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Review

Carbapenem and colistin resistance in Enterobacteriaceae in Southeast Asia: Review and mapping of emerging and overlapping challenges

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ABSTRACT

Carbapenem-resistant Enterobacteriaceae infections have spread globally, leaving polymyxins, including colistin, as 'last-resort treatments'. Emerging colistin resistance raises the spectre of untreatable infections. Despite this threat, data remain limited for much of the world, including Southeast Asia where only 3 of 11 nations submitted data on carbapenem and colistin resistance for recent World Health Organization (WHO) reports. To improve our understanding of the challenge, we utilised broad strategies to search for and analyse data on carbapenem and colistin resistance among *Escherichia coli* and *Klebsiella* in Southeast Asia. We found 258 studies containing 526 unique reports and document carbapenem-resistant *E. coli* and *Klebsiella* in 8 and 9 of 11 nations, respectively. We estimated carbapenem resistance proportions through meta-analysis of extracted data for nations with ≥100 representative isolates. Estimated resistance among *Klebsiella* was high (>5%) in four nations (Indonesia, Philippines, Thailand and Vietnam), moderate (1–5%) in two nations (Malaysia and Singapore) and low (<1%) in two nations (Cambodia and Brunei). For *E. coli*, resistance was generally lower but was high in two of seven nations with ≥100 isolates (Indonesia and Myanmar). The most common carbapenemases were NDM metallo-β-lactamases and OXA β-lactamases. Despite sparse data, polymyxin resistance was documented in 8 of 11 nations, with *mcr-1* being the predominant genotype. Widespread presence of carbapenem and polymyxin resistance, including their overlap in eight nations, represents a continuing risk and increases the threat of infections resistant to both classes. These findings, and remaining data gaps, highlight the urgent need for sufficiently-resourced robust antimicrobial resistance surveillance.

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1. Introduction

Antimicrobial agents are essential to medicine and public health, from treatment of common infections to supportive care for surgery, malignancies and transplantation [1]. However, microorganisms have biological capabilities to resist antimicrobials, leading to antimicrobial resistance (AMR). Genes conferring AMR are often encoded on mobile genetic elements, facilitating their rapid spread. Thus, it is no surprise that the extensive use of antibiotics in humans and agriculture [2,3] is contributing to an increase in infections with multidrug-resistant organisms (MDROs) [1,4,5]. At the same time, development of drugs to treat MDROs has lagged, raising the threat of untreatable infections [1]. As a result, AMR is a global threat [4,6] posing catastrophic risks to health and development [7].

Among the most problematic MDROs, classified both by the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) as an urgent threat [8,9], are carbapenem-resistant Enterobacteriaceae (CRE) [2]. CRE are most commonly associated with healthcare settings [10] but may also be community-acquired [11–13]. Carbapenems are broad-spectrum antibiotics effective against most resistant Gram-negative organisms and are generally reserved for the treatment of serious infections when resistance to alternative antibiotics is documented or suspected [11,14]. However, as resistant organisms have become more common, in particular those expressing extended-spectrum β-lactamases (ESBLs), use of carbapenems has grown [2], as has carbapenem resistance [15]. CRE become resistant through a variety of mechanisms, most importantly by expressing carbapenemases, enzymes encoded on mobile genetic elements that also frequently carry genes conferring resistance to other antibi-

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otics. Whilst there are many carbapenemases, the most common are class A *Klebsiella pneumoniae* carbapenemases (KPCs), class B metallo-β-lactamases (MBLs) including IMP, NDM and VIM types, and class D OXA β-lactamases [16]. CRE infections are difficult to treat, have caused severe outbreaks [17–19] and are associated with excess costs [20] and mortality [21].

Polymyxin antibiotics, including colistin (polymyxin E) and polymyxin B, hereinafter referred to together as polymyxin(s), are often termed antibiotics of 'last resort' as they are among the few, sometimes only, available agent(s) active against CRE [7,22,23]. However, in addition to chromosomal mutations associated with resistance to polymyxin(s) [24], increasing reports document the global spread of resistance-conferring plasmids [25], posing the risk that, if present together with carbapenemases, microorganisms may become untreatable with most or all antibiotics [26,27]. Understanding the prevalence and spread of such MDROs is critical to informing public health and medical interventions [5,9,28,29]. The WHO has initiated the Global Antimicrobial Resistance Surveillance System (GLASS) [5,7] and encourages surveillance as a key objective in national AMR action plans [30]. Whilst participation is rapidly growing, currently there are only 48 nations reporting AMR data, of which just 11 are lower-middle- or low-income countries [2,28]. Thus, there continue to be major gaps in data globally [5,28,31].

Historically, Asia has experienced a high burden of infectious diseases, now including ESBL-producing and carbapenem-resistant organisms [15,32]. In this region, as in many others, challenges in access to health care and diagnostics may contribute to misuse of antibiotics, sometimes of poor quality and/or accessed without prescription [33]. Widespread use in food production of antibiotic classes important to human health, including polymyxin(s) [3,34,35], may contribute to AMR [3,36], and there have been increasing reports of Enterobacteriaceae isolated from humans and animals in Asia carrying plasmid-mediated *mcr* genes conferring polymyxin resistance [32,37,38], making tracking of resistance critical [39].

Southeast Asia has often been particularly challenged by emerging infections [40–42]. When data were sought on CRE for the WHO's 2014 surveillance report, information was reported for 7 of 11 Southeast Asian nations [5] but was limited except for 3 nations with national surveillance systems (Malaysia [43], the Philippines [44] and Thailand [45]). Only these three nations reported data in WHO's more recent reports [7,28] and, as a result, widespread data gaps remain. Two reviews published in 2016 document carbapenem resistance in the region as well as a variety of carbapenemase genotypes [32,36] but provide limited national data. Similarly, a recent review documented the global spread of resistance to polymyxin(s) but reported information from only 4 of 11 Southeast Asian countries [24]. We recently showed that similar data gaps regarding CRE in Africa could be addressed in part through broad data searching, extraction, analysis and mapping, enhancing our understanding of regional CRE [46]. The present study uses further refined approaches to help address gaps in our understanding of carbapenem and polymyxin resistance among *Escherichia coli* and *Klebsiella* spp. in Southeast Asia and provides a comprehensive database and maps, including areas where overlapping resistance may increase the risk of organisms acquiring resistance to both drug classes.

2. Methods

2.1. Sources

A comprehensive search was conducted for data from 11 Southeast Asian nations (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste and Vietnam) based on the United Nations geoscheme [47]. Searches were initiated using four scientific databases (Embase, Global Health, PubMed and Web of Science). These were supplemented by review of relevant citations found in identified studies as well as meta-analyses and by examination of ProMED-mail, ResistanceMap and HealthMap [48–50]. Google Scholar was used to identify open-source data from countries that yielded <4 reports from scientific databases. All reports available from 1 January 1996 to 30 June 2018 were searched.

2.2. Search strategy

Searches were structured to broadly capture data on *E. coli* and *Klebsiella* spp. isolates from humans for which carbapenem and/or polymyxin(s) susceptibility and/or genotyping was reported from Southeast Asian nations. Boolean search strings were constructed, iteratively tested and refined to optimise sensitivity while, to the degree feasible, enhancing specificity (Supplementary Table S1). The strings (search operators capitalised) followed a general structure of place (e.g. terms for Southeast Asia OR country names) AND terms for AMR (including general OR specific AMR terms OR synonym drug terms) AND species/mechanisms (including resistance enzymes and plasmid-mediated genotypes). Final strings also contained MeSH terms found to improve sensitivity and specificity. Human subject filters were used when available. Manual searches were performed for data on chromosomal mutations associated with colistin resistance, including in the *mgrB, phoPQ* and *pmrAB* genes. Manual Google Scholar searches were conducted using terms specific to organism, place and drug class for five countries (Brunei, Cambodia, Laos, Myanmar and Timor-Leste) where database searches resulted in <4 reports. Google Scholar searches followed the structure of 'country name' AND ('carbapenem' or 'colistin' or 'polymyxin B') AND '*E. coli* OR *Klebsiella*' AND 'susceptibility OR resistance'. To reduce irrelevant hits, Google Scholar searches contained negation operators excluding '*Acinetobacter*' OR '*Salmonella*' as well as patents and citations.

2.3. Data collation

Two authors (MDM and LMT) independently evaluated all of the results. Studies were screened based on title, allowing exclusion of irrelevant material. The reviewers then examined the abstracts and full-text of all other studies. Inclusion criteria required that studies contained unique information regarding carbapenem and/or polymyxin susceptibility and/or related genotypes among isolates of *E. coli* and/or *Klebsiella* spp. from humans as well as a description of the study design and sampling, including population, place and testing methods. Both conventional scientific and publicly available 'grey literature' (e.g. non-peer-reviewed publications, reports, abstracts, web-based data or conference proceedings) that met the inclusion criteria were eligible. Both reviewers extracted and coded data from studies meeting the inclusion criteria, resolving discordant results by consensus. A third author (JLG) arbitrated remaining questions through mutual agreement. If more than one study reported identical or overlapping data, the most complete study was utilised unless overlapping reports included unique details, in which case both were included on separate lines in the database without dual reporting of any data.

2.4. Database construction and data entry

A structured Microsoft Excel (Microsoft Corp., Redmond, WA, USA) template with pre-defined attributes, building on that utilised for CRE in Africa [46], was developed for data entry and coding (Supplementary Table S2). The following were extracted and entered: location; dates of study and publication; study duration;

population type; age; specimen/sample type; type of study; organism studied and, for each organism, presence or absence of any carbapenem and/or polymyxin resistance; number of isolates; percentage resistance [carbapenems and/or polymyxin(s)]; and resistance genotypes detected. Populations were classified as from acute (e.g. hospital) or chronic (e.g. long-term care) facilities or as community-based (samples specifically obtained from outpatients, from community-based surveillance, or solely within 48 h of admission to a healthcare facility), or as travellers (from individuals following international travel). Selected subpopulations, if studied, were defined by clinical attributes (e.g. pregnant, intensive care unit, clinical syndrome). WHO age classification (infant, child, adolescent, adults [51]) was utilised where feasible. In cases where authors characterised participants as neonates or elderly, the authors' classification was used. Study type was classified as clinical laboratory-based (based on diagnostic specimens), case series (focused on a specific subpopulation of patients and where clinical information was included defining patients beyond demographics), outbreaks (specimens obtained during an outbreak of resistant infections) or surveillance (defined here strictly as studies evaluating susceptibility among colonising organisms rather than samples obtained for clinical diagnosis). When a study provided potentially important findings, but uncertainties were present relevant to our analyses, the authors were contacted, when possible, for clarification (see the Acknowledgments section).

Reports that focused on specific subsets of laboratory isolates selected for their resistance were coded noting selection criteria utilised (e.g. for ESBL or CRE). Because many reports of *Klebsiella* included multiple species or were not speciated, and because resistance was similar across *Klebsiella* spp., results for *Klebsiella* isolates, while reported by species in the database, were aggregated for analyses. Where the results of susceptibility testing to multiple carbapenems were reported, the value for the drug with the highest percentage resistance was used to represent overall resistance. Isolates reported as having intermediate susceptibility were classified as resistant. For studies that presented susceptibility with results disaggregated by ESBL status (e.g. carbapenem resistance among ESBL-producing versus non-ESBL-producing isolates), data were re-aggregated to reflect resistance in the whole population of isolates. Documentation of specific carbapenemase or polymyxin resistance-associated genes, while recorded and mapped, was not required to consider as resistant those isolates reported as phenotypically resistant. Thus, reported data include both phenotypic and/or genotypic resistance. For quality control, all entries were reviewed by two authors (MDM and LMT), and a third author (JLG) reviewed one-third of the entries through systematic random sampling.

2.5. Data analyses

2.5.1. Presence of antimicrobial resistance and/or specific resistance genotypes

Any report of one or more carbapenem- and/or polymyxin-resistant *E. coli* or *Klebsiella* isolate, or of a resistance-associated genotype, contributed to defining the presence of carbapenem or polymyxin resistance in a nation. This could include data derived from either population-based studies or from studies of outbreaks, case series, highly selected subpopulations, or isolates selected for their known carbapenem, polymyxin or other resistance.

2.5.2. Crude national resistance proportion estimates

To estimate overall crude resistance proportions for *E. coli* and *Klebsiella* at the country level, data from studies with ≥20 isolates studied for resistance to carbapenem(s) or with ≥10 isolates for polymyxin(s), and deemed to be reasonably 'generalisable' (i.e. representative of individuals in overall healthcare populations), were aggregated and analysed across studies. These analyses excluded data from outbreaks and from studies reporting resistant isolates in highly selected subpopulations of patients (e.g. burn injury, oncology, transplantation etc.) that typically have levels of resistance greater than general acute-care populations. Similarly, data reporting resistance among organisms specifically selected for their resistance to antibiotics were not considered generalisable and those data, while contributing to defining the presence or absence of resistance (and of specific genotypes) in a location, were also excluded from national resistance estimates. To enhance the contemporary relevance of carbapenem resistance estimates, they were calculated using data from studies reporting samples obtained from 2010 onward. Due to a paucity of data, crude resistance proportions for polymyxin(s) were calculated using aggregated data from all available years. If the total of generalisable *E. coli* or *Klebsiella* isolates tested for susceptibility to carbapenems or polymyxin(s) in a nation was ≥100, we calculated that nation's mean and, across qualifying studies, median resistance proportions using R v.3.5.2 [52]. When the total of generalisable isolates for a nation was <100, a category of either 'Insufficient isolates – Resistance detected' or 'Insufficient isolates – Resistance not detected' was assigned. For nations with ≥100 generalisable isolates of *E. coli* or *Klebsiella*, a crude estimated median resistance category was assigned as follows: low, <1%; moderate, 1–5%; or high, >5%.

For the three countries with surveillance reporting of carbapenem resistance (Malaysia [43], Philippines [44] and Thailand [45]), data were extracted and analysed (Supplementary Table S3) to determine mean resistance over available time periods most analogous to the 2010–2017 samples included in our analyses in order to allow general comparison of surveillance findings with estimates from our study.

2.6. Geocoding and mapping

ArcGIS Desktop 10.6 (ESRI, Redlands, CA, USA) was used to map estimated crude resistance proportions and detected genotypes at the national level.

2.7. Data sharing

The supplementary material, including all study data and data elements extracted for analyses (Supplementary Table S2), are available through Mendeley (http://dx.doi.org/10.17632/8tnhz8wfk8.2).

3. Results

3.1. Data characteristics

The searches of PubMed, Embase, Web of Science and Global Health returned 5459 documents for screening, of which 251 (4.6%) met the inclusion criteria. Five additional studies [53–57] were identified through review of citations in included studies, meta-analyses or reviews. Two additional studies [58,59] were identified through Google Scholar. Altogether, 258 eligible studies were identified and included data from all 11 Southeast Asian countries. ResistanceMap displayed some additional data from surveillance being developed in Vietnam (Supplementary Table S3). All but one document (in French) were in English. Further details regarding search outputs are provided in Supplementary Fig. S1.

Because many studies either included both *E. coli* and *Klebsiella* isolates or data from more than one population, each study could yield more than one unique data report. Thus, 258 study documents yielded 526 data reports, each then extracted and coded as a separate line in the database. Of the 526 data reports, 21

Table 1
Key data attributes[a].

Age group	*N* (%)	Population type	*N* (%)	Study type	*N* (%)	Specimen type	*N* (%)	Species	*N* (%)
Adolescent	14 (2.7%)	Community	114 (21.7%)	Case series	126 (24.0%)	Bile	4 (0.8%)	*Escherichia coli*	255 (48.5%)
Adult	150 (28.5%)	HC-acute	428 (81.4%)	Clinical laboratory	355 (67.5%)	Blood	98 (18.6%)	*Klebsiella pneumoniae*	230 (43.7%)
All	68 (12.9%)	HC-chronic	4 (0.8%)	Outbreak	3 (0.6%)	CSF	2 (0.4%)	*Klebsiella* spp.	41 (7.8%)
Child	41 (7.8%)	HC-unknown	29 (5.5%)	Surveillance	42 (8.0%)	Multiple	197 (37.5%)		
Elderly	7 (1.3%)	Travellers	5 (1.0%)			Other	2 (0.4%)		
Infant	21 (4.0%)					Pus	5 (1.0%)		
Neonate	19 (3.6%)					Rectal swab	17 (3.2%)		
Unknown	250 (47.5%)					Respiratory	27 (5.1%)		
						Stool	48 (9.1%)		
						Tissue	8 (1.5%)		
						Unknown	57 (10.8%)		
						Urine	75 (14.3%)		
						Wound	9 (1.7%)		

HC, healthcare; CSF, cerebrospinal fluid.
[a] Number (%) of 526 unique data reports including the indicated subgroups. In some categories, the total is >526 as reports may contain multiple subgroups.

Table 2
Available reports on *Escherichia coli* and *Klebsiella* spp. carbapenem and polymyxin resistance and related genes.

Nation and references	All reports on named species (reports identifying resistance or genes related to resistance)			
	Carbapenems		Polymyxins[a]	
	E. coli	*Klebsiella*	*E. coli*	*Klebsiella*
Brunei [5,17,57]	1 (0)	3 (2)	0	1 (0)
Cambodia [5,54,59,80–82,85–94]	13 (2)	13 (6)	3 (3)	2 (1)
Indonesia [95–113]	15 (7)	18 (7)	1 (1)	1 (0)
Laos [5,34,35,76,114–116]	3 (0)	3 (0)	2 (2)	2 (2)
Malaysia [55,58,60,63,67,83,102,117–150]	20 (7)	37 (26)	3 (3)	6 (3)
Myanmar [5,72,74,151–155]	6 (5)	5 (4)	2 (0)	1 (0)
Philippines [56,60,66,102,127,139,140,156–173]	22 (6)	22 (13)	0	1 (1)
Singapore [18,53,69,70,78,79,102,103,127,139,140, 142,162,164,165,167,174–207]	37 (22)	45 (30)	9 (2)	10 (6)
Thailand [23,35,56,60,64–66,68,71,73,75,84,102,104,114,125,127,139,140,142,208–270]	88 (43)	84 (46)	25 (14)	16 (8)
Timor-Leste [271]	1 (0)	1 (0)	0	0
Vietnam [56,60,77,104,127,139,140,272–302]	34 (16)	32 (26)	6 (5)	5 (4)
All reporting nations	240 (108)	263 (160)	51 (30)	45 (25)

[a] Colistin and polymyxin B.

(4.0%) were from grey literature. Although we found reports published in all years searched, 75% were from 2010–2018. Three countries (Thailand, Vietnam and Singapore) accounted for nearly two-thirds of reports; in contrast, Myanmar, Brunei and Timor-Leste accounted for only 3%. Moreover, 53% of reports were based on specimens from a single institution, 44% were from multiple institutions and 3% did not specify.

