Molecular epidemiology of carbapenem-resistant Enterobacterales in Thailand, 2016–2018

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Abstract

Background: Carbapenem-resistant Enterobacterales (CRE) is a global threat. Enterobacterales develops carbapenem resistance through several mechanisms, including the production of carbapenemases. We aim to describe the prevalence of Carbapenem-resistant Enterobacterales (CRE) with and without carbapenemase production and distribution of carbapenemase-producing (CP) genes in Thailand using 2016–2018 data from a national antimicrobial resistance surveillance system developed by the Thailand National Institute of Health (NIH).

Methods: CRE was defined as any Enterobacterales resistant to ertapenem, imipenem, or meropenem. Starting in 2016, 25 tertiary care hospitals from the five regions of Thailand submitted the first CRE isolate from each specimen type and patient admission to Thailand NIH, accompanied by a case report form with patient information. NIH performed confirmatory identification and antimicrobial susceptibility testing and performed multiplex polymerase chain reaction testing to detect CP-genes. Using 2016–2018 data, we calculated proportions of CP-CRE, stratified by specimen type, organism, and CP-gene using SAS 9.4.

Results: Overall, 4,296 presumed CRE isolates were submitted to Thailand NIH; 3,946 (93%) were confirmed CRE. Urine (n = 1622, 41%) and sputum (n = 1380, 35%) were the most common specimen types, while blood only accounted for 323 (8%) CRE isolates. The most common organism was Klebsiella pneumoniae (n = 2660, 72%), followed by Escherichia coli (n = 799, 22%). The proportion of CP-CRE was high for all organism types (range: 85–98%). Of all CRE isolates, 2909 (80%) had one CP-gene and 629 (17%) had > 1 CP-gene. New Delhi metallo-beta-lactamase (NDM) was the most common CP-gene, present in 2392 (65%) CRE isolates. K. pneumoniae carbapenemase (KPC) and Verona integron-encoded metallo-β-lactamase (VIM) genes were not detected among any isolates.

Conclusion: CP genes were found in a high proportion (97%) of CRE isolates from hospitals across Thailand. The prevalence of NDM and OXA-48-like genes in Thailand is consistent with pattern seen in Southeast Asia, but different from that in the United States and other regions. As carbapenemase testing is not routinely performed in Thailand, hospital staff should consider treating all patients with CRE with enhanced infection control measures; in line

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Introduction
Antimicrobial resistance (AMR) is a global health prior-
ity considering its association with high morbidity and 
mortality and increased healthcare costs [1–3]. The bur-
den of AMR is growing worldwide with transmission 
often occurring in healthcare settings due to poor in-
fection control practices and inappropriate use of anti-
microbials. The threat of AMR is particularly concern-
ing in low- and middle-income countries such as Thailand 
who AMR contributes to approximately 38,000 deaths 
per year and additional US$1.2 billion in healthcare costs 
[4]. Thailand’s AMR burden has increased over the past 
two decades, likely a result of excessive and inappropriate 
use of antimicrobials and poor sanitation [5–7].

Carbapenem-resistant Enterobacterales (CRE) are 
an especially concerning AMR threat because they are 
resistant to many last-resort antibiotics, making it dif-
ficult to treat and leading to high mortality rates. CRE 
are often the result of healthcare transmission and 
associated with risk factors such as previous antibiotic 
use, prolonged hospitalization, and medical device use 
[8–11]. CRE develops antibiotic resistance through sev-
eral mechanisms, including through the production of 
carbapenemases, enzymes that degrade carbapenem 
antibiotics. Evidence suggests distinct differences in the 
edemiology of CRE with and without carbapenemase 
production. Carbapenemase producing CRE (CP-CRE) 
are more virulent and are associated with higher levels 
of antimicrobial resistance, worse outcomes, and more 
rapid spread, while noncarbapenemase-producing CRE 
(non-CP-CRE) have been associated with asymptomatic 
carriage and perhaps less person-to-person transmission 
[12–14]. For this reason, CP-CRE have been identified as 
an important target for prevention sometimes warrant-
ing enhanced infection control interventions [15].

