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Antimicrobial susceptibility testing and antibiotic consumption results from 16 hospitals in Viet Nam: The VINARES project 2012–2013

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ABSTRACT

Objective: To establish a hospital-based surveillance network with national coverage for antimicrobial resistance (AMR) and antibiotic consumption in Viet Nam.
Methods: A 16-hospital network (Viet Nam Resistance: VINARES) was established and consisted of national and provincial-level hospitals across the country. Antimicrobial susceptibility testing results from routine clinical diagnostic specimens and antibiotic consumption data in Defined Daily Dose per 1000 bed days (DDD/1000 patient-days) were prospectively collected and analysed between October 2012 and September 2013.
Results: Data from a total of 24 732 de-duplicated clinical isolates were reported. The most common bacteria were: *Escherichia coli* (4437 isolates, 18%), *Klebsiella* spp. (3290 isolates, 13%) and *Acinetobacter* spp. (2895 isolates, 12%). The hospital average antibiotic consumption was 918 DDD/1000 patient-days. Third-generation cephalosporins were the most frequently used antibiotic class (223 DDD/1000 patient-days, 24%), followed by fluoroquinolones (151 DDD/1000 patient-days, 16%) and second-generation cephalosporins (112 DDD/1000 patient-days, 12%). Proportions of antibiotic resistance were high: 1098/1580 (69%) *Staphylococcus aureus* isolates were methicillin-resistant (MRSA); 115/344 isolates (33%) and 90/358 (25%) *Streptococcus pneumoniae* had reduced susceptibility to penicillin and ceftriaxone, respectively. A total of 180/2977 (6%) *E. coli* and 242/1526 (16%) *Klebsiella pneumoniae* were resistant to imipenem, respectively; 602/1826 (33%) *Pseudomonas aeruginosa* were resistant to ceftazidime and 578/1765 (33%) to imipenem. Of *Acinetobacter* spp. 1495/2138 (70%) were resistant to carbapenems and 2/333 (1%) to colistin.
Conclusions: These data are valuable in providing a baseline for AMR among common bacterial pathogens in Vietnamese hospitals and to assess the impact of interventions.

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1. Introduction

Antimicrobial resistance (AMR) among common bacterial pathogens is a recognised global health threat, leading to a significant increase in healthcare costs, treatment failures and deaths [1]. The issue is more pressing in low-income and middle-income countries (LMICs) like Viet Nam, where the burden of resistant infections is disproportionate, while data and evidence on the exact burden and epidemiology are scarce [2].

Overuse and inappropriate use of antibiotics is an important driver for the emergence and spread of AMR. The World Health Organization (WHO) introduced a six-point policy package on World Health Day 2011, including surveillance of antimicrobial resistance and use and rational antimicrobial use [3]. This served as the framework for the Global Action Plan and most National Action Plans composed by member states. The WHO also published a comprehensive set of recommendations to track antimicrobial use and resistance in bacteria, and to ensure a better use of antibiotics and reduce antimicrobial use in animal husbandry [4]. In Viet Nam, there is substantial overuse of antimicrobial drugs, both in the animal health sector and in the human health sector in hospitals and the community [5,6]. An observational study of antibiotic sales in northern Viet Nam showed high proportions of transactions at pharmacies that included antibiotics: 24% in urban sites and 30% in rural sites; the large majority were without prescription [7].

Since 1988, a number of national and international efforts have been made to implement AMR surveillance in Viet Nam, on different scales. Table 1 describes the objectives, scale and results of each project. The Viet Nam Resistance network (VINARES) was launched in 2012 as a collaboration between the Ministry of Health, Vietnamese Infectious Diseases Society, Oxford University Clinical Research Unit-Viet Nam (OUCRU), and Linköping University, Sweden, together with 16 hospitals across the country [8]. This study describes the antimicrobial sensitivity testing (AST) results from clinical specimen isolates from the microbiology laboratories, and antimicrobial consumption data from the VINARES hospitals' pharmacies between October 2012 and September 2013. These results provide an update on earlier results published in the situation analysis [6] and recommendations for data collection improvement to use as evidence for design and implementation of targeted interventions to tackle antibacterial overuse and resistance in Viet Nam.

2. Materials and methods

2.1. Data collection

The VINARES network was previously described [8]. Sixteen hospitals were included: seven in the northern, three in the central and six in the southern region of Viet Nam. These include national-level (n = 7) and provincial-level (n = 9) hospitals; two tropical

Table 1
Result of antimicrobial resistant surveillance programs and studies in Viet Nam from 1988–2011.

