Epidemiology and Burden of Multidrug-resistant Bacterial Infection in a Developing Country

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ABSTRACT

Little is known about the excess mortality caused by multidrug-resistant (MDR) bacterial infection in low- and middle-income countries (LMICs). We retrospectively obtained microbiology laboratory and hospital databases of nine public hospitals in northeast Thailand from 2004 to 2010, and linked these with the national death registry to obtain the 30-day mortality outcome. The 30-day mortality in those with MDR community-acquired bacteraemia, healthcare-associated bacteraemia, and hospital-acquired bacteraemia were 35% (549/1,555), 49% (247/500), and 53% (640/1,198), respectively. We estimate that 19,122 of 45,209 (43%) deaths in patients with hospital-acquired infection due to MDR bacteria in Thailand in 2010 represented excess mortality caused by MDR. We demonstrate that national statistics on epidemiology and burden of MDR in LMICs could be improved by integrating information from readily available databases. The prevalence and mortality attributable to MDR in Thailand are high. This is likely to reflect the situation in other LMICs.

INTRODUCTION

The emergence of antimicrobial resistance (AMR) is of major medical concern, particularly in low- and middle-income countries (LMICs).[1,2] In LMICs, antibiotic use is increasing with rising incomes, affordable antimicrobials and the lack of stewardship in hospital and poor control of over-the-counter sales. This is driving the emergence and spread of multidrug-resistant (MDR) pathogens in community and hospital settings. Hospital data from LMICs suggest that the cumulative incidence of community-acquired Extended-Spectrum Beta-Lactamase (ESBL) producing *Escherichia coli* and *Klebsiella pneumoniae* infections are increasing over time.[3,4] A recent report from the International Nosocomial Infection Control Consortium (INICC) also showed that the prevalence of AMR organisms causing hospital-acquired infections (HAI) in ICUs in LMICs is much higher than those in the United States (US).[5]

Attributable mortality, generally defined as the difference in mortality between those with and without the condition of interest, is an important parameter used to estimate the burden of AMR. In the US, it is estimated that mortality from infection attributable to AMR is 6.5%,[6] leading to an estimate of 23,000 deaths attributable to AMR each year.[7] In the European Union, it is estimated that the number of deaths attributable to selected antibiotic-resistant bacteria is about 25,000 each year.[8] There is limited information on mortality attributable to AMR in LMICs. The

mortality attributable to ventilator-associated pneumonia in ICUs in Colombia, Peru, and Argentina is estimated to be 17%, 25%, and 35%, and is associated with a high percentage of AMR organisms.[9-11] The mortality attributable to ESBL and methicillin-resistance *Staphylococcus aureus* (MRSA) is estimated to be 27% and 34% in neonatal sepsis in Tanzania,[12] which has been used to postulate an estimate that 58,319 deaths could be attributable to ESBL and MRSA in India alone.[2] In an effort to harmonize the surveillance systems of AMR, a joint initiative between the European Centre for Disease Prevention and Control (ECDC) and the Centres for Disease Prevention and Control (CDC) have developed standard definitions of multidrug-resistance (MDR).[13]

We recently combined large data sets from multiple sources including microbiology databases, hospital admission databases, and the national death registry from a sample of ten public hospitals in northeast Thailand from 2004 to 2010.[3,14] We defined community-acquired bacteraemia (CAB) as the isolation of a pathogenic bacterium from blood taken in the first 2 days of admission and without a hospital stay in the 30 days prior to admission, healthcare-associated bacteraemia (HCAB) as the isolation of a pathogenic bacterium from blood taken in the first 2 days of admission and with a hospital stay within 30 days prior to the admission, and hospital-acquired bacteraemia (HAB) as the isolation of a pathogenic bacterium from blood

77 taken after the first 2 days of admission.[3,14] We reported an increase in the incidence of CAB,
78 HCAB and HAB over the study period, and that bacteraemia was associated with high case
79 fatality rates (37.5%, 41.8% and 45.5%, respectively).[3,14] Here, we apply ECDC/CDC standard
80 definitions of MDR to this large data set to evaluate the prevalence, trends, and mortality
81 attributable to MDR bacteria isolated from the blood. We then estimate the number of deaths
82 attributable to MDR in Thailand nationwide.
83
84 **RESULTS**
85 We contacted all 20 provincial hospitals in Northeast Thailand to participate in the study. All
86 provincial hospitals were equipped with all basic medical specialties and intensive care units
87 (ICUs). Agreement was obtained from 15 (75%) hospitals, of which ten had hospital databases
88 and microbiological laboratory databases as electronic files in a readily accessible format.[3,14] Of
89 these ten hospitals, nine had databases of antimicrobial susceptibility testing results as
90 electronic files for the study (Figure 1). The median bed number for the nine hospitals included
91 in the analysis was 450 beds (range 300 to 1,000 beds). Of these, three had data available for
92 the period 2004-2010, two between 2007-2010, three between 2008-2010 and one between
93 2009-2010. Overall, 1,803,506 admission records from 1,255,571 patients were evaluated. A
94 total of 20,803 (1.2%) admission records had at least one blood culture positive for pathogenic

organisms during admission. Of 10,022 patients with first episodes of bacteraemia caused by *S. aureus, Enterococcus* spp, *E. coli, K. pneumoniae, P. aeruginosa* and *Acinetobacter* spp., 226 patients (2%) were excluded because the causative organisms were tested for susceptibility to fewer than three antimicrobial categories. Therefore, a total of 9,796 first episodes of bacteraemia caused by *S. aureus* (n=1,881)*, Enterococcus* spp (n=342), *E. coli* (n=4,279)*, K. pneumoniae* (n=1,661)*, P aeruginosa* (n=568), and *Acinetobacter* spp. (n=1,065) were evaluated in the analysis. The proportion of bacteria being MDR was highest in HAB and lowest in CAB for all organisms (all p<0.001 except for *Enterococcus* spp., Table 1).

Staphylococcus aureus

Of CAB, HCAB and HAB caused by *S. aureus*, 8%, 28%, and 50% were caused by MDR *S. aureus*, respectively (p<0.001). Almost all MDR *S. aureus* were MRSA (92% [357/389], Table 2). We did not observe a trend in the proportion of *S. aureus* bacteremia being caused by MRSA (Figure 2). Vancomycin non-susceptible *S. aureus* was found in <1% of tested isolates (6/1,380).

***Enterococcus* species**

MDR *Enterococcus* spp. were not found in CAB (0/176) and HCAB (0/49), while 3% (4/117) of *Enterococcus* spp. causing HAB were MDR. Of CAB caused by *Enterococcus* spp., 15% (20/134) and 23% (35/153) was non-susceptible to ampicillin and gentamicin, respectively (Table3), while 42% (34/81) and 62% (63/101) of HAB caused by *Enterococcus* spp. were non-susceptible to those agents, respectively (both p<0.001). Vancomycin non-susceptible *Enterococcus* spp. was found in 4% of tested isolates (15/338).

Escherichia coli

Of CAB, HCAB and HAB caused by *E. coli*, 35%, 58% and 63% were caused by MDR *E. coli*, respectively (p<0.001). Of *E. coli* causing CAB, 79% (2,246/2,843), 16% (501/3,076), 24% (728/3,000), 58% (1,738/3,007), and 17% (559/3,346) were non-susceptible to commonly-used antimicrobials for community-acquired infections such as ampicillin, cefotaxime, ciprofloxacin, trimethoprim-sulphamethoxazole, and gentamicin, respectively (Table 4). From 2004 to 2010, the proportions of community-acquired *E. coli* bacteraemia being caused by *E. coli* non-susceptible to extended-spectrum cephalosporins rose from 5% (9/169) to 23% (186/815) (p=0.04) (Figure 3). The proportions of healthcare-associated and hospital-acquired *E. coli* bacteraemia being caused by *E. coli* non-susceptible to extended-spectrum cephalosporins were high (44% [204/465] and 52% [190/368], respectively), but a significant trend over time

was not observed (p=0.18 and p=0.63, respectively). Carbapenem non-susceptible *E. coli* was found in <1% of tested isolates (12/3,838).

