REVIEW

ANTIMICROBIAL RESISTANCE AMONG PATHOGENIC BACTERIA IN SOUTHEAST ASIA

Endang Sri Lestari[1], Juliëtte A Severin[2] and Henri A Verbrugh[2]

[1]Department of Clinical Microbiology, School of Medicine, Diponegoro University/ Dr Kariadi Teaching Hospital, Semarang, Indonesia; [2]Department of Medical Microbiology and Infectious Diseases, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Abstract. Antimicrobial drug resistance is a problem in both developing and developed countries, in hospitals as well as in the community. Much data exists about antimicrobial resistance in Southeast Asia, but this information is fragmented, being published in different papers from different countries over several decades. We reviewed all available information about antimicrobial resistance in Southeast Asia using the PubMed database, concentrating on bacteria that commonly cause infection. From January 1, 1995 to January 1, 2007, 97 reports were published with accurate data regarding resistance patterns among the major pathogens. Thailand was the country where most of the published data were found. No reports were published for East Timor. From the available data, the following trends were observed: 1) there was a high prevalence of resistance to penicillin among *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*; 2) pathogens causing diarrheal diseases are now often resistant to inexpensive, older antibiotics; 3) among Enterobacteriaceae and nonfermenting gram-negative bacteria, resistance to virtually all antibiotic classes has been reported, but it is unclear whether multidrug resistant gram-negative bacteria have emerged as a major problem; 4) the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is not clear; in some countries, such as Singapore, MRSA is endemic in the health care system. This review shows that antimicrobial resistance to pathogenic bacteria has been and still is on the rise in Southeast Asia. However, there is great variation in resistance by hospital, patient type and country.

Keywords: pathogenic bacteria, antimicrobial resistance, Southeast Asia

Correspondence: Dr Endang Sri Lestari, Department of Clinical Microbiology, School of Medicine, Diponegoro University / Dr Kariadi Hospital, Jl Dr Soetomo 16 - 18, Semarang 50231, Indonesia.
Tel: + 62 24 8452931; Fax: + 62 024 8452931
E-mail: endang_sri_lestari@yahoo.com

INTRODUCTION

Antimicrobial drug resistance is a worldwide problem in both developing and developed countries (Tenover and Hughes, 1996; Goldman and Huskins, 1997; Bax *et al*, 2001; Wang and Ho, 2003;

Okeke *et al*, 2005b), in hospitals as well as in the community (Cohen, 1994; Okeke *et al*, 2005a). Infections with resistant bacteria adversely affect treatment outcomes, treatment costs, disease spread and duration of illness (Okeke *et al*, 2005b). In 2001, the World Health Organization (WHO) launched the first global strategy to counter this phenomenon; one of the recommendations of this strategy is to monitor trends in antimicrobial resistance using standardized microbiological methods. Much data exists about the emergence of antimicrobial resistance in Southeast (SE) Asian countries, but this information is fragmented, since it has been published in different papers from different countries over several decades.

SE Asia is geographically divided into two regions, namely Mainland SE Asia and Maritime SE Asia. Mainland SE Asia includes Cambodia, Lao People's Democratic Republic or Lao PDR, Myanmar, Thailand and Vietnam. Maritime SE Asia includes Brunei, East Timor, Indonesia, Malaysia, the Philippines, and Singapore. The region is a mix of developed and developing countries, with East Timor and Myanmar belonging to the least developed countries according to the United Nations Conference on Trade and Development (www.unctad.org).

For the present review we gathered and evaluated all available information in Pubmed on the presence or emergence of antimicrobial resistance among bacterial species that commonly cause infection in SE Asian countries to present an integrated overview of the situation in this region.

SEARCH STRATEGY

A review of the literature was conducted using the PubMed database. The search strategy was a combination of the following keywords, subjects and title words: "antimicrobial resistance", "antibiotic resistance", "MRSA" and "ESBL" and SE Asian countries including "Brunei Darussalam" or "Brunei", "Cambodia", "Indonesia", "Lao People's Democratic Republic" or "Laos" or "Lao PDR", "Malaysia", "Myanmar" or "Burma", "Philippines", "Singapore", "Thailand", "Timor Leste" or "East Timor" and "Vietnam". Articles published between January 1, 1995 and January 1, 2007 were included. Articles and abstracts were limited to studies written in English only. Studies were classified / extracted by species, country, year of publication, year of sample collection, sources, method of antimicrobial susceptibility testing, quality control, number of strains and percent resistance for each species against tested antimicrobial agents. A scoring system was developed for inclusion and exclusion of papers: use of quality control strains (0=no/not described and 1=yes), antimicrobial susceptibility testing according to an internationally approved method, such as that published by the Clinical Laboratory Standards Institute (CLSI) (*eg*, disk diffusion, E-test, micro/macro/agar dilution) (0=no and 2= yes) and use of a well evaluated method for identification [*eg*, Vitek (bioMérieux), Phoenix (Becton Dickinson), API (bioMérieux), molecular] (0=no; 1=yes). Only papers with a total score of 2 or more were included for analysis. A minimum number of 10 isolates had to be tested per species to be included in our review (Cornaglia *et al*, 2004). Only major pathogenic bacterial species among humans were included, except for *Mycobacterium* spp. Data representing a mix of strains from several countries were not included. Clinical material and non-clinical material

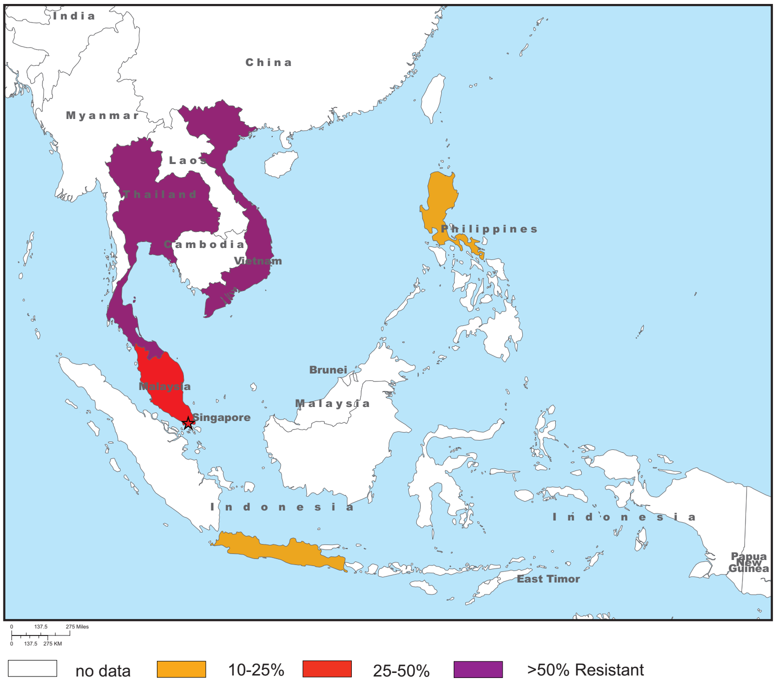

Fig 1–Prevalence of penicillin-non-susceptible *S. pneumoniae* (PNSP) in SE Asian countries, 1995-2007.

were analyzed separately (Tables 1 and 2). Intermediate resistance was not classified as resistance. When resistance data for a bacterial species were available from only one country, these were excluded.

Figures were created to present trends in resistance among the most important pathogens over the years by country. For each country, data collected during the same period but published in different articles or journals were merged. When isolates were collected during a period of more than one year, the median year was chosen to reflect the whole period. When the year of sample collection could not be extracted from the text, the year of publication was used instead.

For mapping purposes, data from multiple sites in geographically small countries were merged into one figure. Data from multiple sites in large countries were presented separately.

RESISTANCE AMONG GRAM-POSITIVE BACTERIA

Streptococcus pneumoniae

S. pneumoniae is a major pathogen causing various infections in children and adults, including pneumonia, meningitis, otitis media and septicemia (Song *et al*, 1999). Antibacterial resistance among pneumococci is increasing worldwide, primarily against betalactams and macrolides (Song *et al*, 2004b,c). The prevalences of penicillin-non-susceptible *S. pneumoniae* (PNSP) in SE Asian countries are presented in Fig 1 and Fig 2a. The data were mainly obtained from studies by the Asian Network for Surveillance of Resistant Pathogens (ANSORP), and a number of other studies. In Malaysia, the PNSP rate increased from 9% in 1996 to 39% in 2000. In Singapore, PNSP levels increased from 23% and 24% in 1996 and 1997, respectively, to more than 40% in the year 2000 and beyond. In Thailand, the rate of PNSP was stably high, ranging from 47% in 1997 to 69% in 2000. In Vietnam, the rate of PNSP was >50% in the 1990s: 61% in 1996, 53% in 1997 and 50% in 1998. In 2001, a strikingly high resistance rate of 92% was found in an ANSORP study (Song *et al*, 2004b,c). In 1996, 21% of *S. pneumoniae* sputum culture isolates in Jakarta, Indonesia, were PNSP. In the Philippines, PNSP prevalence was 21% in 2000 (Fig 2a). Compared to many European countries, the prevalence of PNSP in SE Asia is high. In the UK, Denmark, Norway, Sweden,

Table 1
References available per species of organisms isolated from clinical material in Southeast Asian countries.

No	Organisms	Brunei	Cambodia	Indonesia	Lao PDR	Malaysia	Myanmar	Phillippines	Singapore	Thailand	East Timor	Vietnam
1	*Streptococcus pneumoniae*			Song *et al*, 1999		Lee *et al*, 2001; Song *et al*, 1999, 2004b,c		Lee *et al*, 2001; Song *et al*, 2004b,c	Christiansen *et al*, 2004; Koh and Lin 1997; Lee *et al*, 2001; Soh *et al*, 2000; Song *et al*, 1999; 2004b,c	Chokephaibulkit *et al*, 2000, Critchley *et al*, 2002; Jones *et al*, 2002; Song *et al*, 1999, 2004b,c; Lee *et al*, 2001		Lee *et al*, 2001; Song *et al*, 1999, 2004b,c
2	*Enterococcus* spp					Raja *et al*, 2005, Raja, 2007			Chiew, 1997	Danchaivijitr *et al*, 2005		
3	*Staphylococcus aureus*			Song *et al*, 2004a	Phetsouvanh *et al*, 2006	Cheong *et al*, 1995; Raja, 2007; Rohani *et al*, 2000		Bell *et al*, 2002a; Christiansen *et al*, 2004; Song, *et al*, 2004a	Bell *et al*, 2002a; Christiansen *et al*, 2004; Song *et al*, 2004a	Song *et al*, 2004a		Song *et al*, 2004a
4	CoNS								Kumarasinghe *et al*, 1995	Danchaivijitr *et al*, 2005		
5	*Haemophilus influenzae*								Tee *et al*, 1996	Critchley *et al*, 2002		
6	*Neisseria gonorrhoeae*	WHO, 1997a,b; Tapsall, 2000; WHO, 2001, 2002, 2003, 2005, 2006a,b	WHO, 1997a,b	Djajakusumah *et al*, 1998; Donegan *et al*, 2006; Ieven *et al*, 2003; Lesmana *et al*, 2001; Su *et al*, 2003; Sutrisna *et al*, 2006	WHO, 2002, 2003, 2005, 2006a,b	WHO, 1997a,b, 1998; Tapsall, 2000; WHO, 2001, 2002, 2003, 2006a,b		Klausner *et al*, 1999; Knapp, *et al*, 1997a,b; WHO, 1997a,b; 1998; Tapsall, 2000; WHO, 2001, 2002, 2003, 2005, 2006a,b	WHO, 1997a,b; 1998; Tapsall, 2000; WHO, 2001, 2002, 2003, 2005, 2006a,b	Knapp *et al*, 1997a,b		WHO, 1997a,b; 1998; Tapsall, 2000; WHO, 2001, 2002, 2003, 2006a,b; Jones *et al*, 2006

7	*E. coli*			Lewis *et al*, 1999	Phetsouvanh *et al*, 2006	Cheong *et al*, 1995; Raja, 2007; Wong *et al*, 2003		Bell *et al*, 2002b; Christiansen *et al*, 2004; Hirakata *et al*, 2005	Bell *et al*, 2002b; Kumarasinghe *et al*, 1996; Kumarasinghe *et al*, 1995; Chiew, 2004; Hirakata *et al*, 2005	Biedenbach *et al*, 1999; Danchaivijitr *et al*, 2005; Apisarnthanarak, and Murdy, 2006; Srifuengfung *et al*, 2005; Girlich *et al*, 2001; Jitsurong and Yodsawat, 2006		
8	Enterotoxigenic *E. coli* ETEC			Subekti *et al*, 2003						Isenbarger *et al*, 2002		Isenbarger *et al*, 2002
9	*Klebsiella pneumoniae*				Phetsouvanh *et al*, 2006	Raja, 2007		Bell *et al*, 2002b	Bell *et al*, 2002b	Kusum *et al*, 2004		
10	*Klebsiella* spp			Lewis *et al*, 1999				Johnson, *et al*, 1999	Kumarasinghe, *et al*, 1995, 1996	Biedenbach *et al*, 1999; Isenbarger *et al*, 2002; Angkititrakul *et al*, 2005; Srifuengfung *et al*, 2005a,b		
11	*Salmonella* spp			Oyofo *et al*, 2002a,b	Phetsouvanh *et al*, 2006	Lee *et al*, 2003		Johnson *et al*, 1999		Biedenbach *et al*, 1999; Isenbarger *et al*, 2002; Angkititrakul *et al*, 2005; Srifuengfung *et al*, 2005a,b		
12	*Shigella* spp			Oo, 1995; Oyofo *et al*, 2002a,b; Tjaniadi *et al*, 2003		Hoe *et al*, 2005				Isenbarger *et al*, 2002		Isenbarger *et al*, 2002; Iversen *et al*, 2003
13	*Proteus* spp					Raja, 2007		Johnson *et al*, 1999	Kumarasinghe *et al*, 1995	Biedenbach *et al*, 1999		
14	*Enterobacter* spp			Lewis *et al*, 1999				Bell *et al*, 2002b; Johnson *et al*, 1999	Bell *et al*, 2002b; Kumarasinghe *et al*, 1996; Kumarasinghe *et al*, 1995	Biedenbach *et al*, 1999		

Table 1 (Continued).