Project	Year	Scale	Vietnamese sites	Description	Result of program
NPSAR (former ASTS) [25] [26]	1988–2006	Viet Nam	9 (in 1988) 31 (1993)	NPSAR – implemented by MoH – was a national surveillance program for AMR. Bacteria causing infectious diseases in inpatients and outpatients were isolated and tested for antibiotic susceptibility.	*E. coli* producing ESBL: 7.7% (42/548) *K. pneumoniae* producing ESBL: 23.7% (115/485)
ANSORP [27]	1996	Asia	1	Children's Hospital 2, HCMC, participated in a project of surveillance for pneumococcal resistance among clinical *S. pneumoniae* isolates that were collected from 14 centres in 11 countries in Asia and the Middle East between 2000 and 2001.	Proportion of penicillin non-susceptibility *S. pneumoniae* (71.4%) in Viet Nam, highest among participant countries. Amoxicillin/clavulanic acid (AMC) resistance rate was 22.2%.
ANSORP [28]	2004–2006	Asia	1	A prospective, multinational surveillance study with molecular typing analysis that was performed to understand the changing epidemiology of *S. aureus* infections in Asian countries.	University of Medicine and Pharmacy in HCMC, Viet Nam reported that hospital-acquired and community-acquired *S. aureus* were 74.1% and 30.1%, respectively. Second highest rates of MRSA among participants, lower than Sri Lanka.
Multi-center evaluation study on *S. aureus* bacteraemia [19]	2008–2009	Global	3	This study assessed the variation in management and adherence to treatment guidelines of *S. aureus* bacteraemia treated consecutively over 1 year in eight centres in the United Kingdom, three in Viet Nam and one in Nepal.	80 patients (19%) from Viet Nam had methicillin-resistant *S. aureus* bacteraemia.
GARP [6]	2009	Global	15	GARP-Viet Nam and the University of Oxford collaborated with the Vietnamese MoH to set up new antibiotic resistance surveillance program. A cross-sectional study was performed to collect antibiotic resistance and antibiotic use data from 15 participating hospitals 2009.	*E. coli* resistant to cefuroxime (30–80%), to SXT from 60–80%. *E. coli* and *K. pneumoniae* producing ESBL were 15–57% and 7–73%, respectively. 40% of *Pseudomonas aeruginosa* and 60% of *Acinetobacter* spp. were resistant to ceftazidime.
SOAR [22]	2009–2011	Global	11	A study on AMR surveillance of respiratory pathogens. Isolates of *S. pneumoniae* and *H. influenzae* were obtained from clinical materials taken from adults and paediatric patients with community-acquired respiratory infections.	47.8% and 93.1% of *S. pneumoniae* were non-susceptible to penicillin and resistant to azithromycin. 40.5% of *H. influenzae* produced β-lactamase. Resistances to AMC for *S. pneumoniae* and *H. influenzae* were low (3.1% and 2.6%, respectively).
SMART [29]	2009–2011	Global	4	A study on antimicrobial susceptibility rates in aerobic Gram-negative bacteria causing intra-abdominal infections in Viet Nam (2 sites in HCMC and 2 sites in Hanoi).	ESBL positive in *E. coli* and *K. pneumoniae* were 48.1% and 39.5%, respectively. 7.7% of 13 *P. aeruginosa* isolates were resistant to ceftazidime but none to ciprofloxacin.

Abbreviations: AMR, antimicrobial resistance; NPSAR, National Program for Surveillance in Antimicrobial Resistance; ASTS, antimicrobial sensitivity testing study; MoH, Ministry of Health; ESBL, extended spectrum beta-lactamase; AMC, amoxicillin/clavulanic acid; ANSORP, Asian Network for Surveillance of Resistant Pathogens; HCMC, Ho Chi Minh City; MRSA, methicillin-resistant *Staphylococcus aureus* (*S. aureus*); GARP, Global Antibiotic Resistance Partnership; SXT, trimethoprim/sulfamethoxazole; SOAR, Survey of Antibiotic Resistance; SMART, Study for Monitoring Antimicrobial Resistance Trends; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenza*, *Haemophilus influenzae*; *P. aeruginosa*, *Pseudomonas aeruginosa*.

diseases, two paediatric and one surgical hospital(s) (Fig. 1). Antibiotic consumption was reported monthly by the pharmacy department. Each department was provided with a laptop and an Excel file to enter the details of antibiotic consumption in the intensive care unit (ICU) and whole hospital. In a few cases, patients had to buy outside medicine that was not available in the pharmacy department (e.g. colistin). This situation was ignored in this study, but it did not affect the results as it was very rare.