Klebsiella pneumoniae

Of CAB, HCAB and HAB caused by *K. pneumoniae,* 14%, 36%, and 66% were caused by MDR *K. pneumoniae*, respectively (p<0.001). Of *K. pneumoniae* causing CAB, 16% (146/902), 16% (143/894), 23% (198/876), and 9% (94/999) were non-susceptible to cefotaxime, ciprofloxacin, trimethoprim-sulphamethoxazole and gentamicin, respectively (Table 5). From 2004 to 2010, the proportions of community-acquired *K. pneumoniae* bacteraemia being caused by *K. pneumoniae* non-susceptible to extended-spectrum cephalosporins rose from 12% (6/50) to 24% (64/263) (p=0.04) (Figure 4). The proportions of healthcare-associated and hospital-acquired *K. pneumoniae* bacteraemia being caused by *K. pneumoniae* non-susceptible to extended-spectrum cephalosporins were also high (40% [71/177] and 71% [304/431], respectively), but a significant trend over time was not observed (p=0.16 and p=0.35, respectively). Carbapenem non-susceptible *K. pneumoniae* was found in <1% of tested isolates (11/1,555).

Pseudomonas aeruginosa

Of CAB, HCAB and HAB caused by *P. aeruginosa,* 5%, 10%, and 25% were caused by MDR *P. aeruginosa*, respectively (p<0.001). Of *P. aeruginosa* causing HAB, 38% (68/179), 27% (48/177), 23% (39/169) and 26% (42/164) were non-susceptible to commonly-used antimicrobials for HAI such as ceftazidime, amikacin, ciprofloxacin and carbapenems, respectively (Table 6). We did not observe a trend in the proportions of *P. aeruginosa* being caused by *P. aeruginosa* that were non-susceptible to any specific antibiotic group (Figure 5).

***Acinetobacter* species.**

Of CAB, HCAB and HAB caused by *Acinetobacter* spp., 28%, 50%, and 75% were caused by MDR *Acinetobacter* spp., respectively (p<0.001). Of *Acinetobacter* spp. causing HAB, 75% (377/500), 63% (310/495), 67% (322/481) and 64% (315/490) were non-susceptible to ceftazidime, amikacin, ciprofloxacin and carbapenems, respectively (Table 7). There was borderline evidence that the proportion of hospital-acquired *Acinetobacter spp.* bacteremia being caused by *Acinetobacter spp.* non-susceptible to carbapenem rose from 49% (19/39) in 2004 to 65% (70/108) in 2010 (p=0.10) (Figure 6). Non-susceptibility to colistin was observed in 3% of tested isolates (2/63).

Mortality attributable to MDR

166 The 30-day mortality in patients with CAB, HCAB and HAB caused by MDR bacteria was 35%
167 (549/1,555), 49% (247/500), and 53% (640/1,198), compared with 32% (1,595/4,924), 37%
168 (264/716), and 42% (383/903) in CAB, HCAB, and HAB caused by non-MDR bacteria,
169 respectively (Figure 7). In the final multivariable logistic regression model, gender, age group,
170 year of admission and time to bacteraemia (for HAB) were included (Supplementary file 2).
171
172 If excess mortality in patients infected with MDR bacteria after adjusting for confounding factors
173 in the final multivariable model is assumed to be caused by MDR, the mortality attributable to
174 MDR was 7% (95%CI 4% to 10%, p<0.001) in CAB, 15% (95%CI 5% to 24%, p<0.001) in
175 HCAB and 15% (95%CI 2% to 27%, p<0.001) in HAB (Figure 2). Heterogeneity between
176 different organisms was clearly observed in HAB (p<0.001), and borderline evidence of
177 heterogeneity was observed in HCAB (p=0.09). The heterogeneity observed in HCAB and HAB
178 was largely caused by MDR *Acinetobacter* spp. (Figure 7B and 7C). Mortality attributed to MDR
179 was highest for hospital-acquired MDR *Acinetobacter* bacteraemia (41%).
180
181 Using our estimated mortality attributed to MDR bacteraemia (Figure 7C) and national statistics
182 of HAI caused by MDR bacteria, we further estimated that 19,122 of 45,209 (43%) deaths in
183 patients with HAI due to MDR bacteria in Thailand in 2010 represented excess mortality caused

184 by MDR (Table 8). All parameters used to estimate the number of excess deaths in Thailand are
185 shown in Supplementary file 2.
186
187 **DISCUSSION**
188 This study presents detailed antimicrobial susceptibility data on common pathogenic bacteria,
189 the association of MDR with infection acquisition (community-acquired, healthcare-associated
190 and hospital-acquired), and excess mortality from MDR in a developing country. Our estimate of
191 excess deaths caused by MDR in HAI patients in Thailand (19,122 deaths per year in a country
192 of about 66 million population in 2010) is large compared to those estimated in USA (23,000
193 death per year in a country of 316 million population in 2013)[7] and the European Union (25,000
194 deaths per year in EU of about 500 million population in 2007).[8] Our study highlights the need
195 for public health officials and international health organizations to improve systems to track and
196 reduce the burden of AMR in LMICs. Our estimated mortality for those with MDR HAI (45,209,
197 Table 2) is higher than those previously published by Pumart et al. (38,481)[15], probably because
198 we used 30-day mortality rather than in-hospital mortality.
199
200 *Acinetobacter* spp. is increasingly recognized as an important cause of HAI,[16,17] and our study
201 confirms the importance of this species as a leading cause of hospital-acquired MDR infection in

202 a developing tropical country.[14,18] The high mortality observed in MDR *Acinetobacter* spp.
203 bacteraemia is because treatment options are limited and those available are associated with
204 toxicity.[19] The high proportions of *S. aureus*, *E. coli* and *K. pneumoniae* bactaeremia being
205 caused by MRSA and *E. coli* and *K. pneumoniae* non-susceptible to extended-spectrum
206 cephalosporins, respectively, are consistent with previous reports from other tropical countries.[9-
207 11] The rising proportions of community-acquired *E. coli* and *K. pneumoniae* bacteremia being
208 caused by *E. coli* and *K. pneumoniae* non-susceptible to extended-spectrum cephalosporins,
209 and the rising proportion of hospital-acquired *Acinetobacter* bacteraemia being causing
210 *Acinetobacter* non-susceptible to carbapenem suggest that the burden of AMR in Thailand is
211 deteriorating over time.
212
213 A limitation of this study is that more complete clinical data were not available. Mortality
214 attributable to MDR could be overestimated if MDR infection was associated with more severely
215 ill patients in ICUs. However, our estimated attributable mortality is comparable to the previous
216 reports. For example, our estimated mortality attributable to MDR *Acinetobacter* bacteraemia
217 (40.6%) is comparable to the mortality attributable to imipenem resistant *Acinetobacter*
218 bacteraemia reported by Kwon *et al.* in Korea (41.1%), which was adjusted by severity of
219 illness.[20,21] In addition, data on hospitalization in other hospitals not participating in the study (for

example, a smaller community hospital or a private hospital in the province) were not available, which could have resulted in a misclassification of CAB, HCAB and HAB in some cases. We also note that data on attributable mortality from different countries is difficult to compare because of the differing study designs. For example, our mortality outcome is the overall 30-day mortality, including both directly and indirectly contributed to MDR, while an EU study only considered directly attributable deaths.[8] The p values for trends were generated by the stratification method; therefore, the analysis was not biased towards the increasing availability of the hospital data over the study period. Nonetheless, the trends could be affected by an increasing use of blood culture, changes in antimicrobial agents tested for susceptibility, and greater standardization of laboratory methodologies over time.[23] It is likely that burdens of MDR similar to that observed in our study are present in many secondary and tertiary hospitals in tropical LMICs, particularly where extended-spectrum cephalosporins and carbapenem are widely used. Nonetheless, resources for diagnostics, methodologies used in the laboratories, and study designs need to be carefully considered when performing a comparison between different settings.

Despite the increasing global focus on AMR in LMICs, considerable gaps remain in our understanding of the scale of the problem. We have demonstrated that the integration of information from readily available routinely collected databases can provide valuable information on the trends and mortality attributable to AMR in Thailand. The methodology used in our study could be applied to explore the burden of AMR in other LMICs where microbiological facilities and hospital admission database are available.

