Evaluation of the coverage of three antibiotic regimens for neonatal sepsis in the hospital setting across Asian countries

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Key points

Question: What is the antibiotic coverage offered by empiric neonatal sepsis treatment with aminopenicillin/gentamicin, third-generation cephalosporins and meropenem in Asian countries?

Findings: In this decision-analytical model based on a decision-tree, 8376 isolates from 10 countries were used to estimate coverage. Meropenem generally had the highest coverage (64% India - 91% Cambodia) followed by ampicillin/gentamicin (36% Indonesia - 81% Laos) and cefotaxime or ceftriaxone (18% Indonesia - 75% Laos). In all countries except Laos and Nepal, meropenem coverage was significantly higher than that of the other two regimens.

Meaning: Non-carbapenems may provide limited empiric neonatal sepsis coverage in many Asian countries.

Tweet

Non-carbapenems provide low cover of neonatal sepsis in some Asian countries. Could this explain high meropenem use and further worsen resistance?

Abstract

Importance: Worrying levels of antimicrobial resistance in neonatal bloodstream isolates are being reported globally, including in Asia. Local hospital antibiogram data may include too few isolates to meaningfully examine the expected coverage of antibiotic regimens.

Objective: To assess the coverage offered by three regimens for empiric treatment of neonatal sepsis in Asian countries.

Design: We conducted a modelling study to estimate coverage of three pre-specified regimens based on a weighted-incidence syndromic combination antibiogram (WISCA). Relevant data to parameterize the models were identified from a systematic search of Ovid Medline ® and Embase.

Setting: Data from Asian countries published from 2014 onwards were of interest.

Participants: Only data on blood culture isolates from neonates with sepsis, bloodstream infection or bacteraemia reported from the relevant setting were included.

Exposure: The pre-specified regimens of interest were ampicillin/gentamicin, cefotaxime or ceftriaxone, and meropenem. The relative incidence of different bacteria and their antimicrobial susceptibility to antibiotics relevant for determining expected concordance with these regimens were extracted.

Main outcomes: Coverage was calculated based on a decision-tree model incorporating relative bacterial incidence and antimicrobial susceptibility of relevant isolates. Data on seven bacteria most commonly reported in included studies were used for estimating coverage, which was reported at country level.

Results: Data from 48 studies reporting on 10 countries and 8376 isolates were used. Individual countries reported 51 (Vietnam) to 6284 (India) isolates. Coverage varied considerably between countries. Meropenem was generally estimated to provide the highest coverage ranging from 64% in India (95% credible interval 62.6-64.4%) to 91% in Cambodia

(95%CrI 86.2-94.4%). Ampicillin/gentamicin coverage was lower than that of meropenem in all countries except Laos (81%, 95%CrI 71.1-89.7%) and Nepal (74.3%, 95%CrI: 70.3-78.2%), where 95% credible intervals for ampicillin/gentamicin and meropenem were overlapping. Third-generation cephalosporin coverage was lowest of the three regimens in all countries. The coverage difference between ampicillin/gentamicin and meropenem for countries with non-overlapping 95% credible intervals ranged from -15.9% in China to -52.9% in Indonesia.

Conclusions and relevance: Non-carbapenem regimens may provide limited coverage for empiric treatment of neonatal sepsis in many Asian countries. Alternative regimens must be studied to limit carbapenem consumption.

Role of funding source

No specific funding was received for this piece of analysis. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Introduction

While overall maternal and child mortality have substantially reduced since the early 2000s, neonatal mortality from bacterial infection has remained high with nearly half a million estimated annual deaths from neonatal sepsis.[1] Most of these deaths occur in low and middle-income countries (LMICs), including many thousands in Asia.[2]

The case-fatality rate of culture-positive neonatal sepsis episodes was nearly 50% in a recent prospective cohort study of more than 13,500 live births in India.[3] Recent systematic reviews indicate a high level of bacterial resistance to WHO-recommended empiric treatment regimens for serious neonatal and pediatric infections in LMICs, especially in bloodstream isolates.[4-7] Globally, antimicrobial resistance is estimated to be implicated in up to a third of annual neonatal sepsis deaths.[8]