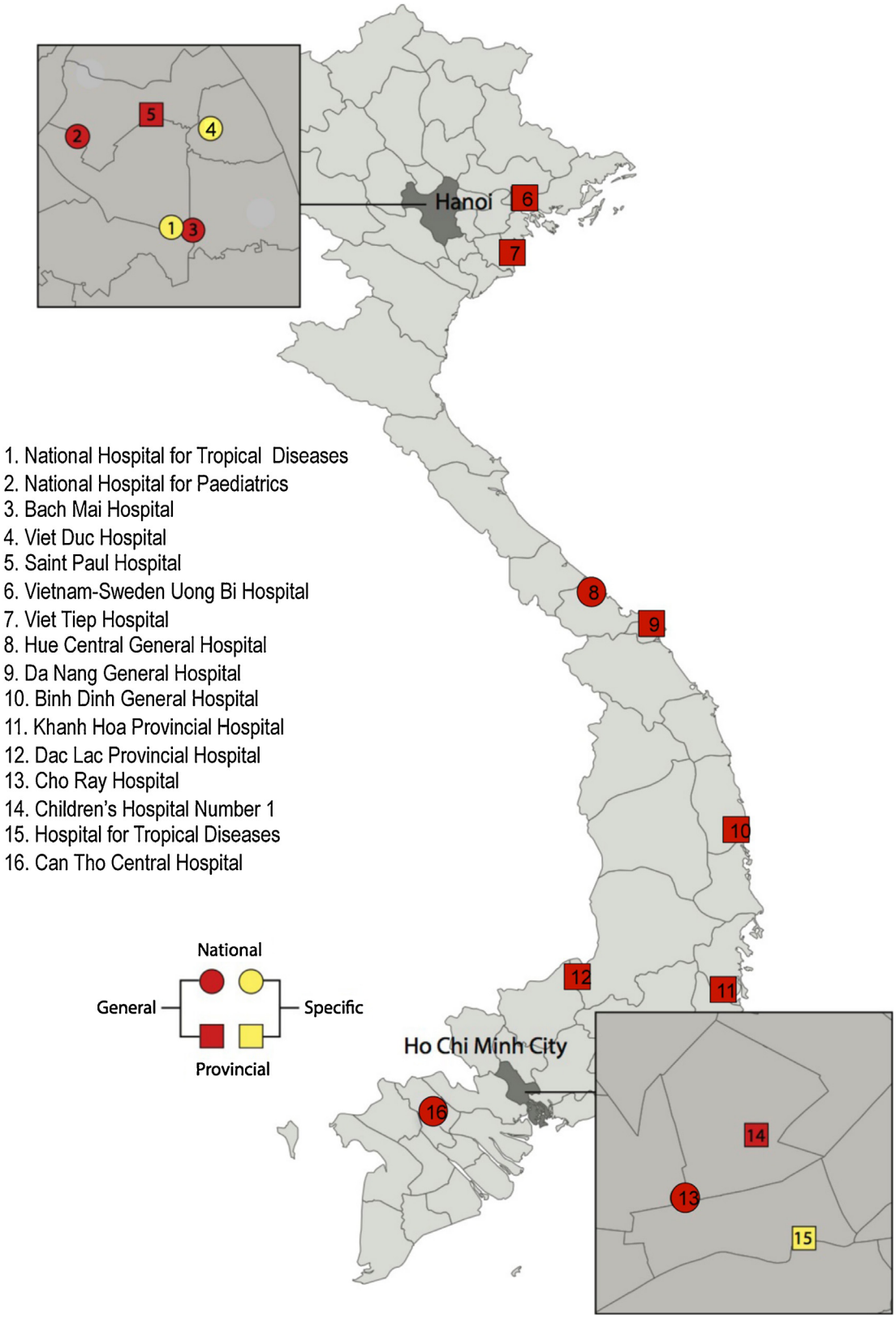

Fig. 1. Location, specialty and type of the 16 participating hospitals in the project.

A baseline laboratory assessment was conducted at the 16 participating hospitals. Laboratories were provided with American Type Culture Collection (ATCC) reference strains for internal quality control and were enrolled into the monthly UK NEQAS identification and AST external quality assessment programme. Each laboratory performed identification and susceptibility tests on an isolate that was sent monthly by UK NEQAS, and uploaded the result on their website. UK NEQUAS assessed the test results and returned the report to OUCRU. Each laboratory was provided with a laptop, surveillance database software (WHONET) [9], and up-to-date Vietnamese-translated Clinical Laboratory Standards Institute (CLSI) guidelines (M100-S22) [10]. Staff from all participating sites were trained during several workshops on microbiology methods and the use of WHONET. A helpdesk was set up to address any issues throughout the project. Reported data, including AST results from bacterial isolates from clinical specimens sent in for routine diagnostics and hospital-wide antibiotic consumption in the 16 participating hospitals, were sent monthly from October 2012 to September 2013. The AST results were entered manually into WHONET or exported from automated AST as VITEK2 (bioMérieux, Marcy l'Étoile, France) or LABCONN (Labsoft, Viet Nam) using BacLink (provided with WHONET). There were four hospitals that used automated systems, 11 used manual and one used both. A configuration file was developed for each laboratory to convert data. Both AST and antimicrobial usage data were submitted regularly or on request by email.

All duplicate isolates for the same patient (identical specimen type and bacterium) in the AST dataset were excluded following WHO recommendations [11]. Results obtained by disk diffusion (DD) and minimum inhibitory concentration (MIC) methods were combined. If both were performed, the MIC result was used. Reported resistance rates are the proportion of bacteria with the AST showing resistance (result = R). Intermediate susceptible isolates (result = I) were not considered as resistant. Results were accepted, analysed and reported as is and, generally, no confirmatory testing of unexpected results or rare phenotypes in reference or central laboratories was performed according to current practice in most LMICs.