Additional attributes of the reports are shown in Table 1. Reports were evenly distributed by species, with 48.5% including data on *E. coli* and 51.5% on *Klebsiella* spp. Over two-thirds (67.5%) were from clinical laboratory-based studies, 24.0% from case series, 8.0% from surveillance and 0.6% from outbreaks. The most common isolate sources were multiple types (37.5%), blood (18.6%) and urine (14.3%). Subjects included adults in 28.5% of reports, all ages in 12.9%, children in 7.8%, infants in 4.0%, neonates in 3.6%, adolescents in 2.7% and elderly in 1.3%, whilst age was not specified in 47.5% of reports. Most reports (81.4%) included isolates from acute healthcare settings, 21.7% included community-based settings, 5.5% included unspecified healthcare settings, 1.0% included travellers and 0.8% included chronic healthcare. The geographic distribution of the data is represented graphically in Fig. 1 and the reports are further detailed, including references, in Table 2.

3.2. Carbapenem resistance: overview

Carbapenem resistance in either *E. coli* or *Klebsiella* spp. was reported from 9 of the 11 countries studied (Brunei, Cambodia, Indonesia, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam). All isolates from Laos and Timor-Leste were carbapenem-susceptible. Carbapenem resistance in *E. coli* was reported from 8 of 11 countries (Cambodia, Indonesia, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam), whilst the same eight countries plus Brunei reported resistance among *Klebsiella* spp. Table 3 presents detailed national-level data on carbapenem resistance from all years studied, including whether resistance was reported, specific carbapenemase genotypes were detected and, for all samples from generalisable studies, percent mean resistance.

3.2.1. Carbapenem susceptibility and resistance among more recent *Escherichia coli* isolates

Table 4 presents carbapenem resistance data from reports including samples collected from 2010 onwards. The data shown include mean, range and, for the 8 countries reporting on *E. coli* carbapenem susceptibility testing from which ≥100 generalisable isolates were tested, estimated national resistance proportions (median resistance across qualifying studies) and resulting resistance categories of low (<1%), medium (1–5%) or high (>5%). For *E. coli*, Myanmar, with median resistance estimated across reports of 8.2% [based on 46/666 (6.9%) resistant isolates overall] was classified as in the high category. Resistance in Indonesia was also estimated as high with a median of 5.4% [based on 107/904 (11.8%) resistant isolates]. Cambodia, Malaysia, Philippines, Singapore, Thailand and Vietnam all had estimated median resistance in *E. coli*

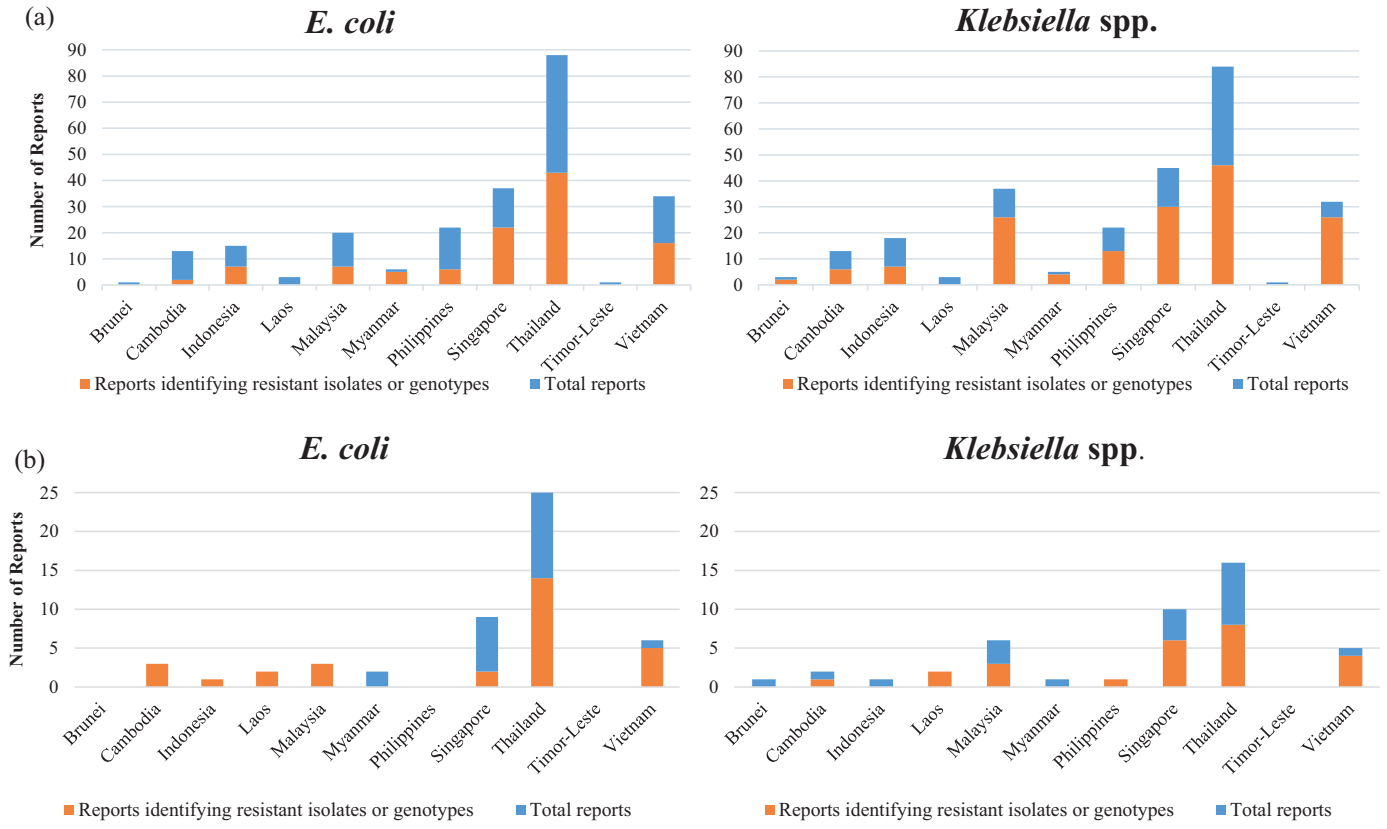

Fig. 1. Number of reports on (a) carbapenem susceptibility and (b) polymyxin susceptibility of *Escherichia coli* and *Klebsiella* spp. isolates in Southeast Asian nations.

of <1% and were classified in the low category. No carbapenem-resistant *E. coli* isolates were reported from Brunei, Laos or Timor-Leste. No isolates were studied from Brunei from 2010 onwards and the low numbers studied from Laos (78 isolates) and Timor-Leste (49 isolates) did not support estimation of resistance proportions. The resistance data for *E. coli* are mapped in Fig. 2a.

3.2.2. Carbapenem susceptibility and resistance among more recent *Klebsiella* isolates

Eight of eleven nations had ≥100 generalisable *Klebsiella* isolates studied, of which four had high estimated median carbapenem resistance. Vietnam had the highest median resistance of 10.1% [based on studies including 142 (10.4%) of 1364 resistant isolates], followed by the Philippines with a median of 8.7% [based on 53 (7.7%) of 692 isolates], Indonesia at 6.4% [based on 30 (12.3%) of 244 isolates] and Thailand at 5.2% [based on 98 (6.0%) of 1631 isolates]. Countries estimated as having moderate median carbapenem resistance included Malaysia at 4.05% and Singapore at 2%, whilst Cambodia and Brunei were classified as low. There were no reports of carbapenem-resistant *Klebsiella* from Laos or Timor-Leste, however both had <100 isolates studied and thus were classified as having 'Insufficient isolates – Resistance not detected'. Finally, although we did not identify reports of phenotypic carbapenem resistance among *Klebsiella* isolates from Myanmar, we did find reports of the presence of NDM-4 and -7 genotypes (see Table 3 and Section 3.2.3) and Myanmar was therefore classified as 'Insufficient isolates – Resistance detected'. The resistance data for *Klebsiella* are mapped in Fig. 2b.

3.2.3. General comparability of findings with available national surveillance data

Our study focused on the utilisation of non-traditional data to help address gaps where sufficient surveillance data are not available. For this reason, and because at least some of the data sources are likely to have included data also reported as part of national surveillance, we did not include in our analyses surveillance system reports from Malaysia [43], the Philippines [44] or Thailand [45], or abbreviated available laboratory surveillance data from Vietnam [49]. We did extract those available national surveillance data from Malaysia, Philippines and Thailand from similar timeframes to permit general comparison with our resistance estimates. The median carbapenem resistance estimates based on the studies included in our analyses are, in fact, broadly similar to mean resistance as reported in surveillance data (Supplementary Table S3). Consistent with surveillance data, carbapenem resistance in Malaysia was estimated through our analyses as low (<1%) among *E. coli* and moderate (1–5%) among *Klebsiella* spp. Also consistent, carbapenem resistance in the Philippines, Thailand and Vietnam was estimated as high (>5%) among *Klebsiella* spp. However, for the Philippines, Thailand and Vietnam there was lower overall carbapenem resistance estimated among *E. coli* using the data included in our analyses compared with available surveillance data.

3.2.4. Carbapenem resistance genotypes

Carbapenemase genotypes were included in 114 data reports, with specific carbapenemases identified in all nine countries from which phenotypic resistance was reported (Table 3). No genotypic studies were available from Laos or Timor-Leste. Among *E. coli*, NDM genotypes were most commonly detected and were reported from Malaysia (NDM-1), Myanmar (NDM-1, -4, -5 and -7), Philippines (NDM-1, -7 and -unspecified), Singapore (NDM-1, -7 and -unspecified), Thailand (NDM-1 and -5) and Vietnam (NDM-1, -4 and -5). OXA genotypes were reported among *E. coli* isolates from Cambodia (OXA-48), Myanmar (OXA-181), Singapore (OXA-23, -48, -181 and -unspecified), Thailand (OXA-48 and -181) and

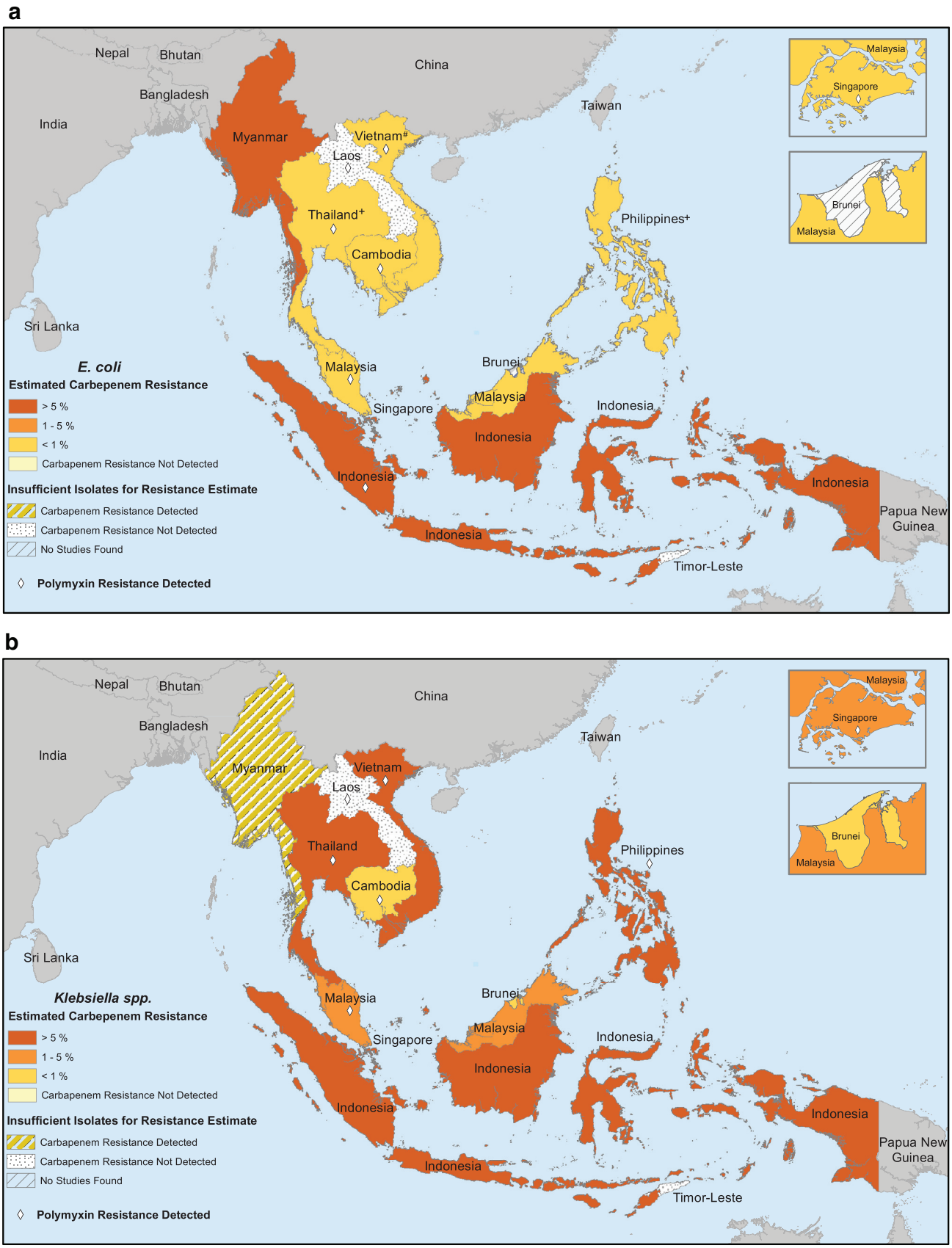

Fig. 2. Estimated median national carbapenem resistance proportions for (a) *Escherichia coli* and (b) *Klebsiella* spp. based on including samples from 2010–2017. For nations with ≥100 isolates from qualifying studies (see Methods), median proportions across studies were calculated. Where there were <100 isolates, data were deemed insufficient to estimate proportions and resistance is represented as either detected or not. +, national surveillance data indicates resistance in the moderate (1–5%) category [44,45]. See Section 3.2.3, Discussion and Supplementary Table S3. # Limited surveillance data indicates resistance in the high (>5%) category [49]. See Section 3.2.3, Discussion and Supplementary Table S3.

Table 3
Carbapenem resistance (R) and resistance-related genotypes in *Escherichia coli* and *Klebsiella* spp. isolates: data from all years.

Nation	No. of reports	Specimens in all reports	Any R	Findings in reports from all study years meeting criteria for generalisability					Genes identified
				Reports meeting criteria	Specimens meeting criteria	Specimens range	Resistant specimens	Resistant specimens (%)	
Brunei									
E. coli	1	4	N	0	0	–[a]	0	0	
Klebsiella	3	1062	Y	1	1038	–	8	0.8	OXA-232
Cambodia									
E. coli	13	1814	Y	10	1217	26–337	0	0	OXA-48
Klebsiella	13	1956	Y	7	465	32–142	4	0.9	OXA-48
Indonesia									
E. coli	15	1100	Y	10	1075	25–280	107	10.0	
Klebsiella	18	495	Y	8	416	30–80	33	7.9	NDM-1
Laos									
E. coli	3	138	N	2	132	54–78	0	0	
Klebsiella	3	26	N	0	0	–	0	0	
Malaysia									
E. coli	20	2301	Y	8	2108	22–1642	86	4.1	NDM-1
Klebsiella	37	2823	Y	16	1947	23–656	69	3.5	KPC-2, -6; IMP-4, -8; NDM-Unsp., -1, -5; OXA-48, -232
Myanmar									
E. coli	6	721	Y	3	666	20–426	46	6.9	NDM-1, -4, -5, -7; OXA-181
Klebsiella	5	80	Y	1	58	–	5	8.6	NDM-4, -7
Philippines									
E. coli	22	1399	Y	10	1205	36–319	1	0.1	IMP-4, -32; NDM-Unsp., -1, -7
Klebsiella	22	1353	Y	11	1123	20–292	58	5.2	KPC-2; IMP-4, -32, NDM-Unsp., -1, -7
Singapore									
E. coli	37	14717	Y	13	14378	25–12287	47	0.3	KPC-Unsp., -2; IMP-Unsp., -1, -8; NDM-Unsp., -1, -7; OXA-Unsp., -23, -48, -181
Klebsiella	45	9345	Y	15	8627	26–7000	112	1.3	KPC-Unsp., -2; IMP-Unsp., -1, -4; NDM-Unsp., -1, -5; OXA-Unsp., -48, -181, -232; VIM-Unsp., -1
Thailand									
E. coli	88	73658	Y	57	72357	20–33338	314	0.4	KPC-13; IMP-Unsp., -14; NDM-1, -5; OXA-48, -181
Klebsiella	84	20666	Y	47	17944	20–5483	289	1.6	IMP-Unsp., -14, -27; NDM-Unsp., -1, -4, -5; OXA-48, -181, -232
Timor-Leste									
E. coli	1	49	N	1	49	–	0	0	
Klebsiella	1	18	N	0	0	–	0	0	
Vietnam									
E. coli	34	5841	Y	18	5131	21–1370	96	1.9	KPC-Unsp., -2; NDM-1, -4, -5; OXA-Unsp., -48
Klebsiella	32	2401	Y	18	2146	20–438	203	9.5	KPC-2; NDM-1, -4; OXA-Unsp., -48; VIM-Unsp.

N, no; Y, Yes; Unsp., unspecified.
[a] – Data not available.

Vietnam (OXA-48 and -unspecified). IMP genotypes were reported in *E. coli* from the Philippines (IMP-4 and -32), Singapore (IMP-1, -8 and -unspecified) and Thailand (IMP-14 and -unspecified). The same KPC genotypes (KPC-2 and -unspecified) were reported in *E. coli* both from Singapore and Vietnam, and KPC-13 was reported in Thailand. The same carbapenemase genotypes were detected in *Klebsiella* isolates, with the addition of VIM (VIM-1 and -unspecified) reported from Singapore and Vietnam; OXA-232 reported from Brunei, Malaysia, Singapore and Thailand; OXA-48 reported from Malaysia; IMP-4 reported from Singapore; and IMP-27 reported from Thailand. All genotypes identified in Southeast Asia are listed in Table 3 by nation and are mapped in Fig. 3.

Table 4
Carbapenem resistance (R) in *Escherichia coli* and *Klebsiella* spp. isolates from studies including samples from 2010 and later.