Clinicians and guideline-setting bodies can be assisted in selecting optimal empiric antibiotic regimens by knowing the coverage of alternative regimens.[9] Regimen "coverage" reflects the proportion of infection episodes that would be treated by the regimen at a stage when the causative pathogen is not yet known, therefore incorporating the frequency of different causative bacteria and their resistance patterns. Several techniques are available to estimate coverage. One example is the weighted-incidence syndromic combination antibiogram (WISCA).[9-11] This estimates coverage by accounting for the relative incidence of different bacteria and their resistance patterns for a specific infection syndrome, in this case neonatal sepsis. Coverage can be estimated for both single drug and combination treatment regimens.

International guidelines provide recommendations for the empiric antibiotic treatment of neonatal bacterial infections and should aim to provide adequate coverage in target settings, especially LMICs.[12] The objective of this study was therefore to evaluate the coverage offered by three pre-specified antibiotic regimens based on WISCAs and focusing on Asia, a region with high prevalence of bacterial resistance.

Methods

We estimated coverage using data on antimicrobial resistance identified from a systematic review of the literature, which were used to create WISCAs for each country with reported data.[9] Reporting followed the Consolidated Health Economic Evaluation Reporting Standards checklist, as this is broadly applicable to any decision-model based analyses (eAppendix).[13]

Regimens selected for coverage estimation

The three regimens evaluated in this study were: (i) aminopenicillin/gentamicin (WHO-recommended first-line treatment, alternative benzylpenicillin or cloxacillin plus gentamicin), (ii) third-generation cephalosporin (WHO-recommended second-line treatment, assumed to be cefotaxime or ceftriaxone, not ceftazidime) and (iii) meropenem.[12] The latter regimen was evaluated because it has now been reported to be the most commonly used empiric treatment in lower and middle-income settings for neonatal sepsis.[14]

Identification of relevant data for parameter estimation

A systematic search of the literature was conducted in Ovid Medline ® and in Embase on 23rd January 2019. Using both free text and MeSH terms, publications on "sepsis" and "antibiotic resistance" and ("neonates" or infants") and "Asia" were identified (eAppendix). The review was registered on the PROSPERO database (CRD42019126027). Given rising antimicrobial resistance, and in order to obtain contemporaneous estimates we arbitrarily limited the search to manuscripts published from 2014 onwards. No additional limits were applied. Studies were reviewed against pre-specified eligibility criteria and data extracted using a standardized pre-piloted form implemented in REDCap™ (eAppendix).[15]

Extracted data for WISCA calculation included information on the total number of bacterial isolates from relevant blood cultures, the number of isolates of specific bacterial species or genera, the number of isolates tested for susceptibility to the antibiotics relevant for

establishing coverage offered by the pre-specified regimens of interest and the number found to be susceptible to these. We excluded bacteria known to frequently represent contamination rather than true infection, most importantly coagulase-negative staphylococci.[16] Exclusion of coagulase-negative staphylococci is likely to result in the overestimation of coverage for beta-lactam based regimens due to very high expected rates of methicillin resistance of 66% to over 90%.[17,18]

Estimation of WISCA parameters

Tables containing the parameter values required for coverage estimation were created by country and regimen. The relative incidence parameters were based only on bacteria reported as contributing to neonatal sepsis in more than 50% of the eligible studies. This meant estimated coverage was based on the most important and frequent pathogens identified in blood cultures from neonates in the target region. Including rare pathogens within the WISCA would have a minimal impact on the estimated coverage and including those likely to be contaminants or unusual pathogens (potentially observed as part of unidentified outbreaks) could introduce substantial bias. For the bacteria identified in this way, their relative incidence was based on the frequency reported in the studies. Similarly, regimen susceptibility was derived directly from reported data with the number of tested isolates representing the denominator. Details of the assumptions for determining susceptibility of pathogens to each regimen are provided in the eAppendix.

Data analysis: Modelling regimen coverage

Regimen coverage was estimated using a previously described Bayesian WISCA.[9] This approach has various advantages: It addresses the typical clinical approach of treating an infection syndrome, often with incomplete knowledge about the frequency of causative bacteria and their susceptibilities. The Bayesian WISCA also explicitly deals with intrinsic

resistance and handles imprecision due to small sample size or incomplete susceptibility testing data.