No	Organisms	Brunei	Cambodia	Indonesia	Lao PDR	Malaysia	Myanmar	Phillippines	Singapore	Thailand	East Timor	Vietnam
15	*Serratia* spp			Lewis *et al*, 1999				Johnson *et al*, 1999		Biedenbach *et al*, 1999		
16	*Citrobacter* spp							Johnson *et al*, 1999;		Biedenbach *et al*, 1999		
17	*Campylobacter jejuni*			Oyofo *et al*, 2002a,b; Tjaniadi *et al*, 2003						Isenbarger *et al*, 2002		Isenbarger *et al*, 2002
18	*Pseudomonas aeruginosa*			Lewis *et al*, 1999		Cheong, *et al*, 1995; Raja, 2007; Raja and Singh, 2007		Johnson *et al*, 1999; Christiansen *et al*, 2004	Kumarasinghe *et al*, 1995,1996	Biedenbach *et al*, 1999; Srifuengfung *et al*, 2005; Thongpi-yapoom *et al*, 2004		Le *et al*, 2006
19	*Acinetobacter* spp			Lewis *et al*, 1999				Johnson *et al*, 1999	Kumarasinghe *et al*, 1995,1996	Biedenbach *et al*, 1999; Danchaivijitr *et al*, 2005		
20	*Burkholderia pseudomallei*				Phetsouvanh *et al*, 2006	Koay *et al*, 1997				Wuthiekanun *et al*, 2005		

Table 2
References available for species of potentially pathogenic organisms isolated by screening in Southeast Asian countries.

No	Organisms	Brunei	Cambodia	Indonesia	Lao PDR	Malaysia	Myanmar	Phillippines	Singapore	Thailand	East Timor	Vietnam
1	*Streptococcus pneumoniae*					Lee *et al*, 2001; Malik *et al*, 1998		Lee *et al*, 2001	Lee *et al*, 2001	Lee *et al*, 2001		Lee *et al*, 2001; Parry *et al*, 2000; Schultsz *et al*, 2007
2	*E. coli*							Nys *et al*, 2004		Hanson *et al*, 2002		

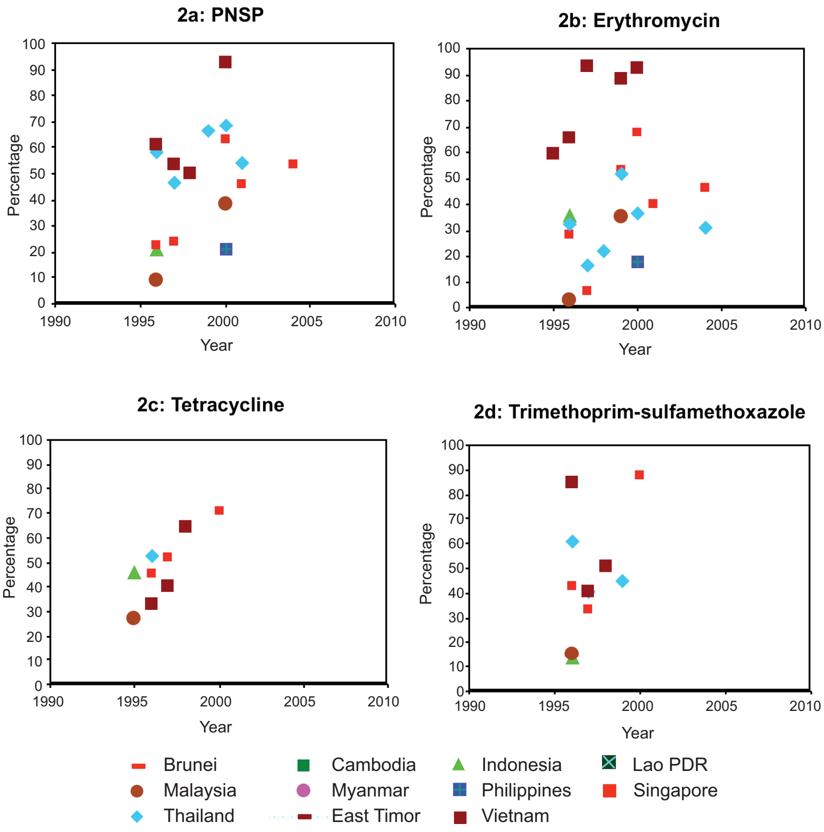

Fig 2–Resistance among *S. pneumoniae* from SE Asia.

(Fig 2c). In 1995, tetracycline resistance was 46% in Indonesia and 27% in Malaysia. In 1996, 52% of Thai isolates were resistant to tetracycline (Fig 2c).

In Singapore, Thailand and Vietnam, trimethoprim-sulfamethoxazole resistance rates were more than 30% (Fig 2d). In Indonesia and Malaysia, trimethoprim-sulfamethoxazole levels of resistance in 1996 were 14% and 15%, respectively (Fig 2d).

Additional data on the antimicrobial resistance among *S. pneumoniae* are presented in Table 3.

and The Netherlands, prevalences are 1-5%, and in Iceland 5-10% (www.rivm.nl/earss/database).

Erythromycin resistance among *S. pneumoniae* isolates from Malaysia was only 3% in 1996, but increased to 35% in 1999 (Fig 2b). In Vietnam, the level of erythromycin resistance increased from 59% in 1995 to over 65% in 1996 and thereafter. In Thailand, erythromycin resistance rates among *S. pneumoniae* ranged from 16% to 52%. In Singapore, erythromycin resistance increased as well (Fig 2b). The resistance rate in Indonesia was 36% in 1996 and in the Philippines 18% in 2000 (Fig 2b).

Resistance to tetracycline increased over the years in Singapore and Vietnam

***Enterococcus* spp**

In general, enterococci are regarded as low grade pathogens, but in the hospital setting these bacteria have emerged as an important cause of nosocomial infections. Enterococci are intrinsically resistant to a large number of antibiotics, and can easily acquire new mechanisms of resistance. Ampicillin is the antibiotic of choice for the treatment of enterococcal infections, and vancomycin is an alternative agent. Ciprofloxacin, erythromycin, tetracycline and chloramphenicol may exhibit *in vitro* activity, but clinical success is limited. *Enterococcus* spp from wounds in diabetic feet in Malaysia had resistance rates of 50% for erythromycin, 25% for

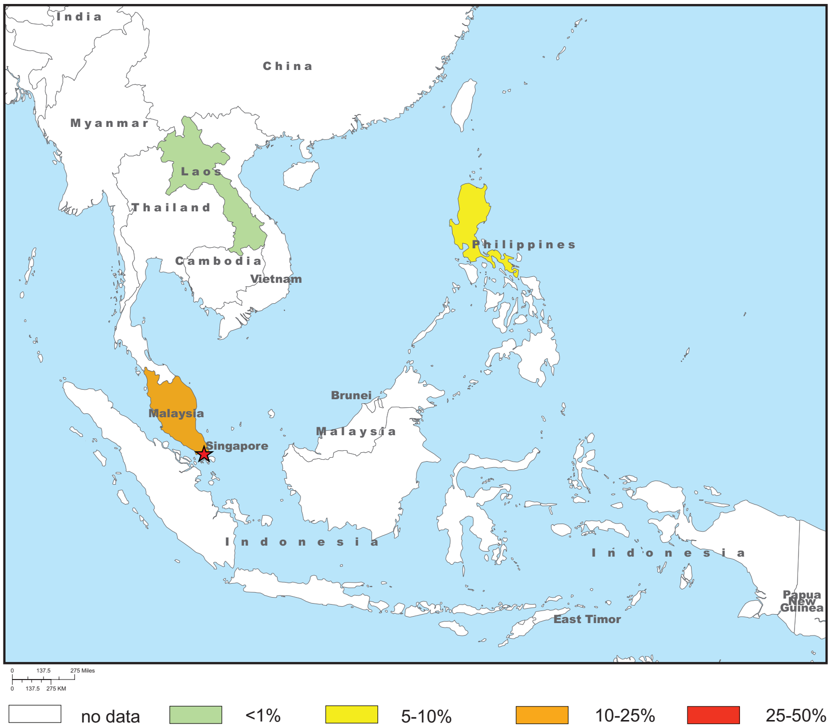

Fig 3–Prevalence of methicillin-resistant *S. aureus* (MRSA) in SE Asian countries, 1995-2007.

trimethoprim-sulfamethoxazole, 17% for ampicillin, 8% for imipenem and 0% for penicillin and vancomycin (Raja, 2007). In a multicenter study in Thailand in 2002-2003, the resistance of *Enterococcus* spp from community- and hospital-acquired infections was 36% to ampicillin, 47% to gentamicin, 4% to vancomycin, 69% to ciprofloxacin, and 76% to erythromycin (Danchaivijitr *et al*, 2005). Vancomycin-resistant enterococci, first described in the late 1980s in Europe and now a major problem in hospitals in the USA, were documented in case reports from Singapore in 1996 (Ang *et al*, 1996) and 1997 (Chiew, 1997), and from Malaysia in 2005 (Raja, 2007), but the full extent of the phenomenon in SE Asia is unknown.

Staphylococcus aureus

S. aureus is a major cause of both hospital- and community-acquired infections, in developed and developing countries (Archer, 1998; Nickerson *et al*, 2009). A study in Lao PDR found *S. aureus* was the second most common cause of bacteremia, and was associated with a mortality rate of 17% (Phetsouvanh *et al*, 2006). Treatment of *S. aureus* infections is becoming increasingly more complicated due to the emergence of various types of antimicrobial resistance worldwide. Methicillin-resistant *S. aureus* (MRSA) strains are of most concern since these are resistant to all betalactam antibiotics and in many cases to other groups of antimicrobials as well, especially in the hospital setting. Data regarding the prevalences of MRSA in SE Asia were available from Lao PDR (Phetsouvanh *et al*, 2006), Malaysia (Cheong *et al*, 1995; Rohani *et al*, 2000; Raja, 2007), the Philippines (Bell and Turnidge, 2002; Christiansen *et al*, 2004), and Singapore (Tan *et al*, 1998; Bell and Turnidge, 2002; Christiansen *et al*, 2004). Overall, rates of MRSA ranged from 0% in Lao PDR and 7% in the Philippines to 25% in Malaysia and 39% in Singapore (Fig 3 and Table 4).