Nation	No. of reports	Specimens in all reports	Any R	Findings in reports from 2010–2017 meeting criteria for generalisability							Resistance estimate category
				Reports meeting criteria	Specimens meeting criteria	Specimens range	Resistant specimens	Resistant specimens (%)	Resistant range (%)	Median R (%)	
Brunei											
E. coli	0	–[a]	–	–	–	–	–	–	–	N/A[b]	No studies found
Klebsiella	2	1043	Y	1	1038	–	8	0.8	–	0.8	Low (<1%)
Cambodia											
E. coli	6	1105	Y	3	508	36–337	0	0	–	0	Low (<1%)[c]
Klebsiella	8	1677	Y	3	203	34–87	1	0.5	0–3	0	Low (<1%)[c]
Indonesia											
E. coli	10	913	Y	7	904	25–280	107	11.8	0–28.2	5.37	High (>5%)
Klebsiella	11	317	Y	4	244	49–80	30	12.3	0–28.8	6.4	High (>5%)
Laos											
E. coli	2	84	N	1	78	–	0	0	–	N/A[b]	Insufficient isolates – Resistance not detected
Klebsiella	3	26	N	0	0	–	0	0	–	N/A[b]	Insufficient isolates – Resistance not detected
Malaysia											
E. coli	3	189	Y	1	183	–	0	0	–	0	Low (<1%)[c]
Klebsiella	14	1301	Y	5	730	53–321	50	6.8	3.2–43.4	4.05	Moderate (1–5%)
Myanmar											
E. coli	5	705	Y	3	666	20–426	46	6.9	3.64–15	8.2	High (>5%)
Klebsiella	3	75	Y	1	58	–	5	8.6	–	N/A[b]	Insufficient Isolates – Resistance detected[c]
Philippines											
E. coli	7	857	Y	4	853	174–319	1	0.1	0–0.3	0	Low (<1%)[c,d]
Klebsiella	10	726	Y	4	692	110–292	53	7.7	0–13.8	8.7	High (>5%)
Singapore											
E. coli	18	1618	Y	3	1328	79–1075	22	1.7	0–2	0	Low (<1%)[d]
Klebsiella	24	1560	Y	4	926	104–515	48	5.2	1.8–7.8	2.0	Moderate (1–5%)
Thailand											
E. coli	33	3252	Y	15	2460	22–543	21	0.9	0–4.5	0.4	Low (<1%)[d]
Klebsiella	27	2072	Y	11	1631	49–317	98	6.0	0–27	5.2	High (>5%)
Timor-Leste											
E. coli	1	49	N	1	49	–	0	0	–	N/A[b]	Insufficient isolates – Resistance not detected
Klebsiella	1	18	N	0	0	–	0	0	–	N/A[b]	Insufficient isolates – Resistance not detected
Vietnam											
E. coli	25	3559	Y	13	3477	23–1370	67	1.9	0–5.1	0	Low (<1%)[d,e]
Klebsiella	22	1480	Y	12	1364	20–345	142	10.4	0–55	10.1	High (>5%)

[a] – Data not available.
[b] Insufficient isolates (<100) for carbapenem resistance estimate.
[c] Only genotypic resistance reported.
[d] National surveillance data indicate resistance in the moderate (1–5%) category [44,45]. See Section 3.2.3, Discussion and Supplementary Table S3.
[e] National surveillance data indicate resistance in the high (>5%) category [49]. See Section 3.2.3, Discussion and Supplementary Table S3.

3.3. Polymyxin resistance: overview

We located 58 studies regarding susceptibility and/or resistance to polymyxin(s) among *E. coli* and/or *Klebsiella*, together providing data from 10 of 11 Southeast Asian countries. Despite the relative paucity of studies and limited number of isolates studied compared with studies on carbapenems, phenotypic resistance to polymyxin(s) in *E. coli* and/or *Klebsiella* was reported from 8 of 11 countries and specific resistance-related genotypes from 7 countries (Table 5). Myanmar was the single country where testing was performed but resistance was not detected among either *E. coli* (240 samples tested) or *Klebsiella* spp. (only 7 samples tested).

3.3.1. Polymyxin resistance among Escherichia coli isolates

Escherichia coli isolates resistant to polymyxin(s) were reported from seven countries (Cambodia, Indonesia, Laos, Malaysia, Singapore, Thailand and Vietnam), whereas all *E. coli* isolates from Myanmar were reported as susceptible (Table 5). No studies were identified of samples from Brunei, Philippines or Timor-Leste. Crude median resistance proportions were estimated for the four countries where data from ≥100 isolates from generalisable reports were available (Cambodia, Myanmar, Thailand and Vietnam). Vietnam was categorised in the moderate resistance category with estimated median resistance across available reports of 3.6%. Cambodia, with an estimated median resistance proportion of

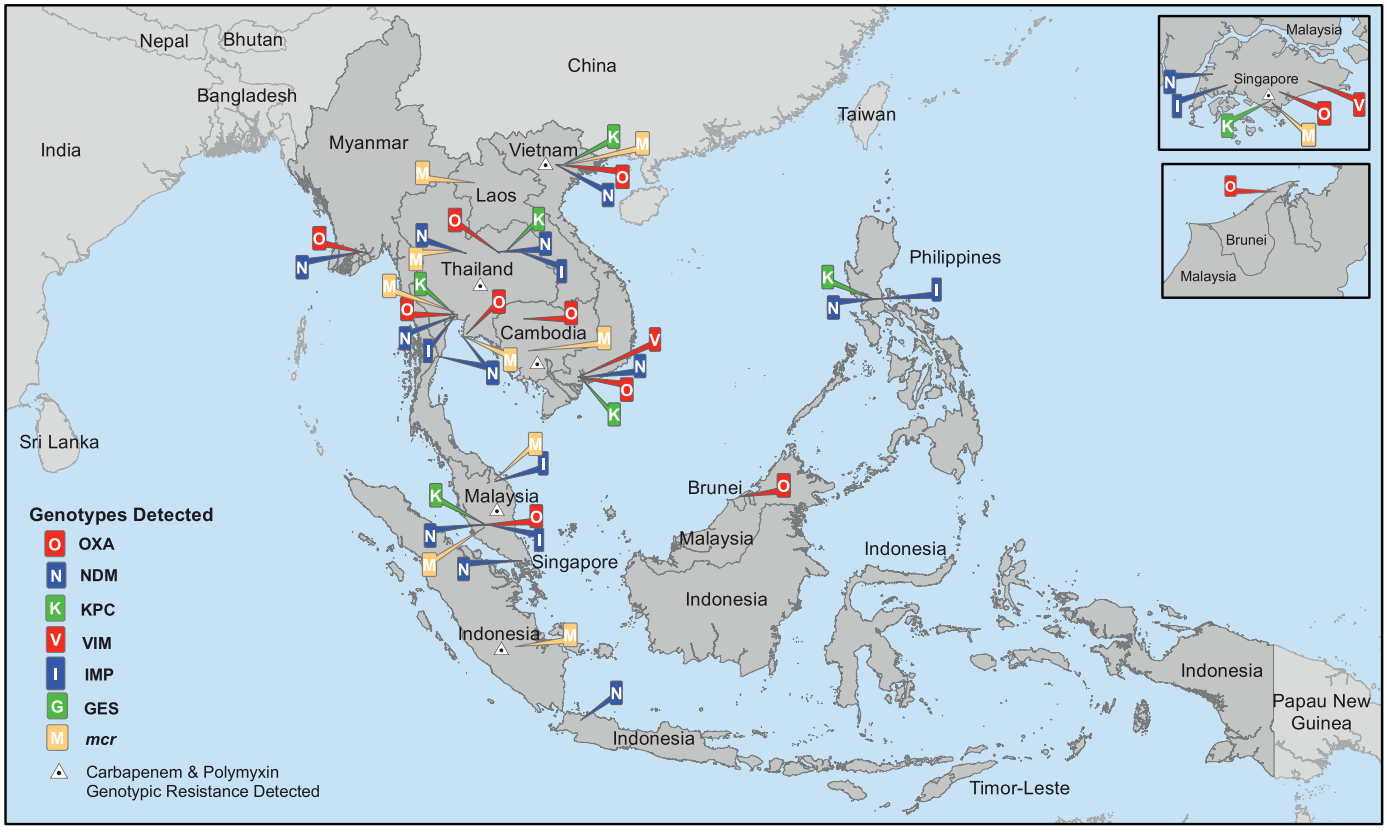

Fig. 3. Carbapenem and polymyxin(s) resistance genotypes.

0.8%, was categorised as low. Whilst significant resistance was documented in Thailand (mean 2.9% of 1396 isolates), the estimated median resistance across all studies of representative isolates was 0% and therefore Thailand was categorised in the low category. As noted, resistance to polymyxin(s) was not detected in Myanmar (categorised as 'Resistance not detected'). Sufficient isolates to support resistance estimates were not available from Indonesia, Laos, Malaysia or Singapore. However, both phenotypic resistance and the *mcr-1* genotype were identified and these countries were classified as 'Insufficient isolates – Resistance detected'. Polymyxin resistance data for *E. coli* are mapped at the national level in Fig. 4a.

3.3.2. Polymyxin resistance among Klebsiella isolates

At least some relevant data on *Klebsiella* isolates were available from 10 of 11 nations (except Timor-Leste). Phenotypic resistance to polymyxin(s) was reported from seven nations (Cambodia, Laos, Malaysia, Philippines, Singapore, Thailand and Vietnam), and genotypic resistance from five of the seven (those other than Cambodia and Philippines). Reports from three nations (Brunei, Indonesia and Myanmar) did not identify resistance but included few isolates (five, one and seven, respectively). Polymyxin resistance proportions for *Klebsiella* were estimated for three nations. Laos and Vietnam were categorised as high with median resistance proportions of 5.8% and 6.4%, respectively. In Thailand, whilst 4.6% of 920 isolates were resistant, median resistance across all representative studies was 0.66% and therefore Thailand was classified in the low category. The remaining countries did not have sufficient isolates to support resistance estimates and were classified as 'Insufficient isolates – Resistance detected' (Cambodia, Malaysia, Philippines and Singapore) or 'Insufficient isolates – Resistance not detected' (Brunei, Indonesia and Myanmar). The polymyxin resistance data for *Klebsiella* are mapped at the national level in Fig. 4b.

3.3.3. Polymyxin resistance genotypes

mcr-1 was the most common polymyxin genotype detected both among *E. coli* and *Klebsiella* isolates. Polymyxin resistance genotypes were reported among *E. coli* isolates from seven countries, including Cambodia (*mcr-1*), Indonesia (*mcr-1*), Laos (*mcr-1*), Malaysia (*mcr-1*), Singapore (*mcr-1*), Thailand (*mcr-1, -2* and *-3*) and Vietnam (*mcr-1*). Among *Klebsiella* isolates, polymyxin resistance genotypes were reported from five countries, including Laos (*mcr-1*), Malaysia (*mcr-1*), Singapore (*mcr-1*), Thailand (*mcr-1* and *-3*) and Vietnam (*mcr-3*). Chromosomal mutations in *mgrB* were reported with colistin resistance among *Klebsiella* isolates from three countries (Laos, Thailand and Vietnam). All genotypes identified in Southeast Asia are listed in Table 5 by nation and are mapped in Fig. 3.

3.3.4. Documented geographic overlap of carbapenem and polymyxin resistance

Geographic overlap of phenotypic carbapenem and polymyxin resistance among *E. coli* or *Klebsiella* was documented in eight nations (all except Laos, Myanmar and Timor-Leste). Overlapping genotypic resistance was documented in six of the same eight nations (Cambodia, Indonesia, Malaysia, Singapore, Thailand and Vietnam), with specific overlaps between NDM carbapenemases and *mcr* in five (Indonesia, Malaysia, Singapore, Thailand and Vietnam).

4. Discussion

Whilst nations in Southeast Asia are developing capacity to detect and respond to AMR threats, major gaps remain in the data required to guide public health and medicine. Building on approaches developed to address similar gaps in Africa [46], we found, analysed and mapped diverse data on resistance to carbapenems and polymyxin(s) in Southeast Asia. The findings doc-

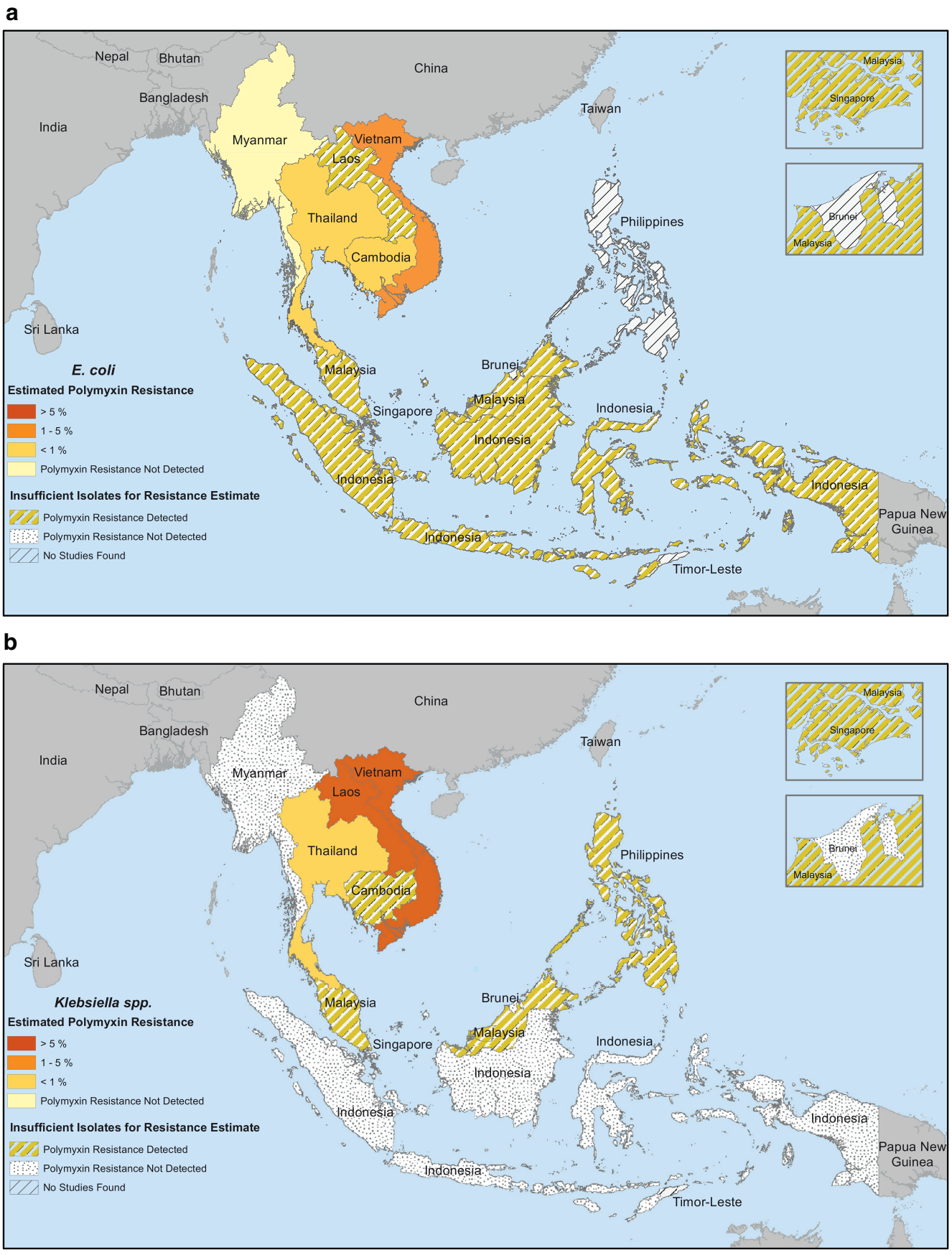

Fig. 4. Estimated median national polymyxin(s) resistance proportions for (a) *Escherichia coli* and (b) *Klebsiella* spp. For nations with ≥100 isolates from qualifying studies (see Methods), median proportions across studies were calculated. Where there were <100 isolates, data were deemed insufficient to estimate proportions and resistance is represented as either detected or not.

Table 5
Polymyxin (colistin and polymyxin B) resistance (R) and resistance-related genotypes in *Escherichia coli* and *Klebsiella* spp. isolates.

Nation	No. of reports	Specimens in all reports	Any R	Findings in reports from all study years meeting criteria for generalisability								Genes identified
				Reports meeting criteria	Specimens meeting criteria	Specimens range	Resistant specimens	Resistant specimens (%)	Resistant range (%)	Median R (%)	Resistance estimate category	
Brunei												
E. coli	0	–[a]	–	–	–	–	–	–	– –	–	No studies found	
Klebsiella	1	5	N	0	0	–	–	–	– –	N/A[b]	Insufficient isolates – Resistance not detected	
Cambodia												
E. coli	3	199	Y	1	130	–	1	0.8	– –	0.8	Low (<1%)	*mcr-1*
Klebsiella	2	49	Y	2	49	17–32	1	2.0	0 3.1	N/A[b]	Insufficient isolates – Resistance detected	
Indonesia												
E. coli	1	1	Y	0	0	–	–	–	– –	–	Insufficient isolates – Resistance detected[c]	*mcr-1*
Klebsiella	1	1	N	0	0	–	0	0	– –	N/A[b]	Insufficient isolates – Resistance not detected	
Laos												
E. coli	2	12	Y	0	0	–	–	–	–	–	Insufficient isolates – Resistance detected[c]	*mcr-1*
Klebsiella	2	194	Y	1	190	–	11	5.8	–	5.8	High (>5%)	*mcr-1, mgrB* mutation
Malaysia												
E. coli	3	30	Y	1	24	–	1	4.2	–	N/A[b]	Insufficient isolates – Resistance detected	*mcr-1*
Klebsiella	6	86	Y	2	69	17–52	12	17.4	0–23.1	N/A[b]	Insufficient isolates – Resistance detected[c]	*mcr-1*
Myanmar												
E. coli	2	240	N	2	240	20–220	0	0	0	0	Resistance not detected	
Klebsiella	1	7	N	0	0	–	0	0	–	N/A[b]	Insufficient isolates – Resistance not detected	
Philippines												
E. coli	0	–	–	–	–	–	–	–	–	–	No studies found	
Klebsiella	1	4	Y	0	0	–	–	–	–	–	Insufficient isolates – Resistance detected	
Singapore												
E. coli	9	37	Y	1	13	–	0	0	0	N/A[b]	Insufficient isolates – Resistance detected[c]	*mcr-1*
Klebsiella	10	92	Y	3	38	11–16	1	2.6	0–6	N/A[b]	Insufficient isolates –Resistance detected[c]	*mcr-1*
Thailand												
E. coli	25	1737	Y	10	1396	12–543	41	2.9	0–8.8	0	Low (<1%)	*mcr-1, -2, -3*
Klebsiella	16	1154	Y	6	920	16–317	42	4.6	0–7.6	0.66	Low (<1%)	*mcr-1, -3, mgrB* mutation
Timor-Leste												
E. coli	0	–	–	–	–	–	–	–	–	–	No studies found	
Klebsiella	0	–	–	–	–	–	–	–	–	–	No studies found	
Vietnam												
E. coli	6	1395	Y	1	1370	–	49	3.6	–	3.6	Moderate (1–5%)	*mcr-1*
Klebsiella	5	407	Y	1	345	–	22	6.4	–	6.4	High (>5%)	*mcr-3, mgrB* mutation

[a] – Data not available.
[b] Insufficient isolates (<100) for polymyxin resistance estimate.
[c] Genotypic resistance only.

ument carbapenem-resistant *E. coli* and *Klebsiella* spp. in most Southeast Asian nations; 8/11 for *E. coli* and 9/11 for *Klebsiella*. Furthermore, through analysis of data from nations with ≥100 generalisable samples collected in more recent studies, we estimated and mapped median national carbapenem resistance proportions for *E. coli* and *Klebsiella* spp. Estimated resistance for *Klebsiella* was high (>5%) in four nations (Indonesia, Philippines, Thailand and Vietnam), moderate (1–5%) in two (Malaysia and Singapore) and low (<1%) in two (Cambodia and Brunei). In contrast, for *E. coli* estimated resistance was high in two (Indonesia and Myanmar) of eight nations with sufficient isolates tested and was low in the remaining six (Cambodia, Malaysia, Philippines, Singapore, Thailand and Vietnam). These findings extend and update both the WHO's published reports [5,7,28] and available reviews [32,36].