In brief, the WISCA gives the expected levels of therapeutic coverage for an antibiotic regimen; in our case, regimens used to treat neonates with sepsis. ¨The WISCA can be represented as a decision tree (eAppendix). Combining the probabilities along the regimen tree branches generates coverage estimates from relative bacterial incidence and proportions of each included pathogen susceptible to the antibiotic regimen. In essence, the WISCA is a weighted average of the susceptibilities of the bacteria, with the weights defined by their relative incidence.

The observed data on pathogen incidence and their susceptibility to the three regimens were combined with an appropriate Bayesian prior distribution that corresponded to our pre-study beliefs about these parameters. We had no strong prior belief about the relative incidence of the pathogens nor for the majority of what level of susceptibility there might be within a country, and a non-informative prior was used in these cases. However, in some circumstances, specific pathogens were expected to have intrinsic resistance to the regimen, and consequently not to have susceptibility regardless of reported susceptibility testing results.[19,20] In these situations, an informative prior was used to dominate the observed data. Based on EUCAST recommendations, enterococci as well as *Acinetobacter* spp. and *Pseudomonas* spp. were assumed to be intrinsically resistant to recommended third-generation cephalosporins and therefore not susceptible to regimen (ii).[19,20]

The value of the pathogen incidence and pathogen–regimen susceptibility parameters were defined as probability distributions to reflect the uncertainty in their respective values. The relative incidence of pathogens was modelled using a Dirichlet distribution and the susceptibility parameters were defined as beta distributions. 95% credible intervals (95%CrI)

for the coverage estimates were calculated using Monte Carlo simulation, based on 1000 runs (eAppendix). All modelling was undertaken using Stata® 13.1 and Microsoft Excel® 2010.

Ethics

As only published data were used in the analysis, no formal ethical review was required.

Results

Description of dataset

The literature review included data from 48 publications (eAppendix) representing 52 centres in ten Asian countries (one centre in Cambodia, five China, thirty-three India, one Indonesia, one Laos, one Malaysia, six Nepal, two Pakistan, one Taiwan, one Vietnam). Thirty-four of 52 centres were university or tertiary hospitals, 10/52 were non-teaching or district hospitals (9 in India, 1 in China) and 8/52 were maternity or paediatric hospitals (1 in Cambodia, 2 in China, 4 in Nepal and 1 in Vietnam).

Ten papers were published in 2014, 13 in 2015, ten in 2016, eight in 2017, six in 2018 and one in 2019. For the majority of publications, the observation period started 2010 or later (32/48), with the earliest start date being 1 January 1990 (eAppendix). Five publications did not report calendar dates for their observation period, but four of five indicated its duration. The median observation period was 2 years, with the shortest and longest periods being 2 months and 12 years, respectively.

Most publications (33/48) reported on bloodstream isolates from neonates with clinical community-acquired or nosocomial sepsis. Another 12/48 publications based reporting on microbiologically defined bacteraemia. Only four publications focused on either nosocomial or community-acquired infections (2/48 each). Reporting of information on sample processing, including species identification, antibiotic susceptibility testing methods and interpretive guidelines was variable (eAppendix).

Reported bloodstream isolates

Individual publications included between 15 and 2112 isolates with a median of 98 isolates (eAppendix). The following bacteria were most frequently reported as contributing to neonatal sepsis or bacteraemia: *E. coli* (46/48 publications), *Klebsiella* spp. and *S. aureus* (45/48 each), *Pseudomonas* spp. (35/48), *Acinetobacter* spp. (32/48), *Enterobacter* spp. (26/48), and *Enterococcus* spp. (25/48). In addition, coagulase-negative staphylococci were reported in 40 of 48 publications. All other bacteria, including *Citrobacter* spp and *Streptococcus agalactiae*, were reported in less than half the publications. Based on the pre-specified criteria, *E. coli*, *Klebsiella* spp. *S. aureus*, *Pseudomonas* spp., *Acinetobacter* spp., *Enterobacter* spp. and *Enterococcus* spp. were selected for antibiotic regimen coverage estimation.