In Malaysia, the MRSA rate was 0% from a variety of specimens from non-hospitalized patients in 1992, 40% among various clinical specimens in 1996 and 16% among isolates from diabetic foot cultures in 2004. In Lao PDR, no MRSA

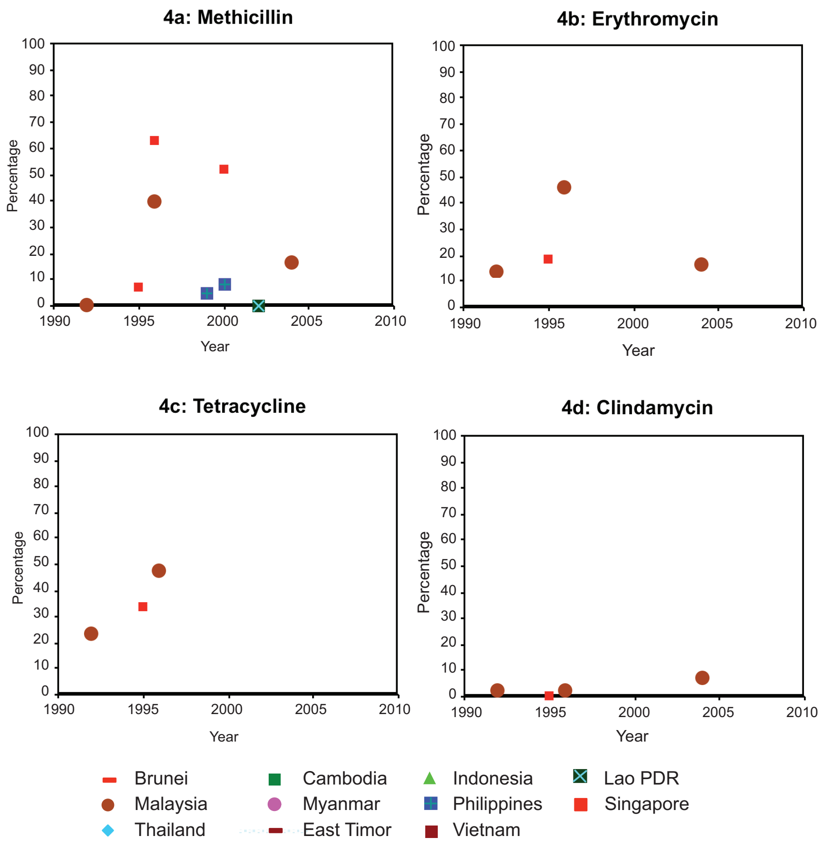

Fig 4–Resistance among *S. aureus* from SE Asia.

infections. In 1997, the first clinical isolate of *S. aureus* with reduced susceptibility to vancomycin was reported from Japan (Centers for Disease Control and Prevention, 1997). Subsequently, vancomycin intermediately susceptible *S. aureus* (VISA) and heterogenous resistance to vancomycin (hVISA) have been identified in many parts of the world. In a study by Song *et al* (2004a) heterointermediate resistance to vancomycin was found among MRSA isolates from the Philippines (4%), Vietnam (2%), Singapore (2%) and Thailand (2%), but not among MRSA strains from Indonesia (Song *et al*, 2004a) or Malaysia (Rohani *et al*, 2000; Raja, 2007). In the Malaysian studies, the disk diffusion method was used, which is an inaccurate method to assess intermediate resistance to vancomycin.

was found among blood culture isolates from patients with community-acquired bacteremia.

SENTRY is an international antimicrobial surveillance program that documents resistance patterns in bacteria isolated predominantly from hospitalized patients. Between April 1998 and December 1999, MRSA accounted for 5% of all *S. aureus* isolates from the Philippines and 62% of isolates from Singapore. From 1999 to 2001, these rates were 8% and 52% for the Philippines and Singapore, respectively (Fig 4a). In another study from Singapore of skin infections in 1995-1996, 7% of *S. aureus* isolates were MRSA.

Vancomycin, a glycopeptide, is the cornerstone for treating invasive MRSA

In Malaysia, overall resistance rate to tetracycline, erythromycin, and clindamycin among *S. aureus* were 39, 33, and 2%, respectively. Tetracycline resistance varied from 23% in 1992 to 47% in 1996 (Fig 4c). Erythromycin resistance rates varied from 13% in 1992 to 46% in 1996 then 16% in 2004 (Fig 4b). Clindamycin resistance was 2% in 1992 and 1996, and 7% in 2004 (Fig 4d). In 1995, in Singapore, 19% of *S. aureus* isolates were resistant to erythromycin,

Table 3
Overall resistance rates among *S. pneumoniae* from clinical samples.

Antibiotic	Indonesia (% R)	Malaysia (% R)	Philippines (% R)	Singapore (% R)	Thailand (% R)	Vietnam (% R)
Penicillin I	3	8	21	14	29	26
Penicillin	18	18	0	36	30	41
Erythromycin	36	26	18	45	29	76
Tetracycline	46	27		59	52	52
Chloramphenicol	6	9		28	18	87
Ciprofloxacin		5	9	6	4	5
Trimethoprim-sulfamethoxazole	42	15		59	50	61
Cefepime						6
Ceftriaxone		2	0	0	5	2
Imipenem					0	0
Clindamycin				11		
Azithromycin					45	61
Cefuroxime	3	30	0	23	48	74
Cefotaxime	3			8	21	17
Clarithromycin					55	
Moxalactam		0	0	0	0	0
Gatifloxacin		0	0	0	0	0
Levofloxacin		0	0	0	0	0
Amoxicillin					0	
Ceftibuten					42	
Roxithromycin					30	

I, intermediately susceptible; R, resistant

34% to tetracycline, and 0% to clindamycin. However, in none of these studies was an induction test performed to check for inducable resistance, thus resistance rates for clindamycin could be higher. Additional data regarding resistance of *S. aureus* is presented in Table 4. From many countries in SE Asia information on resistance data of *S. aureus* is lacking.

Coagulase-negative staphylococci (CoNS)

CoNS are the most frequently reported pathogens in nosocomial bloodstream infections (Jarvis and Martone, 1992; Kloos and Bannerman, 1994). Patients with CoNS infections are usually immunocompromised, with indwelling or implanted foreign bodies. Resistance to antibiotics in CoNS is of concern, especially methicillin resistance encoded by the *mecA* gene, because there is evidence of horizontal transfer of the *mecA* containing staphylococcal cassette chromosome among staphylococcal species (Hanssen *et al*, 2004). In SE Asia, only data from Singapore and Thailand are available. In a university hospital in Singapore, CoNS had a high incidence of resistance to gentamicin (38%), erythromycin (38%), trimethoprim-sulfamethoxazole (29%), methicillin (25%), and fusidic acid (22%), but vancomycin resistance was not found (Kumarasinghe *et al*, 1995). In

Table 4
Overall resistance rates among *S. aureus* clinical samples.

Antibiotic	Indonesia (% R)	Lao PDR (% R)	Malaysia (% R)	Philippines (% R)	Singapore (% R)	Thailand (% R)	Vietnam
Methicillin		0	25	7	39		
Penicillin		88	91		94		
Erythromycin		59	33		0		
Tetracycline			39				
Fucidic acid			7		7		
Chloramphenicol		21	3				
Ciprofloxacin				60	97		
hVISA[a]	0		0	4	2	2	2
Rifampicin			0				
Trimethoprim-sulfamethoxazole		22	5		55		
Cefepime	0					0	
Cefpirome	0					0	
Ceftazidime	14			7		6	
Ceftriaxone	0					0	
Imipenem	0						
Clindamycin			2				
Telithromycin	3						
Amikacin					0		
Gentamicin		2					

[a] hVISA, heterogenous vancomycin intermediately susceptible *S. aureus*.

Thailand, resistance rates were 36% for gentamicin, 43% for erythromycin, 40% for trimethoprim-sulfamethoxazole, 57% for oxacillin, and 1% for vancomycin (Danchaivijitr *et al*, 2005). Resistance to methicillin is much more prevalent in the USA (78%) and other parts of the world (74%) (Jones *et al*, 2007a). Similarly, erythromycin resistance was found in 71% of CoNS from the USA and 65% from other parts of the world (Jones *et al*, 2007b).

RESISTANCE AMONG GRAM-NEGATIVE BACTERIA

Haemophilus influenzae

Accurate data regarding susceptibilities of *H. influenzae* in SE Asia were available from Singapore and Thailand. Results of 318 isolates, obtained during 1993-1994 in Singapore, were reported by Tee and Lin (1996). Resistance rates to ampicillin and trimethoprim-sulfamethoxazole were 41% and 38%, respectively. Resistance rates to chloramphenicol, cefuroxime, and ceftriaxone were 11, 2, and 0%, respectively. In Thailand, 305 isolates from respiratory samples were studied. Beta-lactamase production was present in 45% of isolates, with 135 of these being ampicillin-resistant. Resistance to trimethoprim-sulfamethoxazole was prevalent (50%) as well. All isolates were susceptible to amoxicillin-clavulanic acid, cefuroxime, ceftriaxone, azithromycin and levofloxacin (Tee and Lin, 1996; Critchley *et al*, 2002).

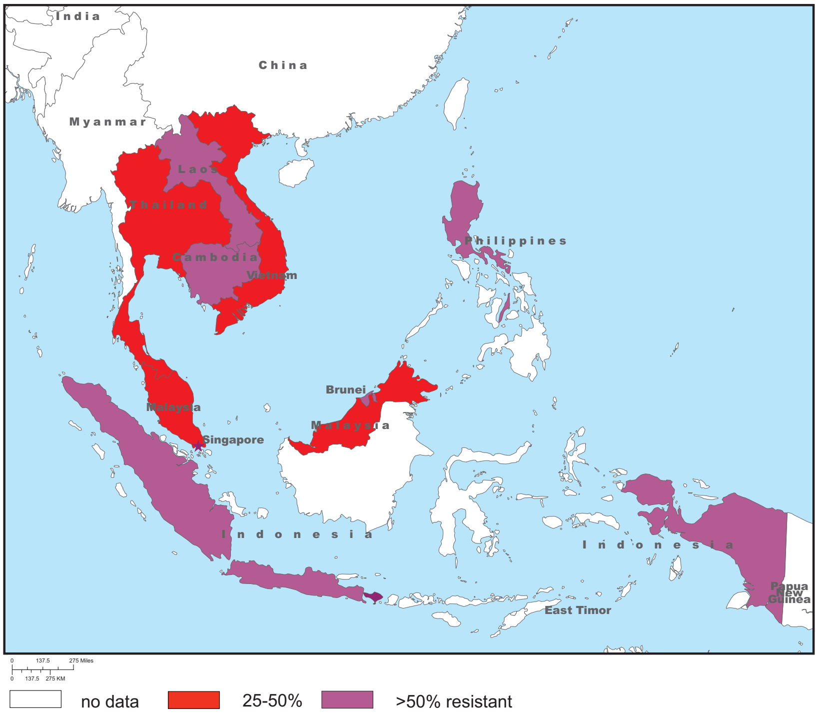

Fig 5–Prevalence of penicillinase-producing *N. gonorrhoeae* (PPNG) in SE Asian countries, 1995-2007.

The production of beta-lactamase is the most common mechanism of ampicillin resistance expressed by *H. influenzae*, with wide geographical variation (Tristram *et al*, 2007). One international surveillance study of almost 3,000 strains from 1999 to 2000 showed an overall prevalence of beta-lactamase-positive strains of 17%, but ranging from as low as 3% in Germany to as high as 65% in South Korea (Hoban and Felminghem, 2002). Compared to European countries, North and South America, ampicillin resistance rates in Singapore and Thailand were high. Resistance to trimethoprim-sulfamethoxazole is common worldwide (Hoban and Felminghem, 2002).