The most commonly detected carbapenemase genotypes were NDM MBLs (with NDM-1 predominant), which were reported in *E. coli* from six nations and *Klebsiella* spp. from seven nations. Given that South Asia was an early site for reports of the $bla_{\text{NDM-1}}$ gene [32], it is possible that geographic proximity has played a role in its extensive spread in the region. OXA genotypes were reported

in *E. coli* from five nations and *Klebsiella* spp. from six nations. KPC-, IMP- and VIM-related genotypes, whilst less common, were also reported. Jean et al. [60] have previously reported NDM- and IMP-carrying Enterobacteriaceae predominantly from Vietnam and the Philippines, with OXA also present in the region. The data assembled here extend those findings and demonstrate that NDM and OXA carbapenemases are widespread, with multiple other carbapenemase families present.

Reports evaluating resistance to polymyxin(s), for which susceptibility is not routinely tested, were more limited. However, we were able to capture data regarding 10 of 11 nations (all except Timor-Leste) documenting resistance to polymyxin(s) among *E. coli* and/or *Klebsiella* spp. in 8/11 (73%) nations. Due to the scarcity of data, we could only estimate median resistance across studies for five countries with ≥100 generalisable isolates tested. Among *E. coli*, Vietnam had moderate estimated median resistance (1–5%), whilst in Cambodia and Thailand resistance was estimated as low (<1%), and no resistant isolates were reported from Myanmar. For *Klebsiella*, Laos and Vietnam had high estimated median resistance (>5%), whilst estimated median resistance in Thailand was low (<1%). In addition to documenting the geographic spread of colistin resistance, our analysis assembles genotypic data identifying plasmid-mediated *mcr* genes, most often *mcr-1*, among *E. coli* in seven Southeast Asian nations and *Klebsiella* in five nations, in contrast to a 2017 review [24] that identified *mcr-1* in *E. coli* and *Klebsiella* from five and one nation, respectively. Studies captured in our analyses also documented *mgrB* chromosomal mutations among *Klebsiella* isolates in three nations.

Resistance to polymyxin(s) is especially worrisome when present in areas with substantial existing carbapenem resistance. Co-carriage of *mcr* with plasmid-derived carbapenemases, particularly MBLs predominant in Southeast Asia, could result in essentially pandrug-resistant organisms with dire consequences [61]. Thus, it is concerning that we could identify, even in the face of limited available data, overlapping carbapenem and polymyxin resistance in eight nations, including overlapping bla_{NDM} and *mcr* in five (Indonesia, Malaysia, Singapore, Thailand and Vietnam) all with substantial carbapenem resistance.

Whilst these findings improve our understanding of carbapenem and polymyxin resistance among Enterobacteriaceae in Southeast Asia, there are limitations that merit emphasis. First, whilst mostly derived from and reflective of acute-care populations, the data originate from diverse sources employing a variety of study designs and laboratory methods. These heterogeneities have been addressed, in part, through pre-defined inclusion criteria, data elements and data extraction. Several known factors may contribute to potential overestimation of resistance, including that laboratories performing testing are likely to support higher complexity care and to be located in urban areas or regional hubs. In addition, there is inherent bias towards reporting positive results. To help address reporting bias, we used search strategies enhanced for finding negative data, including not requiring either that carbapenems or polymyxin(s) be the focus of studies or that resistance be reported.

Conversely, some factors may contribute to potential underestimation of resistance. These include lags in reporting such that samples were typically collected 1–2 years or more prior to publication. It is reassuring that three-quarters of the data were from studies published after 2010 and approximately one-half from after 2014. In an effort to better reflect contemporary rates, we estimated carbapenem resistance using only reports including sample dates from 2010–2017. However, one must use caution and not project findings beyond the specific settings and time periods reflected by the database. The few nations where CRE and/or polymyxin-resistant Enterobacteriaceae were not detected should not be assumed to be free of resistance. Most such countries had a low number of isolates studied, suggesting that resistance may be undetected due to limited power. Furthermore, increasing resistance in the last several years may imply that, as additional contemporary data become available, carbapenem or colistin resistance could be detected.

Despite such caveats, we believe that the carbapenem resistance estimates calculated are reasonably reflective of those found in healthcare settings during the period 2010–2017, as further supported by the overall general correlation of the estimates with available surveillance data. Similarly, abbreviated data reported for Vietnam from 2016 [49] show rates of polymyxin resistance for *E. coli* and *Klebsiella* similar to those in our report. An exception to these correlations was that for the Philippines, Thailand and Vietnam there was lower overall carbapenem resistance estimated among *E. coli* in our analysis compared with surveillance reports. The reason(s) for this discrepancy is not clear, particularly given general concordance for *Klebsiella*, but may include differences in populations and, most likely, the relative paucity in our database of samples from 2014 and later for these nations. It is also possible that changes in thresholds for interpretation of susceptibility testing could account for a portion of recent reported increases in resistance [62].

The intrinsic limitations of the available data do not alter the fundamental findings presented, namely the widespread presence of CRE and polymyxin-resistant Enterobacteriaceae, and corresponding transferrable resistance genotypes, across most of Southeast Asia, including the documented overlap of transferrable genotypes in six nations, five with both bla_{NDM} and *mcr* genes. These circumstances create conditions that increase the future risk of carbapenem and polymyxin resistance, both individually and in combination. The study also highlights major remaining gaps in data from many nations, both historical and contemporary, and strongly supports the need for sufficiently resourced and robust national AMR surveillance.

Declaration of Competing Interest

None declared.

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Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.07.019.

References

[1] Luepke KH, Suda KJ, Boucher H, Russo RL, Bonney MW, Hunt TD, et al. Past, present, and future of antibacterial economics: increasing bacterial resistance, limited antibiotic pipeline, and societal implications. Pharmacotherapy 2017;37:71–84. doi:10.1002/phar.1868.

[2] Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance—the need for global solutions. Lancet Infect Dis 2013;13:1057–98. doi:10.1016/S1473-3099(13)70318-9.

[3] Zellweger RM, Carrique-Mas J, Limmathurotsakul D, Day NPJ, Thwaites GE, Baker S, et al. A current perspective on antimicrobial resistance in Southeast Asia. J Antimicrob Chemother 2017;72:2963–72. doi:10.1093/jac/dkx260.

[4] Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health 2014;2:1458. doi:10.3389/fpubh.2014.00145.

[5] World Health Organization (WHO). Antimicrobial resistance: global report on surveillance. Geneva, Switzerland: WHO; 2014.

[6] Keynan Y, Rubinstein E. The changing face of *Klebsiella pneumoniae* infections in the community. Int J Antimicrob Agents 2007;30:385–9. doi:10.1016/j.ijantimicag.2007.06.019.

[7] World Health Organization (WHO). Global Antimicrobial Resistance Surveillance System (GLASS) report: early implementation 2016–2017. Geneva, Switzerland: WHO; 2018.

[8] World Health Organization (WHO). *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. Geneva, Switzerland: WHO; 2017.

[9] US Centers for Disease Control and Prevention (CDC). *Antibiotic resistance threats in the United States, 2013*. Atlanta, GA: CDC; 2013.

[10] US Centers for Disease Control and Prevention (CDC). *Carbapenem-resistant Enterobacteriaceae in healthcare settings*. Atlanta, GA: CDC. https://www.cdc.gov/hai/organisms/cre/index.html [accessed 10 July 2018].

[11] Rahal JJ. The role of carbapenems in initial therapy for serious Gram-negative infections. Crit Care 2008;12(Suppl 4):S5. doi:10.1186/cc6821.

[12] Salomão MC, Guimarães T, Duailibi DF, Perondi MBM, Letaif LSH, Montal AC, et al. Carbapenem-resistant Enterobacteriaceae in patients admitted to the emergency department: prevalence, risk factors, and acquisition rate. J Hosp Infect 2017;97:241–6. doi:10.1016/j.jhin.2017.08.012.

[13] Kelly AM, Mathema B, Larson EL. Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. Int J Antimicrob Agents 2017;50:127–34. doi:10.1016/j.ijantimicag.2017.03.012.

[14] Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother 2011;55:4943–60. doi:10.1128/AAC.00296-11.

[15] Sidjabat HE, Paterson DL. Multidrug-resistant *Escherichia coli* in Asia: epidemiology and management. Expert Rev Anti Infect Ther 2015;13:575–91. doi:10.1586/14787210.2015.1028365.

[16] Diene SM, Rolain J-M. Carbapenemase genes and genetic platforms in Gram-negative bacilli: Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* species. Clin Microbiol Infect 2014;20:831–8. doi:10.1111/1469-0691.12655.

[17] Momin M, Liakopoulos A, Phee M, Wareham D. Emergence and nosocomial spread of carbapenem-resistant OXA-232-producing *Klebsiella pneumoniae* in Brunei Darussalam. J Glob Antimicrob Resist 2017;9:96–9. doi:10.1016/j.jgar.2017.02.008.

[18] Alenton L, Hsann MY, Tambyah P, Lin R, Ng KS, Rethanam S, et al. OXA-181-carbapenemase producing *Klebsiella pneumoniae*: an emerging threat? The first reported nosocomial outbreak in Singapore. Antimicrob Resist Infect Control 2013;2(Suppl 1):O48. doi:10.1186/2047-2994-2-S1-O48.

[19] Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis 2013;13:785–96. doi:10.1016/S1473-3099(13)70190-7.

[20] Bartsch SM, McKinnell JA, Mueller LE, Miller LG, Gohil SK, Huang SS, et al. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. Clin Microbiol Infect 2017;23 48.e9–16. doi:10.1016/j.cmi.2016.09.003.

[21] McConville TH, Sullivan SB, Gomez-Simmonds A, Whittier S, Uhlemann A-C. Carbapenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study. PLoS One 2017;12:e0186195. doi:10.1371/journal.pone.0186195.

[22] Tang SS, Apisarnthanarak A, Hsu LY. Mechanisms of β-lactam antimicrobial resistance and epidemiology of major community- and healthcare-associated multidrug-resistant bacteria. Adv Drug Deliv Rev 2014;78:3–13. doi:10.1016/J.ADDR.2014.08.003.

[23] Olaitan AO, Morand S, Rolain JM. Emergence of colistin-resistant bacteria in humans without colistin usage: a new worry and cause for vigilance. Int J Antimicrob Agents 2016;47:1–3. doi:10.1016/j.ijantimicag.2015.11.009.

[24] Jeannot K, Bolard A, Plésiat P. Resistance to polymyxins in Gram-negative organisms. Int J Antimicrob Agents 2017;49:526–35. doi:10.1016/j.ijantimicag.2016.11.029.

[25] Antoniadou A, Kontopidou F, Poulakou G, Koratzanis E, Galani I, Papadomichelakis E, et al. Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multiclonal cluster. J Antimicrob Chemother 2007;59:786–90. doi:10.1093/jac/dkl562.

[26] Chen L, Todd R, Kiehlbauch J, Walters M, Kallen A. Notes from the field: pan-resistant New Delhi metallo-β-lactamase-producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016. MMWR Morb Mortal Wkly Rep 2017;66:33. doi:10.15585/mmwr.mm6601a7.

[27] Krapp F, Ozer EA, Qi C, Hauser AR. Case report of an extensively drug-resistant *Klebsiella pneumoniae* infection with genomic characterization of the strain and review of similar cases in the United States. Open Forum Infect Dis 2018;5 ofy074. doi:10.1093/ofid/ofy074.

[28] World Health Organization (WHO). Global Antimicrobial Resistance Surveillance System (GLASS) report: early implementation 2017–2018. Geneva, Switzerland: WHO; 2019.

[29] Review on Antimicrobial Resistance. Antimicrobial resistance: tackling a crisis for the health and wealth of nations; 2014.

[30] World Health Organization (WHO); Food and Agriculture Organization of the United Nations (FAO). Antimicrobial resistance: a manual for developing national action plans. WHO/FAO; 2016.

[31] Tacconelli E., Sifakis F., Harbarth S., Schrijver R., van Mourik M., Voss A., et al. Surveillance for control of antimicrobial resistance. Lancet Infect Dis 2017:99–106. doi: 10.1016/S1473-3099(17)30485-1.

[32] Hsu L-Y, Apisarnthanarak A, Khan E, Suwantarat N, Ghafur A, Tambyah PA. Carbapenem-resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. Clin Microbiol Rev 2016;30:1–22. doi:10.1128/CMR.00042-16.

[33] Chereau F, Opatowski L, Tourdjman M, Vong S. Risk assessment for antibiotic resistance in South East Asia. BMJ 2017;358:j3393. doi:10.1136/BMJ.J3393.

[34] Rolain J-M, Kempf M, Leangapichart T, Chabou S, Olaitan AO, Le Page S, et al. Plasmid-mediated *mcr-1* gene in colistin-resistant clinical isolates of *Klebsiella pneumoniae* in France and Laos. Antimicrob Agents Chemother 2016;60:6994–5. doi:10.1128/AAC.00960-16.

[35] Olaitan AO, Diene SM, Kempf M, Berrazeg M, Bakour S, Gupta SK, et al. Worldwide emergence of colistin resistance in *Klebsiella pneumoniae* from healthy humans and patients in Lao PDR, Thailand, Israel, Nigeria and France owing to inactivation of the PhoP/PhoQ regulator *mgrB*: an epidemiological and molecular study. Int J Antimicrob Agents 2014;44:500–7. doi:10.1016/j.ijantimicag.2014.07.020.

[36] Suwantarat N, Carroll KC. Epidemiology and molecular characterization of multidrug-resistant Gram-negative bacteria in Southeast Asia. Antimicrob Resist Infect Control 2016;5:15. doi:10.1186/s13756-016-0115-6.

[37] Kluytmans J. Plasmid-encoded colistin resistance: *mcr*-one, two, three and counting. Euro Surveill 2017;22 pii: 30588. doi:10.2807/1560-7917.ES.2017.22.31.30588.

[38] Liu Y-Y, Wang Y, Walsh TR, Yi L-X, Zhang R, Spencer J, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2016;16:161–8. doi:10.1016/S1473-3099(15)00424-7.

[39] Nguyen-Viet H, Chotinun S, Schelling E, Widyastuti W, Khong NV, Kakkar M, et al. Reduction of antimicrobial use and resistance needs sectoral-collaborations with a One Health approach: perspectives from Asia. Int J Public Health 2017;62(Suppl 1):3–5. doi:10.1007/s00038-016-0933-6.

[40] Walther BA, Boëte C, Binot A, By Y, Cappelle J, Carrique-Mas J, et al. Biodiversity and health: lessons and recommendations from an interdisciplinary conference to advise Southeast Asian research, society and policy. Infect Genet Evol 2016;40:29–46. doi:10.1016/j.meegid.2016.02.003.

[41] Coker RJ, Hunter BM, Rudge JW, Liverani M, Hanvoravongchai P. Emerging infectious diseases in Southeast Asia: regional challenges to control. Lancet 2011;377:599–609. doi:10.1016/S0140-6736(10)62004-1.

[42] World Health Organization (WHO). Combating emerging infectious diseases in the South-East Asia Region. Geneva, Switzerland: WHO; 2005.

[43] Institute for Medical Research, Ministry of Health Malaysia. *National surveillance of antimicrobial resistance, Malaysia*2018. http://www.imr.gov.my/en/component/content/article/75-english-content/national-collabration/1469-nsar-main.html [accessed 31 August 2018].

[44] Department of Health Philippines. *Antimicrobial Resistance Surveillance Reference Laboratory, Philippines*2018. http://arsp.com.ph/reference/ [accessed 31 August 2018].

[45] National Institute of Health Department of Medical Sciences. *National Antimicrobial Resistance Surveillance Center, Thailand* 2018. http://narst.dmsc.moph.go.th/ [accessed 31 August 2018].

[46] Mitgang EA, Hartley DM, Malchione MD, Koch M, Goodman JL. Review and mapping of carbapenem-resistant Enterobacteriaceae in Africa: using diverse data to inform surveillance gaps. Int J Antimicrob Agents 2018;52:372–84. doi:10.1016/j.ijantimicag.2018.05.019.