Parameter values: isolates reported and susceptibility

In total, 11467 isolates were reported with the greatest number coming from India (6284), China (2043), Pakistan (1875) and Nepal (640) (Table 1). Given the small number of reported isolates from Taiwan (36) and Malaysia (29), antibiotic regimen coverage was not estimated for these two countries.

Most reported isolates (8584/11467, 75%) were from university or tertiary hospitals, with non-teaching or district hospitals contributing 11% (1319/11467) and maternity or paediatric hospitals contributing another 14% (1564/11467).

The proportion of reported isolates contributing to antibiotic regimen coverage estimation ranged from 92% (1723/1875) in Pakistan to 44% (905/2043) in China. Disregarding coagulase-negative staphylococci, the proportion of reported bacterial isolates contributing to coverage estimation ranged from 98% (51/52) in Vietnam to 70% (905/1302) in China.

Availability of susceptibility testing information for aminopenicillin/gentamicin coverage ranged from 69% (623/905) in China to 100% in Indonesia (Table 2). For third-generation cephalosporins, this was available for 100% in Cambodia and Indonesia to 76% (39/51) in Vietnam (Table 3). For meropenem, available susceptibility testing information ranged from 100% in Indonesia to 60% (295/489) in Nepal (Table 4).

Coverage estimates at country level

Coverage was consistently lowest for third-generation cephalosporin monotherapy with some variation across the individual countries ranging from 56.6% (95%CrI 52.2-60.7%) in Nepal to 17.9% (95%CrI 11.7-24.7%) in Indonesia (Figure 1). Similarly, while meropenem had the highest estimated coverage in each country, the proportion of neonates for which it would prove effective empiric treatment varied considerably from 90.6% (95%CrI 86.2-94.4%) in Cambodia to 64.0% (95%CrI 62.6-65.4%) in India (Figure 1). Aminopenicillin/gentamicin tended to offer the second highest level of coverage within each country behind meropenem. Nonetheless, there was again considerable variability in country-level estimates from 74.3% (95%CrI 70.3-78.2%) in Nepal to 35.9% (95%CrI 27.7-44.0%) in Indonesia (Figure 1).

Aminopenicillin/gentamicin coverage was higher than that offered by third generation cephalosporins in China (60.6%, 95%CrI 54.2-67.5% vs. 44.2%, 95%CrI 40.9-47.9%), India (45.1%, 95%CrI 43.7%-46.6% vs 30.4%, 95%CrI 29.2-31.6%), Indonesia (35.9%, 95%CrI 27.7-44.0% vs 17.9%, 95%CrI 11.7-24.7%) and Nepal (74.3%, 95%CrI 70.3%-78.2% vs 56.6%, 95%CrI 52.2%-60.7%), whereas there was greater uncertainty about whether or not the differences observed for Cambodia (47.4%, 95%CrI 38.1-56.6% vs 32.6%, 95%CrI 25.8-39.9%), Laos (81.0%, 95%CrI 71.1-89.7% vs 75.0%, 95%CrI 64.8-84.1%), Pakistan (42.2%, 95%CrI 39.1-45.0% vs 37.4%, 95%CrI 34.4-40.3%) and Vietnam (36.2%, 95%CrI 24.5-49.0% vs 21.5%, 95%CrI 12.0-32.9%) were due to chance variation.

Meropenem coverage was higher than aminopenicillin/gentamicin coverage in Cambodia (90.6% vs 47.4%), China (76.5% vs 60.6%), India (64% vs 45.1%), Indonesia (88.8% vs 35.9%), Pakistan (88.1% vs 42.2%) and Vietnam (84.1% vs 36.2%) based on non-overlapping 95%CrI. The largest percentage difference in coverage was observed in Indonesia (Δ52.9%), Pakistan (Δ 45.9%) and Cambodia (Δ43.2%). For meropenem and third-generation cephalosporins, the percentage difference was largest for Indonesia (Δ70.9%), Vietnam (Δ62.6%) and Cambodia (Δ58%). Of note, for Laos and Nepal imprecision around estimated meropenem coverage, which was comparable to aminopenicillin/gentamicin with overlapping 95%CrI, was largely due to low proportions of isolates (40/64, 63% for Laos; 295/489, 60% for Nepal) contributing to the meropenem susceptibility parameter.