MATERIALS AND METHODS

Study Population

From 2004 to 2010, Thailand was classified as a lower-middle income country with an average income of $4,782 per person per year in 2010.[22] Northeast Thailand consists of 20 provinces covering 170,226 km^2 and had an estimated population of 21.4 million in 2010. A large proportion of the population in this area lives in rural settings, with most adults engaging in agriculture with an emphasis on rice farming. Healthcare in Thailand is mainly provided by government-owned hospitals. Each province has a provincial hospital, which provides services and care to individuals within its catchment area. Additionally, provincial hospitals act as referral hospitals for smaller community hospitals for severely ill patients. All provincial hospitals receive

254 comparable resources, which are proportional to the respective populations of the provinces.
255 Provincial hospitals, unlike smaller community hospitals, are equipped with a microbiology
256 laboratory capable of performing bacterial culture using standard methodologies for bacterial
257 identification and susceptibility testing provided by the Bureau of Laboratory Quality and
258 Standards, Ministry of Public Health (MoPH), Thailand.[23] During the study period, antimicrobial
259 susceptibility was determined in all study hospitals using the disc diffusion method according to
260 Clinical and Laboratory Standards Institute (CLSI).[24]
261
262 **Study Design**
263 We conducted a retrospective, multicentre surveillance study of all provincial hospitals in
264 Northeast Thailand. From the hospitals that agreed to participate, data were collected from
265 microbiology and hospital databases between January 2004 and December 2010. Hospital
266 number (HN) and admission number (AN) were used as a record linkage between the two
267 databases and to identify individuals who had repeat admissions. The death registry for
268 Northeast Thailand was obtained from the Ministry of Interior (MoI), Thailand, and used to
269 identify patients who were discharged from hospital but died at home shortly after, which is a
270 common practice in Thailand.[3,14] Ethical permission for this study was obtained from the Ethical
271 and Scientific Review Committees of the Faculty of Tropical Medicine, Mahidol University, and

of the MoPH, Thailand. Written consent was given by the directors of the hospitals to use their routine hospital database for research. Consent was not sought from the patients as this was a retrospective study, and the Ethical and Scientific Review Committees approved the process.

Data Collection

The microbiology laboratory data collected included hospital number (HN), admission number (AN), specimen type, specimen date, culture result, and antibiotic susceptibility profile (antibiogram). We consulted with study sites when the results of antimicrobial susceptibility testing were unclear. Hospital admission data were collected from the routine in-patient discharge report, which is regularly completed by attending physicians and reported to the MoPH, Thailand, as part of the national morbidity and mortality reporting system. The data collected included HN, AN, national identification 13-digit number, admission date, and discharge date. Date of death was also extracted from this record. Data collected from the national death registry obtained from the MoI included the national identification 13-digit number and the date of death.

Definitions

289 Bacteraemia was classified as CAB, HAB and HCAB as described previously.[3,14] Polymicrobial
290 infection was defined in patients who had more than one species of pathogenic organisms
291 isolated from the blood during the same episode, and was excluded from the analysis.
292 Information on the incidence of CAB, HCAB and HAB from all pathogenic organisms has been
293 published previously.[3,14]
294
295 The 30-day mortality of CAB and HCAB was defined as death within 30 days of the admission
296 date. The 30-day mortality of HAB was determined on the basis of a record of death within 30
297 days of the positive blood culture taken as recorded in the routine hospital database or by a
298 record of death in the national death registry. In the event that a patient had more than one
299 episode of bacteraemia, only the first episode was included in the study.
300
301 The standard definition of MDR proposed by ECDC/CDC was used.[13] In brief, MDR was defined
302 as non-susceptibility to at least one agent in three or more antimicrobial categories. Additionally,
303 methicillin-resistant *Staphylococcus aureus* (MRSA) were automatically described as MDR.[13]
304
305 **Statistical Analysis**

306 Pearson's chi-squared test and Fisher's Exact test were used to compared categorical
307 variables. A non-parametric test for trends was used to assess change in prevalence of
308 antimicrobial resistance over time stratified by hospital (using the npt_s command in STATA).
309
310 Mortality of patients with a first episode of HAB, HCAB and HAB caused by *S. aureus,*
311 *Enterococcus* spp., *E. coli, K. pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter* spp.
312 were evaluated in relation to MDR. We selected these organisms based on guidelines for MDR
313 proposed by ECDC/CDC,[13] and the fact that *E. coli* and *K. pneumoniae* were the most common
314 causes of bacteraemia caused by *Enterobacteriaceae* in our setting.[3,14] Isolates tested for less
315 than three antimicrobial categories were excluded from the analysis because they were not
316 applicable to ECDC/CDC standard definitions of MDR. To examine the association between
317 MDR and mortality, we performed a multivariable logistic regression analysis adjusting for a
318 priori selected baseline confounders. To take account of the fact that patients with CAB, HCAB,
319 and HAB were different populations with different definitions of 30-day mortality, we applied
320 models to each group (CAB, HCAB and HAB) separately. Multivariable logistic regression
321 models were developed using a purposeful selection method.[25] Potential confounding variables
322 evaluated included age, gender and admission year. In the model for HAB, time to bacteremia
323 was also evaluated as a potential confounder because there was evidence suggesting that time

to HAI was associated with mortality from HAI.[26,27] Time to bacteremia was defined as the duration between hospital admission and the date positive blood culture was taken. All models were stratified by hospital.

The mortality attributable to MDR was calculated using adjusted odds ratios (aORs) estimated by the final multivariable logistic regression models. If X was the observed mortality in patients with MDR infection, the estimated odds of mortality if they were infected with non-MDR organisms (O) would be (1/aOR)*(X/(1-X)). Assuming that excess mortality was due to MDR, then the mortality attributable to MDR would be the absolute difference between mortality in patients with MDR infection (X) and the predicted mortality if they were infected with non-MDR organisms (O/(1+O)), which would be X – (O/(1+O)).[28,29] Heterogeneity between different organisms within each group of patients (CAB, HCAB, and HAB) was assessed using the chi-squared test, and the percentage of variation due to heterogeneity (I-square) was calculated.

The number of deaths attributable to MDR in Thailand was determined using methodology described previously.[8] Data used included our estimated mortality attributable to MDR bacteraemia and cumulative incidence of HAI bacteraemia, lower respiratory track infection (LRTI), urinary tract infection (UTI), skin and soft tissue infection (SSTI), and other sites of

infection caused by MDR *S. aureus, E. coli, K. pneumoniae*, *P. aeruginosa,* and *Acinetobacter* spp. in Thailand in 2010, which have been described previously.[15] Death attributable to MDR *Enterococcus* spp. was not included as the cumulative incidence of MDR *Enterococcus* infection in Thailand was not available.[15] Attributable mortality by site of infection (LRTI, UTI, SSTI and other site) was estimated by applying correction factors corresponding to the relative mortality from infections of those sites compared to bacteraemia.[30] All analyses were performed using STATA version 14.0 (StataCorp LP, College station, Texas, USA).

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Competing Interests

We declare that no competing interests exist.

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Figure legends

Figure 1. Location of participating hospitals. These were situated in (1) Nong Khai, (2) Udon Thani, (3) Nakhon Phanom, (4) Chaiyaphum, (5) Mukdahan, (6) Yasothon, (7) Burirum, (8) Sisaket, and (9) Ubon Ratchathani provinces.

Figure 2. Trends in proportions of *Staphylococcus aureus* bacteremia being caused by MRSA in Northeast Thailand. (A) community-acquired, **(B)** healthcare-associated and **(C)** hospital-acquired *Staphylococcus aureus* bacteremia

Figure 3. Trends in proportions of *Escherichia coli* bacteremia being caused by *E. coli* non-susceptible to extended-spectrum cephalosporins in Northeast Thailand. (A) community-acquired, **(B)** healthcare-associated and **(C)** hospital-acquired *E. coli* bacteremia.

Figure 4. Trends in proportions of *Klebsiella pneumoniae* bacteremia being caused by *K. pneumoniae* non-susceptible to extended-spectrum cephalosporins in Northeast Thailand. (A) community-acquired, **(B)** healthcare-associated and **(C)** hospital-acquired *K. pneumoniae* bacteremia.