[47] United Nations Statistics Division (UNSD). *Methodology*. https://unstats.un.org/unsd/methodology/m49/ [accessed 8 November 2018].
[48] International Society for Infectious Diseases. *ProMED-mail*. https://www.promedmail.org/ [accessed 8 April 2019].
[49] Center for Disease Dynamics, Economics & Policy. *ResistanceMap – antibiotic resistance*. https://resistancemap.cddep.org/AntibioticResistance.php [accessed 17 April 2019].
[50] HealthMap. *HealthMap – virus and contagious disease surveillance*. https://healthmap.org/en/ [accessed 16 April 2019].
[51] World Health Organization (WHO). Definition of key terms. Geneva, Switzerland: WHO; 2013.
[52] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
[53] Teo J, Ngan G, Balm M, Jureen R, Krishnan P, Lin R. Molecular characterization of NDM-1 producing Enterobacteriaceae isolates in Singapore hospitals. West Pac Surveill Response J 2012;3:19–25. doi:10.5365/wpsar.2011.2.4.010.
[54] Rammaert B, Goyet S, Beauté J, Hem S, Te V, Try PL, et al. *Klebsiella pneumoniae* related community-acquired acute lower respiratory infections in Cambodia: clinical characteristics and treatment. BMC Infect Dis 2012;12:3. doi:10.1186/1471-2334-12-3.
[55] Nurul Atifah MA, Loo HK, Subramaniam G, Wong EH, Selvi P, Ho SE, et al. Faecal prevalence of extended-spectrum β-lactamase (ESBL)-producing coliforms in a geriatric population and among haematology patients. Malays J Pathol 2005;27:75–81.
[56] Peirano G, Bradford PA, Kazmierczak KM, Badal RE, Hackel M, Hoban DJ, et al. Global incidence of carbapenemase-producing *Escherichia coli* ST131. Emerg Infect Dis 2014;20:1928–31. doi:10.3201/eid2011.141388.
[57] Abdul Kadir KA, Satyavani M, Pande K. Bacteriological study of diabetic foot infections. Brunei Int Med J 2012;8:19–26.
[58] Mustafa M, Balingi J. Urinary tract infections in a Sabah General Hospital. IOSR J Pharm Biol Sci 2012;1:2278–3008. doi:10.9790/3008-0164448.
[59] van Aartsen JJ, Moore CE, Parry CM, Turner P, Phot N, Mao S, et al. Epidemiology of paediatric gastrointestinal colonisation by extended spectrum cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolates in north-west Cambodia. BMC Microbiol 2019;19:59. doi:10.1186/s12866-019-1431-9.
[60] Jean SS, Hsueh PR, Korman T, Ellem J, George N, Coombs G, et al. Distribution of ESBLs, AmpC β-lactamases and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal and urinary tract infections in the Asia-Pacific region during 2008–14: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). J Antimicrob Chemother 2017;72:166–71. doi:10.1093/jac/dkw398.
[61] Manohar P, Shanthini T, Ayyanar R, Bozdogan B, Wilson A, Tamhankar AJ, et al. The distribution of carbapenem- and colistin-resistance in Gram-negative bacteria from the Tamil Nadu region in India. J Med Microbiol 2017;66:874–83.
[62] Rennie RP, Jones RN. Effects of breakpoint changes on carbapenem susceptibility rates of Enterobacteriaceae: results from the SENTRY Antimicrobial Surveillance Program, United States, 2008 to 2012. Can J Infect Dis Med Microbiol 2014;25:285–7.
[63] Hamzan NI, Yean CY, Rahman RA, Hasan H, Rahman ZA. Detection of bla_{IMP4} and bla_{NDM1} harboring *Klebsiella pneumoniae* isolates in a university hospital in Malaysia. Emerg Health Threats J 2015;8:8–12. doi:10.3402/ehtj.v8.26011.
[64] Prombhul S, Tribuddharat C, Laikijrung P, Aranya C, Bamrungsri N, Mekviwattanawong S. New variant of an imipenemase, IMP-32, in *Klebsiella pneumoniae* from a fatal case of a Thai patient. J Med Microbiol 2016;65:572–3. doi:10.1099/jmm.0.000252.
[65] Luvsansharav UO, Hirai I, Nakata A, Imura K, Yamauchi K, Niki M, et al. Prevalence of and risk factors associated with faecal carriage of CTX-M β-lactamase-producing Enterobacteriaceae in rural Thai communities. J Antimicrob Chemother 2012;67:1769–74. doi:10.1093/jac/dks118.
[66] Kazmierczak KM, Rabine S, Hackel M, McLaughlin RE, Biedenbach DJ, Bouchillon SK, et al. Multiyear, multinational survey of the incidence and global distribution of metallo-β-lactamase-producing Enterobacteriaceae and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2016;60:1067–78. doi:10.1128/AAC.02379-15.
[67] Gan H, Rajasekaram G, Eng WWH, Kaniappan P, Dhanoa A. Whole-genome sequences of two carbapenem-resistant *Klebsiella quasipneumoniae* strains isolated from a tertiary hospital in Johor, Malaysia. Genome Announc 2017;5 e00768-17.
[68] Jaruratanasirikul S, Wongpoowarak W, Jullangkoon M, Samaeng M. Population pharmacokinetics and dosing simulations of imipenem in serious bacteraemia in immunocompromised patients with febrile neutropenia. J Pharmacol Sci 2015;127:164–9. doi:10.1016/j.jphs.2014.12.003.
[69] Chen YT, Lin AC, Siu LK, Koh TH. Sequence of closely related plasmids encoding bla_{NDM-1} in two unrelated *Klebsiella pneumoniae* isolates in Singapore. PLoS One 2012;7:3–8. doi:10.1371/journal.pone.0048737.
[70] La MV, Jureen R, Lin RTP, Teo JWP. Unusual detection of an *Acinetobacter* class D carbapenemase gene, bla_{OXA-23}, in a clinical *Escherichia coli* isolate. J Clin Microbiol 2014;52:3822–3. doi:10.1128/JCM.01566-14.
[71] Niumsup PR, Tansawai U, Na-udom A, Jantapalaboon D, Assawatheptawee K, Kiddee A, et al. Prevalence and risk factors for intestinal carriage of CTX-M-type ESBLs in Enterobacteriaceae from a Thai community. Eur J Clin Microbiol Infect Dis 2017;37:69–75. doi:10.1007/s10096-017-3102-9.
[72] Myat TO, Prasad N, Thinn KK, Win KK, Htike WW, Zin KN, et al. Bloodstream infections at a tertiary referral hospital in Yangon, Myanmar. Trans R Soc Trop Med Hyg 2014;108:692–8. doi:10.1093/trstmh/tru151.
[73] Netikul T, Kiratisin P. Genetic characterization of carbapenem-resistant Enterobacteriaceae and the spread of carbapenem-resistant *Klebsiella pneumonia* ST340 at a university hospital in Thailand. PLoS One 2015;10:e0139116. doi:10.1371/journal.pone.0139116.
[74] Sugawara Y, Akeda Y, Sakamoto N, Takeuchi D, Motooka D, Nakamura S, et al. Genetic characterization of bla_{NDM}-harboring plasmids in carbapenem-resistant *Escherichia coli* from Myanmar. PLoS One 2017;12:e0184720. doi:10.1371/journal.pone.0184720.
[75] Musikatavorn K, Chumpengpan C, Sujinpram C. Risk factors of extended-spectrum β-lactamase-producing Enterobacteriaceae bacteremia in Thai emergency department: a retrospective case–control study. Asian Biomed 2011;5:129–38. doi:10.5372/1905-7415.0501.016.
[76] Stoesser N, Xayaheuang S, Vongsouvath M, Phommasone K, Elliott I, Del Ojo Elias C, et al. Colonization with Enterobacteriaceae producing ESBLs in children attending pre-school childcare facilities in the Lao People's Democratic Republic. J Antimicrob Chemother 2015;70:1893–7. doi:10.1093/jac/dkv021.
[77] Phu VD, Wertheim HFL, Larsson M, Nadjm B, Dinh Q-D, Nilsson LE, et al. Burden of hospital acquired infections and antimicrobial use in Vietnamese adult intensive care units. PLoS One 2016;11:e0147544. doi:10.1371/journal.pone.0147544.
[78] Vasoo S, Cunningham SA, Cole NC, Kohner PC, Menon SR, Krause KM, et al. In vitro activities of ceftazidime–avibactam, aztreonam–avibactam, and a panel of older and contemporary antimicrobial agents against carbapenemase-producing Gram-negative bacilli. Antimicrob Agents Chemother 2015;59:7842–6. doi:10.1128/AAC.02019-15.
[79] Chia G, Kum JQ, Marimuthu K, Fong PB, Ang B. Identifying patients at high risk for carbapenem-resistant Enterobacteriaceae at admission: nurse-led or doctor-led? Infect Control Hosp Epidemiol 2016;37:238–9. doi:10.1017/ice.2015.288.
[80] Vlieghe ER, Huang TD, Phe T, Bogaerts P, Berhin C, De Smet B, et al. Prevalence and distribution of β-lactamase coding genes in third-generation cephalosporin-resistant Enterobacteriaceae from bloodstream infections in Cambodia. Eur J Clin Microbiol Infect Dis 2015;34:1223–9. doi:10.1007/s10096-015-2350-9.
[81] Turner P, Pol S, Soeng S, Sar P, Neou L, Chea P, et al. High prevalence of antimicrobial-resistant Gram-negative colonization in hospitalized Cambodian infants. Pediatr Infect Dis J 2016;35:856–61. doi:10.1097/INF.0000000000001187.
[82] Fox-Lewis A, Takata J, Miliya T, Lubell Y, Soeng S, Sar P, et al. Antimicrobial resistance in invasive bacterial infections in hospitalized children, Cambodia, 2007–2016. Emerg Infect Dis 2018;24:841–51. doi:10.3201/eid2405.171830.
[83] Kor SB, Choo QC, Chew CH. New integron gene arrays from multiresistant clinical isolates of members of the Enterobacteriaceae and *Pseudomonas aeruginosa* from hospitals in Malaysia. J Med Microbiol 2013;62:412–20. doi:10.1099/jmm.0.053645-0.
[84] Chayakulkeeree M, Junsriwong P, Keerasuntonpong A, Tribuddharat C, Thamlikitkul V. Epidemiology of extended-spectrum β-lactamase producing Gram-negative bacilli at Siriraj Hospital, Thailand, 2003. Southeast Asian J Trop Med Public Health 2005;36:1503–9.
[85] Taitt CR, Leski TA, Heang V, Ford GW, Prouty MG, Newell SW, et al. Antimicrobial resistance genotypes and phenotypes from multidrug-resistant bacterial wound infection isolates in Cambodia. J Glob Antimicrob Resist 2015;3:198–204. doi:10.1016/j.jgar.2015.05.006.
[86] Stoesser N, Mathers AJ, Moore CE, Day NPJ, Crook DW. Colistin resistance gene *mcr-1* and pHNSHP45 plasmid in human isolates of *Escherichia coli* and *Klebsiella pneumoniae*. Lancet Infect Dis 2016;16:285–6. doi:10.1016/S1473-3099(16)00010-4.
[87] Moore CE, Sona S, Poda S, Putchhat H, Kumar V, Sopheary S, et al. Antimicrobial susceptibility of uropathogens isolated from Cambodian children. Paediatr Int Child Health 2016;36:113–17. doi:10.1179/2046905515Y.0000000008.
[88] Stoesser N, Emary K, Soklin S, Peng KA, Sophal S, Chhomrath S, et al. The value of intermittent point-prevalence surveys of healthcare-associated infections for evaluating infection control interventions at Sngkor Hospital for Children, Siem Reap, Cambodia. Trans R Soc Trop Med Hyg 2013;107:248–53. doi:10.1093/trstmh/trt005.
[89] Phe T, Vlieghe E, Reid T, Harries AD, Lim K, Thai S, et al. Does HIV status affect the aetiology, bacterial resistance patterns and recommended empiric antibiotic treatment in adult patients with bloodstream infection in Cambodia? Trop Med Int Health 2013;18:485–94. doi:10.1111/tmi.12060.
[90] Smit PW, Stoesser N, Pol S, van Kleef E, Oonsivilai M, Tan P, et al. Transmission dynamics of hyper-endemic multi-drug resistant *Klebsiella pneumoniae* in a Southeast Asian neonatal unit: a longitudinal study with whole genome sequencing. Front Microbiol 2018;9:1197. doi:10.3389/fmicb.2018.01197.
[91] Hout B, Oum C, Men P, Vanny V, Supaprom C, Heang V, et al. Drug resistance in bacteria isolated from patients presenting with wounds at a nonprofit surgical center in Phnom Penh, Cambodia from 2011–2013. Trop Dis Travel Med Vaccines 2015;1:4. doi:10.1186/s40794-015-0006-5.
[92] Vlieghe ER, Phe T, De Smet B, Chhun Veng H, Kham C, Lim K, et al. Bloodstream infection among adults in Phnom Penh, Cambodia: key pathogens and resistance patterns. PLoS One 2013;8:e59775. doi:10.1371/journal.pone.0059775.
[93] Ruppé E, Hem S, Lath S, Gautier V, Ariey F, Sarthou JL, et al. CTX-M β-lactamases in *Escherichia coli* from community-acquired urinary tract in-

fections, Cambodia. Emerg Infect Dis 2009;15:741–8. doi:10.3201/eid1505.071299.
[94] Caron Y, Chheang R, Puthea N, Soda M, Boyer S, Tarantola A, et al. β-Lactam resistance among Enterobacteriaceae in Cambodia: the four-year itch. Int J Infect Dis 2018;66:74–9. doi:10.1016/j.ijid.2017.10.025.
[95] Wikaningtyas P, Sigit JI, Sukandar EY, Gunawan I. Profile of antibiotic resistance and usage pattern in ICU of private hospital in Bandung, Indonesia. Int J Pharm Pharm Sci 2015;7:160–2.
[96] Murni IK, Duke T, Daley AJ, Kinney S, Soenarto Y. Antibiotic resistance and mortality in children with nosocomial bloodstream infection in a teaching hospital in Indonesia. Southeast Asian J Trop Med Public Health 2016;47:983–93.
[97] Gunawan H, Sugiri U, Nurhasanah, Makarti K, Suwarsa O. Oral clindamycin as drug of choice for scabies patients with secondary bacterial infections in West Java, Indonesia. Am J Infect Dis 2018;14:45–50. doi:10.3844/ajidsp.2018.45.50.
[98] Kitagawa K, Shigemura K, Yamamichi F, Alimsardjono L, Rahardjo D, Kuntaman K, et al. International comparison of causative bacteria and antimicrobial susceptibilities of urinary tract infections between Kobe, Japan, and Surabaya, Indonesia. Jpn J Infect Dis 2018;71:8–13. doi:10.7883/yoken.JJID.2017.233.
[99] Radji M, Putri CS, Fauziyah S. Antibiotic therapy for diabetic foot infections in a tertiary care hospital in Jakarta, Indonesia. Diabetes Metab Syndr 2014;8:221–4. doi:10.1016/j.dsx.2014.09.006.
[100] Karuniawati A, Saharman YR, Lestari DC. Detection of carbapenemase encoding genes in Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* isolated from patients at Intensive Care Unit Cipto Mangunkusumo Hospital in 2011. Acta Med Indones 2013;45:101–6.
[101] Chien JMF, Koh TH, Chan KS, Chuah THC, Tan TT. Successful treatment of NDM-1 *Klebsiella pneumoniae* bacteraemia in a neutropenic patient. Scand J Infect Dis 2012;44:312–14. doi:10.3109/00365548.2011.633549.
[102] Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, et al. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med 2011;184:1409–17. doi:10.1164/rccm.201102-0349OC.
[103] Cheong HS, Chung DR, Park M, Kim SH, Ko KS, Ha YE, et al. Emergence of an extended-spectrum β-lactamase-producing serotype K1 *Klebsiella pneumoniae* ST23 strain from Asian countries. Epidemiol Infect 2017;145:990–4. doi:10.1017/S0950268816003113.
[104] von Wintersdorff CJH, Wolffs PFG, van Niekerk JM, Beuken E, van Alphen LB, Stobberingh EE, et al. Detection of the plasmid-mediated colistin-resistance gene *mcr-1* in faecal metagenomes of Dutch travellers. J Antimicrob Chemother 2016;71:3416–19. doi:10.1093/jac/dkw328.
[105] Sasongkowati R, Chitraningtyas D, Suliati, Christyaningsih J. The study on the susceptibility of *Enterococcus faecalis* and *Klebsiella ozaenae* cause UTI to antibiotics in East Java, Indonesia. Res J Pharm Biol Chem Sci 2015;6:1539–44.
[106] Lewis MT, Biedenbach DJ, Jones RN. In vitro evaluation of cefepime and other broad-spectrum β-lactams against bacteria from Indonesian medical centers. The Indonesia Antimicrobial Resistance Study Group. Diagn Microbiol Infect Dis 1999;35:285–90.
[107] Severin JA, Lestari ES, Kloezen W, Lemmens-den Toom N, Mertaniasih NM, Kuntaman K, et al. Faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae among humans in Java, Indonesia, in 2001–2002. Trop Med Int Health 2012;17:455–61. doi:10.1111/j.1365-3156.2011.02949.x.
[108] Radji M, Fauziah S, Aribinuko N. Antibiotic sensitivity pattern of bacterial pathogens in the intensive care unit of Fatmawati Hospital, Indonesia. Asian Pac J Trop Biomed 2011;1:39–42. doi:10.1016/S2221-1691(11)60065-8.
[109] Severin JA, Mertaniasih NM, Kuntaman K, Lestari ES, Purwanta M, Lemmens-Den Toom N, et al. Molecular characterization of extended-spectrum β-lactamases in clinical *Escherichia coli* and *Klebsiella pneumoniae* isolates from Surabaya, Indonesia. J Antimicrob Chemother 2010;65:465–9. doi:10.1093/jac/dkp471.
[110] Sari IP, Nuryastuti T, Wahyono D. The study of multidrug-resistance in neonatal intensive care unit at the central Java hospital. Asian J Pharm Clin Res 2017;10:80. doi:10.22159/ajpcr.2017.v10s2.19495.
[111] Bagus Wasito E, Shigemura K, Osawa K, Fardah A, Kanaida A, Raharjo D, et al. Antibiotic susceptibilities and genetic characteristics of extended-spectrum β-lactamase-producing *Escherichia coli* isolates from stools of pediatric diarrhea patients in Surabaya, Indonesia. Jpn J Infect Dis 2017;70:378–82. doi:10.7883/yoken.JJID.2016.234.
[112] Pradipta IS, Sandiana AT, Halimah E, Diantini A, Lestari K, Abdulah R. Microbial and resistance profile in isolate from adult sepsis patients: an observational study at an Indonesian private hospital during 2009–2012. Int J Pharm Sci Rev Res 2013;19:24–9.
[113] Sugianli AK, Ginting F, Kusumawati RL, Pranggono EH, Pasaribu AP, Gronthoud F, et al. Antimicrobial resistance in uropathogens and appropriateness of empirical treatment: a population-based surveillance study in Indonesia. J Antimicrob Chemother 2017;72:1469–77. doi:10.1093/jac/dkw578.
[114] Olaitan AO, Chabou S, Okdah L, Morand S, Rolain J-M. Dissemination of the *mcr-1* colistin resistance gene. Lancet Infect Dis 2016;16:147. doi:10.1016/S1473-3099(15)00540-X.
[115] Stoesser N, Crook DW, Moore CE, Phetsouvanh R, Chansamouth V, Newton PN, et al. Characteristics of CTX-M ESBL-producing *Escherichia coli* isolates from the Lao People's Democratic Republic, 2004–09. J Antimicrob Chemother 2012;67:240–1. doi:10.1093/jac/dkr434.
[116] Olaitan AO, Thongmalayvong B, Akkhavong K, Somphavong S, Paboriboune P, Khounsy S, et al. Clonal transmission of a colistin-resistant *Escherichia coli* from a domesticated pig to a human in Laos. J Antimicrob Chemother 2015;70:3402–4. doi:10.1093/jac/dkv252.
[117] Ariffin N, Hasan H, Ramli N, Ibrahim NR, Taib F, Rahman AA, et al. Comparison of antimicrobial resistance in neonatal and adult intensive care units in a tertiary teaching hospital. Am J Infect Control 2012;40:572–5. doi:10.1016/j.ajic.2012.02.032.
[118] Baskaran ND, Gan GG, Adeeba K, Sam IC. Bacteremia in patients with febrile neutropenia after chemotherapy at a university medical center in Malaysia. Int J Infect Dis 2007;11:513–17. doi:10.1016/j.ijid.2007.02.002.
[119] Ariffin H, Navaratnam P, Kee TK, Balan G. Antibiotic resistance patterns in nosocomial Gram-negative bacterial infections in units with heavy antibiotic usage. J Trop Pediatr 2004;50:26–31. doi:10.1093/tropej/50.1.26.
[120] Raja NS. Microbiology of diabetic foot infections in a teaching hospital in Malaysia: a retrospective study of 194 cases. J Microbiol Immunol Infect 2007;40:39–44.
[121] Lim KT, Yeo CC, Yasin RM, Balan G, Lin Thong K. Characterization of multidrug-resistant and extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* strains from Malaysian hospitals. J Med Microbiol 2009;58:1463–9. doi:10.1099/jmm.0.011114-0.
[122] Lim K-T, Yasin R, Yeo C-C, Puthucheary S, Thong K-L. Characterization of multidrug resistant ESBL-producing *Escherichia coli* isolates from hospitals in Malaysia. J Biomed Biotechnol 2009;2009:165637. doi:10.1155/2009/165637.
[123] Zainol Abidin NZ, Sulong A, Alfizah H, Muttaqillah NAS, Ding CH. Molecular detection of the New Delhi metallo-β-lactamase-1 gene in Enterobacteriaceae isolates in a tertiary medical centre. Malays J Pathol 2015;37:227–32.
[124] Zaidah AR, Mohammad NI, Suraiya S, Harun A. High burden of carbapenem-resistant Enterobacteriaceae (CRE) fecal carriage at a teaching hospital: cost-effectiveness of screening in low-resource setting. Antimicrob Resist Infect Control 2017;6:426. doi:10.1186/s13756-017-0200-5.
[125] Wise MG, Estabrook MA, Sahm DF, Stone GG, Kazmierczak KM. Prevalence of *mcr*-type genes among colistin-resistant Enterobacteriaceae collected in 2014–2016 as part of the INFORM global surveillance program. PLoS One 2018;13:e0195281. doi:10.1371/journal.pone.0195281.
[126] Yap PSX, Ahmad Kamar A, Chong CW, Yap IKS, Thong KL, Choo YM, et al. Intestinal carriage of multidrug-resistant Gram-negative bacteria in preterm-infants during hospitalization in neonatal intensive care unit (NICU). Pathog Glob Health 2016;110:238–46. doi:10.1080/20477724.2016.1229884.
[127] Karlowsky JA, Hoban DJ, Hackel MA, Lob SH, Sahm DF. Resistance among Gram-negative ESKAPE pathogens isolated from hospitalized patients with intra-abdominal and urinary tract infections in Latin American countries: SMART 2013–2015. Braz J Infect Dis 2017;21:343–8. doi:10.1016/j.bjid.2017.03.006.
[128] Yu CY, Ang GY, Chin PS, Ngeow YF, Yin WF, Chan KG. Emergence of *mcr-1*-mediated colistin resistance in *Escherichia coli* in Malaysia. Int J Antimicrob Agents 2016;47:504–5. doi:10.1016/j.ijantimicag.2016.04.004.
[129] Sia KJ, Tang IP, Prepageran N. Antibiotic sensitivity and spectrum of bacterial isolates in otorhinolaryngological infection: a retrospective study. Med J Malaysia 2013;68:6–9.
[130] Ahmad N, Hashim R, Shukor S, Khalid KNM, Shamsudin F, Hussin H. Characterization of the first isolate of *Klebsiella pneumoniae* carrying New Delhi metallo-β-lactamase and other extended spectrum β-lactamase genes from Malaysia. J Med Microbiol 2013;62:804–6. doi:10.1099/jmm.0.050781-0.
[131] Ibrahim N, Wajidi MF, Yusof MY, Tay ST. The integron prevalence of extended-spectrum β-lactamase producing enterobacterial isolates in a Malaysian teaching hospital. Trop Biomed 2011;28:668–71.
[132] Ho WS, Balan G, Puthucheary S, Kong BH, Lim KT, Tan LK, et al. Prevalence and characterization of multidrug-resistant and extended-spectrum β-lactamase-producing *Escherichia coli* from pediatric wards of a Malaysian hospital. Microb Drug Resist 2012;18:408–16. doi:10.1089/mdr.2011.0222.
[133] Palasubramaniam S, Muniandy S, Navaratnam P. Resistance to extended-spectrum β-lactams by the emergence of SHV-12 and the loss of OmpK35 in *Klebsiella pneumoniae* and *Escherichia coli* in Malaysia. J Microbiol Immunol Infect 2009;42:129–33.
[134] Subramaniam G, Palasubramaniam S, Navaratnam P. SHV-5 extended-spectrum-β-lactamases in clinical isolates of *Escherichia coli* in Malaysia. Indian J Med Microbiol 2006;24:205–7.
[135] Parasakthi N, Vadivelu J, Ariffin H, Iyer L, Palasubramaniam S, Arasu A. Epidemiology and molecular characterization of nosocomially transmitted multidrug-resistant *Klebsiella pneumoniae*. Int J Infect Dis 2000;4:123–8. doi:10.1016/S1201-9712(00)90072-9.
[136] Halder D, Haque ME, Zabidi MH, Kamaruzzaman A. Nosocomial bacterial sepsis in babies weighing 1000–1499 g in Kelantan. Med J Malaysia 1999;54:52–7.
[137] Ariffin H, Navaratnam P, Mohamed M, Arasu A, Abdullah WA, Lee CL, et al. Ceftazidime-resistant *Klebsiella pneumoniae* bloodstream infection in children with febrile neutropenia. Int J Infect Dis 2000;4:21–5.
[138] Low YM, Yap IKS, Abdul Jabar K, Md Yusof MY, Chong CW, Teh CSJ. Genotypic and metabolic approaches towards the segregation of *Klebsiella pneumoniae* strains producing different antibiotic resistant enzymes. Metabolomics 2017;13:1–13. doi:10.1007/s11306-017-1201-3.
[139] Lob S, Hackel M, Biedenbach D, Sahm D, Badal R. Trends in ESBL-production and susceptibility for *E. coli* from urinary tract infections in Southeast Asia: SMART 2010–2013. In: Abstracts from the 10th International Symposium on

