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Short Communication

Escherichia coli ST410 among humans and the environment in Southeast Asia

Maya L. Nadimpalli[a], Agathe de Lauzanne[b], Thong Phe[c], Laurence Borand[b], Jan Jacobs[d,e], Laetitia Fabre[f], Thierry Naas[g], Simon Le Hello[f,h], Marc Stegger[i,*]

[a] *Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases Unit (B2PHI), Inserm, Université de Versailles Saint-Quentin-en-Yvelines, Institut Pasteur, Université Paris-Saclay, Paris, France*
[b] *Epidemiology and Public Health Unit, Institut Pasteur in Cambodia, Phnom Penh, Cambodia*
[c] *Sihanouk Hospital Center of HOPE, Phnom Penh, Cambodia*
[d] *Institute of Tropical Medicine, Antwerp, Belgium*
[e] *Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium*
[f] *Enteric Bacterial Pathogens Unit, Institut Pasteur, Paris, France*
[g] *Bacteriology-Hygiene Unit, Assistance Publique/Hôpitaux de Paris, Bicêtre Hospital, Université Paris-Sud, Le Kremlin-Bicêtre, France*
[h] *EA 2656, Groupe de Recherche sur l'Adaptation Microbienne (GRAM 2.0), Université de Caen Normandie, Caen, France*
[i] *Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Copenhagen, Denmark*

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ABSTRACT

Escherichia coli ST410 (*Ec*-ST410) is an emerging, multidrug-resistant clone. Recent investigations of its global epidemiology and evolution have been based almost exclusively on isolates from Europe and North America. It is unclear whether Southeast Asian-origin *Ec*-ST410 (SEA-*Ec*-ST410) belong to these same clones or represent regionally disseminated variants. Antimicrobial resistance mechanisms among SEA-*Ec*-ST410 were characterised, and whether they belonged to regional variants was investigated by contextualising them within a global collection. Seven *Ec*-ST410 were identified among a recent collection of expanded-spectrum cephalosporin-resistant *E. coli* recovered from 91 healthy women (stool) and 26 infected patients (blood and urine) living in Phnom Penh, Cambodia. Nine additional *Ec*-ST410 genomes were identified from Thailand ($n=7$) and Vietnam ($n=2$) through EnteroBase and PubMed searches. The assembled genomes were characterised and a SNP-based phylogenetic tree was created comparing these 16 SEA-*Ec*-ST410 with a previously published *Ec*-ST410 collection, primarily sourced from Europe (97/128) and North America (24/128). SEA-*Ec*-ST410 belonged to several distinct branches within previously described clonal clades. SEA-*Ec*-ST410 within the B3/*H*24Rx sublineage encoded $bla_{CTX\text{-}M\text{-}55}$ (8/12) and F18:A-:B1 plasmid replicons (6/12), neither of which were detected among other *Ec*-ST410 belonging to this clade. Three of four SEA-*Ec*-ST410 within the B4/*H*24RxC sublineage lacked both $bla_{OXA\text{-}181}$ and an IncX3 plasmid replicon that were harboured by 97% and 100% of all other *Ec*-ST410 in this sublineage ($n=64$), respectively. In conclusion, *Ec*-ST410 are present in Southeast Asia following multiple introductions. The unique pattern of antimicrobial resistance elements harboured by SEA-*Ec*-ST410 suggests independent circulation in the region.

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1. Introduction

Escherichia coli sequence type 410 (*Ec*-ST410) is an emerging multidrug-resistant pathogen. Two major sublineages are currently circulating in Europe and North America, including a fluoroquinolone- and extended-spectrum cephalosporin (ESC)-resistant clade (i.e. B3/*H*24Rx) that emerged in the 1980s, and a carbapenem-resistant clone that emerged from that around 2003 (i.e. B4/*H*24RxC) [1,2]. Given its high transmissibility, its ability to persist in the gut and its capacity to cause recurrent infections, *Ec*-ST410 may be a 'high-risk' clone, similar to *Ec*-ST131 [1].