Figure 5. Trends in proportions of *Pseudomonas aeruginosa* bacteremia being caused by *P. aeruginosa* non-susceptible to carbapenem in Northeast Thailand. (A) community-acquired, **(B)** healthcare-associated and **(C)** hospital-acquired *Pseudomonas aeruginosa* bacteremia.

Figure 6. Trends in proportions of *Acinetobacter* spp bacteremia being caused by *Acinetobacter* spp non-susceptible to carbapenem in Northeast Thailand. (A) community-acquired, **(B)** healthcare-associated and **(C)** hospital-acquired *Acinetobacter* spp bacteremia.

Figure 7. Forest plot of mortality in patients with MDR bacteremia compared with non-MDR bacteremia in Northeast Thailand. (A) Community-acquired bacteraemia. **(B)** Healthcare-associated bacteraemia. **(C)** Hospital-acquired bacteraemia.

Figure 7 – source data 1

Table 1. Proportions of bacteraemias being caused by multidrug-resistant (MDR) variants of those bacteria.

Pathogens	Community-acquired bacteraemia (CAB)	Healthcare-associated bacteraemia (HCAB)	Hospital-acquired bacteraemia (HAB)	P values
MDR *Staphylococcus aureus*	94/1176 (8%)	73/259 (28%)	222/446 (50%)	<0.001
MDR *Enterococcus* spp	0/176 (0%)	0/49 (0%)	4/117 (3%)	0.02
MDR *Escherichia coli*	1177/3382 (35%)	288/494 (58%)	252/403 (63%)	<0.001
MDR *Klebsiella pneumoniae*	146/1010 (14%)	71/196 (36%)	301/455 (66%)	<0.001
MDR *Pseudomonas aeruginosa*	13/286 (5%)	10/103 (10%)	45/179 (25%)	<0.001
MDR *Acinetobacter* spp	125/449 (28%)	58/115 (50%)	374/501 (75%)	<0.001

Table 2. Antibiogram of *S. aureus* causing bacteremia in Northeast Thailand.

Antibiotic category	Antibiotic agents	CAB (n=1176 patients)	HCAB (n=259 patients)	HAB (n=446 patients)	P values
Aminoglycosides	Gentamicin	24/484 (5%)	16/84 (19%)	66/151 (44%)	<0.001
Ansamycins	Rifampin	2/129 (2%)	1/19 (5%)	0/38 (0%)	0.37
Anti-MRSA cephalosporins	Ceftaroline	NA	NA	NA	-
Cefamycins	Oxacillin *	80/1145 (7%)	67/247 (27%)	210/441 (48%)	<0.001
Fluoroquinolones	Ciprofloxacin	3/45 (7%)	2/8 (25%)	4/10 (40%)	0.01
	Moxifloxacin	NA	NA	NA	-
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	99/1139 (9%)	57/251 (23%)	185/438 (42%)	<0.001
Fucidanes	Fusidic acid	33/618 (5%)	4/170 (2%)	12/291 (4%)	0.26
Glycopeptides	Vancomycin **	4/833 (0.5%)	0/190 (0%)	2/357 (1%)	0.86
	Teicoplanin	2/66 (3%)	1/17 (6%)	0/17 (0%)	0.72
	Telavancin	NA	NA	NA	-
Glycylcyclines	Tigecycline	NA	NA	NA	-
Lincosamides	Clindamycin	118/1147 (10%)	77/251 (31%)	202/438 (46%)	<0.001
Lipopeptides	Daptomycin	NA	NA	NA	-
Macrolides	Erythromycin	138/1116 (12%)	76/240 (32%)	222/429 (52%)	<0.001
Oxazolidinones	Linezolid	0/81 (0%)	0/16 (0%)	0/32 (0%)	-
Phenicols	Chloramphenicol	6/86 (7%)	4/24 (17%)	2/14 (14%)	0.21
Phosphonic acids	Fosfomycin	14/361 (4%)	10/66 (15%)	24/141 (17%)	<0.001
Streptogramins	Quinupristin-dalfopristin	NA	NA	NA	-
Tetracyclines	Tetracycline	NA	NA	NA	-
	Doxycycline	NA	NA	NA	-
	Minocycline	NA	NA	NA	-
MDR		94/1176 (8%)	73/259 (28%)	222/446 (50%)	<0.001

NOTE: Data are number of isolates demonstrating non-susceptible to the antimicrobial over the total number of isolates tested (%). CAB=Community-acquired bacteraemia, HCAB=Healthcare-associated bacteraemia, HAB= Hospital-acquired bacteraemia, and NA=Not available. The first isolate of each patient was used. MDR (one or more of these have to apply): (i) an MRSA is always considered MDR by virtue of being an MRSA (ii) non-susceptible to ≥1 agent in ≥3 antimicrobial categories.

* Defined by using a 30 µg cefoxitin disc and an inhibition zone diameter of <21 mm.

** Defined by using a 30 µg vancomycin disc and an inhibition zone diameter of <15 mm.

Table 3. Antibiogram of *Enterococcus* spp. causing bacteraemia in Northeast Thailand.

Antibiotic category	Antibiotic agents	CAB (n=176 patients)	HCAB (n=49 patients)	HAB (n=117 patients)	P values
Aminoglycosides	Gentamicin (high level)	35/153 (23%)	24/45 (53%)	63/101 (62%)	<0.001
Streptomycin	Streptomycin (high level)	NA	NA	NA	-
Carbapenems*	Imipenem	NA	NA	NA	-
	Meropenem	1/1 (100%)	NA	3/5 (60%)	>0.99
	Doripenem	NA	NA	NA	-
Fluoroquinolones	Ciprofloxacin	37/44 (84%)	9/10 (90%)	31/37 (84%)	>0.99
	Levofloxacin	5/18 (28%)	1/6 (17%)	11/15 (73%)	0.01
	Moxifloxacin	NA	NA	NA	-
Glycopeptides	Vancomycin	9/176 (5%)	0/49 (0%)	6/113 (5%)	0.27
	Teicoplanin	0/11 (0%)	0/4 (0%)	0/10 (0%)	-
Glycylcyclines	Tigecycline	NA	NA	NA	-
Lipopeptides	Daptomycin	NA	NA	NA	-
Oxazolidinones	Linezolid	0/8 (0%)	0/2 (0%)	0/4 (0%)	-
Penicillins	Ampicillin	20/134 (15%)	6/37 (16%)	34/81 (42%)	<0.001
Streptogramins*	Quinupristin-dalfopristin	NA	NA	NA	-
Tetracycline	Doxycycline	NA	NA	NA	-
	Minocycline	NA	NA	NA	-
MDR		0/176 (0%)	0/49 (0%)	4/117 (3%)	0.02

NOTE: Data are number of isolates demonstrating non-susceptible to the antimicrobial over the total number of isolates tested (%). CAB=Community-acquired bacteraemia, HCAB=Healthcare-associated bacteraemia, HAB= Hospital-acquired bacteraemia, and NA=Not available. The first isolate of each patient was used. MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.

*Intrinsic resistance in *E. faecium* against carbapenems and in *E. faecalis* against streptogramins. When a species has intrinsic resistance to an antimicrobial category, that category is removed prior to applying the criteria for the MDR definition and is not counted when calculating the number of categories to which the bacterial isolate is non-susceptible.

Table 4. Antibiogram of *E. coli* causing bacteraemia in Northeast Thailand.