Neisseria gonorrhoeae

Gonorrhea is among the most prevalent sexually transmitted diseases throughout much of the world (Tapsall, 2005, 2006; Workowski *et al*, 2008). Complications of urogenital infections include pelvic infammatory disease in women, leading to infertility, chronic pelvic pain, ectopic pregnancy and conjunctivitis in the newborn of infected mothers. Effective antibiotic treatment is an essential component to controling the disease. The epidemiology of antimicrobial resistance guides decisions about gonococcal treatment recommendations. Data regarding antimicrobial resistance among *N. gonorrhoeae* isolates was available for Indonesia, Thailand, the Philippines, Brunei, Lao PDR, Malaysia, Singapore and Vietnam. The latter six countries participate in the WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Program (WPR GASP) that has monitored gonococcal resistance since 1992. Resistance to penicillins, which may be the result of penicillinase production (PPNG) or aggregation of a number of chromosomally mediated mechanisms (CMRNG), is widespread and at high levels in SE Asia. The PPNG prevalences are shown in Figs 5 and 6a. Although the PPNG prevalence in Malaysia was 39%, the total rate of resistance to penicillin was 48%. In Brunei, the overall rate of resistance to penicillin was 64% (Table 5). There was considerable regional variation in the distribution of high-level plasmid-mediated tetracycline

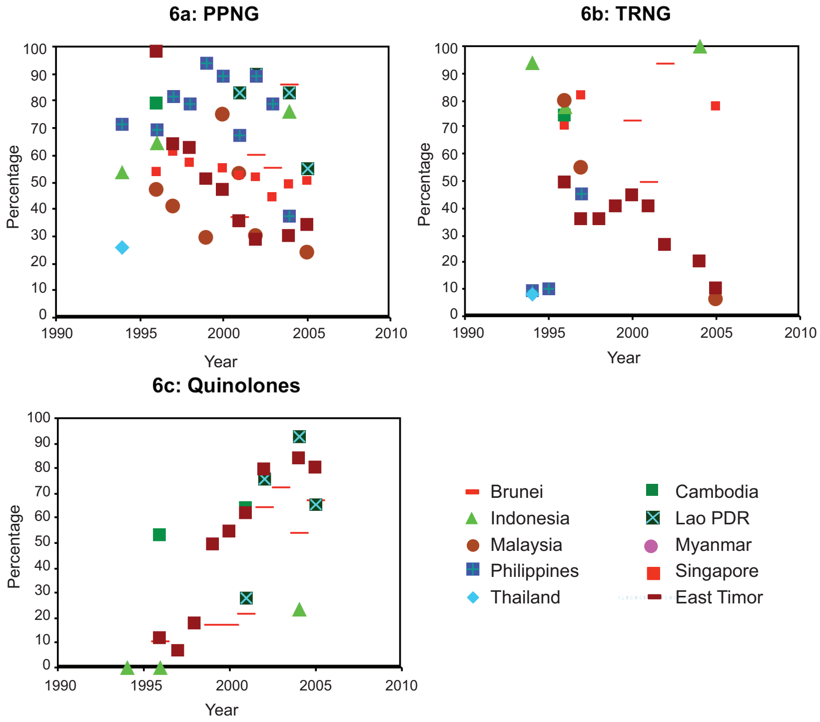

Fig 6–Resistance among *N. gonorrhoeae* from SE Asia.

resistance (TRNG) (Fig 6b). Rates ranged from 6% in Malaysia (2005) to 100% in Bali and East-Java, Indonesia (2004) (Donegan *et al*, 2006; Sutrisna *et al*, 2006; WHO, 2006). In the Philippines, an increase in tetracycline resistance was observed from 8% in 1994 to 30% in 2005 (Knapp *et al*, 1997a; WHO, 2006). Quinolone resistance among gonococci, the result of chromosomal changes in *gyrA* or *parC* genes, has been increasing in SE Asia since 1993, as shown by WHO WPR GASP data. At first, strains "less sensitive" to quinolones were observed. Infections with these strains were treated with an increased dose of the fluoroquinolone. Subsequent strains were detected with higher MICs: these were not amenable to therapy even with higher-dose regimens. In 2005, more than 50% of isolates were resistant or less susceptible to quinolones in Brunei, Lao PDR, Singapore and Vietnam (WHO, 2006). Other countries in SE Asia with high rates of decreased susceptibility to quinolones, but not part of the WHO WPR GASP study, included Indonesia (50% in 2004) and Thailand (22% in 1994-1995) (Fig 6c) (Knapp *et al*, 1997b; Donegan *et al*, 2006; Sutrisna *et al*, 2006). Resistance to penicillin, tetracycline and quinolones is now so widespread in most SE Asian countries that these have become unreliable as a first-line treatment for gonococcal disease. Alternatives include third-generation cephalosporins, spectinomycin (injectible) and azithromycin. Strains with a decrease in susceptibility to third-generation cephalosporins have been detected in recent WHO WPR GASP surveys, but exact prevalences have not been reported. Spectinomycin resistance is only rarely observed. In Jakarta, this antibiotic is now used as a first-line therapy. However, when extensively used, resistance emerges quickly, as occurred in the mid-1980s. Data regarding azithromycin resistance from SE Asia is scarce. In 2004, no resistance to this macrolide was observed in isolates from Denpasar, Indonesia (Donegan *et al*, 2006; Sutrisna *et al*, 2006).

ENTEROBACTERIACEAE

Escherichia coli

E. coli isolates exist as normal flora in

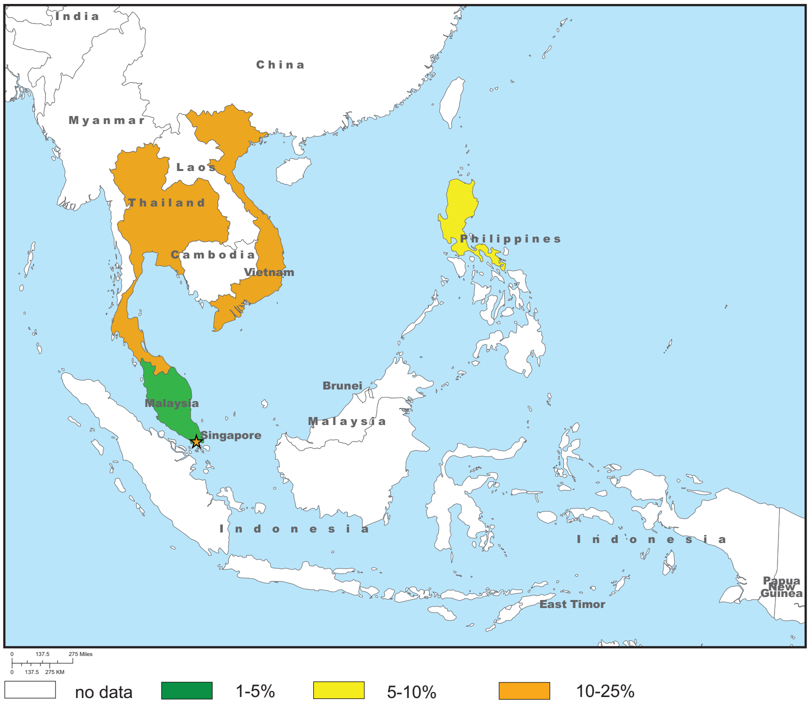

Fig 7–Prevalence of ESBL-producing *E. coli* in SE Asian countries, 1995-2007.

the gut of humans and animals and were originally susceptible to many antimicrobial agents. However, selective pressure by repeated exposure to antibiotics has led to the development of resistance (Wong *et al*, 2003). In SE Asia, many studies have assessed antimicrobial resistance among *E. coli* (Figs 7, 8). The overall prevalence of ampicillin resistance was ≥50%, much higher than other countries of the world (Erb *et al*, 2007). The emergence of fluoroquinolone resistance among gram-negative rods is, however, a phenomenon seen worldwide. In Malaysia, ciprofloxacin resistance increased from 0% in 1992 (Cheong *et al*, 1995) to 29% in 2004 (Raja, 2007). An increase in ciprofloxacin resistance has also been observed in Singapore and Thailand (Fig 8b). In the Philippines, the resistance rate to ciprofloxacin was the highest among SE Asian countries, 54% in 1998, but in this analysis only extended spectrum beta-lactamase (ESBL)-positive *E. coli* isolates were included. The association between ESBL production and quinolone resistance has been recognized worldwide (Bell *et al*, 2002).

Aminoglycosides, such as gentamicin, are important antibiotics for the empiric treatment of severe infections suspected to be caused by aerobic gram-negative rods. In Malaysia, gentamicin resistance increased from 1% in 1992 to 30% in 2004. In Singapore, the gentamicin resistance rate was ≤10% in 1992 and 1994, but more recent data are not available. The highest resistance rate described in SE Asian reports was among ESBL-positive isolates from the Philippines (46% in 1998). No resistance to gentamicin was found among *E. coli* from the blood of HIV-positive patients in Thailand in 1997 (Fig 8c). However, resistance to trimethoprim-sulfamethoxazole was high in this collection (100%). Among ESBL-positive isolates from the Philippines, the resistance rate was 92%. Fig 8d shows resistance to trimethoprim-sulfamethoxazole in Malaysia increased from 34% in 1992 to 71% in 2004. This is much higher than the prevalences described in Europe or the Americas (Erb *et al*, 2007).

Additional resistance data are presented in Table 6. No data were available from Brunei, Cambodia, Lao PDR, Myanmar or Vietnam.

Table 5
Overall resistance rates among *N. gonorrhoeae* clinical samples.

Antibiotic	Brunei (% R)	Lao PDR (% R)	Cambodia (% R)	Indonesia (% R)	Malaysia (% R)	Philippines (% R)	Singapore (% R)	Thailand (% R)	Vietnam (% R)
Penicillin	64	98	79	66	48	84	58		29
Ciprofloxacin				30.6					
Trimethoprim-sulfamethoxazole				0					
Ceftriaxone				0					
Ofloxacin				0					
Norfloxacin				0					
PPNG	65	80	79	68	39	76	54	26	47
TRNG	68	98	74	86	61	14	74	8	33
Spectinomycin	0		0	0	0	0	0	0	
Kanamycin				0				22	
Norfloxacin				0					
Thiamphenicol				3					
Cefotaxime				0					
Cefixime				0					
Cefoxitin				0					
Azithromycin				0					
QRNG	45	50	56	23	13	55	24		51

PPNG, penicillinase-producing *N. gonorrhoeae*; TRNG, high-level plasmid-mediated tetracycline-resistant *N. gonorrhoeae*; QRNG, quinolone-resistant *N. gonorrhoeae*; R, resistant

Table 6
Overall resistance rates among *E. coli* clinical samples.

Antibiotic	Indonesia (% R)	Lao PDR (% R)	Malaysia (% R)	Philippines (% R)	Singapore (% R)	Thailand (% R)
Tetracycline			62	92		
Chloramphenicol		38	25			40
Ciprofloxacin			2	54	2	36
Gentamicin		8	2	46	7	0
Trimethoprim-sulfamethoxazole			36	92	35	100
Cefepime	3					0
Cefpirome	0			1		0
Ceftazidime	10	64	0	4	3	14
Ceftriaxone	3	8	0	2	2	1
Imipenem	0		0	0	2	0
Pefloxacin			2			
Amikacin			0	8	0	9
Netilmicin			0			0
Nitrofurantoin			3		10	
Ampicillin		75	53		50	85
Ampicillin-sulbactam			23		24	64
Amoxicillin-clavulanic acid			18		23	58
Cefazolin						33
Cefuroxime			0			
Cefotaxime			0			8
Kanamycin			15			
Piperacillin	7		41		24	0
Piperacillin-tazobactam			2	2		
Ofloxacin			2			
Cephalothin			17			
Tobramycin			1	77		
Nalidixic acid		13	2			
Aztreonam			3			
Carbenicillin			46			
Cefoperazone			7			
Cefoperazone-sulbactam					0	
Ticarcillin			48			
Trimethoprim			37			
Cefalexin					47	

R, resistance

Enterotoxigenic *E. coli* (ETEC)

The antimicrobial resistance among ETEC, an important cause of diarrhea in developing countries, particularly among young childern, was studied in three SE Asian countries: Indonesia (Subekti *et al*, 2003), Thailand (Isenbarger *et al*, 2002) and Vietnam (Isenbarger *et al*, 2002). The prevalence of resistance to tetracycline was 81, 43, and 65%; to chloramphenicol

Table 7
Overall resistance rates among Enterotoxigenic *E. coli* (ETEC) clinical samples.

Antibiotic	Indonesia (% R)	Thailand (% R)	Vietnam (% R)
Tetracycline	88	43	65
Chloramphenicol	61	13	17
Ciprofloxacin	0	2	0
Trimethoprim-sulfamethoxazole	63	51	63
Ceftriaxone	0		
Azithromycin		4	3
Ampicillin	78	54	67
Norfloxacin	0		
Cephalothin	87		
Nalidixic acid	0	3	0

R, resistance

61, 13, and 17%; to trimethoprim-sulfamethoxazole 63, 51, and 63%; and to ampicillin 78, 54, and 67% in Indonesia, Thailand and Vietnam, respectively. Resistance to ciprofloxacin, azithromycin, and nalidixic acid was <5% (Table 7).

Klebsiella pneumoniae

Studies regarding the prevalence of antimicrobial resistance among *K. pneumoniae* isolates were available from Malaysia (Raja, 2007), Lao PDR (Phetsouvanh *et al*, 2006), the Philippines (Bell *et al*, 2002), Singapore (Bell *et al*, 2002), and Thailand (Kusum *et al*, 2004) (Figs 9, 10). The latter three studies only involved ESBL-positive isolates. Not surprisingly, ciprofloxacin resistance was prevalent in the Philippines (62%), Thailand (29%) and Singapore (22%). Among *K. pneumoniae* isolates from diabetic feet in Malaysia, the resistance rate to ciprofloxain was 9%, to nalidixic acid 17%, and to trimethoprim-sulfamethoxazole 26%. Resistance to aminoglycosides was also present among ESBL-positive isolates. Twenty-six percent of isolates from the Philippines and 6% from Thailand were resistant to amikacin (Fig 10d).

Although there has been a rapid global spread of carbapenemase-producing *K. pneumoniae*, imipenem resistance was not present in Malaysia, the Philippines, Singapore or Thailand (Fig 10c).

Additional resistance data is shown in Table 8.