Whether *Ec*-ST410 circulating in Southeast Asia are repeat introductions of these same sublineages or represent regionally disseminated variants remains unclear. Prior clonal expansions of *Ec*-ST410 were preceded by widespread antibiotic selection pressure [1], which is exceptionally high in Southeast Asia owing to antibiotic misuse and extensive environmental pollution [3]. The prevalence and diversity of extended-spectrum β-lactamase (ESBL)- and

* Corresponding author.
E-mail address: mtg@ssi.dk (M. Stegger).

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carbapenemase-encoding genes circulating among healthy persons in Southeast Asia also differs from Europe and North America [4–6]. Importantly, regional *Ec*-ST410 variants could disseminate globally. Already, travel to Southeast Asia has been linked to imported *Ec*-ST410 infections [7].

The primary aim of this study was to characterise the diversity of antimicrobial resistance mechanisms among Southeast Asian-origin *Ec*-ST410 (SEA-*Ec*-ST410). The second aim was to investigate whether SEA-*Ec*-ST410 belonged to unique, regionally disseminated variants by contextualising them within a global collection.

2. Materials and methods

2.1. Bacterial isolates

Ec-ST410 were identified from recently described collections of ESC-resistant *E. coli* from healthy women and infected patients living in Phnom Penh, Cambodia [8]. Healthy women were screened for ESC-resistant *E. coli* faecal carriage between April 2015 and December 2016 as part of a community-based cohort study of bacterial infections among young children in low-income countries [9]. *Escherichia coli* infection isolates were available from patients admitted to the Sihanouk Hospital Center of HOPE (Phnom Penh, Cambodia) between November 2015 and December 2016. *Escherichia coli* from all infection types were stored in 2015; primarily *E. coli* from bloodstream infections were stored in 2016.

2.2. Antimicrobial susceptibility testing

The susceptibility of Cambodian-origin *Ec*-ST410 to 21 antibiotics was determined by the Kirby–Bauer disk diffusion assay (see Supplementary Table S1 for a list of the antibiotics used). Inhibition zone diameter interpretations were based on 2016 European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards (v 6.0) [10].

2.3. Whole-genome sequencing analyses

All ESC-resistant *E. coli* from both collections were previously sequenced by the Mutualized Microbiology Platform (P2M) of the Pasteur International Bioresources network (PIBnet) [8]. One strain was re-sequenced at Statens Serum Institut (Copenhagen, Denmark) using previously described methods to achieve sufficient genome quality for phylogenetic analysis [1]. Genome characterisation, including multilocus sequence typing (MLST) assignment, are described in the Supplementary methods. Individual accession numbers are available in Supplementary Table S2.

Additional, publicly available *Ec*-ST410 genomes from mainland Southeast Asia (i.e. Burma, Cambodia, Laos, Malaysia, Thailand and Vietnam) were identified by searching EnteroBase (http://enterobase.warwick.ac.uk; accessed 15 October 2018). PubMed (accessed 15 October 2018) was also searched using the search terms '*Escherichia coli*', 'whole genome' and ['Burma' or 'Myanmar' or 'Cambodia' or 'Laos' or 'Malaysia' or 'Thailand' or 'Vietnam'] to identify genomes for which country metadata may not be listed on EnteroBase. Only genomes for which raw reads were available were included.

Single nucleotide polymorphisms (SNPs) identified by the Northern Arizona SNP Pipeline (NASP) v.1.0.0 were used to build a phylogenetic tree comparing SEA-*Ec*-ST410 with a previously published *Ec*-ST410 collection primarily sourced from Europe (97/128) and North America (24/128) but also including isolates from South America ($n=2$), Africa ($n=1$), the Middle East ($n=1$) and Asia ($n=3$; 1 each from Japan, Singapore and Nepal) [1,11]. Briefly, duplicate regions of the reference chromosome of *Ec*-ST410 isolate AMA1167 (GenBank accession no. **CP024801**) were identified with NUCmer v.3.1. Duplicate regions were then masked from downstream analysis. Raw read files of all 144 genomes were aligned using the Burrows–Wheeler Aligner (BWA), and SNPs were identified using GATK UnifiedGenotyper [11,12]. Gubbins v.2.3.4 was used to remove recombination signals in the resulting SNP alignment file [13]. The final phylogenetic tree was generated using PHyML with smart-model selection and annotated using iTOL (http://itol.embl.de) [14].