Carbapenemase enzymes are encoded by genes on 
mobile genetic elements, such as plasmids, which are 
highly transmissible between organisms and increase the 
potential spread of resistance. There are several genes 
encoding different carbapenemases, including Kleb-
siella pneumoniae carbapenemase (KPC) which is the 
most common carbapenemase in the United States and 
New Delhi metallo-beta-lactamase (NDM) which was 
first identified in a traveler returning from India but has 
now spread worldwide. Others include Verona integrin-
encoded metallo-β-lactamase (VIM) and imipenemase 
(IMP) which are most prevalent in Southern Europe 
and Asia and oxacillinase-48 (OXA-48) which is most 
prevalent in the Mediterranean region, Europe, and India 
[16].

The National Antimicrobial Resistance Surveillance 
center, Thailand (NARST) which is managed by Thai-
land’s National Institute of Health (NIH), was established 
in 1998 and includes 92 hospital laboratories from all 
five regions of Thailand. NARST data show the overall 
percentage of K. pneumoniae isolates resistant to mer-
openem increased from 0.4% in 2000 to 6.5% in 2016 and 
the overall percentage of Escherichia coli isolates resistant 
to meropenem increased from 0.6 to 1.6% during the 
same period [6]. In August 2016, with growing concerns 
about AMR and CRE burden and antimicrobial effective-
ness, the Ministry of Public Health of Thailand endorsed 
a National Strategic Plan on AMR to reduce the mortal-
ity, morbidity, and economic impact of AMR.

NARST contains limited information on resistance 
genes because resistance mechanism testing is not rou-
tinely performed at participating hospital laboratories. 
NIH established the Enhanced Incorporation of Global 
and National AMR (EIGNA) Surveillance System to 
to understand the distribution of resistance genes and iden-
tify novel resistance genes among CRE in Thailand. We 
analyzed 2016–2018 EIGNA data to better understand 
the distribution of resistance genes and identify novel 
resistance genes among CP-CRE in Thailand.

Methods
EIGNA includes 25 of 92 hospital laboratories partici-
pating in NARST surveillance from all five regions of 
Thailand; 21 (84%) of the labs are regional, tertiary care 
hospitals (Table 3). These laboratories were chosen based 
on their history of timely and complete submission of 
NARST data, the presence of competent laboratory per-
formance based on external quality assessments and site 
visits, and a functional infection prevention and control 
(IPC) program.

Hospital laboratories performed Gram stains, cul-
tures, biochemical tests, and antimicrobial susceptibil-
ity testing (AST) using disk diffusion and/or E-test on 
routine clinical specimens from hospitalized patients. 
CRE was defined as any Enterobacterales isolate resist-
ant to ertapenem, imipenem, or meropenem according 
to CLSI M100-S26 standards [17]. Participating hospitals 
were instructed to submit the first CRE isolate from each 
 specimen type and each patient admission to the NIH 
along with a case report form (CRF) containing patient 
demographics, admission date, discharge date, previous
antibiotic exposure, patient comorbidities, and outcome of hospitalization.

NIH repeated AST using disk diffusion. E-test was done to confirm CRE for isolates that had discordant results. CRE isolates confirmed by NIH underwent multiplex polymerase chain reaction (PCR) to detect five carbapenemase-producing (CP) genes, including blaKPC, blaNDM, blaOXA-48-like, blaVIM, and blaIMP [18]. As colistin is a drug of last resort for serious infections due to multidrug resistant organisms, PCR testing was also done to detect blaMCR-1 (i.e., plasmid-mediated mobilized colistin resistance). Since hyperproduction of AmpC β-lactamase combined with altered membrane permeability can result in carbapenem resistance [12, 19, 20], routine PCR testing for blaAmpC was started for CRE isolates in the middle of this surveillance period and included testing for some isolates from 2017 and all isolates from 2018. Isolates negative by PCR for the six targeted genes were tested using modified Carbapenem Inactivation Method (mCIM) [21] for carbapenemase production and with commercial AMR Direct Flow Chip Kit (Master Diagnostica, Seville, Spain) [22] to confirm the absence of targeted CP genes and the presence of any additional CP genes.