Antibiotic category	Antibiotic agents	CAB (n= 3382 patients)	HCAB (n= 494 patients)	HAB (n= 403 patients)	P values
Aminoglycosides	Gentamicin	559/3346 (17%)	166/484 (34%)	178/398 (45%)	<0.001
	Tobramycin	NA	NA	NA	-
	Amikacin	72/2685 (3%)	26/397 (7%)	32/326 (10%)	<0.001
	Netilmicin	68/1394 (5%)	25/259 (10%)	42/254 (17%)	<0.001
Anti-MRSA cephalosporins	Ceftaroline	NA	NA	NA	-
Antipseudomonal penicillins + β lactamase inhibitors	Ticarcillin-clauvanic acid	NA	NA	NA	-
	Piperacillin-tazobactam	23/511 (5%)	10/103 (10%)	15/89 (17%)	<0.001
Carbapenems	Ertapenem	4/1325 (<1%)	1/235 (<1%)	4/205 (2%)	0.02
	Imipenem	3/2449 (<1%)	0/386 (0%)	3/344 (1%)	0.04
	Meropenem	0/1988 (0%)	1/314 (<1%)	1/244 (<1%)	0.05
Non-extended spectrum cephalosporins	Cefazolin	468/1095 (43%)	115/174 (66%)	80/102 (78%)	<0.001
	Cefuroxime	219/1438 (15%)	96/226 (42%)	102/202 (50%)	<0.001
Extended-spectrum cephalosporins	Cefotaxime	501/3076 (16%)	199/455 (44%)	185/361 (51%)	<0.001
	Ceftazidime	392/3020 (13%)	165/446 (37%)	164/351 (47%)	<0.001
	Cefepime	30/293 (10%)	12/42 (29%)	18/53 (34%)	<0.001
Cephamycins	Cefoxitin	36/1200 (3%)	16/215 (7%)	16/195 (8%)	<0.001
	Cefotetan	NA	NA	NA	-
Fluoroquinolones	Ciprofloxacin	728/3000 (24%)	221/452 (49%)	171/384 (45%)	<0.001
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	1738/3007 (58%)	294/442 (67%)	225/350 (64%)	<0.001
Glycylcyclines	Tigecycline	0/7 (0%)	NA	0/1 (0%)	-
Monobactams	Aztreonam	NA	NA	NA	-
Penicillins	Ampicillin	2246/2843 (79%)	371/420 (88%)	301/342 (88%)	<0.001
Penicillins + β lactamase inhibitors	Amoxicillin-clavulanic acid	790/3074 (26%)	191/463 (41%)	158/373 (42%)	<0.001
	Ampicillin-sulbactam	83/296 (28%)	18/48 (38%)	12/25 (48%)	0.06
Phenicols	Chloramphenicol	14/63 (22%)	1/4 (25%)	3/5 (60%)	0.14
Phosphonic acids	Fosfomycin	NA	NA	NA	-
Polymyxins	Colistin *	2/34 (6%)	0/6 (0%)	1/6 (17%)	0.61
MDR		1177/3382 (35%)	288/494 (58%)	252/403 (63%)	<0.001

NOTE: Data are number of isolates demonstrating non-susceptible to the antimicrobial over the total number of isolates tested (%). CAB=Community-acquired bacteraemia, HCAB=Healthcare-associated

524 bacteraemia, HAB= Hospital-acquired bacteraemia, and NA=Not available. The first isolate of each
525 patient was used. MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.
526 * Defined by using an inhibition zone of <11 mm.
527

528 **Table 5. Antibiogram of *K. pneumoniae* causing bacteraemia in Northeast Thailand.**

Antibiotic category	Antibiotic agents	CAB (n= 1010 patients)	HCAB (n= 196 patients)	HAB (n=455 patients)	P values
Aminoglycosides	Gentamicin	94/999 (9%)	53/193 (27%)	265/444 (60%)	<0.001
	Tobramycin	NA	NA	NA	-
	Amikacin	17/815 (2%)	12/157 (8%)	109/398 (27%)	<0.001
	Netilmicin	20/450 (4%)	23/112 (21%)	124/320 (39%)	<0.001
Anti-MRSA cephalosporins	Ceftaroline	NA	NA	NA	-
Antipseudomonal penicillins + β lactamase inhibitors	Ticarcillin-clauvanic acid	NA	NA	NA	-
	Piperacillin-tazobactam	24/166 (14%)	14/32 (44%)	73/121 (60%)	<0.001
Carbapenems	Ertapenem	2/432 (0%)	1/100 (1%)	5/264 (2%)	0.17
	Imipenem	1/778 (0%)	1/164 (1%)	2/408 (0%)	0.24
	Meropenem	0/583 (0%)	1/113 (1%)	2/317 (1%)	0.10
Non-extended spectrum cephalosporins	Cefazolin	76/319 (24%)	30/60 (50%)	101/127 (80%)	<0.001
	Cefuroxime	81/478 (17%)	35/98 (36%)	161/231 (70%)	<0.001
Extended-spectrum cephalosporins	Cefotaxime	146/902 (16%)	71/173 (41%)	298/424 (70%)	<0.001
	Ceftazidime	124/927 (13%)	63/176 (36%)	295/430 (69%)	<0.001
	Cefepime	5/100 (5%)	8/22 (36%)	25/51 (49%)	<0.001
Cephamycins	Cefoxitin	15/396 (4%)	10/95 (11%)	14/230 (6%)	0.03
	Cefotetan	NA	NA	NA	-
Fluoroquinolones	Ciprofloxacin	143/894 (16%)	66/176 (38%)	187/430 (43%)	<0.001
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	198/876 (23%)	69/171 (40%)	219/407 (54%)	<0.001
Glycylcyclines	Tigecycline	NA	NA	NA	-
Monobactams	Aztreonam	NA	NA	NA	-
Penicillins + β lactamase inhibitors	Amoxicillin-clavulanic acid	131/945 (14%)	68/183 (37%)	291/443 (66%)	<0.001
	Ampicillin-sulbactam	20/105 (19%)	9/17 (53%)	23/38 (61%)	<0.001
Phenicols	Chloramphenicol	4/19 (21%)	0/2 (0%)	0/3 (0%)	>0.99
Phosphonic acids	Fosfomycin	NA	NA	NA	-
Polymyxins	Colistin *	0/6 (0%)	0/2 (0%)	0/5 (0%)	-
MDR		146/1010 (14%)	71/196 (36%)	301/455 (66%)	<0.001

529 NOTE: Data are number of isolates demonstrating non-susceptible to the antimicrobial over the total

530 number of isolates tested (%). CAB=Community-acquired bacteraemia, HCAB=Healthcare-associated

bacteraemia, HAB= Hospital-acquired bacteraemia, and NA=Not available. The first isolate of each patient was used. MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.

* Defined by using an inhibition zone of <11 mm.

536 **Table 6. Antibiogram of *P. aeruginosa* causing bacteraemia in Northeast Thailand.**

Antibiotic category	Antibiotic agents	CAB (n=286 patients)	HCAB (n=103 patients)	HAB (n=179 patients)	P values
Aminoglycosides	Gentamicin	29/235 (12%)	13/88 (15%)	60/140 (43%)	<0.001
	Tobramycin	NA	NA	NA	-
	Amikacin	27/284 (10%)	13/100 (13%)	48/177 (27%)	<0.001
	Netilmicin	8/155 (5%)	5/67 (7%)	34/120 (28%)	<0.001
Antipseudomonal carbapenems	Imipenem	14/238 (6%)	6/86 (7%)	37/154 (24%)	<0.001
	Meropenem	9/163 (6%)	8/73 (11%)	24/125 (19%)	0.001
	Doripenem	2/17 (12%)	0/3 (0%)	2/2 (100%)	0.04
Antipseudomonal cephalosporins	Ceftazidime	29/280 (10%)	16/103 (16%)	68/179 (38%)	<0.001
	Cefepime	2/36 (6%)	2/18 (11%)	10/28 (36%)	0.01
Antipseudomonal fluoroquinolones	Ciprofloxacin	24/275 (9%)	12/101 (12%)	39/169 (23%)	<0.001
	Levofloxacin	0/1 (0%)	1/1 (100%)	1/1 (100%)	>0.99
Antipseudomonal penicillins + β lactamase inhibitors	Ticarcillin-clauvanic acid	NA	NA	NA	-
	Piperacillin-tazobactam	8/85 (9%)	6/38 (16%)	8/46 (17%)	0.37
Monobactams	Aztreonam	NA	NA	NA	-
Phosphonic acids	Fosfomycin	1/1 (100%)	NA	NA	-
Polymyxins	Colistin	0/7 (0%)	0/3 (0%)	1/7 (14%)	>0.99
	Polymyxin B	NA	NA	NA	-
MDR		13/286 (5%)	10/103 (10%)	45/179 (25%)	<0.001