3. Results

3.1. Escherichia coli ST410 isolates

Seven *Ec*-ST410 were identified among recent collections of ESC-resistant *E. coli* from healthy women ($n=4$) and infected patients ($n=3$) in Phnom Penh, described in detail elsewhere [8]. Among 130 healthy women screened between April 2015 and December 2016, 91 (70.0%) were colonised with ESC-resistant *E. coli*. *Ec*-ST410 was the fourth most common ST (4/91). Among Phnom Penh-based patients admitted to Sihanouk Hospital Center of HOPE between November 2015 and December 2016, three were treated for *E. coli* infections between November–December 2015. Two (67%) of these three *E. coli* infections were ESC-resistant; both were *Ec*-ST410 cultured from urine. Moreover, 23 Phnom Penh-based patients were treated for bloodstream *E. coli* infection in 2016; 15 (65%) of these bloodstream *E. coli* infections were ESC-resistant, and *Ec*-ST410 was detected once. The characteristics of colonised and infected persons are listed in Supplementary Tables S3 and S4, respectively. Antimicrobial susceptibility profiles for the seven Cambodian-origin *Ec*-ST410 are given in Supplementary Table S5.

Nine additional *Ec*-ST410 genomes were identified from Thailand ($n=7$) and Vietnam ($n=2$) through the literature search. *Ec*-ST410 from Thailand were cultured from human infections (6/7) and canal water <20 km from a major hospital (1/7) [15]. Both *Ec*-ST410 from Vietnam were cultured from human faecal swabs.

Overall, 16 SEA-*Ec*-ST410 from Cambodia ($n=7$), Thailand ($n=7$) and Vietnam ($n=2$) were included in this study.

3.2. Antimicrobial resistance genes

All 16 SEA-*Ec*-ST410 encoded ESBL genes, plasmid-encoded AmpC cephalosporinase genes, or a combination of both (Supplementary Table S5). The ESBL-encoding genes $bla_{\text{CTX-M-55}}$ (8/16) and $bla_{\text{CTX-M-15}}$ (7/16) predominated and occurred among isolates both from colonised individuals and infected patients. The carbapenemase-encoding genes $bla_{\text{NDM-5}}$ ($n=2$) and $bla_{\text{OXA-181}}$ ($n=1$) were primarily detected among infection isolates and were never present concurrently.

In addition to β-lactamases, all 16 isolates harboured chromosomal mutations conferring fluoroquinolone resistance (amino acid substitutions in *gyrA, parC* and *parE*) as well as tetracycline resistance genes [*tet*(A) or *tet*(B)]. Most strains harboured genes conferring resistance to trimethoprim/sulfamethoxazole (*sul* and *dfrA* variants) and azithromycin [*mph*(A)]. Acquired resistance genes encoding colistin or fosfomycin resistance were not detected in any SEA-*Ec*-ST410 isolates. Among the seven Cambodian-origin *Ec*-ST410 (for which antimicrobial susceptibility testing was performed), complete concordance was observed between genotypic and phenotypic resistance (Supplementary Table S5).

3.3. Plasmid replicons

Most SEA-*Ec*-ST410 isolates harboured IncF-type plasmid replicons (combination of IncFII, IncFIA and IncFIB) as well as up to three additional plasmid replicon types (Supplementary Table S5).