For isolates with evidence of carbapenemase production but no CP gene identified, whole-genome sequencing was conducted by isolating DNA from overnight cultures with a DNeasy Blood and Tissue kit (Qiagen, Hilden, Germany) and quantifying the extracted DNA using the Qubit dsDNA HS Assay Kit (Invitrogen), both according to the manufacturer's protocols. Genomic libraries were generated with the QIAGEN® QIAseq FX DNA Library Kit (Qiagen, Hilden, Germany) following to the manufacturer's protocol. The Whole-genome sequencing (WGS) was carried out using the Illumina® MiSeq platforms to obtain 250-bp paired-end reads chemistry (Illumina, California, United States) according to manufacturer's instructions. The 250-bp paired-end reads was de novo assembled using the CLC Genomics Workbench 12.0.2 (Qiagen, Aarhus, Denmark) using defaults settings except that the minimum contig size threshold was set to 500 bp in length.

EIGNA data from September 2016 through August 2018 were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC). Proportions of CP-CRE isolates among CRE isolates were calculated and stratified by specimen type, organism, and carbapenemase-producing gene. For the analysis of patient characteristics, isolate data was deduplicated by including CRF information from the first isolate submitted. However, for one patient whose first isolate was CP-CRE negative and subsequent isolates were CP-CRE positive, the first CP-CRE isolate was...

Fig. 1 Testing results of Enterobacterales surveillance isolates submitted, Thailand, 2016–2018. *1 additional CRE isolate with no genotype results available was not included in the analysis
included and prior non-CP-CRE isolates were excluded. Clinical characteristics were calculated for CP-CRE and non-CP-CRE patients and compared using the Wilcoxon-Mann–Whitney test for continuous variables and chi-square and Fisher’s exact tests for categorical variables.

Results
A total of 4296 presumed CRE isolates were submitted to NIH by participating hospital laboratories and 3946 (92%) isolates from 3748 patients were confirmed by NIH as CRE [Fig. 1], with 224 patients having multiple CRE isolates of different specimen types or pathogens. Urine and sputum were the most common specimen types (41% from urine, 35% from sputum), while blood accounted for only 8% of all CRE specimens. K. pneumoniae (73%) and E. coli (21%) were the most common organisms among all confirmed CRE isolates [Table 1].

Of 3748 patients with confirmed CRE, 2368 (63%) were collected more than two calendar days after admission (suggesting healthcare onset [HO]), 2502 (67%) had antibiotic exposures during 14 days prior to specimen collection, and 885 (24%) died during hospitalization. For the 3724 (99%) with information on age available, median age was 66 years (IQR: 52–77). Of the 3031 (80%) with information on length of stay (LOS) available, median LOS was 20 days (IQR: 9–39). Of the 3318 (80%) with information on duration from admission to specimen collection date available, median duration was 10 days (IQR: 2–23) [Table 2].

Of 3,946 CRE isolates, 3,844 (97%) tested positive for at least one CP gene and the proportion of CP-CRE for all Enterobacterales species ranged from 89 to 100% [Table 1]. These CP-CRE isolates were submitted from 25 hospitals across all five geographic regions of Thailand, with 21 of these hospitals (84%) having > 500 beds [Table 3], and the percentage of CRE isolates with a CP gene ranging from 94–100% across hospitals and 97–99% across all regions [Additional file 1: Table 1]. On univariate analysis, there were no statistically significant differences between CP-CRE and non-CP-CRE patients with regard to age, gender, use of any antibiotic during the two weeks prior to culture, HO status, total length of hospital stay, length of stay before or after specimen collection, or death during hospitalization [Table 2].