2.2. Data analysis

The number and proportion of nine indicator bacteria — *Acinetobacter* spp., *Pseudomonas aeruginosa* (*P. aeruginosa*), *Haemophilus influenzae* (*H. influenzae*), *Escherichia coli* (*E. coli*), *Klebsiella* spp., *Staphylococcus aureus* (*S. aureus*), *Enterobacter* spp., *Enterococcus faecium* (*E. faecium*), and *Streptococcus pneumoniae* (*S. pneumoniae*) – were described overall by patient age group, sex and specimen type.

An *S. aureus* isolate was counted as multi-resistant (MRSA) if it tested resistant to oxacillin or cefoxitin in screening. Similarly, *S. pneumoniae* isolates were counted as reduced susceptibility to penicillin if resistance to oxacillin by disk diffusion was reported (also if unconfirmed by MIC testing). Resistance rates were reported for all specimens combined and for a subgroup of invasive isolates from blood and cerebrospinal fluid (CSF). The proportion assessed by disk diffusion or MIC was reported if applicable. A sample was considered resistant to an antibiotic class if it was resistant to at least one antibiotic agent in that class, as per CLSI guidelines.

Antibiotic consumption was summarised in number of Defined Daily Dose per 1000 bed days (DDD/1000 patient-days). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, which can be obtained from the WHO Antimicrobial DDD Quick Reference List [12]. The DDD/1000 patient-days was calculated by antibiotic class and did not depend on bed size of hospital.

For each bacteria-antibiotic pair, the resistant proportion was calculated as the ratio between the number of resistant isolates and number of tested isolates for that drug. All hospitals were anonymised and coded from H1 to H16. R software (version 3.1.11) was used for the analysis [13].

3. Results

3.1. Distribution of bacteria and antibiotics

The AST results were reported for 26 808 isolates from the VINARES network between October 2012 and September 2013. After de-duplication and removal of fungi, 24 732 bacterial isolates were included in the analysis.

The most commonly isolated organisms were: *E. coli* (4437 isolates, 18%); *Klebsiella* spp. (3290 isolates, 13%) – including 2206 *K. pneumoniae* isolates (9%); *Acinetobacter* spp. (2895 isolates, 12%) – including 1668 *Acinetobacter baumannii* (*A. baumannii*) isolates (7%); *P. aeruginosa* (2326 isolates, 9%); *S. aureus* (2039 isolates, 8%); *Enterobacter* spp. (1067 isolates, 4%); *S. pneumoniae* (813 isolates, 3%); *H. influenzae* (404 isolates, 2%); and *E. faecium* (98 isolates, 1%). Gram-negative bacteria accounted for 69% (17 065 isolates) and Gram-positive for 31% (7667 isolates). Sputum was the most frequently reported specimen (3625 isolates, 15%) followed by blood (3222 isolates, 13%). Of the total isolates, 11% were recovered from blood and CSF.

The distribution of isolates by gender and age of patient and type of specimen for the nine indicator bacteria is summarised in Supplementary Table S1. Among 17 369 common bacteria, a higher proportion was isolated from male (66%) than from female patients (34%), reflecting the usual hospital population in Viet Nam. *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter* spp. (including *A. baumannii*) were mainly reported from adults aged >20 years, while *S. aureus* and *S. pneumoniae* were more commonly reported from children aged ≤10 years.

The distribution of bacteria was separately stratified by hospitals and region (Fig. 2). *Acinetobacter* spp. were mostly found in two major general hospitals (H2 and H4). *H. influenzae* was mainly isolated from children, with >50% from one paediatric hospital (H11). The proportion of *E. coli* was similar across the three regions and, overall, the pathogen distribution also appeared similar across regions.

Antibiotic consumption was separately summarised by hospital and region. One hospital (H2) did not provide consumption data. The average antibiotic consumption was 918 DDD/1000 patient-days per hospital. Hospitals in the central and southern region had similar antibiotic consumption rates (1079 and 1026 DDD/1000 patient-days, respectively), while a lower rate was reported, on average, from hospitals in the northern region (799 DDD/1000 patient-days, after excluding a paediatric hospital). The most commonly used antibiotics were third-generation cephalosporins (223 DDD/1000 patient-days, 24%), fluoroquinolones (151 DDD/1000 patient-days, 16%), second-generation cephalosporins (112 DDD/1000 patient-days, 12%), penicillin combinations (111 DDD/1000 patient-days, 12%), followed by aminoglycosides (54 DDD/1000 patient-days, 6%), penicillins with extended spectrum (53 DDD/1000 patient-days, 6%), fourth-generation cephalosporins (49 DDD/1000 patient-days, 5%), carbapenems (35 DDD/1000 patient-days, 4%) and glycopeptides (10 DDD/1000 patient-days, 1%). Overall, third-generation cephalosporins was the largest group in all regions, followed by fluoroquinolones (Fig. 3). Two-thirds of second-generation cephalosporins were used in the central region.