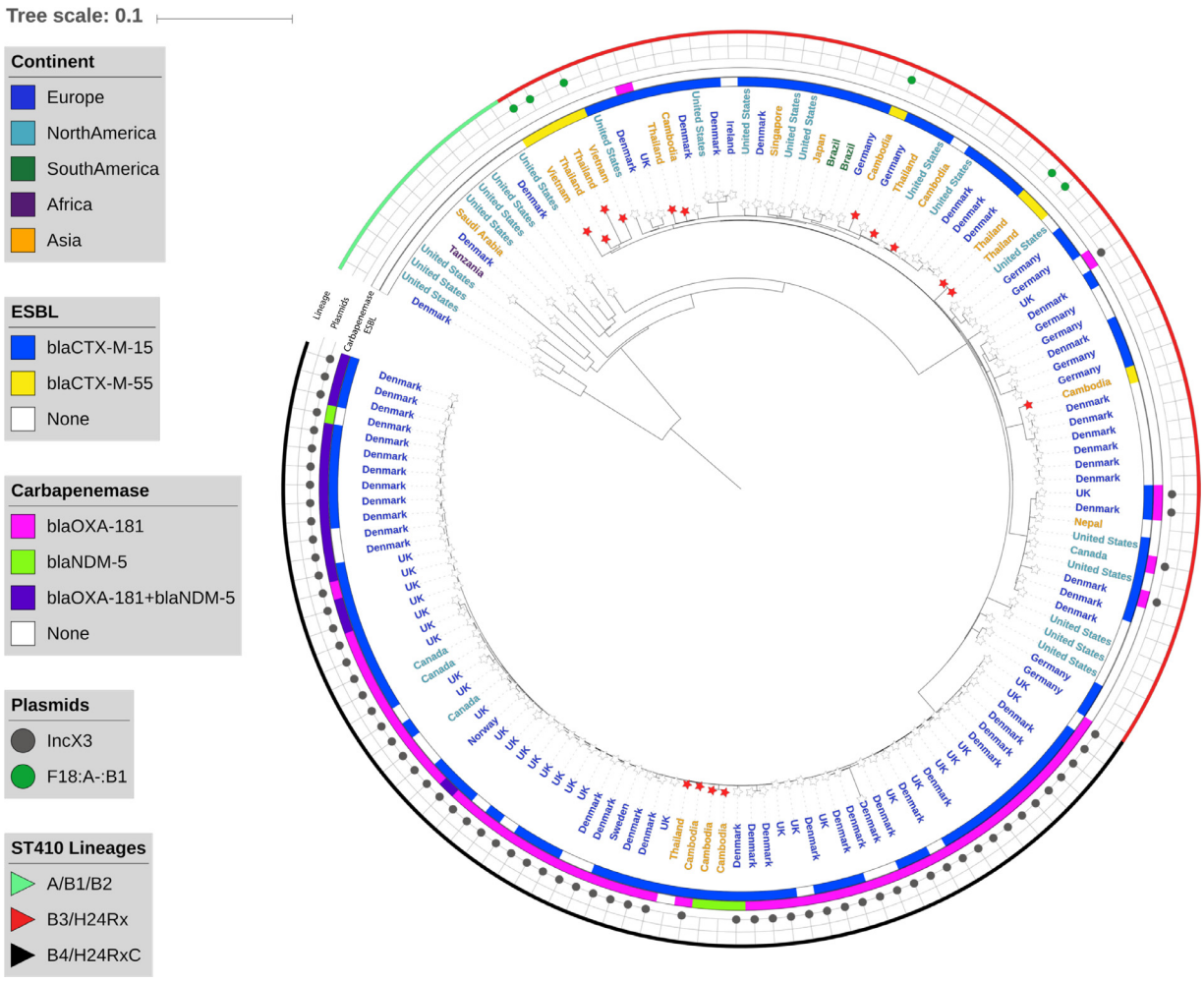

Fig. 1. Rooted maximum-likelihood phylogenetic tree of 144 *Escherichia coli* sequence type 410 (*Ec*-ST410) genomes. The phylogeny is based on 4318 variable sites identified in the *Ec*-ST410 isolates after filtering for recombination. Red stars indicate isolates from mainland Southeast Asia (i.e. Cambodia, Thailand and Vietnam).