ESBL-producing Enterobacteriaceae

ESBL-producing Enterobacteriaceae are an increasing problem worldwide. This emerging resistance phenomenon is discussed separately. Reliable detection of ESBL-producing bacteria includes a screening test followed by a confirmation test. This is, however, not straightforward, because different ESBL enzymes hydrolyze oxymino-cephalosporins at different rates and other mechanisms of resistance may interfere with the tests. Methods for screening and phenotypic confirmatory testing of bacteria other than *E. coli*, *K. pneumoniae*, and *K. oxytoca*, have not yet been determined by the CLSI. Accurate information regarding ESBLs from SE Asia was available for Singapore (Bell *et al*, 2002; Chiew, 2004; Hirakata *et al*, 2005), the Philippines (Bell *et al*, 2002; Hirakata *et al*, 2005), Thailand (Girlich *et al*, 2001; Kusum *et al*, 2004; Apisarnthanarak and Mundy, 2006; Jitsurong and Yodsawat, 2006), Malaysia (Wong *et al*, 2003), and Vietnam (Jones *et al*, 2006) (Figs 7, 8a, 9, 10a). In 1998-1999, confirmed ESBL-producing isolates were present in SE Asia, as reported by the Asia-Pacific group of the SENTRY Antimicrobial Surveillance Program (Bell *et al*, 2002). Among clinical strains of *E. coli*, rates were 5% and 9%, in Singapore and the Philippines, respectively. For *K. pneumoniae*, these rates were 42% and 32%, respectively. During the same period, 11%

Table 8
Overall resistance rates among *K. pneumoniae* clinical samples.

Antibiotic	Lao PDR (%R)	Malaysia (%R)	Philippines (%R)	Singapore (%R)	Thailand (%R)
Tetracycline			53	30	
Ciprofloxacin		9	62	22	31
Gentamicin					47
Trimethoprim-sulfamethoxazole	29	26	89	48	53
Chloramphenicol	33				
Cefepime					100
Ceftazidime		9			100
Ceftriaxone		9			100
Imipenem		0	0	0	0
Amikacin		0	26	0	6
Nitrofurantoin					42
Ampicillin	94	17			
Cefazolin					100
Cefuroxime		13			
Piperacillin		4	24	7	34
Tobramycin			73	78	81
Aztreonam					0
Cefoperazone		13			
Levofloxacin					31
Cefotetan					100
Nalidicid acid	17				

R, resistance

of *E. coli*, 36% of *K. pneumoniae*, and 39% of *K. oxytoca* isolates were ESBL-positive in Singapore. A rapid increase was observed for *K. pneumoniae* in Thailand, from 10% in 1999 in Bangkok to 21% in Pathum Thani (central Thailand) in 2003 and 44% in Songkhla Province (southern Thailand) in 2004. The latter high prevalence was from isolates of blood cultures only, which is of concern, since ESBL-producing strains are associated with poor patient outcomes, probably due to inappropriate first-line treatment. In Kuala Lumpur, Malaysia, and in Ho Chi Minh City, Vietnam, 3% and 19% of *E. coli* isolates, respectively, were ESBL-producing. Overall, the prevalence of ESBLs in SE Asia was higher among *K. pneumoniae* than *E. coli* isolates, consistent with findings elsewhere in the world.

Molecular characterization of clinical strains producing ESBLs was published for Malaysia, Vietnam, Singapore, and Thailand. However, this is beyond the scope of this review.

Salmonella spp

Antimicrobial therapy is not recommended for uncomplicated salmonellosis, but appropriate antibiotics are crucial for patients with invasive infec-

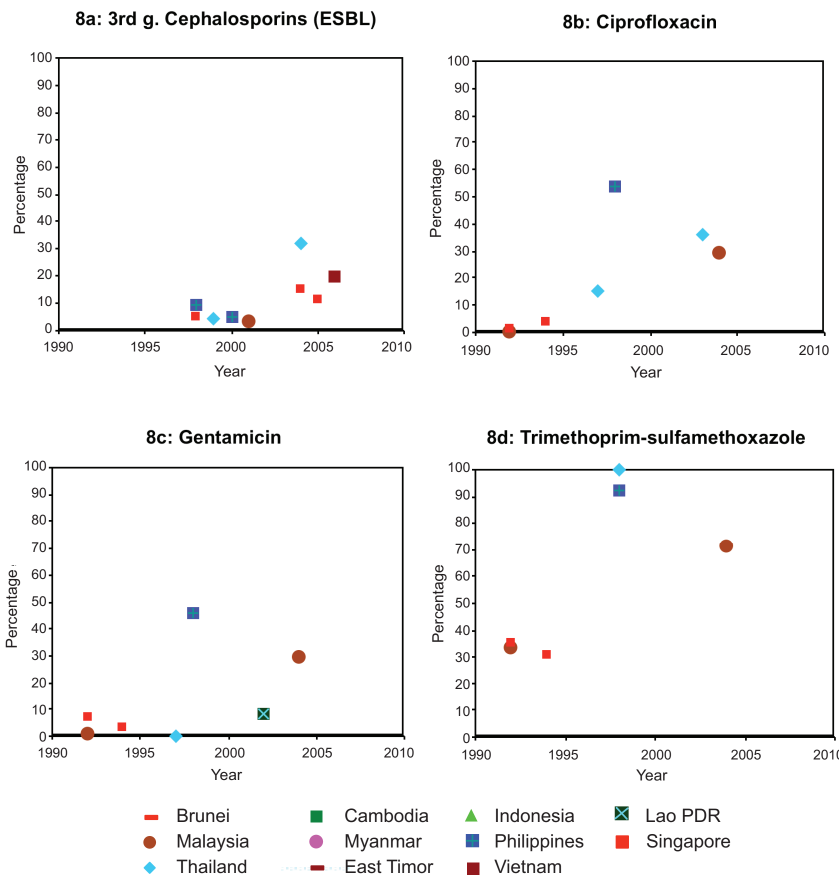

Fig 8–Resistance among *E. coli* from SE Asia.

tions. Fluoroquinolones are the optimal choice for treatment of typhoid fever, but the emergence of resistance to fluoroquinolones suggests their use should be restricted. Traditional first-line drugs should be considered (tetracycline, chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole), or more expensive parenteral ceftriaxone in severe infections. Trends in tetracycline, chloramphenicol, ciprofloxacin, and ampicillin resistance among all *Salmonella* spp are shown in Figs 11a-11d.

Resistance to tetracycline among *Salmonella* spp in Thailand was 58% in 1998 (Isenbarger *et al*, 2002) and 100% in 2003 (Angkititrakul *et al*, 2005). In Malaysia, Vietnam, and Indonesia, tetracycline resistance rates were much lower: 11% in 1995 (Malaysia), 7% in 1998 (Vietnam) and 21-20% in 1998-1999 (Indonesia) (Fig 11a).

Chloramphenicol resistance among Thai *Salmonella* spp decreased slightly over the years, from 35% in 1993, 28% in 1998 to 24% in 2003. In Indonesia, resistance rates remained stable: 16% in 1998 and 13% in 1999. In Lao PDR, Malaysia, and Vietnam, the resistance rates were 12% (2002), 7% (1995), and 0% (1998), respectively (Fig 11b).

Resistance rates to ciprofloxacin were lower than to the other antibiotics tested in this species (range 0-0.5%) (Fig 11c). However, in almost all studies included in our analysis, antimicrobial susceptibility testing was performed using the disk diffusion method. This method does not detect reduced susceptibitly to ciprofloxacin (MIC ≥0.25 μg/ml). In a Finnish study of *Salmonella* isolates from travelers returning from abroad, reduced fluoroquinolone susceptibility was particularly seen among isolates from travelers returning from SE Asia (Thailand, Indonesia, Malaysia) (Hakanen *et al*, 2001). In all these isolates a point mutation in the

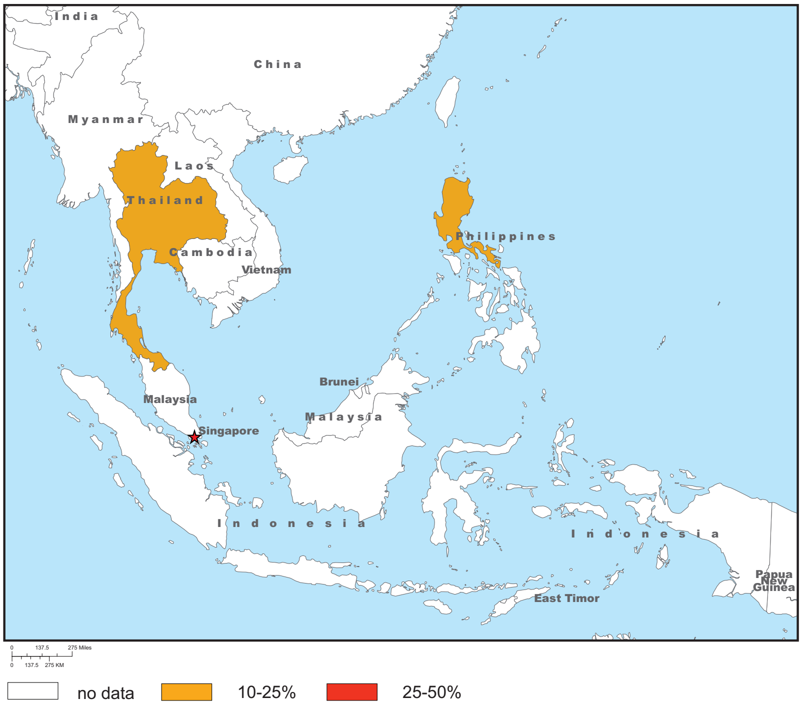

Fig 9–Prevalence of ESBL-producing *K. pneumoniae* in SE Asian countries, 1995-2007.

quinolone-resistance determining region (QRDR) of *gyrA* was present. Such isolates are important to identify, since infections with these should not be treated with standard fluoroquinolone therapy. The CLSI currently recommends nalidixic acid disk diffusion testing for as a marker for the detection of reduced susceptibility of *Salmonella* spp to fluoroquinolones, which was performed in the studies by Oyofo *et al* (2002a,b) and Isenbarger *et al* (2002). In these studies, resistance to nalidixic acid was frequent among Thai isolates (up to 33%), but not present at all among Indonesian isolates.

In Thailand, ampicillin resistance decreased from 37% in 1996 to 30% in 1998 and 10% in 2003. In Indonesia, the rates of resistance remained stable in the late 1990s: 19% in 1998 and 18% in 1999. Lower prevalences of resistance were observed in Malaysia and Vietnam, 1% in 1995 and 0% in 1998, respectively (Fig 11d). The overall resistance rates are shown in Table 9.

In Indonesia, *S.* Typhi isolates were universally susceptible to commonly used antimicrobials (Oyofo *et al*, 2002a,b; Tjaniadi *et al*, 2003), but in Lao PDR, resistance rates to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole were 12, 12, and 11%, respectively (Phetsouvanh *et al*, 2006).

A collection of non-Typhi *Salmonella* isolates was studied in Malaysia with low resistance rates found to tetracycline (11%), chloramphenicol (7%), trimethoprim-sulfamethoxazole (5%), streptomycin (4%) and ampicillin (1%). There was no resistance to ciprofloxacin or kanamycin (Lee *et al*, 2003).

Overall, resistance to quinolones seems to be emerging in SE Asia and resistance to traditional first-line antibiotics is decreasing.

Shigella spp

Worldwide it is estimated shigellosis is responsible for some 600,000 deaths each year, two-thirds of which are in children aged under 10 years (Mintz, 2008). The incidence of shigellosis is the highest in developing countries where the general standard of living and sanitary conditions

Table 9
Overall resistance rates among *Salmonella* spp clinical samples.

Antibiotic	Indonesia (% R)	Lao PDR (% R)	Malaysia (% R)	Philippines (% R)	Thailand (% R)	Vietnam (% R)
Ampicillin	7	12	1		33	0
Amoxicillin					9	
Ciprofloxacin	0				1	0
Chloramphenicol	15	12	7		30	0
Tetracycline	20		11		59	7
Gentamicin			2		2	
Trimethoprim-sulfamethoxazole	10	11	5		31	7
Cefepime				0		
Ceftazidime				0	0	
Ceftriaxone	2	0	0	0	2	
Imipenem				0	0	
Azithromycin					6	7
Amoxicillin-clavulanic acid					4	
Pefloxacin					7	
Amikacin					0	
Netilmicin					46	
Ampicillin-sulbactam					10	
Cefazolin					0	
Cefuroxime					0	
Cefotaxime					1	
Ofloxacin					2	
Kanamycin	10		0			
Piperacillin-tazobactam				0		
Norfloxacin	1				0	
Cephalothin	7					
Nalidixic acid	0				31	0
Colistin	7					
Neomycin	3		4			
Streptomycin					100	
Sulfamethoxazole					100	

R, resistance

are usually poor (Anh *et al*, 2001). *S. flexneri* and *S. sonnei* are the predominant species in developing countries. Antimicrobial treatment can reduce morbidity, mortality and transmission. The antibiotics commonly used are trimethoprim-sulfamethoxazole, tetracycline, ciprofloxacin, chloramphenicol, and ampicillin.