3.2. Antimicrobial susceptibilities

3.2.1. General

The proportion of isolates having AST assessed varied by hospital; more ASTs were performed at national hospitals than in provincial hospitals (Supplementary Table S2). Vancomycin-susceptibility test

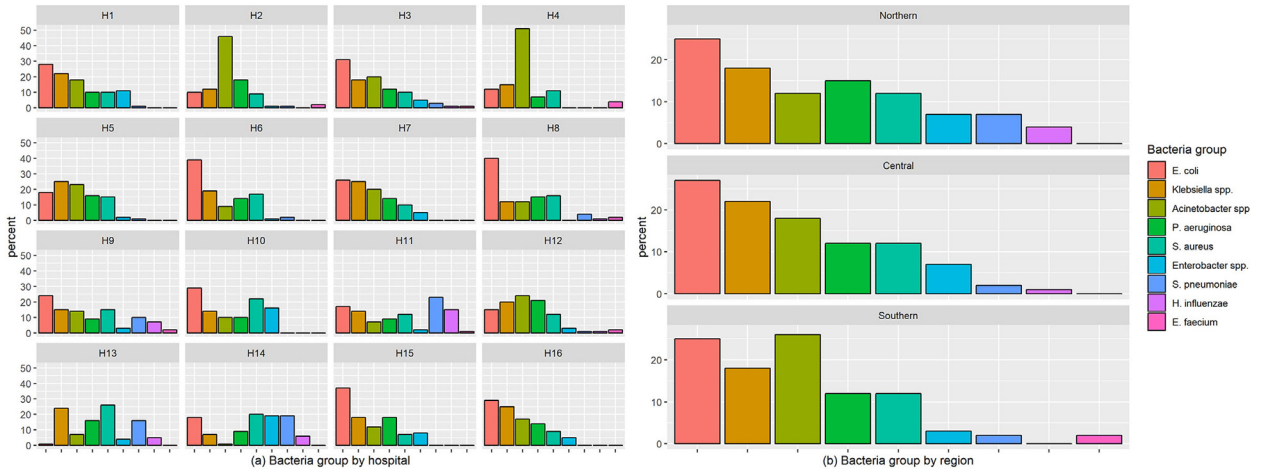

Fig. 2. Distribution of bacteria by hospitals and regions. Sum of each graph is 100%.
Abbreviations: *E. coli*, *Escherichia coli*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *E. faecium*, *Enterococcus faecium*.

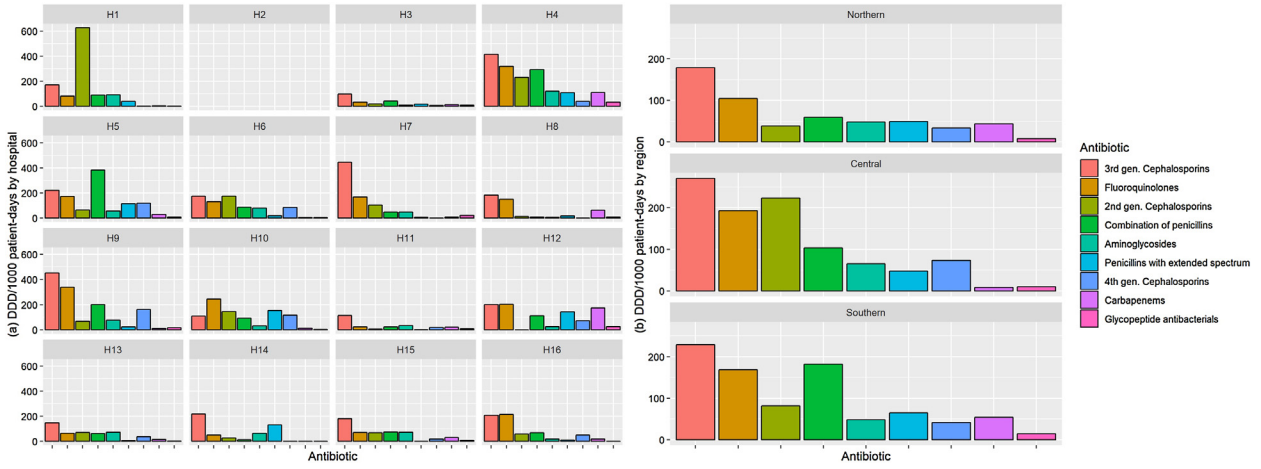

Fig. 3. Distribution of antibiotic consumption by hospitals and regions.

for *E. faecium* and imipenem-susceptibility test for *P. aeruginosa* were most frequently carried out across the hospitals (98% and 76%, respectively). Four hospitals (H3, H4, H8, H12) had tested >95% of reported isolates.

