordance with local laboratory protocol.
- **Step 3**: If organism identification belongs to Enterobacteriaceae family and carbapenem susceptibility results suggest intermediate susceptibility or resistance, according to local interpretive criteria inform clinical microbiologist and infection prevention and control team of latest results.
- **Step 4**: Set up two slopes of the suspect isolate – Retain one slope locally.
- **Step 5**: Send the second slope to a reference laboratory along with a photocopy of completed page 3 of enhanced patient surveillance form – Laboratory information.

Updated Interim National Recommendations on Carbapenem Resistant Enterobacteriaceae (CRE) screening in Acute Healthcare Facilities in Ireland, July 6th 2011 www.hpsc.ie