Most $bla_{\text{CTX-M-15}}$-encoding isolates harboured IncF replicons with pMLST F1:A1:B49 (4/7). In contrast, most $bla_{\text{CTX-M-55}}$-encoding isolates harboured IncF replicons with pMLST F18:A-:B1 (6/8). One of eight $bla_{\text{CTX-M-55}}$-encoding isolates did not harbour any IncF-type plasmid replicon; only IncX1 and IncR replicons were detected.

Among the three carbapenemase-encoding isolates, both $bla_{\text{NDM-5}}$-encoding isolates harboured an IncF (pMLST F1:A1:B49) plasmid replicon. The $bla_{\text{OXA-181}}$-encoding isolate harboured an IncX3 replicon in addition to IncF (pMLST F1:A1:B49).

3.4. Southeast Asian-origin *Escherichia coli* ST410 in a global context

SEA-*Ec*-ST410 belonged to previously described clonal clades, i.e. B3/*H*24Rx and B4/*H*24RxC [1] (Fig. 1). SEA-*Ec*-ST410 belonging to B3/*H*24Rx ($n = 12$) occurred across several distinct and unrelated branches, whilst SEA-*Ec*-ST410 belonging to B4/*H*24RxC ($n = 4$) clustered closely together.

SEA-*Ec*-ST410 encoded different antimicrobial resistance genes and plasmid replicon patterns compared with European and North American-origin genomes from either lineage (Fig. 1). First, 8 of 12 SEA-*Ec*-ST410 belonging to the B3/*H*24Rx sublineage encoded the $bla_{\text{CTX-M-55}}$ gene. Neither the $bla_{\text{CTX-M-55}}$ gene nor associated F18:A-:B1 plasmid replicons were detected among *Ec*-ST410 belonging to B3/*H*24Rx from other parts of the world. Second, three of four SEA-*Ec*-ST410 that clustered within the B4/*H*24RxC clade lacked both the $bla_{\text{OXA-181}}$ gene and its IncX3 plasmid backbone. In contrast, all other *Ec*-ST410 belonging to this sublineage harboured an IncX3 plasmid replicon (64/64), and most also encoded the $bla_{\text{OXA-181}}$ gene (62/64). We were unable to detect any carbapenemase-encoding genes in one SEA-*Ec*-ST410 genome lacking $bla_{\text{OXA-181}}$/IncX3 plasmid replicon (a urinary isolate from Thailand), although the other two encoded $bla_{\text{NDM-5}}$ (both from Cambodia).

4. Discussion

Recent studies have described the stepwise emergence of increasingly drug-resistant clades of *Ec*-ST410 in Europe and North America [1,2]. Here we characterised *Ec*-ST410 from colonised humans, infected patients and the environment from three Southeast Asian countries, i.e. Cambodia ($n = 7$), Thailand ($n = 7$) and Vietnam ($n = 2$), to determine whether *Ec*-ST410 circulating in that region are repeat introductions of the same B3/*H*24Rx and B4/*H*24RxC lineages detected elsewhere or represent regionally disseminated variants. Phylogenetic analysis revealed that SEA-*Ec*-ST410 belonging to B3/*H*24Rx ($n = 12$) were largely unrelated to each other, suggesting that this lineage is highly mobile and has likely been introduced to Southeast Asia through several independent events. On the other hand, SEA-*Ec*-ST410 belonging to B4/*H*24RxC ($n = 4$) clustered closely together, suggesting that the isolates characterised may have descended from a single introduction to the region. The

patterns of antimicrobial resistance elements harboured by SEA-*Ec*-ST410 belonging to both lineages were distinct from European and North American isolates, supporting independent circulation in Southeast Asia.