Fig. 4 illustrates the resistant proportions of each bacteria-antibiotic combination and its relationship with the amount of antibiotic used and the number of isolates. Second-generation cephalosporins are not included in Fig. 4 because most hospitals did not test for these. More than 50% of Enterobacteriaceae were resistant to third-generation cephalosporins and fluoroquinolones. Carbapenem-resistant proportions were highest among *Acinetobacter* spp. (around 75%), followed by *P. aeruginosa* (around 50%) and lowest in Enterobacteriaceae (around 25%). *S. aureus* and *E. faecium* were susceptible to vancomycin, but the susceptibility results of *E. faecium* should be interpreted with caution because of the low numbers. *S. pneumoniae* was susceptible, while nearly 50% of *H. influenzae* were resistant to combinations of penicillins.

3.2.2. Antimicrobial susceptibility testing results of Gram-positive bacteria

Table 2 shows the AST results for *S. aureus*, *S. pneumoniae* and *E. faecium*. *S. aureus* was isolated from 2039 specimens; 258 (13%) were from blood and CSF. Among 1580 tested, 1098 (69%) *S. aureus* isolates were identified as MRSA. Similar resistance rates were observed for isolates from blood and CSF isolates from all specimens. D-test for induced clindamycin resistance was not separately reported, therefore resistance may be underestimated.

The results from 813 *S. pneumoniae* isolates included 87 from blood and CSF. Etests confirmed/were performed in 99% (353/358) of ceftriaxone, 39% (86/221) of penicillin and 54% (349/641) of vancomycin susceptibility tests. A total of 115/344 (33%) *S. pneumoniae* isolates showed reduced susceptibility to penicillin; the corresponding percentage in blood and CSF isolates was 7/30 (23%). *Streptococcus pneumoniae* susceptibility to penicillin was screened using oxacillin disks; 86 isolates were confirmed by penicillin MIC test. Out of 194 oxacillin disk diffusion results showing resistance, 87 (45%) were not confirmed by penicillin susceptibility test. Regarding blood and CSF specimens, there were six isolates confirmed by penicillin MIC test, and they were all susceptible. Ten isolates (2%) of *S. pneumoniae* were resistant to vancomycin (two of 10 resistant isolates were confirmed by Etest). These results were not confirmed in a reference laboratory or molecularly, and this should be interpreted with caution.