In 1984 and 1985, no resistance to trimethoprim-sulfamethoxazole was observed among *Shigella* spp in Myanmar, in 1989 it was 48% and in 1993 63% of isolates were resistant (Fig 12a) (Oo, 1995). In Vietnam, resistance patterns of *Shigella* spp isolates collected between 1989 and 1998 were studied by the National Program for

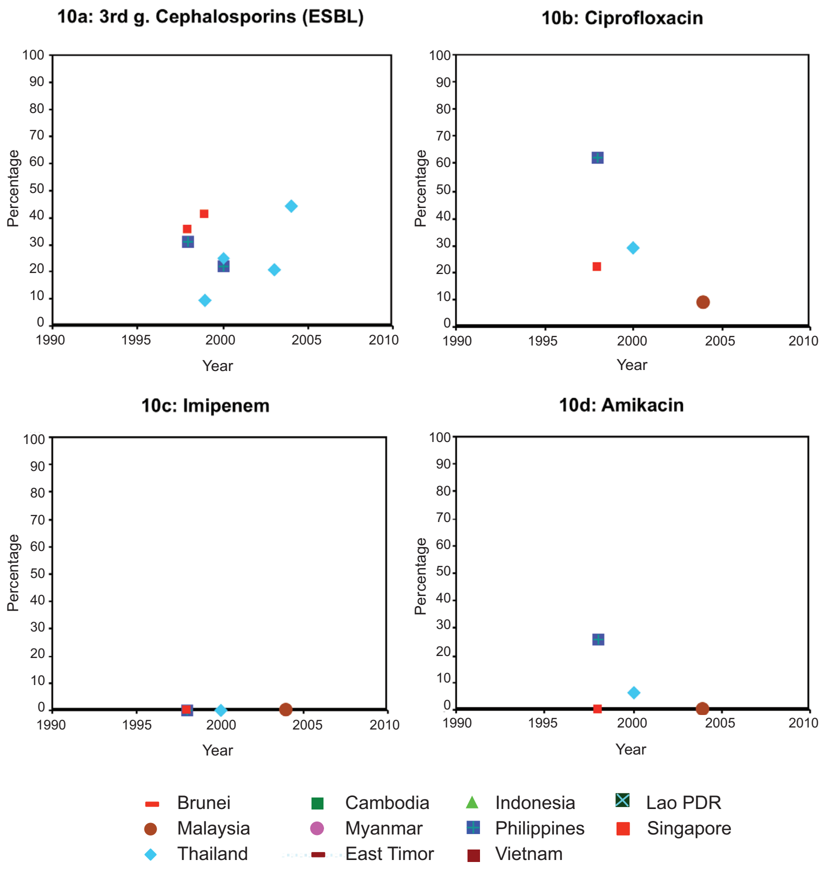

Fig 10–Resistance among *K. pneumoniae* from SE Asia.

Surveillance of Antimicrobial Resistance (NPSAR) (Anh *et al*, 2001). Resistance to trimethoprim-sulfamethoxazole increased from 25% in 1989 to 94% in 1994 and remained >70% thereafter. Trimethoprim-sulfamethoxazole resistance rates were also high in Indonesia (54% in 1998, 73% in 1999, and 67% in 2000) and in Thailand (91% during 1996-1999) (Isenbarger *et al*, 2002) (Fig 12a).

In many countries, tetracycline is not used anymore as empiric therapy for shigellosis due to high resistance rates. High resistance rates have also been seen in SE Asia. In Myanmar, tetracycline resistance among *Shigella* spp increased over the years from 0% in 1980, 41% in 1984, 63% in 1985, 90% in 1991 to 91% in 1993. In Vietnam, the prevalence of resistance has been ≥80% since 1990. In Indonesia, resistance to tetracycline was studied by Oyofo *et al* (2002a,b) and Tjaniadi *et al* (2003). Resistance was 90, 73 and 92% in 1998, 1999 and 2000, respectively. In Thailand, an even higher rate of resistance to tetracycline was observed than in Malaysia and Indonesia during the same period (Fig 12b).

Ciprofloxacin resistance among *Shigella* spp was not found in Vietnam or Indonesia (Fig 12c).

For chloramphenicol, there has been a steady increase in resistance rates over the years in Myanmar: from 0% in 1980, 41% in 1984, 63% in 1985, 75% in 1989, 90% in 1990 to 91% in 1993. In Vietnam, the resistance rates were over 60% (range 63 - 89%). In Indonesia, the prevalence of resistance decreased from 76% in 1998, to 68% in 1999 and finally 15% in 2000. In Thailand and Malaysia, resistance rates were 21% and 5%, respectively, in 1998 (Fig 12d).

Tables 10 and 11 provide additional data regarding *S. flexneri* and *S. sonnei*. Overall, the prevalences of resistance were high for ampicillin, tetracycline,

Table 10
Overall resistance rates among *Shigella flexneri* clinical samples.

Antibiotic	Indonesia (% R)	Thailand (% R)	Vietnam (% R)
Tetracycline	89	96	87
Chloramphenicol	81	61	76
Ciprofloxacin		0	0
Trimethoprim-sulfamethoxazole	66	86	52
Azithromycin		0	5
Ceftriaxone	0		
Neomycin	1		
Ampicillin	83	82	82
Colistin	2		
Kanamycin	0		
Norfloxacin	0		
Cephalothin	12		
Nalidixic acid	0	0	0

R, resistance

chloramphenicol, and trimethoprim-sulfamethoxazole among *S. flexneri* and for tetracycline, chloramphenicol, and streptomycin among *S. sonnei*, which is in agreement with trends observed worldwide (Okeke *et al*, 2005b).

OTHER GLUCOSE FERMENTING GRAM-NEGATIVE BACILLI

Microorganisms belonging to the genera *Proteus*, *Enterobacter*, *Serratia*, and *Citrobacter* are members of the family Enterobacteriaceae, of which the latter three rarely cause infections among healthy hosts, but are common nosocomial pathogens. Most information regarding antimicrobial resistance among these four bacterial species in SE Asia is from Biedenbach *et al* (1999) and Jones *et al* (2002)

Table 11
Overall resistance rates among *Shigella sonnei* clinical samples.

Antibiotic	Indonesia (% R)	Malaysia (% R)	Thailand (% R)	Vietnam (% R)
Tetracycline	36	35	92	60
Chloramphenicol	5	5	3	36
Ciprofloxacin	0		0	0
Trimethoprim-sulfamethoxazole	37	37	97	67
Azithromycin			2	28
Ceftriaxone	0			
Neomycin	0			
Ampicillin	30	7	4	62
Colistin	0			
Kanamycin	0	0		
Norfloxacin	0			
Cephalothin	10			
Nalidixic acid	0		0	0
Streptomycin	63	63		

R, resistance

Table 12
Overall resistance rates among *Proteus* spp clinical samples.

Antibiotic	Malaysia (% R)	Philippines (% R)	Thailand (% R)	Singapore (% R)
Ciprofloxacin	7			1
Trimethoprim-sulfamethoxazole	33			47
Cefepime		0	0	
Cefpirome		0	6	
Ceftazidime	0	2	20	2
Ceftriaxone	2	0	2	
Imipenem	1	4	0	
Amikacin	0			1
Ampicillin	62			60
Ampicillin- sulbactam	12			20
Cefuroxime	5			9
Piperacillin				19
Piperacillin-tazobactam	0	0	0	
Cefoperazone	0			9
Aztreonam				2
Amoxicillin-clavulanic acid				21
Gentamicin				10
Netilmicin				3
Cephalexin				40
Cefuroxime				9
Cefotiam				10
Pefloxacin				2
Norfloxacin				0
Ofloxacin				3
Nalidixic acid				4
Nitrofurantoin				45

R, resistance

along with the Philippines, Thailand, and Indonesia Antmicrobial Resistance Study Group (Biedenbach *et al*, 1999; Johnson *et al*, 1999; Lewis *et al*, 1999). They evaluated the *in vitro* activity of broad-spectrum betalactam antibiotics against isolates of clinical bacteria from the Philippines, Thailand and Indonesia collected in 1998. Infections caused by *Enterobacter*, *Serratia*, and *Citrobacter* should not be treated with third-generation cephalosporins or piperacillin-tazobactam, due to their inducable AmpC enzyme; therefore, the results for these antibiotics from this study are of limited use. Furthermore, the exact origin of the isolates in these studies, community-acquired or hospital-acquired, from an intensive care unit or a general surgery ward, was not indicated. This information is important to properly interprete the results.

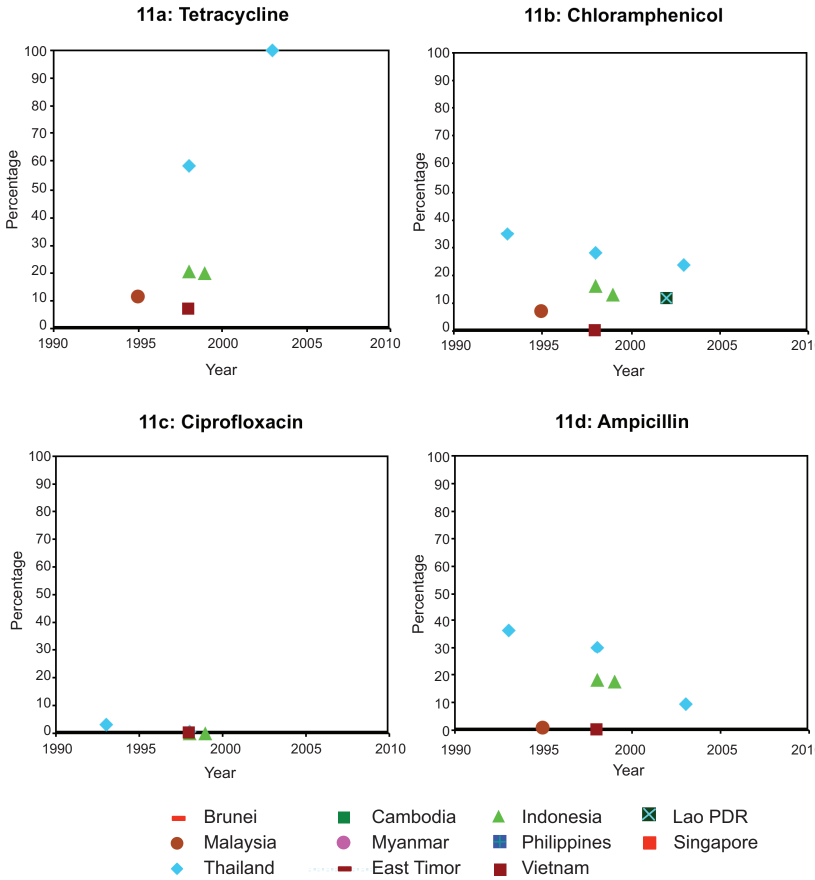

Fig 11–Resistance among *Salmonella* spp from SE Asia.

Proteus spp

Proteus spp are common causes of urinary tract infections, occasionally in normal hosts and common in patients with indwelling catheters. They have been studied for antimicrobial susceptibility in Malaysia (Raja, 2007), Singapore (Kumarasinghe *et al*, 1995), the Philippines (Johnson *et al*, 1999), and Thailand (Biedenbach *et al*, 1999). In Malaysia, *Proteus* spp from diabetic foot infections were analyzed. Of the 42 isolates, 62% were resistant to ampicillin, 33% to trimethoprim-sulfamethoxazole, 27% to ciprofloxacin, 19% to amoxicillin-clavulanic acid, and 10% to gentamicin (Raja, 2007). All isolates remained susceptible to imipenem and amikacin. In Singapore, resistance rates among *Proteus* spp from various clinical specimens to ampicillin, trimethoprim-sulfamethoxazole, nitrofurantoin and ciprofloxacin were 60, 45, 40, and 0%, respectively. In the Philippines and Thailand, isolates remained highly susceptible to broad-spectrum betalactams, except for ceftazidime, to which 20% of the indole-positive Thai isolates were resistant (Table 12).

Enterobacter spp

Data about antimicrobial resistance among *Enterobacter* spp were available from Indonesia (Lewis *et al*, 1999), the Philippines (Johnson *et al*, 1999; Bell *et al*, 2002), Singapore (Kumarasinghe *et al*, 1995, 1996; Bell *et al*, 2002), and Thailand (Biedenbach *et al*, 1999).