The distribution of carbapenemase genes among these isolates can be found in Table 4. Of all 3946 CRE isolates, 2501 (63%) were positive for blaNDM and

Table 1 Frequency of Carbapenem-resistant Enterobacterales (CRE) and Carbapenemase-producing (CP)-CRE isolates by specimen type and organism, Thailand, 2016–2018

| Isolate characteristics | No. CRE isolates (%) | No. CP-CRE isolates (%) | % of CRE with CP gene |
|-------------------------|----------------------|-------------------------|----------------------|
| Specimen type           |                      |                         |                      |
| Urine                   | 1622 (41%)           | 1567 (41%)              | 97                   |
| Sputum                  | 1380 (35%)           | 1351 (35%)              | 98                   |
| Pus                     | 437 (11%)            | 429 (11%)               | 98                   |
| Blood                   | 322 (8%)             | 320 (8%)                | 99                   |
| Other normally sterile site | 77 (2%)            | 75 (2%)                 | 97                   |
| Other                   | 107 (3%)             | 102 (3%)                | 95                   |
| Organism                |                      |                         |                      |
| Klebsiella pneumoniae   | 2888 (73%)           | 2814 (73%)              | 97                   |
| Escherichia coli        | 825 (21%)            | 816 (21%)               | 99                   |
| Enterobacter cloaceae   | 123 (3%)             | 115 (3%)                | 93                   |
| Citrobacter freundii    | 11 (< 1%)            | 11 (< 1%)               | 100                  |
| Other organism          | 99 (3%)              | 88 (2%)                 | 89                   |
| Total                   | 3946                 | 3844                    | 97                   |

Table 2 Characteristics of patients with and without a carbapenemase gene, Thailand, 2016–2018

| Patient characteristic | n (% or IQR)       | CP-CRE | Non-CP-CRE | p value** |
|------------------------|-------------------|--------|------------|-----------|
| All CRE                | CP-CRE            | Non-CP-CRE |
| Median age (N = 3,724) | 66 (52–77)        | 62 (52–77) | 65 (45–79) | 0.75      |
| No. male (N = 3,748)  | 2263 (60)         | 2211 (61) | 53 (54)    | 0.36      |
| No. with any antibiotic 14 days prior (N = 3,748) | 2502 (67) | 2436 (67) | 66 (67)    | 0.98      |
| Median length of stay (LOS) (N = 3,031) | 20 (9–39) | 20 (9–39) | 24 (11–38) | 0.18      |
| Median LOS before specimen collection*** (N = 3,318) | 10 (2–23) | 10 (1–23) | 10 (3–24) | 0.51      |
| Median LOS after specimen collection *** (N = 2,968) | 9 (4–19) | 9 (4–19) | 11 (4–19) | 0.48      |
| No. with healthcare onset (N = 3,748) | 2368 (63) | 2298 (63) | 70 (71)    | 0.12      |
| Death during hospitalization (N = 3,748) | 885 (24) | 864 (24) | 21 (21)    | 0.57      |

*** Wilcoxon–Mann–Whitney test used for numeric variables

** Wilcoxon–Mann–Whitney test used for numeric variables
1892 (48%) were positive for blaOXA-48-like (48%). There were 634 (16%) isolates with coexistence of both blaNDM and blaOXA-48-like genes, seven (< 1%) isolates with coexistence of both blaIMP and blaOXA-48-like genes, and five (< 1%) isolates with coexistence of blaIMP and blaNDM. When stratified by organism, blaNDM remained the most common CP gene across all organisms, except in K. pneumoniae, which had a similar percentage of isolates with blaNDM (55%) and blaOXA-48-like (59%) genes. The highest proportion of blaNDM-positive isolates were among Citrobacter freundii (n = 11, 100%) and E. coli (n = 776, 94%). E. cloacae had the highest proportion of isolates positive for blaIMP (31, 25%). blaKPC and blaVIM genes were not detected among any of the isolates. Of the 102 isolates with no CP gene identified, the most common pathogen was K. pneumoniae (73, 72%). The distribution of CP genes by region is presented in Additional file 1: Table 1.