Antimicrobial Agents and Resistance. Int J Antimicrob Agents 2015;45(Suppl 2):S81. doi:10.1016/S0924-8579(15)30006-6.
[140] Biedenbach D, Lob S, Badal R, Sahm D. Variability of susceptibility and multidrug resistance among *K. pneumoniae* from IAI in Asia/Pacific Countries – SMART 2012–2013. In: Abstracts from the 10th International Symposium on Antimicrobial Agents and Resistance. Int J Antimicrob Agents 2015;45(Suppl 2):S59–143. doi:10.1016/S0924-8579(15)30006-6.
[141] Castanheira M, Griffin MA, Deshpande LM, Mendes RE, Jones RN, Flamm RK. Detection of *mcr-1* among *Escherichia coli* clinical isolates collected worldwide as part of the SENTRY Antimicrobial Surveillance Program during 2014–2015. Antimicrob Agents Chemother 2016;316:806–7. doi:10.1128/AAC.01267-16.
[142] Pfaller MA, Shortridge D, Sader HS, Castanheira M, Flamm RK. Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing healthcare-associated infections in the Asia-Pacific region (minus China, Australia and New Zealand): report from an Antimicrobial Surveillance Programme (2013–2015). Int J Antimicrob Agents 2018;51:181–9. doi:10.1016/j.ijantimicag.2017.09.016.
[143] Palasubramaniam S, Subramaniam G, Muniandy S, Parasakthi N. Extended-spectrum β-lactam resistance due to AmpC hyperproduction and CMY-2 coupled with the loss of OMPK35 in Malaysian strains of *Escherichia coli* and *Klebsiella pneumoniae*. Microb Drug Resist 2007;13:186–90. doi:10.1089/mdr.2007.726.
[144] Mohamed NA, Said HM, Hussin H, Abdul Rahman N, Hashim R. Carbapenem-resistant Enterobacteriaceae: clinico-epidemiological perspective. Trop Biomed 2018;35:300–7.
[145] Mohd Helmi U, Mohd Desa MN, Taib NM, Tengku Jamaluddin TZM, Masri SN. Multiple Ambler class A ESBL genes among *Klebsiella pneumoniae* isolates in a Malaysian district hospital. Trop Biomed 2016;33:109–19.
[146] Kong Z, Low Y, Jabar K, Karunakaran R, Ponnampalavanar S, Chong C, et al. Trends in molecular epidemiology of carbapenem resistant *Klebsiella pneumoniae* in a tertiary hospital in Malaysia. In: Abstracts of the 30th International Congress of Chemotherapy and Infection 2017 (ICC 2017). Int J Antimicrob Agents Chemother 2017;50(Suppl 2):S69–277. doi:10.1016/S0924-8579(17)30423-5.
[147] Palasubramaniam S, Karunakaran R, Gin GG, Muniandy S, Parasakthi N. Imipenem-resistance in *Klebsiella pneumoniae* in Malaysia due to loss of OmpK36 outer membrane protein coupled with AmpC hyperproduction. Int J Infect Dis 2007;11:472–4. doi:10.1016/J.IJID.2007.01.005.
[148] Low Y-M, Yap PS-X, Abdul Jabar K, Ponnampalavanar S, Karunakaran R, Velayuthan R, et al. The emergence of carbapenem resistant *Klebsiella pneumoniae* in Malaysia: correlation between microbiological trends with host characteristics and clinical factors. Antimicrob Resist Infect Control 2017;6:5. doi:10.1186/s13756-016-0164-x.
[149] Al-Marzooq F, Mohd Yusof MY, Tay ST. Molecular analysis of antibiotic resistance determinants and plasmids in Malaysian isolates of multidrug resistant *Klebsiella pneumoniae*. PLoS One 2015;10:e0133654. doi:10.1371/journal.pone.0133654.
[150] Ahmad N, Chong TM, Hashim R, Shukor S, Yin W-F, Chan K-G. Draft genome of multidrug-resistant *Klebsiella pneumoniae* 223/14 carrying KPC-6, isolated from a general hospital in Malaysia. J Genomics 2015;3:97–8. doi:10.7150/jgen.13910.
[151] Myat TO, Hannaway RF, Zin KN, Htike WW, Win KK, Crump JA, et al. ESBL- and carbapenemase-producing Enterobacteriaceae in patients with bacteremia, Yangon, Myanmar, 2014. Emerg Infect Dis 2017;23:857–9. doi:10.3201/eid2305.161100.
[152] Espedido BA, Dimitrijovski B, Van Hal SJ, Jensen SO, Slade AP, Jensen O. The use of whole-genome sequencing for molecular epidemiology and antimicrobial surveillance: identifying the role of IncX3 plasmids and the spread of $bla_{\text{NDM-4-like}}$ genes in the Enterobacteriaceae. J Clin Pathol 2015;68:935–8. doi:10.1136/jclinpath-2015-203044.
[153] Van Hattem JM, Arcilla MS, Bootsma MCJ, Van Genderen PJ, Goorhuis A, Grobusch MP, et al. Prolonged carriage and potential onward transmission of carbapenemase-producing Enterobacteriaceae in Dutch travelers. Future Microbiol 2016;11:857–64. doi:10.2217/fmb.16.18.
[154] Aung MS, San N, Maw WW, San T, Urushibara N, Kawaguchiya M, et al. Prevalence of extended-spectrum β-lactamase and carbapenemase genes in clinical isolates of *Escherichia coli* in Myanmar: dominance of $bla_{\text{NDM-5}}$ and emergence of $bla_{\text{OXA-181}}$. Microb Drug Resist 2018;24:1333–44. doi:10.1089/mdr.2017.0387.
[155] Mon M, Mendes AJ, Silva D, Zin KN, Htike WW, Da Costa PM. Study of multidrug-resistant Gram-negative bacteria isolates obtained from hospitalized patients in Yangon, Myanmar. Myanmar Health Sci Res J 2017;29:151–7.
[156] Kanamori H, Navarro RB, Yano H, Sombrero LT, Capeding MRZ, Lupisan SP, et al. Molecular characteristics of extended-spectrum β-lactamases in clinical isolates of Enterobacteriaceae from the Philippines. Acta Trop 2011;120:140–5. doi:10.1016/j.actatropica.2011.07.007.
[157] Litzow J, Gill C, Mantaring J, Fox M, Mendoza M, Mendoza S, et al. High frequency of multidrug-resistant Gram-negative rods in 2 neonatal intensive care units in the Philippines. Infect Control Hosp Epidemiol 2009;30:543–9. doi:10.1086/597512.
[158] Tian GB, Garcia J, Adams-Haduch JM, Evangelista JP, Destura RV, Wang HN, et al. CTX-M as the predominant extended-spectrum β-lactamases among Enterobacteriaceae in Manila, Philippines. J Antimicrob Chemother 2010;65:584–6. doi:10.1093/jac/dkp480.
[159] Velasco JM, Valderama MT, Peacock T, Warawadee N, Nogrado K, Navarro FC, et al. Carbapenemase-producing Enterobacteriaceae and nonfermentative bacteria, the Philippines, 2013–2016. Emerg Infect Dis 2017;23:1597–8. doi:10.3201/eid2309.161237.
[160] Gangcuangco LM, Alejandria M, Henson KE, Alfaraz L, Ata RM, Lopez M, et al. Prevalence and risk factors for trimethoprim–sulfamethoxazole-resistant *Escherichia coli* among women with acute uncomplicated urinary tract infection in a developing country. Int J Infect Dis 2015;34:55–60. doi:10.1016/j.ijid.2015.02.022.
[161] Peirano G, Lascols C, Hackel M, Hoban DJ, Pitout JDD. Molecular epidemiology of Enterobacteriaceae that produce VIMs and IMPs from the SMART surveillance program. Diagn Microbiol Infect Dis 2014;78:277–81. doi:10.1016/j.diagmicrobio.2013.11.024.
[162] Hsueh PR, Hoban DJ, Carmeli Y, Chen SY, Desikan S, Alejandria M, et al. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. J Infect 2011;63:114–23. doi:10.1016/j.jinf.2011.05.015.
[163] Salvador VBDG, Lozada MCH, Consunji RJ. Microbiology and antibiotic susceptibility of organisms in bile cultures from patients with and without cholangitis at an Asian academic medical center. Surg Infect (Larchmt) 2011;12:105–11. doi:10.1089/sur.2010.005.
[164] Hirakata Y, Matsuda J, Miyazaki Y, Kamihira S, Kawakami S, Miyazawa Y, et al. Regional variation in the prevalence of extended-spectrum β-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998–2002). Diagn Microbiol Infect Dis 2005;52:323–9. doi:10.1016/j.diagmicrobio.2005.04.004.
[165] Bell JM, Turnidge JD, Gales AC, Pfaller MA, Jones RN. Prevalence of extended spectrum β-lactamase (ESBL)-producing clinical isolates in the Asia-Pacific region and South Africa: regional results from SENTRY Antimicrobial Surveillance Program (1998–99). Diagn Microbiol Infect Dis 2002;42:193–8.
[166] Kazmierczak KM, Biedenbach DJ, Hackel M, Rabine S, de Jonge BLM, Bouchillon SK, et al. Global dissemination of bla_{KPC} into bacterial species beyond *Klebsiella pneumoniae* and in vitro susceptibility to ceftazidime–avibactam and aztreonam–avibactam. Antimicrob Agents Chemother 2016;60:4490–500. doi:10.1128/AAC.00107-16.
[167] Bell J, Turnidge J. SENTRY Antimicrobial Surveillance Program Asia-Pacific region and South Africa. Commun Dis Intell Q Rep 2003;27(Suppl):S61–6.
[168] Mendes RE, Mendoza M, Banga Singh KK, Castanheira M, Bell JM, Turnidge JD, et al. Regional resistance surveillance program results for 12 Asia-Pacific nations (2011). Antimicrob Agents Chemother 2013;57:5721–6. doi:10.1128/AAC.01121-13.
[169] Cabrera EC, Rodriguez RD. First report on the occurrence of SHV-12 extended-spectrum β-lactamase-producing Enterobacteriaceae in the Philippines. J Microbiol Immunol Infect 2009;42:74–85.
[170] Valle DL Jr, Cabal ABS, Paclibare PAP, Rivera WL. Enteroaggregative *Escherichia coli* infections among children in a tertiary hospital in the Philippines. Southeast Asian J Trop Med Public Health 2018;49:409–20.
[171] Hsueh PR, Snyder TA, DiNubile MJ, Satischandran V, McCarroll K, Chow JW. In vitro susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). Int J Antimicrob Agents 2006;28:238–43. doi:10.1016/j.ijantimicag.2006.04.010.
[172] Chou A, Roa M, Evangelista MA, Sulit AK, Lagamayo E, Torres BC, et al. Emergence of *Klebsiella pneumoniae* ST273 carrying $bla_{\text{NDM-7}}$ and ST656 carrying $bla_{\text{NDM-1}}$ in Manila, Philippines. Microb Drug Resist 2016;22:585–8. doi:10.1089/mdr.2015.0205.
[173] Johnson DM, Biedenbach DJ, Jones RN. In vitro evaluation of broad-spectrum β-lactams in the Philippines medical centers: role of fourth-generation cephalosporins. The Philippines Antimicrobial Resistance Study Group. Diagn Microbiol Infect Dis 1999;35:291–7.
[174] Venkatachalam I, Teo J, Balm MND, Fisher DA, Jureen R, Lin RTP. *Klebsiella pneumoniae* carbapenemase-producing enterobacteria in hospital, Singapore. Emerg Infect Dis 2012;18:1381–3. doi:10.3201/eid1808.110893.
[175] Kumarasinghe G, Chow C, Chiu C. In vitro activity of meropenem against organisms causing serious infections in a Singapore hospital. Int J Antimicrob Agents 1997;9:121–5.
[176] Tan TY, Ng SY. The in-vitro activity of colistin in Gram-negative bacteria. Singapore Med J 2006;47:621–4.
[177] Teo JQ-M, Ong RT-H, Xia E, Koh T-H, Khor C-C, Lee SJ-Y, et al. *mcr-1* in multidrug-resistant $bla_{\text{KPC-2}}$-producing clinical Enterobacteriaceae isolates in Singapore. Antimicrob Agents Chemother 2016;60:6435–7. doi:10.1128/AAC.00804-16.
[178] Teo JWP, Tan P, La MV, Krishnan P, Tee N, Koh TH, et al. Surveillance trends of carbapenem-resistant Enterobacteriaceae from Singapore, 2010–2013. J Glob Antimicrob Resist 2014;2:99–102. doi:10.1016/j.jgar.2013.11.003.
[179] Harris PNA, Yin M, Jureen R, Chew J, Ali J, Paynter S, et al. Comparable outcomes for β-lactam/β-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused by cefotaxime-resistant *Escherichia coli* or *Klebsiella pneumoniae*. Antimicrob Resist Infect Control 2015;4:14. doi:10.1186/s13756-015-0055-6.
[180] Hsu L-Y, Tan T-Y, Jureen R, Koh T-H, Krishnan P, Tzer-Pin Lin R, et al. Antimicrobial drug resistance in Singapore hospitals. Emerg Infect Dis 2007;13:1944–7. doi:10.3201/eid1312.070299.
[181] Tan TY, Yang HL, Hsien KT, Ng LSY, Tee NWS, Krishnan P, et al. Antibiotic resistance in Gram-negative bacilli: a Singapore perspective. Ann Acad Med Singapore 2008;37:819–25.