The SENTRY Antimicrobial Surveillance Program (1998-1999) found a presumptive ESBL prevalence among *Enterobacter* spp of 11% in Singapore and 2% in the Philippines (Bell *et al*, 2002). Thereafter, the prevalence increased to 44% in Singapore and 35% in the Philippines, for *E. cloacae* (Bell *et al*, 2003). Strains with an ESBL phenotype had high rates of resistance to other antibiotics, such as ciprofloxacin, gentamicin, and trimethoprim-

Table 13
Overall resistance rates among *Enterobacter* spp clinical samples.

Antibiotic	Indonesia (% R)	Philippines (% R)	Singapore (% R)	Thailand (% R)
Cefepime	4	0		4
Cefpirome	0	1		14
Ceftazidime	20	29	8	42
Ceftriaxone	16	9	8	28
Imipenem	0	0	1	0
Piperacillin			21	
Piperacillin- tazobactam	16	5		17
Gentamicin			9	
Ciprofloxacin			2	
Trimethoprim-sulfamethoxazole			43	
Amoxicillin-clavulanic acid			22	
Pefloxacin			2	
Amikacin			3	
Netilmicin			3	
Nitrofurantoin			41	
Ampicillin			60	
Ampicillin- sulbactam			20	
Cefuroxime			20	
Ofloxacin			2	
Norfloxacin			0	
Nalidixic acid			3	
Aztreonam			2	
Cefoperazone			11	
Cefoperazone- sulbactam			0	
Cephalexin			37	
Cefotiam			10	

R, resistance

sulfamethoxazole: 50, 58, and 83%, respectively, in Singapore, and 33, 48, and 91%, respectively, in the Philippines. In two other reports from these two countries, imipenem resistance was not detected (Kumarasinghe *et al*, 1996; Johnson *et al*, 1999). Resistance to aminoglycosides was low among isolates collected from a university hospital in Singapore from 1994 to 1995: 8% for amikacin and 3% for gentamicin, but resistance to ciprofloxacin was 11% and to trimethoprim-sulfamethoxazole 24%.

In Malaysia, *Enterobacter cloacae* from diabetic foot infections were highly susceptible to ciprofloxacin, imipenem, and gentamicin, but more resistant to trimethoprim-sulfamethoxazole (31%) (Raja, 2007).

Among strains from Indonesia and Thailand, imipenem resistance was not detected, but resistance to cefepime, a fourth-generation cephalosporin, was 4% in both countries (Biedenbach *et al*, 1999; Lewis *et al*, 1999). Non-betalactams were

Table 14
Overall resistance rates among *Serratia* spp clinical samples.

Antibiotic	Indonesia (% R)	Philippines (% R)	Thailand (% R)
Cefepime	0	0	2
Cefpirome	0	0	2
Ceftazidime	7	9	22
Ceftriaxone	7	4	11
Imipenem	7	0	0
Piperacillin-tazobactam	0	0	2

R, resistance

Table 15
Overall resistance rates among *Campylobacter jejuni* clinical samples.

Antibiotic	Indonesia (% R)	Thailand (% R)	Vietnam (% R)
Tetracycline	39		
Chloramphenicol	1		
Ciprofloxacin	31	75	1
Trimethoprim-sulfamethoxazole	88		
Ceftriaxone	37		
Azithromycin	0	2	0
Ampicillin	52		
Kanamycin	29		
Norfloxacin	30		
Nalidixic acid		72	1

R, resistance

not tested. Additional information regarding resistance among *Enterobacter* spp is shown in Table 13.

***Serratia* spp**

Antimicrobial resistance among *Serratia* spp has been studied in Indonesia (Lewis *et al*, 1999), the Philippines (Johnson *et al*, 1999), and Thailand (Biedenbach *et al*, 1999). Resistance to cefepime was present among 2% of isolates from Thailand, but not observed in isolates from the Philippines or Indonesia. A worrisome observation was the prevalence of imipenem resistance among Indonesian isolates (7%). Imipenem resistance was not found among isolates from the Philippines or Thailand (Table 14).

***Citrobacter* spp**

Citrobacter spp were studied in 1998 in the Philippines (Johnson *et al*, 1999) and Thailand (Biedenbach *et al*, 1999). Resistance to cefepime was seen in 0% and 6% and to imipenem in 0% and 2% from the Philippines and Thailand, respectively. No data were available regarding susceptibilty of *Citrobacter* spp to non-betalactam antibiotics.

OTHER (GLUCOSE-NON-FERMENTING) BACTERIA

Campylobacter jejuni

Infection due to *Campylobacter jejuni* has been recognized as a frequent cause of bacterial gastroenteritis. Treatment of presumed *Campylobacter* gastroenteritis in otherwise healthy individuals is symptomatic and does not include antibiotics. When antibiotic therapy is indicated, macrolides, quinolones and tetracycline are most often used. Antimicrobial resistance among *Campylobacter jejuni* was studied in Thailand, Vietnam, and Indonesia (Isenbarger *et al*, 2002; Oyofo *et al*, 2002 a,b; Tjaniadi *et al*, 2003). In 1997, resistance to ciprofloxacin was 75% and 1%, respectively, among Thai and Vietnamese isolates, but resistance to azithromycin was low in Thailand (2%) and absent in Vietnam (Isenbarger *et al*, 2002). From Indonesia, there were much data about *Campylobacter*. All reported a similar trend of the emergence of ciprofloxacin-resistant strains (up to 43% in 2000), stable high prevalences of tetracycline resistance (>30%), and no resistance to azithromycin (Table 15).

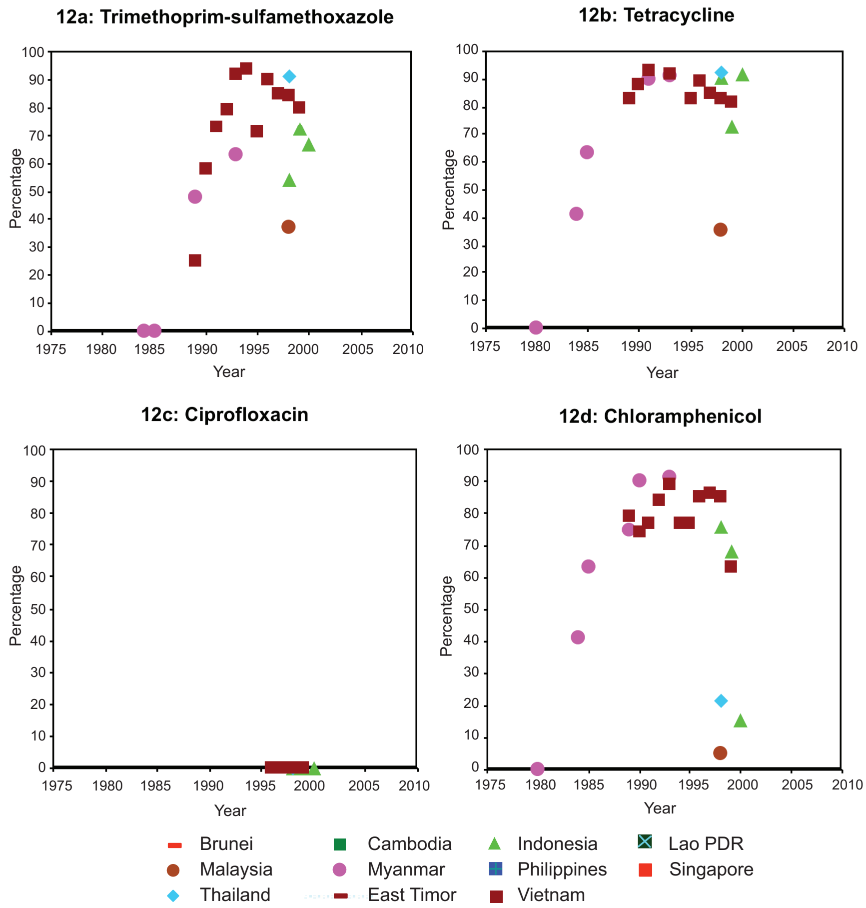

Fig 12–Resistance among *Shigella* spp from SE Asia.

In one Malaysian report of isolates collected in 1992, strains were highly susceptible to various antibiotic classes, including ceftazidime, but during several surveillance studies conducted after 1992, ceftazidime resistance was over 10% in the Philippines, Vietnam, and Malaysia. In Indonesia, resistance to ceftazidime was 7% in 1998 (Lewis *et al*, 1999).

Except for Malaysian strains collected in 1992, ciprofloxacin resistance rates among *Pseudomonas* spp were over 10% in Malaysia (after 1992), Vietnam, Thailand and Singapore. In Malaysia, resistance increased from 1% in 1992 to 11% in 2005. The highest resistance rate was found in Vietnam, 82% in 2000 among isolates causing surgical site infections (Fig 13a).

Imipenem resistance was detected in Malaysian *Pseudomonas* strains in 1992 (1%). Resistance rates of less than 10% were reported in Malaysia (2004), Indonesia, and Vietnam, but in Singapore, the Philippines and Thailand, rates were ≥10% (Fig 13c).

Amikacin resistance in Malaysia was less than 10% (range 3-7%). In Singapore, Thailand, and Vietnam, *Pseudomonas* isolates were more frequently resistant to

Pseudomonas aeruginosa

Pseudomonas aeruginosa strains exhibit intrinsic resistance to several betalactams and may acquire additional resistance mechanisms, such as broad-spectrum beta-lactamases, that further reduce their susceptibilty to antimicrobial drugs. The Vietnamese extended-spectrum beta-lactamase (VEB)-1, first described in a strain from Vietnam, was present in 23% of *Pseudomonas aeruginosa* isolated from Thailand in 1999, causing complete resistance to the oxymino-cephalosporins (Girlich *et al*, 2002). Total resistance to ceftazidime in Thailand increased from 27% in 1999, 52% in 2001 to 40% in 2002 (Fig 13b).

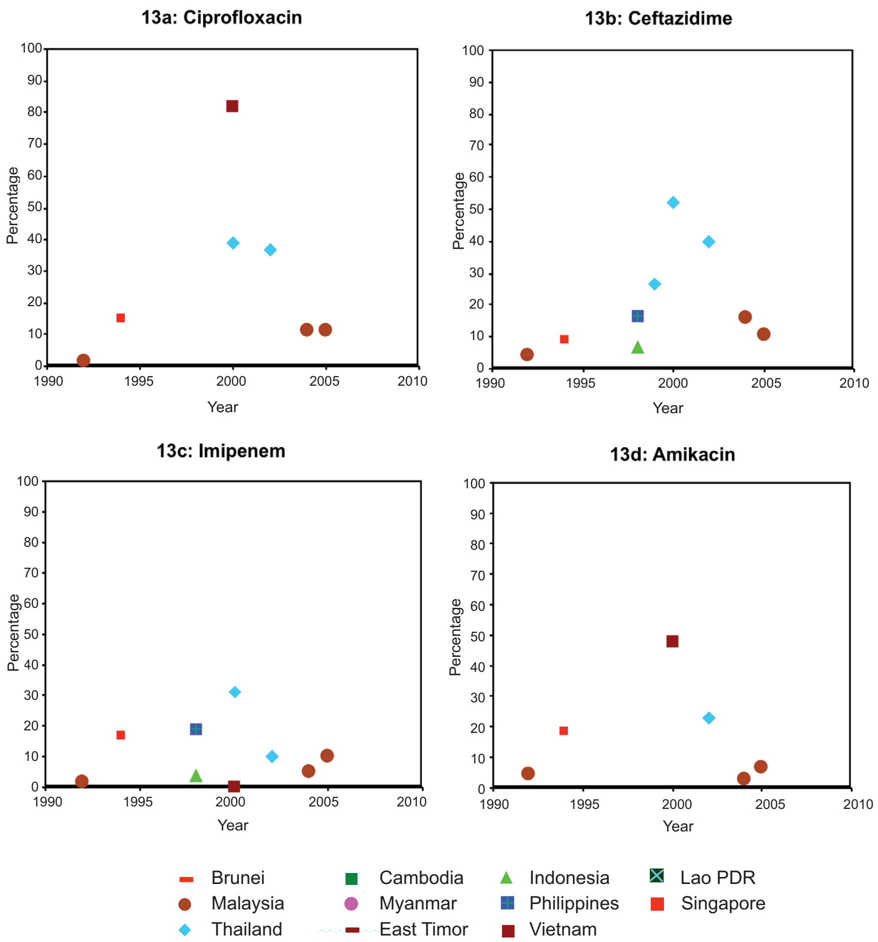

Fig 13–Resistance among *Pseudomonas aeruginosa* from SE Asia.

amikacin. The highest resistance rate was found in Vietnam (48% in 2000) (Fig 13d). None of the reports on resistance among *Pseudomonas* isolates presented prevalences of multi-drug resistance (resistance to three more antibiotic classes) which is a matter of concern in many countries.