### Discussion

The EIGNA surveillance system provides new information about carbapenemase distribution across Thailand. While previous studies show that there is a high burden of CRE in Thailand [6, 7, 23], our analysis demonstrates a high prevalence of CP genes among CRE in Thailand, with 97% of CRE isolates submitted to EIGNA having a CP gene. This estimate is much higher than estimates from other countries, such as the United States and India, where 32% and 28% of CRE are CP-CRE [24, 25]. This is also higher than recent estimates from a smaller study in Thailand which found that 71% of 287 Enterobacteriales isolates from Bangkok were CP-CRE [26]. While these different estimates may reflect differences in the populations being studied, we found CP-CRE isolates from all regions of Thailand and the proportion of CRE with a CP gene was similar across regions. Despite some prior evidence of increased mortality associated with CP-CRE after adjusting for clinical factors [13], we did not identify a specific population at greater risk of CP-CRE based on demographics, prior antibiotic exposure, length

| Facility Characteristic | Total no. facilities (%) | N = 25 |
|------------------------|-------------------------|-------|
| Region                 |                         |       |
| North                  | 6 (24%)                 |       |
| Northeast              | 6 (24%)                 |       |
| East                   | 3 (12%)                 |       |
| Central                | 5 (20%)                 |       |
| South                  | 5 (20%)                 |       |
| Bed size               |                         |       |
| 251–500                | 4 (16%)                 |       |
| 501–750                | 13 (52%)                |       |
| 751–1000               | 7 (28%)                 |       |
| > 1000                 | 1 (4%)                  |       |

### Table 3 Characteristics of participating facilities with Carbapenemase-producing (CP)-CRE isolates, Thailand, 2016–2018

| Organisms               | Total (N = 3946) | N (% of isolates by organism) | P-value |
|-------------------------|------------------|------------------------------|---------|
| Klebsiella pneumoniae   | (N = 2659)       | NDM (63) 1577 (55) 776 (94) 736 (59) 11 (100) 64 (65) < .0001 |         |
| Escherichia coli        | (N = 799)        | OX-48-like 192 (48) 1703 (59) 149 (18) 27 (22) 1 (9) 12 (12) < .0001 |         |
| Enterobacter cloacae    | (N = 113)        | IMP 97 (2) 46 (2) 1 (< 1) 31 (25) 0 (0) 19 (19) < .0001 |         |
| Citrobacter freundii    | (N = 113)        | No CP Gene 102 (3) 74 (3) 9 (1) 18 (16) 0 (0) 1 (1) < .0001 |         |
| Other                   | (N = 102)        | Mcr1 10 (< 1) 5 (< 1) 5 (1) 0 (0) 0 (0) 0 (0) 0.23 |         |

*Not mutually exclusive: 634 had NDM and OXA and 7 had IMP and OXA, 5 had NDM and IMP, 6 Mcr1 and NDM, 3 Mcr1 and OXA-48-like

*No VIM or KPC

P-value using chi-square or Fisher exact test to compare presence of carbapenemase genes and MCR-1 across organisms
of stay, or death, as there was no significant difference when comparing patients with CP-CRE and patients with non-CP-CRE. Yet, the low number of CP-CRE specimens from blood and sterile specimens reflects a low proportion of invasive infections with high mortality.

The distribution of CP genes in Thailand also differs from that found in other parts of the world. The most common CP genes in Thailand were NDM (69%) and OXA-48-like (38%), regardless of organism. These results support other studies showing that NDM is the most common gene in South and Southeast Asia [27–30]. However, this differs from the United States where NDM is present in 3% of isolates and OXA-48-like genes are present in 65% of isolates [25, 30]. KPC is the most common CP gene in the United States, present in 87% of CP-CRE isolates [25, 30], but was not present in any of these isolates from Thailand.

The U.S. Centers for Disease Control and Prevention recommends enhanced infection control measures specifically for CP-CRE compared to non-CP-CRE because of their high propensity to spread. However, testing for the presence of a CP gene is not routinely done in Thailand’s clinical laboratories and reference laboratory testing results are often delayed, hindering their use in guiding infection control measures. Given the high proportion of CP-CRE, clinicians in Thailand that do not have access to genotyping or carbapenemase production testing should consider that any CRE isolate is likely to have a CP gene and use appropriate infection control precautions for all patients with CRE. Testing for specific CP genes is more difficult and less available than testing for the presence of any carbapenemase activity. While there is currently no evidence or recommendation about specific infection control measures associated with specific CP genes, information about CP genes can be useful to guide antimicrobial therapy. NDM is associated with limited treatment options. Newer combination drugs such as meropenem-vaborbactam and imipenem-relebactam are effective against KPC, but not NDM or OXA-48-like carbapenemases. Ceftazidime-avibactam is effective against both KPC and OXA-48-like carbapenemases, but not against NDM [31]. However, the combination of ceftriaxone-avibactam with aztreonam offers a therapeutic advantage against NDM, as well as being effective against KPC and OXA-48-like [32, 33]. The co-existence of multiple carbapenemase genes in the same isolate was frequent but the clinical implication is not well understood and should be further investigated to determine whether these patients have poorer outcomes or should be prioritized for enhanced infection control efforts.