Discussion

We estimated the coverage offered by three antibiotic regimens (aminopenicillin/gentamicin, third-generation cephalosporin alone, recommended as first and second-line regimens by the WHO, respectively, and meropenem) in Asian countries for the empirical treatment of neonatal sepsis caused by seven specified bacteria. The coverage estimates were based on a systematic review of recent studies reporting on the relative incidence of common bacteria and their resistance.

In general, coverage estimates supported the identification of better or worse performing regimens for most countries. Coverage offered by aminopenicillin/gentamicin (WHO-recommended first-line regimen) was below 50% for Cambodia, India, Indonesia, Pakistan and Vietnam, and below 75% for China and Nepal. Even lower coverage was offered by the WHO-recommended second-line third-generation cephalosporin monotherapy regimen: below 50% in all represented countries except Laos (75%) and Nepal (57%). Meropenem coverage was generally highest and above 80% in Cambodia, Indonesia, Pakistan and Vietnam, but <80% in China, Laos and Nepal and as low as 64% in India. Considerable between-country differences were observed for all three regimens, even for countries bordering each other, such as Cambodia, Laos, Thailand and Vietnam.

Coverage estimates are clinically highly relevant for the development of local and national empiric treatment guidelines, incorporating both the relative incidence of bacteria and their susceptibility.[9] This concept has not to our knowledge been previously applied to neonatal sepsis in LMIC settings. Instead, reports have focused on susceptibility for individual pathogen-drug combination, an approach that does not directly incorporate the spectrum of causative bacteria.[4,6,7]

One important question is whether global setting-independent recommendations for empiric neonatal sepsis treatment can be supported in an era of changing and highly variable

297 epidemiology. In some settings difficult to treat pathogens and multidrug resistant isolates
298 now contribute considerably.[3] Stratified guidance moving between recommended regimens
299 according to microbiology and coverage by patient-level factors (e.g. presence of certain
300 underlying conditions or timing of sepsis onset) or setting, may be one solution. One
301 challenge will be the lack of defined coverage thresholds to move between regimens.[21] Given
302 sufficiently large datasets, coverage estimates could help inform such shifting by supporting
303 inferences about true differences between regimens.

304 **Limitations**

305 Our coverage estimates were based on data from predominantly university or teaching
306 hospitals. Infants with complex medical issues and at higher risk of nosocomial bloodstream
307 infections may therefore be overrepresented. At the same time, microbiology data from
308 infants managed in district hospitals are lacking precluding confirmation that presented
309 coverage estimates are applicable to them as well. Clinicians applying WHO
310 recommendations to infants with nosocomial infection or managed in tertiary hospitals would
311 on the basis of our observations need to consider alternatives for this population.

312 We chose to estimate coverage based on pathogens frequently reported across included
313 studies, likely to be associated with severe neonatal sepsis and so-called ESKAPE organisms
314 known to be problematic in terms of emerging antimicrobial resistance.[22] Inclusion of other
315 pathogens would be expected to have a variable impact on expected coverage of considered,
316 leading to either higher or lower estimates. This may be particularly important in individual
317 hospitals with on-going outbreaks where a single bacterial strain is dominant. In such
318 situations regional coverage estimates may not be applicable.

319 Coverage estimation requires a number of assumptions to be made when calculating the
320 susceptibility parameters, such as the incorporation of intrinsic resistance, extrapolations

from susceptibility testing for one representative of an antibiotic class to other members of this class, and the interpretation of multiple testing for one antibiotic class. We based our calculations of regimen susceptibility on EUCAST algorithms, and whenever possible used susceptibility testing information for the specific drug of interest.[19] Importantly, however, all included studies used versions of CLSI interpretive criteria, which may diverge from EUCAST both in breakpoints and assumptions about intrinsic resistance.[23] Debate about the merits and challenges of switching from CLSI to EUCAST, and the implications of such a transition for interpretation of routine data in the context of surveillance is on-going.[23,24]

In order to support coverage estimation, it is important that the microbiological data used are collected in equivalent ways. However, the data used for this analysis may have been subject to various random or systematic errors that could bias the coverage estimates. Possible sources of error include duplicate isolates, contaminants, non-standardized susceptibility testing, combining data from different patient populations (children and adults) and reflex susceptibility testing based on resistance identified in a first-line testing panel.[25] These requirements have important implications for global surveillance initiatives such as the Global Antimicrobial Resistance Surveillance System (http://www.who.int/glass/en/), if data collected are to be used at the interface between surveillance and clinical practice.