537 NOTE: Data are number of isolates demonstrating non-susceptible to the antimicrobial over the total
538 number of isolates tested (%). CAB=Community-acquired bacteraemia, HCAB=Healthcare-associated
539 bacteraemia, HAB= Hospital-acquired bacteraemia, and NA=Not available. The first isolate of each
540 patient was used. MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.
541
542

543 **Table 7. Antibiogram of *Acinetobacter* spp. causing bacteraemia in Northeast Thailand.**

Antibiotic category	Antibiotic agents	CAB (n=449 patients)	HCAB (n=115 patients)	HAB (n=501 patients)	P values
Aminoglycosides	Gentamicin	112/390 (29%)	45/105 (43%)	310/455 (68%)	<0.001
	Tobramycin	NA	NA	NA	-
	Amikacin	123/442 (28%)	45/112 (40%)	310/495 (63%)	<0.001
	Netilmicin	44/203 (22%)	24/64 (38%)	224/381 (59%)	<0.001
Antipseudomonal carbapenems	Imipenem	87/397 (22%)	37/102 (36%)	293/459 (64%)	<0.001
	Meropenem	65/284 (23%)	32/81 (40%)	229/348 (66%)	<0.001
	Doripenem	16/45 (36%)	9/10 (90%)	6/7 (86%)	0.001
Antipseudomonal fluoroquinolones	Ciprofloxacin	84/413 (20%)	53/106 (50%)	322/481 (67%)	<0.001
	Levofloxacin	2/5 (40%)	2/2 (100%)	8/9 (89%)	0.11
Antipseudomonal penicillins + β lactamase inhibitors	Ticarcillin-clauvanic acid	NA	NA	NA	-
	Piperacillin-tazobactam	22/98 (22%)	13/28 (46%)	74/106 (70%)	<0.001
Extended-spectrum cephalosporins	Cefotaxime	242/291 (83%)	89/94 (95%)	407/420 (97%)	<0.001
	Ceftazidime	133/448 (30%)	61/114 (54%)	377/500 (75%)	<0.001
	Cefepime	18/53 (34%)	10/22 (45%)	95/133 (71%)	<0.001
Folate pathway inhibitor	Trimethopri-sulphamethoxazole	119/356 (33%)	55/99 (56%)	333/435 (77%)	<0.001
Penicillins + β lactamase inhibitors	Ampicillin-sulbactam	43/134 (32%)	16/29 (55%)	79/115 (69%)	<0.001
Polymyxins	Colistin *	2/16 (13%)	0/14 (0%)	0/33 (0%)	0.11
	Polymyxin B	NA	NA	NA	-
Tetracyclines	Tetracycline	NA	NA	NA	-
	Doxycycline	NA	NA	NA	-
	Minocycline	NA	NA	NA	-
MDR		125/449 (28%)	58/115 (50%)	374/501 (75%)	<0.001

544 NOTE: Data are number of isolates demonstrating non-susceptible to the antimicrobial over the total
545 number of isolates tested (%). CAB=Community-acquired bacteraemia, HCAB=Healthcare-associated
546 bacteraemia, HAB= Hospital-acquired bacteraemia, and NA=Not available. The first isolate of each
547 patient was used. MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.
548 * Defined by using an inhibition zone of <11 mm.
549
550

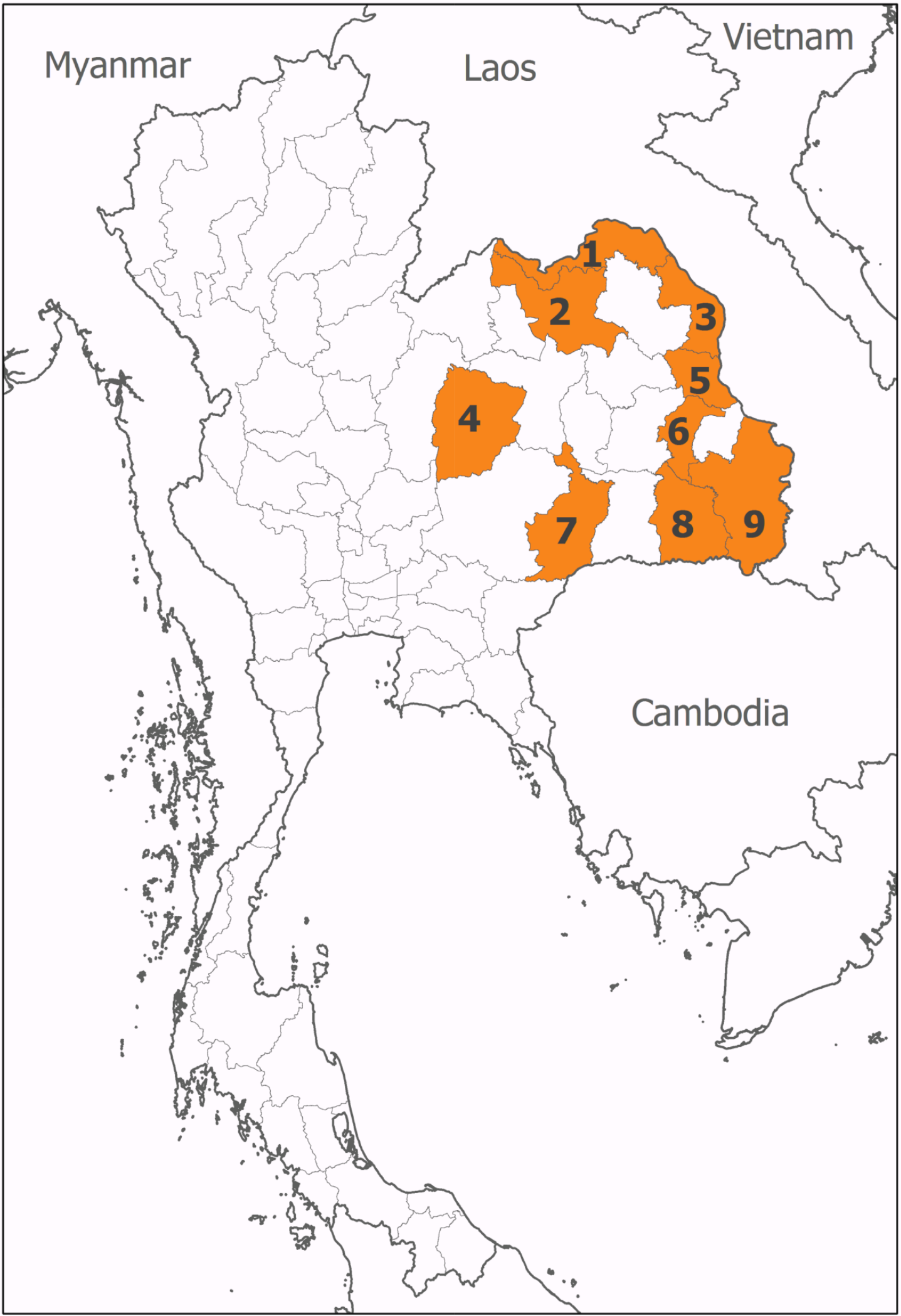
Table 8. Estimates of mortality attributable to multidrug-resistance (MDR) in hospital-acquired infection (HAI) in Thailand

Pathogens	No of patients [a]	Estimated mortality (%) [b]	Estimated mortality if the infections were caused by non-MDR organisms (%) [b, c]	Estimated excess mortality caused by MDR (%) [b, c]
MDR *Staphylococcus aureus*	18,725	8,262 (44%)	5,463 (29%)	2,799 (15%)
MDR *Escherichia coli*	11,116	2,163 (19%)	1,566 (14%)	597 (5%)
MDR *Klebsiella pneumoniae*	15,239	5,267 (35%)	4,979 (33%)	288 (2%)
MDR *Pseudomonas aeruginosa*	6,118	3,966 (65%)	3,696 (60%)	270 (4%)
MDR *Acinetobacter* spp	36,553	25,551 (70%)	10,383 (28%)	15,168 (41%)
Total	87,751	45,209 (52%)	26,087 (30%)	19,122 (22%)

[a] Cumulative incidence of antimicrobial resistant HAI in Thailand 2010 estimated by Pumart et al.[15]

[b] All parameters used to estimate the mortality and excess mortality are shown in Supplementary File 2.