[182] Teo JW, Chew KL, Lin RT. Transmissible colistin resistance encoded by *mcr-1* detected in clinical Enterobacteriaceae isolates in Singapore. Emerg Microbes Infect 2016;5:e87. doi:10.1038/emi.2016.85.

[183] Bahadin J, Teo SS, Mathew S. Aetiology of community-acquired urinary tract infection and antimicrobial susceptibility patterns of uropathogens isolated. Singapore Med J 2011;52:415–20.

[184] Marimuthu K, Venkatachalam I, Khong WX, Koh TH, Cherng BPZ, Van La M, et al. Clinical and molecular epidemiology of carbapenem-resistant Enterobacteriaceae among adult inpatients in Singapore. Clin Infect Dis 2017;64(Suppl 2):S68–75. doi:10.1093/cid/cix113.

[185] Lim TP, Cai Y, Hong Y, Chan ECY, Suranthran S, Teo JQM, et al. In vitro pharmacodynamics of various antibiotics in combination against extensively drug-resistant *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2015;59:2515–24. doi:10.1128/AAC.03639-14.

[186] Teo J, La M, Lin R. Development and evaluation of a multiplex real-time PCR for the detection of IMP, VIM, and OXA-23 carbapenemase gene families on the BD MAX open system. Diagn Microbiol Infect Dis 2016;86:358–61. doi:10.1016/j.diagmicrobio.2016.08.019.

[187] Khong WX, Marimuthu K, Teo J, Ding Y, Xia E, Lee JJ, et al. Tracking inter-institutional spread of NDM and identification of a novel NDM-positive plasmid, pSg1-NDM, using next-generation sequencing approaches. J Antimicrob Chemother 2016;71:3081–9. doi:10.1093/jac/dkw277.

[188] Cai Y, Chua NG, Lim TP, Teo JQM, Lee W, Kurup A, et al. From bench-top to bedside: a prospective in vitro antibiotic combination testing (iACT) service to guide the selection of rationally optimized antimicrobial combinations against extensively drug resistant (XDR) Gram negative bacteria (GNB). PLoS One 2016;11:e0158740. doi:10.1371/journal.pone.0158740.

[189] Marimuthu K, Ng OT, Khong WX, Xia E, Teo Y-Y, Ong RT-H, et al. Reactive infection control strategy for control of New Delhi metallo-β-lactamase (NDM)-producing Enterobacteriaceae analyzed using whole-genome sequencing: hits and misses. Infect Control Hosp Epidemiol 2016;37:987–90. doi:10.1017/ice.2016.92.

[190] Chen Y-T, Siu LK, Tsai Y-K, Lin F-M, Koh TH, Chen J-H. A common flanking region in promiscuous plasmids encoding bla_{NDM-1} in *Klebsiella pneumoniae* isolated in Singapore. Microb Drug Resist 2016;22:109–14. doi:10.1089/mdr.2015.0132.

[191] Choudhury S, Yeng JLW, Krishnan PU. In vitro susceptibilities of clinical isolates of carbapenemase-producing Enterobacteriaceae to fosfomycin and tigecycline. Clin Microbiol Infect 2015;21:e75–6. doi:10.1016/j.cmi.2015.06.005.

[192] Marimuthu K, Teo JWP, Fong PB, Hui Chin JO, Qi KJ, Lye Chien Boon D, et al. First report of emergence of OXA-48 carbapenemase-producing Enterobacteriaceae in Singapore: proactive or reactive infection control strategy? Am J Infect Control 2014;42:577–8. doi:10.1016/j.ajic.2014.01.021.

[193] Koh TH, Cao D, Shan QY, Bacon A, Hsu LY, Ooi EE. Acquired carbapenemases in Enterobacteriaceae in Singapore, 1996–2012. Pathology 2013;45:600–3. doi:10.1097/PAT.0b013e3283650b1e.

[194] Balm MND, La MV, Krishnan P, Jureen R, Lin RTP, Teo JWP. Emergence of *Klebsiella pneumoniae* co-producing NDM-type and OXA-181 carbapenemases. Clin Microbiol Infect 2013;19:E421–3. doi:10.1111/1469-0691.12247.

[195] Teng CP, Chen HH, Chan J, Lye DCB. Ertapenem for the treatment of extended-spectrum β-lactamase-producing Gram-negative bacterial infections. Int J Antimicrob Agents 2007;30:356–9. doi:10.1016/j.ijantimicag.2007.05.016.

[196] Chlebicki M, Oh H. Extended-spectrum β-lactamases in clinical isolates of *Escherichia coli* and *Klebsiella* spp. in a Singapore hospital: clinical spectrum. Ann Acad Med 2004;33:302–6.

[197] Kumarasinghe G, Chow C, Tambyah PA. Widespread resistance to new antimicrobials in a university hospital before clinical use. Int J Antimicrob Agents 2001;18:391–3. doi:10.1016/S0924-8579(01)00418-6.

[198] Kumarasinghe G, Chow C, Chiu C, Cheong YM. In vitro activity of cefoperazone–sulbactam: Singapore experience. Southeast Asian J Trop Med Public Health 1996;27:734–7.

[199] Balm MND, Ngan G, Jureen R, Lin RTP, Teo J. Molecular characterization of newly emerged bla_{KPC-2}-producing *Klebsiella pneumoniae* in Singapore. J Clin Microbiol 2012;50:475–6. doi:10.1128/JCM.05914-11.

[200] Koh T, Sng L, Babini G, Woodford N, Livermore D, Hall L. Carbapenem-resistant *Klebsiella pneumoniae* in Singapore producing IMP-1 β-lactamase and lacking an outer membrane protein. Antimicrob Agents Chemother 2001;45:1939–40. doi:10.1128/AAC.45.6.1939-1940.2001.

[201] Lee EK. Incidence of CAUTI in a new integrated ICU/HD in Singapore over 1 year. Crit Care Shock 2017;20:53–60.

[202] Koh TH, Cao D, Tee NWS, Teo JWP. *Escherichia coli* with bla_{IMP-8} in Singapore. Antimicrob Agents Chemother 2014;58:617. doi:10.1128/AAC.01754-13.

[203] Marimuthu K, Ng TM, Teng C, Lim TP, Koh TH, Yen Tan T, et al. Risk factors and treatment outcome of ertapenem non-susceptible Enterobacteriaceae bacteraemia. J Infect 2013;66:294–6. doi:10.1016/j.jinf.2012.11.010.

[204] Marimuthu K, Teo J, Gan V, Ng WK, Krishnan P, Lye D. Risk factors for locally acquired New Delhi metallo-β-lactamase-1 Enterobacteriaceae in Singapore. Clin Microbiol Infect 2012;18:286–7. doi:10.1111/j.1469-0691.2012.03802.x.

[205] Tay MKX, Lee JYC, Wee IYJ, Oh HML. Evaluation of intensive care unit-acquired urinary tract infections in Singapore. Ann Acad Med Singapore 2010;39:460–5.

[206] Koh TH, Wang G, Koh TY. High-level cefepime resistance in *Escherichia coli* from Singapore producing OXA-1 β-lactamase. Int J Antimicrob Agents 2008;31:382–3. doi:10.1016/J.IJANTIMICAG.2007.11.004.

[207] Balm MND, Ngan G, Jureen R, Lin RTP, Teo JWP. OXA-181-producing *Klebsiella pneumoniae* establishing in Singapore. BMC Infect Dis 2013;13:58. doi:10.1186/1471-2334-13-58.

[208] Lim C, Takahashi E, Hongsuwan M, Wuthiekanun V, Thamlikitkul V, Hinjoy S, et al. Epidemiology and burden of multidrug-resistant bacterial infection in a developing country. Elife 2016;5 pii: e18082. doi:10.7554/eLife.18082.

[209] Chaiwarith R, Nuntachit N, Chittawatanarat K, Bunchoo M, Supparatpinyo K, Oberdorfer P. Surveillance of antimicrobial resistance among bacterial pathogens isolated from hospitalized patients at Chiang Mai University Hospital, 2006–2009. J Infect Dis Antimicrob Agents 2011;28:35–44.

[210] Srifuengfung S, Chokephaibulkit K, Yungyuen T, Tribuddharat C. Bacteremia and antimicrobial susceptibilities in HIV-infected patients at Siriraj Hospital. Southeast Asian J Trop Med Public Health 2005;36:347–51.

[211] Stoesser N, Sheppard AE, Peirano G, Sebra RP, Lynch T, Anson LW, et al. First report of bla_{IMP-14} on a plasmid harboring multiple drug resistance genes in *Escherichia coli* sequence type 131. Antimicrob Agents Chemother 2016;60:5068–71. doi:10.1128/AAC.00840-16.

[212] Biedenbach DJ, Johnson DM, Jones RN. In vitro evaluation of cefepime and other broad-spectrum β-lactams in eight medical centers in Thailand. The Thailand Antimicrobial Resistance Study Group. Diagn Microbiol Infect Dis 1999;35:325–31.

[213] Phongpaichit S, Tunyapanit W, Pruekprasert P. Antimicrobial resistance, class 1 integrons and extended-spectrum β-lactamases in *Escherichia coli* clinical isolates from patients in South Thailand. J Health Sci 2011;57:281–8.

[214] Kiratisin P, Chattammanat S, Sa-Nguansai S, Dansubutra B, Nangpatharapornthawee P, Patthamalai P, et al. A 2-year trend of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in Thailand: an alert for infection control. Trans R Soc Trop Med Hyg 2008;102:460–4. doi:10.1016/j.trstmh.2008.02.005.

[215] Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Clinical and molecular epidemiology of community-onset, extended-spectrum β-lactamase-producing *Escherichia coli* infections in Thailand: a case–case–control study. Am J Infect Control 2007;35:606–12. doi:10.1016/j.ajic.2007.05.008.

[216] Runcharoen C, Raven KE, Reuter S, Kallonen T, Paksanont S, Thammachote J, et al. Whole genome sequencing of ESBL-producing *Escherichia coli* isolated from patients, farm waste and canals in Thailand. Genome Med 2017;9:81. doi:10.1186/s13073-017-0471-8.

[217] Leelasupasri S, Chantaratchada S. Antimicrobial resistance of Gram-negative bacilli in the intensive care units of Phramongkutklao Hospital. J Infect Dis Antimicrob Agents 1998;15:9–14.

[218] Reechaipichitkul W, Phondongnok S, Bourpoern J, Chaimanee P. Causative agents and resistance among hospital-acquired and ventilator-associated pneumonia patients at Srinagarind Hospital, northeastern Thailand. Southeast Asian J Trop Med Public Health 2013;44:490–502.

[219] Sirijatuphat R, Sripanidkulchai K, Boonyasiri A, Rattanaumpawan P, Supapueng O, Kiratisin P, et al. Implementation of Global Antimicrobial Resistance Surveillance System (GLASS) in patients with bacteremia. PLoS One 2018;13:e0190132. doi:10.1371/journal.pone.0190132.

[220] Vading M, Kabir MH, Kalin M, Iversen A, Wiklund S, Nauclér P, et al. Frequent acquisition of low-virulence strains of ESBL-producing *Escherichia coli* in travellers. J Antimicrob Chemother 2016;71:3548–55. doi:10.1093/jac/dkw335.

[221] Srijan A, Margulieux KR, Ruekit S, Snesrud E, Maybank R, Serichantalergs O, et al. Genomic characterization of nonclonal *mcr-1*-positive multidrug-resistant *Klebsiella pneumoniae* from clinical samples in Thailand. Microb Drug Resist 2018;24:403–10. doi:10.1089/mdr.2017.0400.

[222] Malaisri C, Phuphuakrat A, Wibulpolprasert A, Santanirand P, Kiertiburanakul S. A randomized controlled trial of sitafloxacin vs. ertapenem as a switch therapy after treatment for acute pyelonephritis caused by extended-spectrum β-lactamase-producing *Escherichia coli*: a pilot study. J Infect Chemother 2017;23:556–62. doi:10.1016/j.jiac.2017.05.005.

[223] Sukkua K, Manothong S, Sukhumungoon P. Seroprevalence and molecular epidemiology of *EAST1* gene-carrying *Escherichia coli* from diarrheal patients and raw meats. J Infect Dev Ctries 2017;11:220–7. doi:10.3855/jidc.6865.

[224] Paveenkittiporn W, Kerdsin A, Chokngam S, Bunthi C, Sangkitporn S, Gregory CJ. Emergence of plasmid-mediated colistin resistance and New Delhi metallo-β-lactamase genes in extensively drug-resistant *Escherichia coli* isolated from a patient in Thailand. Diagn Microbiol Infect Dis 2017;87:157–9. doi:10.1016/j.diagmicrobio.2016.11.005.

[225] Lunha K, Chanawong A, Lulitanond A, Wilailuckana C, Charoensri N, Wonglakorn L, et al. High-level carbapenem-resistant OXA-48-producing *Klebsiella pneumoniae* with a novel OmpK36 variant and low-level, carbapenem-resistant, non-porin-deficient, OXA-181-producing *Escherichia coli* from Thailand. Diagn Microbiol Infect Dis 2016;85:221–6. doi:10.1016/j.diagmicrobio.2016.03.009.

[226] Koomanachai P, Yungyuen T, Disthaporn P, Kiratisin P, Nicolau DP. Application of pharmacodynamic profiling for the selection of optimal β-lactam regimens in a large university hospital. Int J Infect Dis 2016;46:22–6. doi:10.1016/j.ijid.2016.03.020.

[227] Preechachuawong P, Santimaleeworagun W, Jitwasinkul T, Samret W. Detection of New Delhi metallo-β-lactamase-1-producing *Klebsiella pneumoniae* at a general hospital in Thailand. Southeast Asian J Trop Med Public Health 2015;46:1031–6.

[228] Themphachana M, Kongpheng S, Rattanachuay P, Khianngam S, Singkhamanan K, Sukhumungoon P. Molecular characterization of virulence and antimicrobial susceptibility profiles of uropathogenic *Escherichia*