Acinetobacter spp

Acinetobacter spp – principally *A. baumannii* – are opportunistic pathogens of great concern, especially in intensive care units and for burn patients. *A. baumannii* has shown a remarkable propensity to develop resistance to virtually every antibiotic class (Livermore and Woodford, 2006). Multidrug-resistant (MDR) *A. baumannii* and extensively-resistant *A. baumannii* (XDR) have been reported with increasing frequency from around the world, but recent data from SE Asia are lacking (Doi *et al*, 2009). In a study from the National University Hospital in Singapore of 165 *Acinetobacter* spp isolates collected in 1991, resistance to ceftazidime was almost 50%, to aminoglycosides was 34-54%, to quinolones was 4-21%, and to imipenem was 5% (Kumarasinghe *et al*, 1995). In another study from the same hospital three years later, *Acinetobacter* spp were one of the most commonly isolated gram-negative bacilli from blood cultures (Kumarasinghe *et al*, 1996). The authors reported moderate prevalences of resistance to ceftazidime (23%), piperacillin (26%), gentamicin (27%), ciprofloxacin (26%), and trimethoprim-sulfamethoxazole (15%). Resistance to imipenem and amikacin was less frequent: 7% and 8%, respectively (Kumarasinghe *et al*, 1996). Among Thai isolates collected in 2002 from 24 hospitals across Thailand, resistance rates were much higher: 56% to ceftazidime, 24% to impenem, 52% to amikacin, 56% to ciprofloxacin and 66%

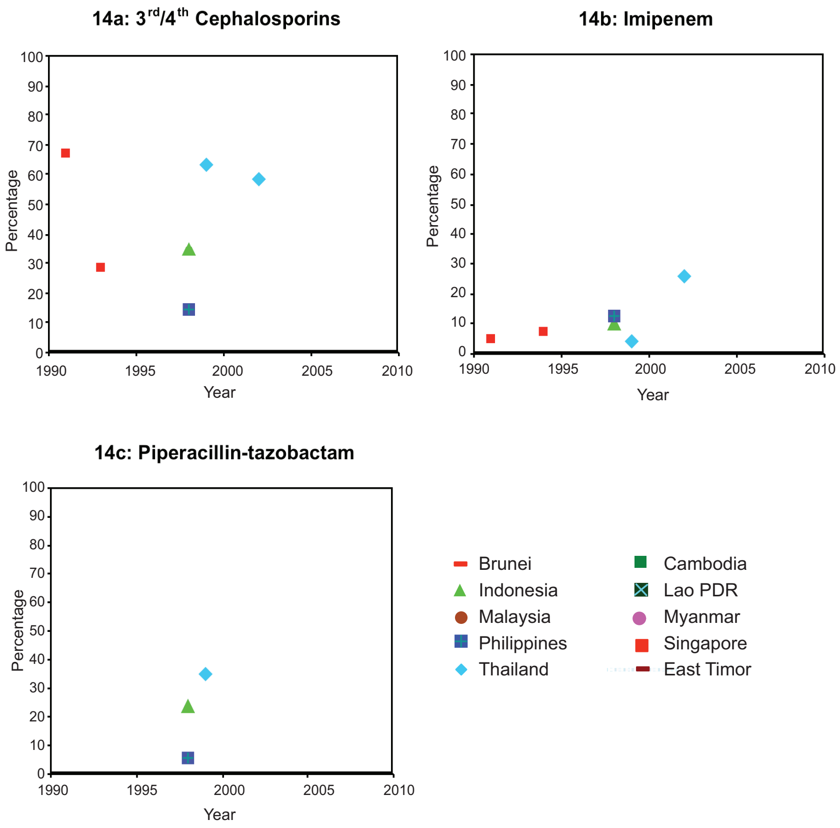

Fig 14–Resistance among *Acinetobacter* spp from SE Asia.

to trimethoprim-sulfamethoxazole, but whether MDR isolates were present is unknown. In this study, the isolates from community-acquired infections were generally more sensitive to antibiotics than those from hospital-acquired infections (Danchaivijitr *et al*, 2005). The data of resistance rates to several broad-spectrum betalactams from Singapore, Thailand, Indonesia, and the Philippines are shown in Fig 14a to 14c. In 1998 imipenem resistance was 10% and 13% in Indonesia and the Philippines, respectively (Fig 14b, Table 16).

Burkholderia pseudomallei

B. pseudomallei, the causative microorganism of melioidosis, an endemic disease in most of SE Asia, has been studied in Lao PDR, Malaysia and Thailand. In Lao PDR, *B. pseudomallei* was isolated from blood cultures in 14 out of 4,460 patients, but the mortality rate in these patients was 60%. The resistance rate to chloramphenicol was 1% and to trimethoprim-sulfamethoxazole 0% (Phetsouvanh *et al*, 2006). In Malaysia, resistance to cefoperazone, a third-generation cephalosporin, was 14%, but to cefoperazone-sulbactam was 0% (Koay *et al*, 1997). In Thailand, resistance to trimethoprim-sulfamethoxazole was 13% by the E-test and 71% by disk diffusion (Wuthiekanun *et al*, 2005).

RESISTANCE AMONG COMMENSALS

Carriage of strains of *S. pneumoniae* has been studied in Malaysia, the Philippines, Singapore, Thailand, and Vietnam and commensal *E. coli* in the Philippines and Thailand.

Carriage of isolates of *S. pneumoniae*

Knowledge of the prevalence of carriage of resistant pneumococci in children is likely to have predictive value in defining the status of resistance in a certain region. The general trend observed among

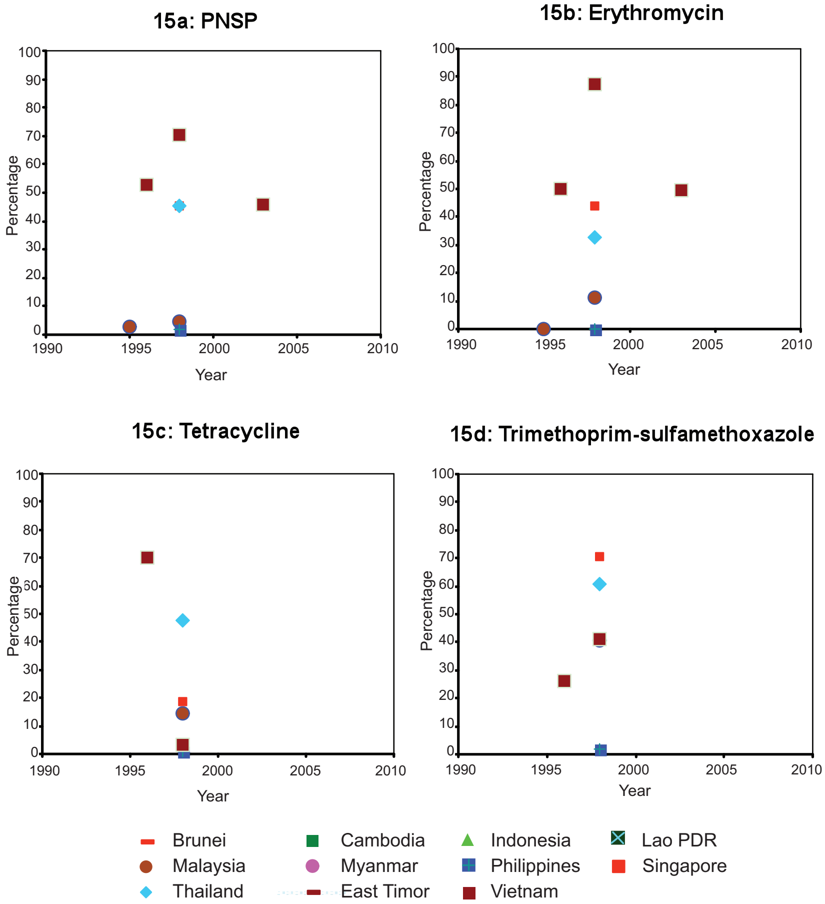

Fig 15–Resistance among *S. pneumoniae* from SE Asia (from non-clinical material).

the different collections studied was resistance to penicillin and erythromycin had reached high levels. In Malaysia, the PNSP rate increased from 3% in 1995 to 5% in 1998. In Vietnam, the prevalence of PNSP increased from 53% in 1996 to 70% in 1998 and decreased thereafter to 46% in 2003. In 1998, the PNSP rate was only 2% in the Philippines, but 46% in Thailand and Singapore (Fig 15a).

Erythromycin resistance in *S. pneumoniae* isolates was found in Malaysia, Vietnam, Singapore, Thailand, and the Philippines, but some geographical variation existed. In Malaysia, resistance to erythromycin was 0% in 1995 and 11% in 1998. In Vietnam, levels of resistance were much higher: 50% in 1996, 88% in 1998 and 49% in 2003. In 1998, resistance rates to erythromycin were 44, 33 and 0%in Singapore, Thailand and the Philippines, respectively (Fig 15b).

For tetracycline, the highest prevalence of resistance was found among Vietnamese pneumococci (70% in 1996). The lowest prevalence was observed in strains from the Philippines (1% in 1998) (Fig 15c). Similarly, prevalences of resistance to trimethoprim-sulfamethoxazole in the SE Asian countries ranged from 2% to 71% and are shown in Fig 15d. Thus, increasing levels of resistance to penicillin and other antimicrobials in carriage isolates of *S. pneumoniae* are consistent with increasing drug resistance among clinical isolates.

Commensal *E. coli*

The fecal flora of the general population represents a potentially large reservoir of antimicrobial-resistant bacteria and mobile genetic elements with resistance genes. Therefore, commensal *E. coli* can be used as an indicator organism for resistance. In Thailand, the antimicrobial resistance profiles of *E.coli* from swine and

Table 16
Overall resistance rates among *Acinetobacter* spp clinical samples.

Antibiotic	Indonesia (% R)	Philippines (% R)	Singapore (% R)	Thailand (% R)
Ciprofloxacin			11	58
Trimethoprim-sulfamethoxazole			40	
Cefepime	19	12	51	
Cefpirome	29	9	60	
Ceftazidime	29	14	41	59
Ceftriaxone	29	21	52	73
Imipenem	10	13	6	24
Pefloxacin		20		
Amikacin			24	54
Netilmicin			32	
Nitrofurantoin			95	
Ampicillin			93	
Ampicillin-sulbactam			6	
Cefuroxim			92	
Ofloxacin			14	
Piperacillin			40	
Piperacillin-tazobactam	24	5		35
Norfloxacin			39	
Nalidixic acid			38	
Cefoperazone			68	
Cefoperazone-sulbactam			0	
Cephalexin			88	
Cefotiam			97	

R, resistance

chicken farm workers were determined. The prevalences of resistance to tetracycline, chloramphenicol, ampicillin and nalidixic acid were 67, 56, 44, and 33%, respectively. All strains were susceptible to ciprofloxacin and ceftriaxone (Hanson, *et al*, 2002). Nys *et al* (2004) studied fecal *E. coli* from healthy adult volunteers from the Philippines; high resistance rates were found for all antibiotics tested, including tetracycline (90%), trimethoprim (84%), ampicillin (81%), chloramphenicol (64%), ciprofloxacin (49%), gentamicin (33%), and cefazolin (21%).

CONCLUSION

Antimicrobial resistance to pathogenic bacteria is on the rise in SE Asia. The high prevalences of resistance to betalactam and non-betalactam antibiotics by *S. pneumoniae* and *N. gonorrhoeae* is of great concern. Pathogens causing diarrheal diseases are now often resistant to inexpensive, older antibiotics. Among Enterobacteriaceae and nonfermenting gram-negative bacteria, resistance to virtually all antibiotic classes have been reported, but whether MDR gram-negative bacteria were a problem is unknown. The picture for MRSA is not fully clear yet as well, but in some countries, such as Singapore, MRSA is endemic in the health care system. There is still much that is unknown. From January 1, 1995 to January 1, 2007, 97 papers were published with accurate data on the resistance patterns among major pathogens. None of these reports contained data from East Timor. From Brunei and Cambodia, only data on *N. gonorrhoeae* were available. From Myanmar, a single report on *Shigella* was available. Thailand is the country with the most published data. Most SE Asian countries have been participating in one of the large international surveillance programs. The Philippines and Singapore are, for example, part of the Asia-Pacific group of the SENTRY Antimicrobial Surveillance Program. In 1996, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) was initiated, and as of 2010, six SE Asian countries were participating. These large international surveys have shown large-scale secular trends, often with high-quality microbiological data. However, from resistance data from other parts of the world, we know there is great variation in resistance rates by hospital and patient type within countries. In a large country, such as Indonesia with more than 17,000 islands, it is likely resistance rates differ between one region and another. Good local data are essential, and for this, good laboratory facilities and qualified personnel are needed.

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