[c] Excess mortality caused by MDR (mortality attributable to MDR) was defined as the difference in mortality of patients with MDR infection and their mortality if they were infected with non-MDR infections.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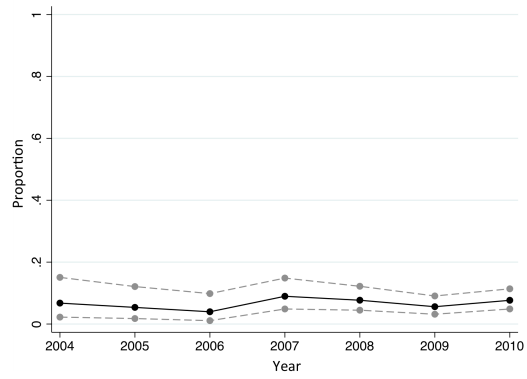
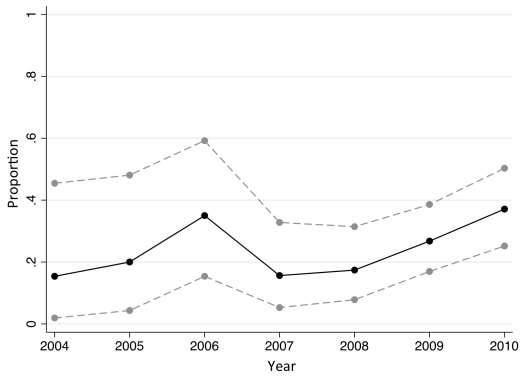


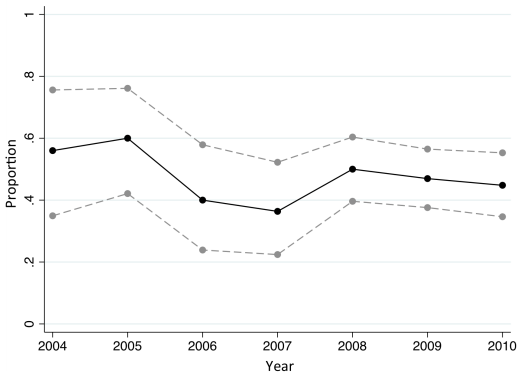
(P value = 0.12, nonparametric test for trend stratified by hospitals)

B



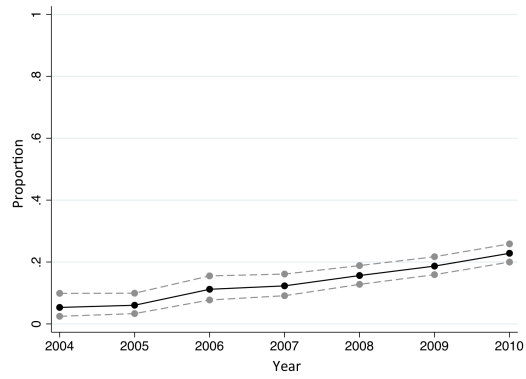
(P value = 0.77, nonparametric test for trend stratified by hospitals)

C



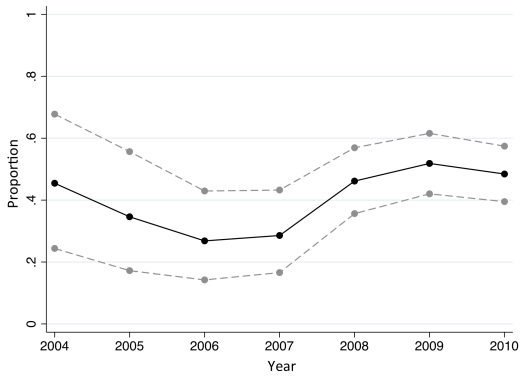
(P value = 0.61, nonparametric test for trend stratified by hospitals)

A



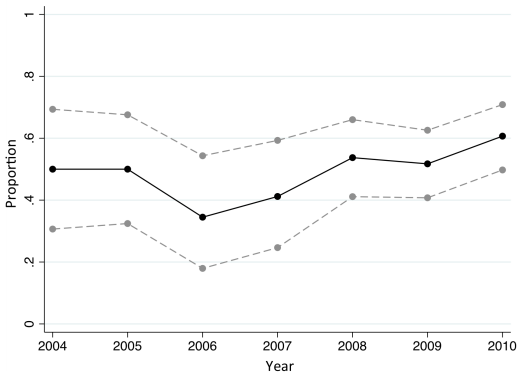
(P value = 0.04, nonparametric test for trend stratified by hospitals)

B



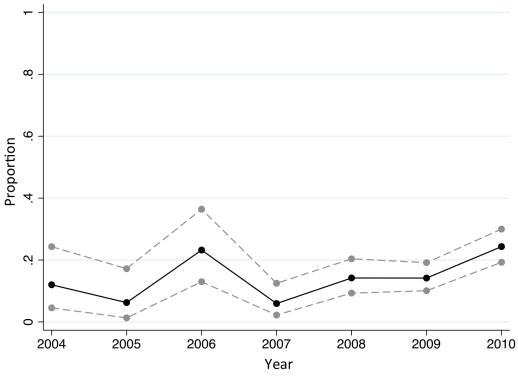
(P value = 0.18, nonparametric test for trend stratified by hospitals)

C



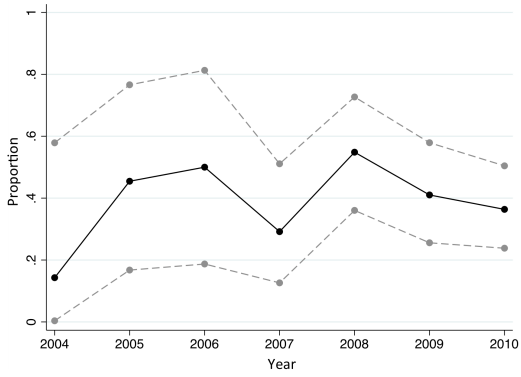
(P value = 0.63, nonparametric test for trend stratified by hospitals)

A



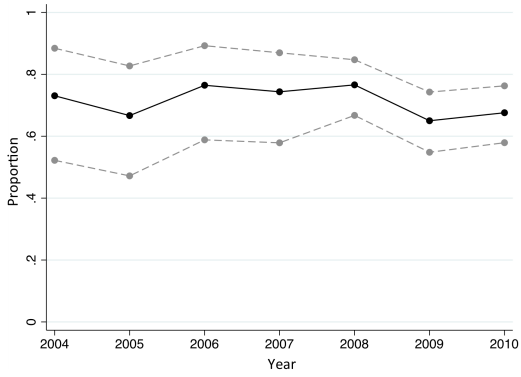
(P value = 0.04, nonparametric test for trend stratified by hospitals)

B

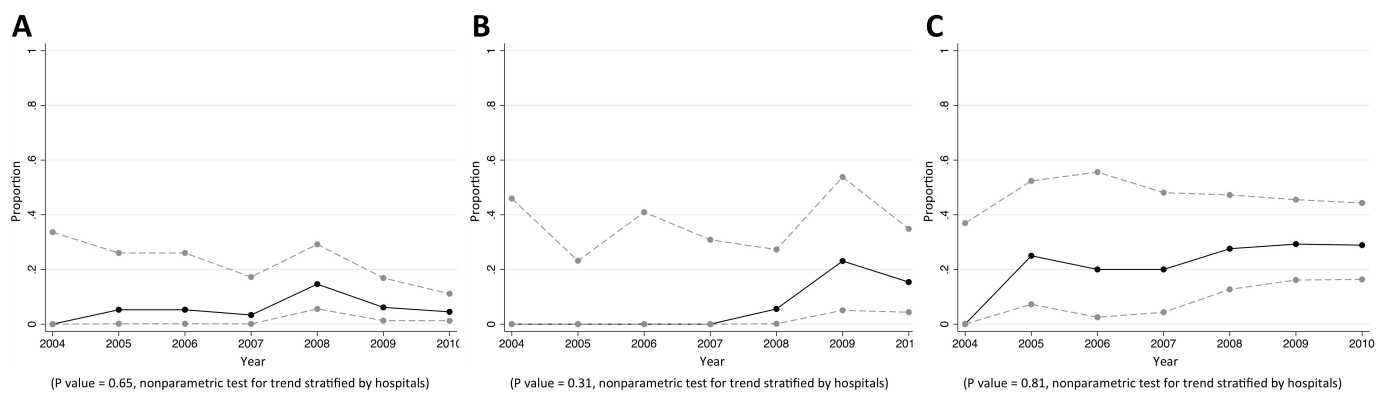


(P value = 0.16, nonparametric test for trend stratified by hospitals)