coli from patients in a tertiary hospital, southern Thailand. Southeast Asian J Trop Med Public Health 2015;46:1021–30.
[229] Pornsinchai P, Chongtrakool P, Diraphat P, Siripanichgon K, Malathum K. Emergency room: an unrecognized source of extended-spectrum β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*. Southeast Asian J Trop Med Public Health 2015;46:51–62.
[230] Sethaphanich N, Santanirand P, Rattanasiri S, Techasaensiri C, Chaisavaneeyakorn S, Apiwattanakul N. Pediatric extended spectrum β-lactamase infection: community-acquired infection and treatment options. Pediatr Int 2016;58:338–46. doi:10.1111/ped.12845.
[231] Themphachana M, Kanobthammakul S, Nakaguchi Y, Singkhamanans K, Yadrak P, Sukhumungoon P. Virulence characteristics and antimicrobial susceptibility of uropathogens from patients on Phuket Island, Thailand. Southeast Asian J Trop Med Public Health 2014;45:1090–8.
[232] Boonyasiri A, Tangkoskul T, Seenama C, Saiyarin J, Tiengrim S, Thamlikitkul V. Prevalence of antibiotic resistant bacteria in healthy adults, foods, food animals, and the environment in selected areas in Thailand. Pathog Glob Health 2014;108:235–45. doi:10.1179/2047773214Y.0000000148.
[233] Netikul T, Sidjabat HE, Paterson DL, Kamolvit W, Tantisiriwat W, Steen JA, et al. Characterization of an IncN2-type bla_{NDM-1}-carrying plasmid in *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST11 and ST15 isolates in Thailand. J Antimicrob Chemother 2014;69:3161–3. doi:10.1093/jac/dku275.
[234] Pasom W, Chanawong A, Lulitanond A, Wilailuckana C, Kenprom S, Puang-Ngern P. Plasmid-mediated quinolone resistance genes, *aac(6′)-Ib*-cr, *qnrS*, *qnrB*, and *qnrA*, in urinary isolates of *Escherichia coli* and *Klebsiella pneumoniae* at a teaching hospital, Thailand. Jpn J Infect Dis 2013;66:428–32. doi:10.7883/yoken.66.428.
[235] Jaruratanasirikul S, Wongpoowarak W, Kositpantawong N, Aeinlang N, Jullangkoon M. Pharmacodynamics of doripenem in critically ill patients with ventilator-associated Gram-negative bacilli pneumonia. Int J Antimicrob Agents 2012;40:434–9. doi:10.1016/j.ijantimicag.2012.07.014.
[236] Rimrang B, Chanawong A, Lulitanond A, Wilailuckana C, Charoensri N, Sribenjalux P, et al. Emergence of NDM-1- and IMP-14a-producing Enterobacteriaceae in Thailand. J Antimicrob Chemother 2012;67:2626–30. doi:10.1093/jac/dks267.
[237] Singtohin S, Chanawong A, Lulitanond A, Sribenjalux P, Auncharoen A, Kaewkes W, et al. CMY-2, CMY-8b, and DHA-1 plasmid-mediated AmpC β-lactamases among clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* from a university hospital, Thailand. Diagn Microbiol Infect Dis 2010;68:271–7. doi:10.1016/j.diagmicrobio.2010.06.014.
[238] Polwichai P, Dejsirilert S, Panpetch S, Sawanpanyalert P, Aswapokee N, Mootsikapun P. Antimicrobial resistance of *Escherichia coli* isolated from urine in Thailand from 2000 to 2005. J Med Assoc Thai 2009;92(Suppl 4):S59–67.
[239] Punpanich W, Tantichattanon W, Wongwatcharapaiboon S, Treeratweeraphong V. In vitro susceptibility pattern of cephalosporin-resistant Gram-negative bacteria. J Med Assoc Thai 2008;91(Suppl 3):S21–7.
[240] Niumsup PR, Tansawai U, Boonkerd N, Polwichai P, Dejsirilert S. Dissemination of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli* in Thai hospitals. J Infect Chemother 2008;14:404–8. doi:10.1007/s10156-008-0642-z.
[241] Suankratay C, Jutivorakool K, Jirajariyavej S. A prospective study of ceftriaxone treatment in acute pyelonephritis caused by extended-spectrum β-lactamase-producing bacteria. J Med Assoc Thai 2008;91:1172–81.
[242] Pongpech P, Naenna P, Taipobsakul Y, Tribuddharat C, Srifuengfung S. Prevalence of extended-spectrum β-lactamase and class 1 integron integrase gene *intI1* in *Escherichia coli* from Thai patients and healthy adults. Southeast Asian J Trop Med Public Health 2008;39:425–33.
[243] Kiratisin P, Apisarnthanarak A, Laesripa C, Saifon P. Molecular characterization and epidemiology of extended-spectrum-β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates causing health care-associated infection in Thailand, where the CTX-M family is endemic. Antimicrob Agents Chemother 2008;52:2818–24. doi:10.1128/AAC.00171-08.
[244] Kiratisin P, Apisarnthanarak A, Saifon P, Laesripa C, Kitphati R, Mundy LM. The emergence of a novel ceftazidime-resistant CTX-M extended-spectrum β-lactamase, CTX-M-55, in both community-onset and hospital-acquired infections in Thailand. Diagn Microbiol Infect Dis 2007;58:349–55. doi:10.1016/j.diagmicrobio.2007.02.005.
[245] Tantracheewathorn T, Vititpatarapak N, Phumisantiphong U. Epidemiologic study of nosocomial bacterial infection of pediatric patients at BMA Medical College and Vajira Hospital. J Med Assoc Thai 2007;90:258–65.
[246] Danchaivijitr S, Dhiraputra C, Rongrungruang Y, Worajitr M, Jintanothaitavorn D. Antimicrobial susceptibility of community and hospital acquired bacteria. J Med Assoc Thai 2005;88(Suppl 10):S14–25.
[247] Srifuengfung S, Yungyuen T, Komolpis P. Bacterial isolation and antimicrobial susceptibilities in patients with infective endocarditis. Southeast Asian J Trop Med Public Health 2004;35:897–901.
[248] Srifuengfung S, Sangsawang M, Komolpis P, Dhiraputra C, Chompanee B. Bacterial pathogens (non-*Mycobacterium*) from sputum culture and antimicrobial susceptibility. Southeast Asian J Trop Med Public Health 1998;29:96–9.
[249] Laolerd W, Akeda Y, Preeyanon L, Ratthawongjirakul P, Santanirand P. Carbapenemase-producing carbapenem-resistant Enterobacteriaceae from Bangkok, Thailand, and their detection by the Carba NP and modified carbapenem inactivation method tests. Microb Drug Resist 2018;24:1006–11. doi:10.1089/mdr.2018.0080.
[250] Pootong A, Mungkornkaew N, Norrapong B, Cowawintaweewat S. Phylogenetic background, drug susceptibility and virulence factors of uropathogenic *E. coli* isolate in a tertiary university hospital in central Thailand. Trop Biomed 2018;35:195–204.
[251] Kiratisin P. Effect of MIC interpretative breakpoint revision on cephalosporin and carbapenem susceptibility among ESBL-producing Enterobacteriaceae. Asian Biomed 2012;6:713–21. doi:10.5372/1905-7415.0605.112.
[252] Tantisiriwat W, Linasmita P. In vitro activity of sitafloxacin and other antibiotics against bacterial isolates from HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University and Samitivej Sukhumvit Hospital. J Med Assoc Thai 2017;100:469–78.
[253] Tiengrim S, Phiboonbanakit D, Thunyaharn S, Tantisiriwat W, Santiwatanakul S, Susaengrat W, et al. Comparative in vitro activity of sitafloxacin against bacteria isolated from Thai patients with urinary tract infections and lower respiratory tract infections. J Med Assoc Thai 2017;100:1061–72.
[254] Winissorn W, Tribuddharat C, Naenna P, Leelarasamee A, Pongpech P. Fluoroquinolone resistance and effect of *qnrA* integron cassettes in *Escherichia coli* clinical isolates in a university hospital. J Infect Dis Antimicrob Agents 2013;30:15–25.
[255] Netikul T, Leelaporn A, Leelarasmee A, Kiratisin P. In vitro activities of fosfomycin and carbapenem combinations against carbapenem non-susceptible *Escherichia coli* and *Klebsiella pneumoniae*. Int J Antimicrob Agents 2010;35:609–10. doi:10.1016/j.ijantimicag.2010.01.021.
[256] Chaikittisuk N, Munsrichoom A. Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children at Queen Sirikit National Institute of Child Health. J Infect Dis Antimicrob Agents 2007;24:107–15.
[257] Apisarnthanarak A, Kiratisin P, Mundy LM. Clinical and molecular epidemiology of healthcare-associated infections due to extended-spectrum β-lactamase (ESBL)-producing strains of *Escherichia coli* and *Klebsiella pneumoniae* that harbor multiple ESBL genes. Infect Control Hosp Epidemiol 2008;29:1026–34. doi:10.1086/591864.
[258] Kiratisin P, Tiengrim S, Yungyuen T, Thamlikitkul V. In vitro activity of colistin and tigecycline against extended-spectrum-β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from patients in Siriraj Hospital. J Infect Dis Antimicrob Agents 2006;23:21–4.
[259] Waiwarawooth J, Jutiworakul K, Joraka W. The prevalence and susceptibility patterns of ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli* in Chonburi Hospital. J Infect Dis Antimicrob Agents 2006;23:57–65.
[260] Netikul T, Sidjabat H, Paterson D, Kiratisin P. Emergence of novel bla_{KPC-13} among carbapenem-resistant Enterobacteriaceae in Thailand. Int J Antimicrob Agents 2014;44:568–9. doi:10.1016/j.ijantimicag.2014.08.005.
[261] Nuramrum S, Chanawong A, Lunha K, Lulitanond A, Sangka A, Wilailuckana C, et al. Molecular characterization of carbapenemase-nonproducing clinical isolates of *Escherichia coli* (from a Thai university hospital) with reduced carbapenem susceptibility. Jpn J Infect Dis 2017;70:628–34. doi:10.7883/yoken.JJID.2017.156.
[262] Chalmers L, Cross J, Chu CS, Phyo AP, Trip M, Ling C, et al. The role of point-of-care tests in antibiotic stewardship for urinary tract infections in a resource-limited setting on the Thailand–Myanmar border. Trop Med Int Health 2015;20:1281–9. doi:10.1111/tmi.12541.
[263] Mongkolrattanothai K, Chokephaibulkit K, Kolatat T, Vanprapar N, Chearskul S, Srihapol N, et al. Nosocomial bloodstream infection in pediatric patients: Siriraj Hospital, Bangkok; 1996–1999. J Med Assoc Thai 2001;84:160–5.
[264] Angkasekwinai N, Werarak P, Chaiyasoot K, Thamlikitkul V. Monitoring of effectiveness and safety of generic formulation of meropenem for treatment of infections at Siriraj Hospital. J Med Assoc Thai 2011;94(Suppl 1):S217–24.
[265] Kusum M, Wongwanich S, Dhiraputra C, Pongpech P, Naenna P. Occurrence of extended-spectrum β-lactamase in clinical isolates of *Klebsiella pneumoniae* in a university hospital, Thailand. J Med Assoc Thai 2004;87:1029–33.
[266] Udomwiboonchai P, Leemingsawat C, Visuthisakchai S, Thamlikitkul V. Prevalence of antibiotic-resistant bacteria colonized in neutropenic patients at Siriraj Hospital. Siriraj Med J 2007;59:344–7.
[267] Tharavichitkul P, Khantawa B, Bousoung V, Boonchoo M. Activity of fosfomycin against extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli* in Maharaj Nakorn Chiang Mai Hospital. J Infect Dis Antimicrob Agents 2005;22:121–6.
[268] Ingviya N, Hortiwakul R, Chayakul P, Thamjarungwong B. Prevalence and susceptibility patterns of *Klebsiella pneumoniae* and *Escherichia coli* producing extended-spectrum β-lactamases in Songklanagarind Hospital, Thailand. J Infect Dis Antimicrob Agents 2003;20:127–34.
[269] Hortiwakul R, Chayakul P, Ingviya N. In vitro activity of cefminox and other β-lactam antibiotics against clinical isolates of extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. J Infect Dis Antimicrob Agents 2006;23:9–14.
[270] Chunhamaneewat S, Punyagupta S. Biliary tract infection: a study of 345 cholecystectomy cases. J Infect Antimicrob Agents 1998;15:123–8.
[271] Marr I, Sarmento N, O'Brien M, Lee K, Gusmao C, de Castro G, et al. Antimicrobial resistance in urine and skin isolates in Timor-Leste. J Glob Antimicrob Resist 2018;13:135–8. doi:10.1016/j.jgar.2017.12.010.
[272] Johansson M, Phuong DM, Walther SM, Hanberger H. Need for improved antimicrobial and infection control stewardship in Vietnamese intensive care units. Trop Med Int Health 2011;16:737–43. doi:10.1111/j.1365-3156.2011.02753.x.
[273] Biedenbach DJ, Bouchillon SK, Hoban DJ, Hackel M, Phuong DM, Nga TTT, et al. Antimicrobial susceptibility and extended-spectrum β-lactamase rates in aerobic Gram-negative bacteria causing intra-abdominal infections in Vietnam: report from the Study for Monitoring Antimicrobial Resistance Trends

(SMART 2009–2011). Diagn Microbiol Infect Dis 2014;79:463–7. doi:10.1016/j.diagmicrobio.2014.05.009.
[274] Hoang PH, Awasthi SP, Do Nguyen P, Nguyen NLH, Nguyen DTA, Le NH, et al. Antimicrobial resistance profiles and molecular characterization of *Escherichia coli* strains isolated from healthy adults in Ho Chi Minh City, Vietnam. J Vet Med Sci 2017;79:479–85. doi:10.1292/jvms.16-0639.
[275] Tran GM, Ho-Le TP, Ha DT, Tran-Nguyen CH, Nguyen TSM, Pham TTN, et al. Patterns of antimicrobial resistance in intensive care unit patients: a study in Vietnam. BMC Infect Dis 2017;17:429. doi:10.1186/s12879-017-2529-z.
[276] Breurec S, Guessennd N, Timinouni M, Le TAH, Cao V, Ngandjio A, et al. *Klebsiella pneumoniae* resistant to third-generation cephalosporins in five African and two Vietnamese major towns: multiclonal population structure with two major international clonal groups, CG15 and CG258. Clin Microbiol Infect 2013;19:349–55. doi:10.1111/j.1469-0691.2012.03805.x.
[277] Nguyen TV, Le PV, Le CH, Weintraub A. Antibiotic resistance in diarrheagenic *Escherichia coli* and *Shigella* strains isolated from children in Hanoi, Vietnam. Antimicrob Agents Chemother 2005;49:816–19. doi:10.1128/AAC.49.2.816-819-2005.
[278] Trang NHT, Nga TVT, Campbell JI, Hiep NT, Farrar J, Baker S, et al. The characterization of ESBL genes in *Escherichia coli* and *Klebsiella pneumoniae* causing nosocomial infections in Vietnam. J Infect Dev Ctries 2013;7:922–8. doi:10.3855/jidc.2938.
[279] Tada T, Tsuchiya M, Shimada K, Nga TTT, Thu LTA, Phu TT, et al. Dissemination of carbapenem-resistant *Klebsiella pneumoniae* clinical isolates with various combinations of carbapenemases (KPC-2, NDM-1, NDM-4, and OXA-48) and 16S rRNA methylases (RmtB and RmtC) in Vietnam. BMC Infect Dis 2017;17:467. doi:10.1186/s12879-017-2570-y.
[280] Tada T, Uechi K, Nakasone I, Shimada K, Nakamatsu M. Emergence of a colistin-resistant *Escherichia coli* clinical isolate harboring *mcr-1* in Japan. Int J Infect Dis 2017;63:21–2. doi:10.1016/j.ijid.2017.07.023.
[281] Thuy DB, Campbell J, Hoang NVM, Trinh TTT, Duong HTH, Hieu NC, et al. A one-year prospective study of colonization with antimicrobial-resistant organisms on admission to a Vietnamese intensive care unit. PLoS One 2017;12:e0184847. doi:10.1371/journal.pone.0184847.
[282] Lan NPH, Hien NH, Le Thi Phuong T, Thanh DP, Thieu NTV, Ngoc DTT, et al. Phenotypic and genotypic characteristics of ESBL and AmpC producing organisms associated with bacteraemia in Ho Chi Minh City, Vietnam. Antimicrob Resist Infect Control 2017;6:105. doi:10.1186/s13756-017-0265-1.
[283] Nakayama T, Kumeda Y, Kawahara R, Yamaguchi T, Yamamoto Y. Carriage of colistin-resistant, extended-spectrum β-lactamase-producing *Escherichia coli* harboring the *mcr-1* resistance gene after short-term international travel to Vietnam. Infect Drug Resist 2018;11:391–5. doi:10.2147/IDR.S153178.
[284] Dat VQ, Vu HN, Nguyen The H, Nguyen HT, Hoang LB, Vu Tien Viet D, et al. Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: aetiology, drug resistance, and treatment outcome. BMC Infect Dis 2017;17:493. doi:10.1186/s12879-017-2582-7.
[285] Phu VD, Nadjm B, Duy NHA, Co DX, Mai NTH, Trinh DT, et al. Ventilator-associated respiratory infection in a resource-restricted setting: impact and etiology. J Intensive Care 2017;5:69. doi:10.1186/s40560-017-0266-4.
[286] Trung NV, Nhung HN, Carrique-Mas JJ, Mai HH, Tuyen HT, Campbell J, et al. Colonization of enteroaggregative *Escherichia coli* and Shiga toxin-producing *Escherichia coli* in chickens and humans in southern Vietnam. BMC Microbiol 2016;16:208. doi:10.1186/s12866-016-0827-z.
[287] Tran HT, Doyle LW, Lee KJ, Dang NM, Graham SM. A high burden of late-onset sepsis among newborns admitted to the largest neonatal unit in central Vietnam. J Perinatol 2015;35:846–51. doi:10.1038/jp.2015.78.
[288] Duong HP, Mong Hiep TT, Hoang DT, Janssen F, Lepage P, De Mol P, et al. Practical problems related to the management of febrile urinary tract infection in Vietnamese children [in French]. Arch Pediatr 2015;22:848–52. doi:10.1016/j.arcped.2015.05.010.
[289] Tran HH, Ehsani S, Shibayama K, Matsui M, Suzuki S, Nguyen MB, et al. Common isolation of New Delhi metallo-β-lactamase 1-producing Enterobacteriaceae in a large surgical hospital in Vietnam. Eur J Clin Microbiol Infect Dis 2015;34:1247–54. doi:10.1007/s10096-015-2345-6.
[290] Kruse AY, Thieu Chuong DH, Phuong CN, Duc T, Graff Stensballe L, Prag J, et al. Neonatal bloodstream infections in a pediatric hospital in Vietnam: a cohort study. J Trop Pediatr 2013;59:483–8. doi:10.1093/tropej/fmt056.
[291] Hoang TH, Wertheim H, Minh NB, Duong TN, Anh DD, Phuong TTL, et al. Carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* strains containing New Delhi metallo-β-lactamase isolated from two patients in Vietnam. J Clin Microbiol 2013;51:373–4. doi:10.1128/JCM.02322-12.
[292] Le TA, Sohn AH, Nguyen PT, Vo TC, Vo VN, Tran Nguyen TH, et al. Microbiology of surgical site infections and associated antimicrobial use among Vietnamese orthopedic and neurosurgical patients. Infect Control Hosp Epidemiol 2006;27:855–62. doi:10.1086/506400.
[293] Berglund B, Hoang NTB, Tärnberg M, Le NK, Svartström O, Khu DTK, et al. Insertion sequence transpositions and point mutations in *mgrB* causing colistin resistance in a clinical strain of carbapenem-resistant *Klebsiella pneumoniae* from Vietnam. Int J Antimicrob Agents 2018;51:789–93. doi:10.1016/j.ijantimicag.2017.11.012.
[294] Berglund B, Hoang NTB, Tärnberg M, Le NK, Welander J, Nilsson M, et al. Colistin- and carbapenem-resistant *Klebsiella pneumoniae* carrying *mcr-1* and bla_{OXA-48} isolated at a paediatric hospital in Vietnam. J Antimicrob Chemother 2018;73:1100–2. doi:10.1093/jac/dkx491.
[295] Hoang TAV, Nguyen TNH, Ueda S, Le QP, Tran TTN, Nguyen TND, et al. Common findings of $bla_{CTX-M-55}$-encoding 104–139 kbp plasmids harbored by extended-spectrum β-lactamase-producing *Escherichia coli* in pork meat, wholesale market workers, and patients with urinary tract infection in Vietnam. Curr Microbiol 2017;74:203–11. doi:10.1007/s00284-016-1174-x.
[296] Cao V, Lambert T, Nhu DQ, Loan HK, Hoang NK, Arlet G, et al. Distribution of extended-spectrum β-lactamases in clinical isolates of Enterobacteriaceae in Vietnam. Antimicrob Agents Chemother 2002;46:3739–43. doi:10.1128/AAC.46.12.3739-3743.2002.
[297] Van P.H., Binh P.T., Ngan L.L.B., Huong P.T.*The resistance of the Gram-negative rods isolated from clinical cases in Vietnam to doripenem*. 2017. http://pctu.edu.vn/vn/the-resistance-of-the-gram-negative-rods-isolated-from-clinical-cases-in-vietnam-to-doripenem-1517623286.html [accessed 23 August 2018].
[298] Viet Hung N, Anh Thu T, Rosenthal VD, Tat Thanh D, Quoc Anh N, Le Bao Tien N, et al. Surgical site infection rates in seven cities in Vietnam: findings of the International Nosocomial Infection Control Consortium. Surg Infect (Larchmt) 2016;17:243–9. doi:10.1089/sur.2015.073.
[299] Ueda S, Ngan BTK, Huong BTM, Hirai I, Tuyen LD, Yamamoto Y. Limited transmission of $bla_{CTX-M-9-type}$-positive *Escherichia coli* between humans and poultry in Vietnam. Antimicrob Agents Chemother 2015;59:3574–7. doi:10.1128/AAC.00517-15.
[300] Nga TTT, Phuong TTL, Phuong TM, Phuong DM, Biedenbach DJ, Narang P, et al. In vitro susceptibility of Gram-negative isolates from patients with urinary tract infections in Vietnam: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). J Glob Antimicrob Resist 2014;2:338–9. doi:10.1016/J.JGAR.2014.04.003.
[301] Trung NT, Hien TTT, Huyen TTT, Quyen DT, Binh MT, Hoan PQ, et al. Simple multiplex PCR assays to detect common pathogens and associated genes encoding for acquired extended spectrum β-lactamases (ESBL) or carbapenemases from surgical site specimens in Vietnam. Ann Clin Microbiol Antimicrob 2015;14:23. doi:10.1186/s12941-015-0079-z.
[302] Le NK, Wertheim H, Vu PD, Khu DTK, Le HT, Hoang BTN, et al. High prevalence of hospital-acquired infections caused by Gram-negative carbapenem resistant strains in Vietnamese pediatric ICUs: a multi-centre point prevalence survey. Medicine (Baltimore) 2016;95:e4099. doi:10.1097/MD.0000000000004099.