Conclusions

Recently, machine learning approaches and more elaborate multivariable Bayesian models using clinical and demographic information combined with microbiological data have been proposed as optimizing selection of empiric antibiotic treatment in sepsis.[26,27] While these may help in selecting patient-adapted regimens, the approach used in our study only requires estimates of pathogen incidence and susceptibility and could already substantially improve clinical decision-making based on routine microbiological data alone, provided that the data used to produce these estimates are of sufficient quality. Our analysis indicates that the

recommendation for third-generation cephalosporin monotherapy as a second-line regimen may no longer be valid for many infants receiving treatment for neonatal sepsis in several Asian countries. Our findings could explain high reported empiric meropenem use a in this population in Asia.[14,28] Evaluation of potential alternatives will be essential to reduce consumption of last-resort antibiotics for the empiric treatment of neonatal sepsis in settings with a high prevalence of antimicrobial resistance.

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Figure legends

Figure 1: Coverage estimates for eight Asian countries.

Point estimates are shown with 95% credible intervals (95%CrI). Non-overlapping 95%CrI indicate likely within-country differences in regimen coverage. Countries are shown together with the overall number of isolates used for estimating coverage.

[a] Highest coverage offered by meropenem (Cambodia: 91%, China: 77%, India 64%, Indonesia 89%, Pakistan 88%, Vietnam 84%)

[b] Highest coverage offered by aminopenicillin/gentamicin combination (Laos 81%, Nepal 74%)

Table 1: Parameter table – literature review relative incidence data

	Cambodia	China	India	Indonesia	Laos	Malaysia	Nepal	Pakistan	Taiwan	Vietnam	Total
	N (% of those contributing to WISCA)*										
E. coli	25 (16%)	300 (33%)	671 (14%)	0	8 (13%)	6 (33%)	50 (10%)	976 (57%)	11 (92%)	2 (4%)	2049 (24%)
Klebsiella spp.	60 (39%)	264 (29%)	1065 (22%)	49 (40%)	9 (14%)	1 (6%)	45 (9%)	159 (9%)	1 (8%)	18 (35%)	1671 (20%)
Enterobacter spp.	18 (11%)	58 (6%)	167 (3%)	20 (17%)	4 (6%)	0	30 (6%)	0	0	6 (12%)	303 (4%)
Acinetobacter spp.	16 (10%)	27 (3%)	992 (21%)	21 (17%)	2 (3%)	0	63 (13%)	0	0	17 (33%)	1138 (14%)
Pseudomonas spp.	6 (4%)	53 (6%)	430 (9%)	31 (26%)	1 (2%)	1 (6%)	25 (5%)	199 (12%)	0	4 (8%)	750 (9%)
S. aureus	33 (21%)	112 (12%)	1235 (26%)	0	37 (58%)	10 (55%)	261 (53%)	388 (23%)	0	4 (8%)	2080 (25%)
Enterococcus spp.	0	91 (10%)	275 (6%)	0	3 (5%)	0	15 (3%)	1 (<1%)	0	0	385 (5%)
	N (% of total reported during observation period)										
Total contributing to WISCA	158 (85%)	905 (44%)	4835 (77%)	121 (54%)	64 (85%)	18 (62%)	489 (76%)	1723 (92%)	12 (33%)	51 (68%)	8376 (73%)
Other (not contributing to WISCA)	27 (15%)	1138 (56%)	1449 (23%)	104 (46%)	11 (15%)	11 (38%)	151 (24%)	152 (8%)	24 (67%)	24 (32%)	3091 (27%)
Coagulase-negative staphylococci (not contributing to WISCA)	0	741 (36%)	980 (16%)	63 (28%)	0	0	137 (21%)	28 (1%)	0	23 (31%)	1972 (17%)

*Percentages may not add to 100% due to rounding.