Most SEA-*Ec*-ST410 belonging to the ancestral B3/*H*24Rx lineage encoded $bla_{CTX\text{-}M\text{-}55}$, an ESBL-encoding gene first reported in Thailand in 2007 and now an increasingly common ESBL type [6,16,17]. SEA-*Ec*-ST410 likely acquired $bla_{CTX\text{-}M\text{-}55}$-harbouring plasmids from other Enterobacteriaceae colonising humans and animals in the region. Most CTX-M-55-producing *Ec*-ST410 encoded F18:A-:B1 plasmid replicons. Conjugative $bla_{CTX\text{-}M\text{-}55}$-harbouring F18:A-:B1 plasmids have previously been isolated from urinary tract *E. coli* infections in China [18]. Other CTX-M-55-producing *Ec*-ST410 encoded IncN, IncI1 and IncX1 plasmids. Conjugative $bla_{CTX\text{-}M\text{-}55}$-harbouring IncN plasmids have been detected among non-typhoidal *Salmonella enterica* from pork in Cambodia, whilst conjugative $bla_{CTX\text{-}M\text{-}55}$-harbouring IncI1 and IncX1 plasmids have been described among urinary tract *E. coli* infections in China and in *E. coli* from pig faeces in Hong Kong, respectively [18–20]. Overall, our finding that the majority of SEA-*Ec*-ST410 belonging to the B3/*H*24Rx lineage have acquired regionally disseminated antimicrobial resistance elements could indicate that it is established in the gut colonisation reservoir. The phylogeny of *Ec*-ST410 from other regions of Asia, especially China, should be investigated in future work.

The majority of SEA-*Ec*-ST410 belonging to the more recent B4/*H*24RxC lineage lacked the IncX3 plasmid replicon and its associated $bla_{OXA\text{-}181}$ gene, which are defining characteristics of this sublineage [1,2]. SEA-*Ec*-ST410 were not basal to the B4/*H*24RxC clade or basally-located within the clade, indicating that they are not the ancestors of this lineage and must have been introduced to Southeast Asia. It is unclear why some SEA-*Ec*-ST410 may have lost this plasmid following introduction to the region, as carbapenems are excessively prescribed [21]. However, $bla_{OXA\text{-}48\text{-}like}$ carbapenemases hydrolyse carbapenems less effectively than bla_{NDM} variants, which are also a more common cause of carbapenem-resistant Enterobacteriaceae infections in Thailand and Vietnam [21]. It is possible that *Ec*-ST410 that solely encode $bla_{NDM\text{-}5}$ have an ecological advantage in the region. However, further work is needed to investigate this hypothesis.

SEA-*Ec*-ST410 also harboured plasmid and resistance gene combinations that have been previously reported. The one OXA-181-producing SEA-*Ec*-ST410 isolate characterised encoded an IncX3 plasmid replicon. Conjugative IncX3 plasmids harbouring $bla_{OXA\text{-}181}$ have been described globally, including in Asia [1,22,23]. Both NDM-5-producing *Ec*-ST410 harboured a single IncF-type plasmid (pMLST F1:A1:B49) and co-produced multiple additional β-lactamases, including CTX-M-15, CMY-2, OXA-1 and TEM-1B. Using the available Illumina short-read sequencing data, we were unable to co-locate these genes on any contigs or determine whether they were chromosomally-encoded or harboured by plasmids. However, other studies characterising NDM-5-producing *Ec*-ST410 through long-read sequencing and plasmid transformation experiments have found that the $bla_{NDM\text{-}5}$, $bla_{CTX\text{-}M\text{-}15}$, $bla_{OXA\text{-}1}$ and $bla_{TEM\text{-}1B}$ genes are harboured by an IncF plasmid (pMLST F1:A1:B49), whilst the $bla_{CMY\text{-}2}$ gene is chromosomally-located [22,24].

Overall, *Ec*-ST410 are present in Southeast Asia likely following multiple introductions. The unique patterns of antimicrobial resistance genes and plasmids encoded by SEA-*Ec*-ST410 are different from clones detected in Europe and North America, indicating independent circulation in the community. The establishment of *Ec*-ST410 in Southeast Asia is of concern given this clone's high potential to acquire resistance to last-resort antibiotics, as antimicrobial resistance is already a major public-health crisis in the region.

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Competing interests

None declared.

Ethical approval

Not required.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.05.024.

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