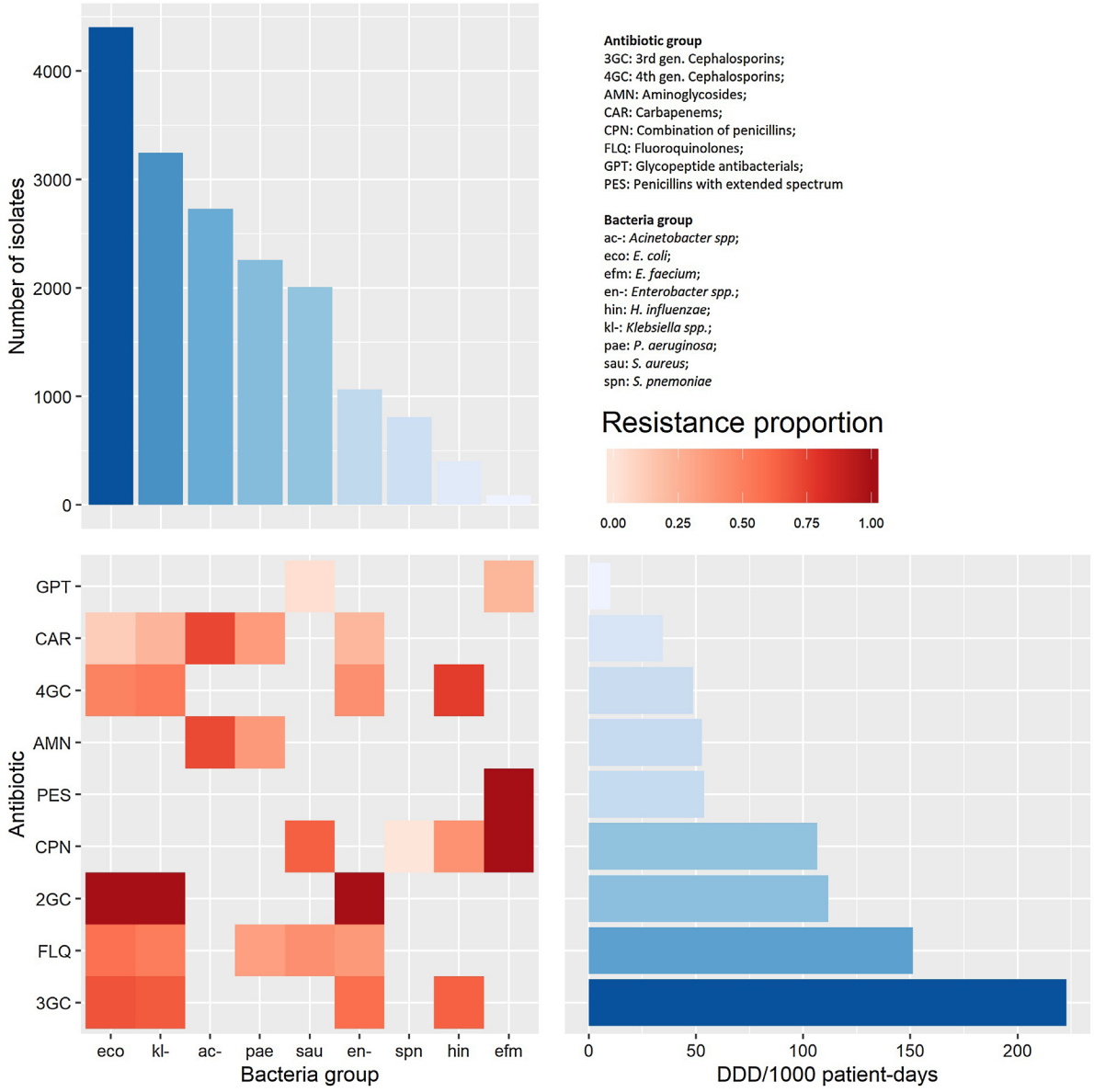

Fig. 4. Resistance rate, number of isolates and number of DDD/1000 patient-days per antibiotic group.
For each bacteria-antibiotic combination, the resistant proportion was shown in bottom left figure; the number of isolates for each organism was in top left and the number of DDD/1000 patient-days of antibiotic group was in bottom right. The resistant proportion was calculated for 15 hospitals that provided antibiotic consumption data. DDD/1000 patient-days figure illustrates the amount of antibiotic used for all bacterial treatment, not for any specific bacteria. Untested or clinically irrelevant bacteria-antibiotic combinations were not shown.

Among 98 *E. faecium* isolates, only one amoxicillin susceptibility test was performed. Of isolates, 78% were vancomycin susceptible, while the proportion of normal-level gentamicin susceptibility was <50%.

3.2.3. Antimicrobial sensitivity testing results of Gram-negative bacteria

Enterobacteriaceae susceptibility for amikacin, cefotaxime, ciprofloxacin, gentamicin, imipenem, tobramycin and trimethoprim/sulfamethoxazole (SXT) are shown in Table 3. Among the 4437 *E. coli* submitted, 527 (12%) were from blood and CSF and 992 (23%) from urine. More than 80% of ASTs for *E. coli* were carried out by disk diffusion. Resistance was >50% for third-generation cephalosporins and fluoroquinolones. Lower resistance levels were seen for imipenem and amikacin. Resistance rates among all isolates were generally higher than proportions observed in blood and CSF isolates ($P < 0.0001$ for cefotaxime and ciprofloxacin; $P = 0.03$ for SXT).

Of the 3290 available *Klebsiella* spp. isolates, 2206 were *K. pneumoniae*. Resistance rates to third-generation cephalosporins and carbapenems were 68% and 16%, respectively. Similar to *E. coli*, proportions of resistance to cefotaxime, ciprofloxacin and SXT were also lower among blood and CSF than all isolates ($P < 0.0001$ for all). Among the 1067 *Enterobacter* spp. isolates (82 from blood and CSF), 21% were resistant to carbapenems.

Table 4 shows the AST results of *Acinetobacter* spp., *P. aeruginosa* and *H. influenzae*. Results from 2895 *Acinetobacter* spp. (including 1668 *A. baumannii*) were submitted. Data on colistin were available from only one hospital and two of 333 isolates were found to be resistant. Results showed very high resistant proportions for all

Table 2
Susceptibility result of Gram-positive bacteria isolated in the VINARES project.

Resistance/tested isolates (%)	*S. aureus*		*S. pneumoniae*		*E. faecium*	
	All specimens (n = 2039)	Blood and CSF (n = 258)	All specimens (n = 813)	Blood and CSF (n = 87)	All specimens (n = 98)	Blood and CSF (n = 24)
MRSA	1098/1580 (69)	145/197 (74)				
Vancomycin	22/823 (3)	2/135 (1)	10/641 (2)	1/74 (1)	21/96 (22)	3/24 (12)
Ciprofloxacin	456/1277 (36)	71/189 (38)	2/12 (17)	0/0 (NT)		
Erythromycin	985/1 315 (75)	103/143 (72)	246/289 (85)	26/29 (90)		
Clindamycin	639/907 (70)	74/118 (63)				
Gentamicin	435/1155 (38)	55/135 (41)			26/46 (57)	8/9 (89)
Levofloxacin	333/852 (39)	40/125 (32)				
SXT	261/1156 (23)	41/141 (29)				
Penicillin			115/344 (33)[a]	7/30 (22)[b]		
Ceftriaxone			90/358 (25)	9/52 (17)		
Amoxicillin					1/1 (100)	0/0 (NT)

Abbreviations: CSF, cerebrospinal fluid; MRSA, methicillin-resistant *Staphylococcus aureus*; SXT, trimethoprim/sulfamethoxazole.
Untested or clinically irrelevant bacteria-antibiotic combinations were not shown.
[a] screened with oxacillin, 86 isolated were confirmed by MIC method and one isolate was resistant to penicillin.
[b] screened with oxacillin, six isolates were confirmed by MIC method and all were susceptible to penicillin.