C



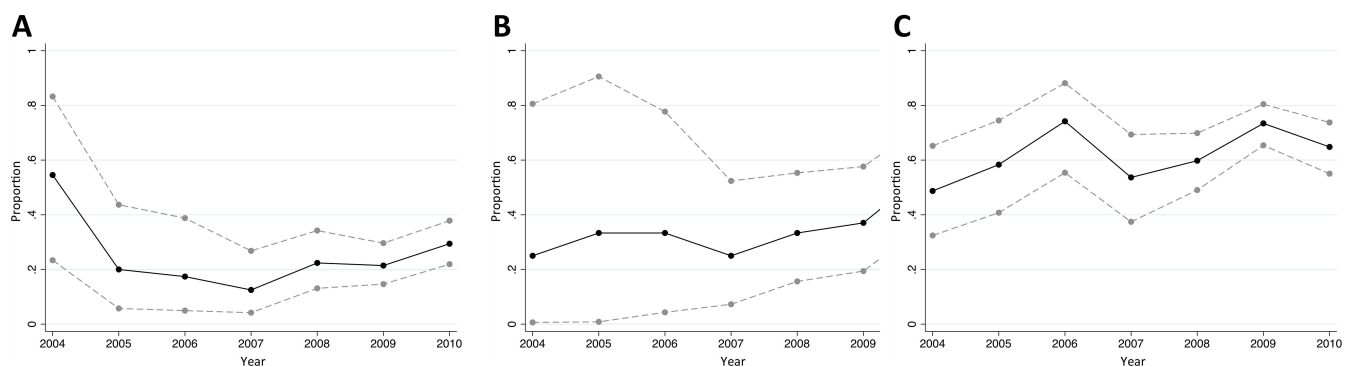
(P value = 0.35, nonparametric test for trend stratified by hospitals)



(P value = 0.65, nonparametric test for trend stratified by hospitals)

(P value = 0.31, nonparametric test for trend stratified by hospitals)

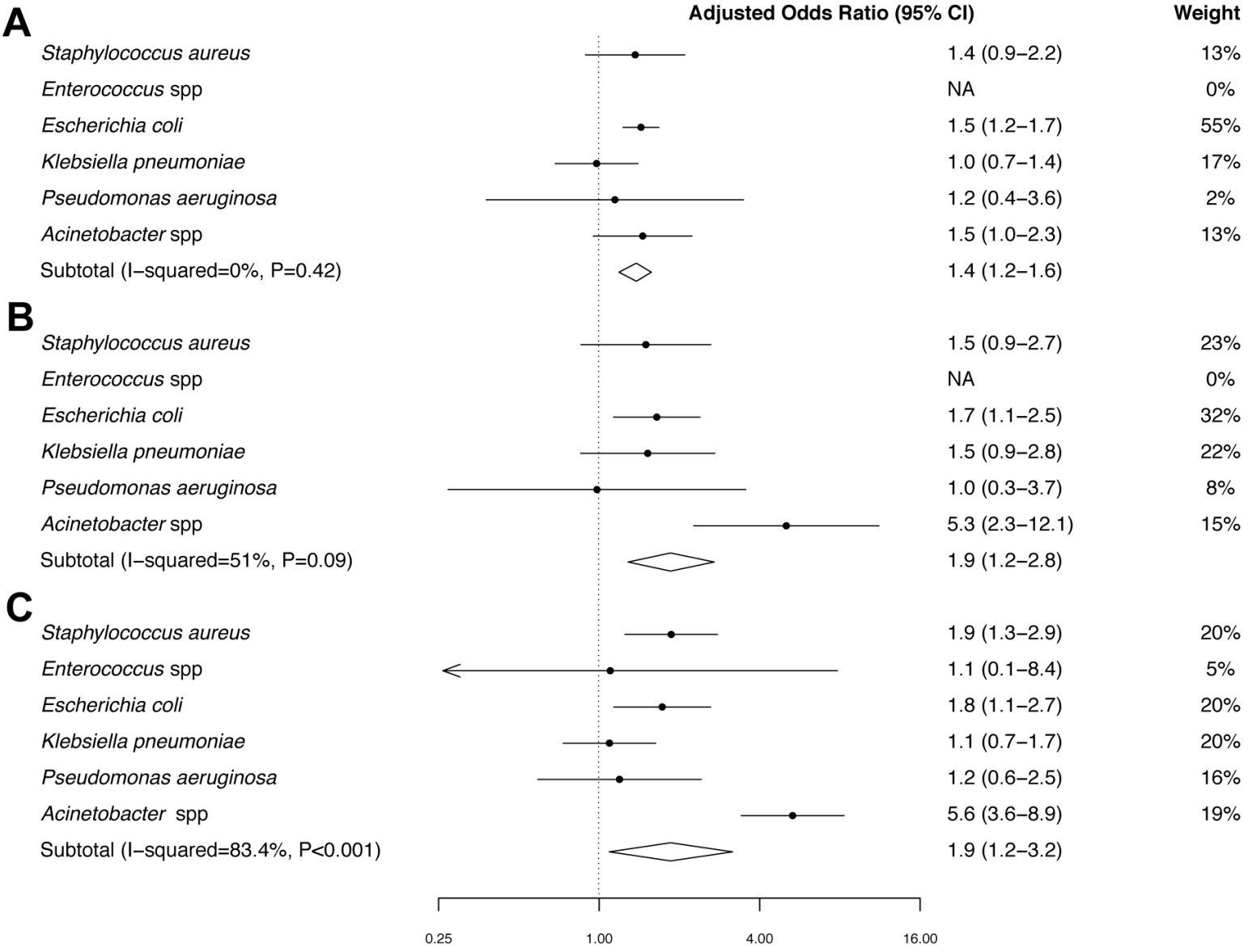
(P value = 0.81, nonparametric test for trend stratified by hospitals)



(P value = 0.98, nonparametric test for trend stratified by hospitals)

(P value = 0.20, nonparametric test for trend stratified by hosp

(P value = 0.10, nonparametric test for trend stratified by hospitals)


A
Adjusted Odds Ratio (95% CI)
Weight
Staphylococcus aureus
1.4 (0.9–2.2)
13%
Enterococcus spp
NA
0%
Escherichia coli
1.5 (1.2–1.7)
55%
Klebsiella pneumoniae
1.0 (0.7–1.4)
17%
Pseudomonas aeruginosa
1.2 (0.4–3.6)
2%
Acinetobacter spp
1.5 (1.0–2.3)
13%
Subtotal (I–squared=0%, P=0.42)
1.4 (1.2–1.6)
B
Staphylococcus aureus
1.5 (0.9–2.7)
23%
Enterococcus spp
NA
0%
Escherichia coli
1.7 (1.1–2.5)
32%
Klebsiella pneumoniae
1.5 (0.9–2.8)
22%
Pseudomonas aeruginosa
1.0 (0.3–3.7)
8%
Acinetobacter spp
5.3 (2.3–12.1)
15%
Subtotal (I–squared=51%, P=0.09)
1.9 (1.2–2.8)
C
Staphylococcus aureus
1.9 (1.3–2.9)
20%
Enterococcus spp
1.1 (0.1–8.4)
5%
Escherichia coli
1.8 (1.1–2.7)
20%
Klebsiella pneumoniae
1.1 (0.7–1.7)
20%
Pseudomonas aeruginosa
1.2 (0.6–2.5)
16%
Acinetobacter spp
5.6 (3.6–8.9)
19%
Subtotal (I–squared=83.4%, P<0.001)
1.9 (1.2–3.2)
0.25
1.00
4.00
16.00