Table 2: Parameter table – susceptibility testing and susceptibility data for aminopenicillin plus gentamicin

	Cambodia			China			India			Indonesia			Laos			Nepal			Pakistan			Vietnam			Total		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
E. coli	25	25	13	300	290	182	671	655	426	0			8	8	6	50	50	31	976	976	340	2	0		2033	2004	998
Klebsiella spp.	60	60	10	264	256	193	1065	1026	402	49	49	3	9	9	7	45	42	23	159	159	36	18	11	2	1669	1612	676
Enterobacter spp.	18	18	8	58	20	11	167	154	42	20	20	18	4	0		30	30	21	0			6	5	3	303	247	103
Acinetobacter spp.	16	0		27	0		992	930	226	21	21	11	2	0		63	62	34	0			17	17	3	1138	1030	274
Pseudomonas spp.	6	0		53	0		430	422	238	31	31	9	1	0		25	23	18	199	199	74	4	4	1	749	679	340
S. aureus	33	33	32	112	56	31	1235	1142	655	0			37	37	37	261	227	195	388	88	63	4	3	3	2070	1586	1016
Enterococcus spp.	0			91	1	0	275	132	44	0			3	0		15	15	12	1	0		0			385	148	56

N=total isolates; T=susceptibility testing available for regimen of interest; S=isolates identified as susceptible on testing.

Table 3: Parameter table – susceptibility testing and susceptibility data for third-generation cephalosporins

	Cambodia			China			India			Indonesia			Laos			Nepal			Pakistan			Vietnam			Total		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
E. coli	25	25	13	300	289	165	671	657	339	0			8	8	7	50	43	25	976	976	317	2	0		2033	1998	866
Klebsiella spp.	60	60	4	264	251	122	1065	1031	346	49	49	2	9	9	6	45	42	12	159	159	52	18	11	1	1669	1612	545
Enterobacter spp.	18	18	1	58	20	14	167	167	59	20	20	17	4	0		30	28	12	0			6	4	1	303	257	104
Acinetobacter spp. †	16	16	0	27	27	0	992	992	0	21	21	0	2	2	0	63	63	0	0			17	17	0	1138	1138	0
Pseudomonas spp. †	6	6	0	53	53	0	430	430	0	31	31	0	1	1	0	25	25	0	199	199	0	4	4	0	749	749	0
S. aureus	33	33	32	112	56	31	1235	1142	655	0			37	37	37	261	227	195	388	88	63	4	3	3	2070	1586	1016
Enterococcus spp. †	0			91	91	0	275	275	0	0			3	3	0	15	15	0	1	1	0	0			385	385	0

N=total isolates; T=susceptibility testing available for regimen of interest; S=isolates identified as susceptible on testing; †indicates not based on susceptibility testing as assumed intrinsically resistant.

Table 4: Parameter table – susceptibility testing and susceptibility data for meropenem

	Cambodia			China			India			Indonesia			Laos			Nepal			Pakistan			Vietnam			Total		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
E. coli	25	24	24	300	289	289	671	439	379	0			8	0		50	3	1	976	811	768	2	0		2033	1566	1461
Klebsiella spp.	60	60	60	264	253	228	1065	882	667	49	49	49	9	0		45	27	27	159	102	87	18	9	9	1669	1382	1127
Enterobacter spp.	18	18	17	58	20	20	167	157	122	20	20	19	4	0		30	16	14	0			6	3	3	303	234	195
Acinetobacter spp.	16	16	14	27	0		992	926	475	21	21	21	2	0		63	7	3	0			17	16	15	1138	986	528
Pseudomonas spp.	6	5	5	53	0		430	415	354	31	31	23	1	0		25	0		199	199	188	4	3	3	749	653	573
S. aureus	33	33	32	112	56	31	1235	1142	655	0			37	37	37	261	227	195	388	88	63	4	3	3	2070	1586	1016
Enterococcus spp. †	0			91	91	0	275	275	0	0			3	3	0	15	15	0	1	1	0	0			385	385	0

N=total isolates; T=susceptibility testing available for regimen of interest; S=isolates identified as susceptible on testing; †indicates not based on susceptibility testing as assumed intrinsically resistant.