**Limitations**

There are several limitations to this study that restrict its generalizability. Participating sites were chosen based on microbiology capacity and surveillance performance to optimize data accuracy but may not reflect a nationally representative sample and gaps in reporting may have resulted in an underestimate of total CRE cases. Different hospital types and locations were included, but regional hospitals (82%), which provide tertiary care and likely have more severely ill patients, were disproportionately represented. Results may also have been biased by inconsistent culturing practices or laboratory testing at participating sites. For example, specimen collection and testing at hospital sites was left to the clinical discretion of each hospital or clinician and therefore not standardized. As a result, some clinicians may have collected samples only from patients with more severe conditions or those who did not respond to initial therapy with first-line antibiotics. Additionally, ertapenem susceptibility testing was not performed at all sites; only 14 (17%) of 84 sites participating in NARST do ertapenem susceptibility testing. As a result, isolates resistant to only ertapenem, which are more likely to be non-CP-CRE, may not have been identified or included in the analysis [34, 35]. Whole-genome sequencing was only conducted on a subset of isolates because of resource accessibility and may have limited detection of additional CP genes.

Clinical data collected as part of the EIGNA surveillance system was limited and did not include information about some risk factors or exposures (e.g., use of indwelling medical devices, prior hospitalizations or healthcare exposures, underlying comorbidities) which may be associated with CP-CRE. Outcome data was only reported for the hospitalization and did not include death after discharge.

**Conclusion**

We found that carbapenemase production is predominant among CRE across Thailand. The distribution of carbapenemase-producing genes and the prevalence of NDM and OXA-48-like genes in Thailand differs from that in the United States and other regions of the world but seems to be consistent with patterns demonstrated by the limited data from Southeast Asia. Our analysis demonstrated a high frequency of established healthcare risk factors and poor outcomes among patients with CP-CRE. Efforts to strengthen clinical laboratory capacity for carbapenemase testing is important to improve early identification and appropriate response by guiding clinical treatment and control measures. Given that current availability of carbapenemase testing results is limited,
all patients with CRE should be considered to have CP-CRE and treated with appropriate use of infection control measures. Ongoing CRE surveillance is necessary to detect new, emerging resistance mechanisms, monitor CRE trends, and determine the effectiveness of control measures in preventing transmission.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13756-021-00950-7.

Additional file 1: Table 1. Presence of carbapenemase* and MCR-1 genes in isolates by region, Thailand, 2016–2018.

Acknowledgements
We would like to thank Dr. Anusak Kerdsin, Faculty of Public Health, Kasetsart University, Chalermprakiat Sakon Nakhon province campus for technical writing advice.

Authors’ contributions
WP: developed the surveillance system and produced the data used for this analysis, was a major contributor in data collection and project methodology; read and approved the final manuscript. ML: analyzed and interpreted the data; drafted the manuscript; read and approved the final manuscript. CaBi: analyzed and interpreted the data; read and approved the final manuscript. NC: advised on development of the surveillance system and collection of the data; all authors read and approved the final manuscript.

Funding
This work was supported by the National Institute of Health, Department of Medical Sciences, Ministry of Public Health, Thailand, and the Division of Global Health Protection, Thailand MOPH-US CDC Collaboration.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This work received a non-research determination by CDC as part of routine surveillance work. The Human Research Ethics Committee of Department of Medical Sciences, Ministry of Public Health reviewed this protocol and judged that this study constituted routine public health activities and therefore did not involve human subject research. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Consent for publication
No individual person’s data was used.

Competing interests
The authors declare that they have no competing interests.

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Received: 16 February 2021 Accepted: 17 May 2021
Published online: 05 June 2021

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