Table 3
Susceptibility results of *Escherichia coli, Klebsiella* spp. and *Enterobacter* spp. isolated in the VINARES project.

Resistance/tested isolates (%)	*Escherichia coli*		*Klebsiella* spp.		*Enterobacter* spp.	
	All specimens (n = 4 437)	Blood and CSF (n = 527)	All specimens (n = 3 290)	Blood and CSF (n = 413)	All specimens (n = 1067)	Blood and CSF (n = 82)
Amikacin	321/2936 (11)	36/394 (9)	638/2163 (29)	61/329 (19)	149/768 (19)	11/58 (19)
Cefotaxime	2342/4192 (56)	240/514 (47)	1479/2227 (66)	101/190 (53)	483/802 (60)	25/48 (52)
Ciprofloxacin	1758/3052 (58)	188/397 (47)	1 222/2305 (53)	139/332 (42)	277/741 (37)	28/63 (44)
Gentamicin	1285/2655 (48)	111/282 (39)	1042/1989 (52)	99/233 (42)	294/760 (39)	21/47 (45)
Imipenem	180/2977 (6)	15/403 (4)	393/2294 (17)	64/361 (18)	144/665 (22)	12/70 (17)
SXT	1994/2803 (71)	196/298 (66)	1242/2 007 (62)	118/236 (50)	360/709 (51)	24/51 (47)
Tobramycin	502/1309 (38)	52/247 (21)	588/1377 (43)	65/236 (28)	142/386 (37)	16/48 (33)

Abbreviations: CSF, cerebrospinal fluid; SXT, trimethoprim/sulfamethoxazole.

Table 4
Susceptibility result of *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Haemophilus influenzae* isolated in the VINARES project.

Resistance/tested isolates (%)	*Acinetobacter* spp.		*P. aeruginosa*		*H. influenzae*	
	All specimens (n = 2895)	Blood and CSF (n = 313)	All specimens (n = 2326)	Blood and CSF (n = 154)	All specimens (n = 404)	Blood and CSF (n = 10)
Amikacin	1347/1993 (68)	82/188 (44)	329/1556 (21)	13/82 (16)		
Cefotaxime					118/270 (44)	5/10 (50)
Ciprofloxacin	1298/1733 (75)	74/207 (36)	496/1527 (32)	33/120 (28)	17/269 (6)	0/10 (0)
Gentamicin	1385/1837 (75)	130/214 (61)	566/1456 (39)	33/106 (31)		
Imipenem	1495/2138 (70)	110/244 (45)	578/1765 (33)	36/129 (28)	33/341 (10)	0/10 (0)
SXT	1258/1799 (70)	86/192 (45)			46/60 (77)	3/5 (60)
Ceftazidime	1650/2146 (77)	124/242 (51)	602/1826 (33)	43/133 (32)		
TCC	771/1128 (68)	47/141 (33)				
AMC					109/276 (39)	2/5 (40)
Erythromycin					3/3 (100)	0/0 (NT)
Ampicillin					160/226 (71)	3/5 (60)

Abbreviations: CSF, cerebrospinal fluid; SXT, trimethoprim/sulfamethoxazole; TCC, ticarcillin/clavulanic acid; AMC, amoxicillin/clavulanic acid.

antibiotics, from 68% (amikacin) to 77% (ceftazidime). Resistant proportions of *Acinetobacter* spp. for imipenem and amikacin in blood and CSF were lower than in other specimens ($P < 0.0001$ for both).

Of the 2326 *P. aeruginosa* submitted isolates, 154 were from blood and CSF. The resistance rate to ceftazidime was 33%, which is similar to blood and CSF specimens. Of the isolates, 33% were resistant to imipenem, while 39% were aminoglycosides-resistant. Blood isolates had lower aminoglycosides-resistance levels in comparison with all isolates ($P = 0.04$).

H. influenzae was isolated from 404 specimens, including 10 from blood and CSF. One hundred and sixty (71%) isolates were resistant to ampicillin. The resistance rates to amoxicillin/clavulanic acid (AMC) and cefotaxime were 39% and 44%, respectively.

4. Discussion

This study described the AST and antibiotic usage results reported from the VINARES network in Viet Nam between 2012 and 2013. Overall, the data showed high proportions of AMR among all tested bacteria across all hospitals in the network. These results also show large variations in the resistant proportions between hospitals. This highlights the importance of continuous monitoring of local antibiotic use and bacterial resistance, which is one of the core strategies in the National Action Plan on combatting

drug resistance [14]. Overall, lower proportions of resistance were found in samples taken among isolates from blood and CSF samples, likely reflecting different proportions of hospital acquired isolates among sample types.

Cephalosporins, fluoroquinolones and penicillin covered 70% of antibiotic use. Hospitals were more likely to use fluoroquinolones and less likely to use cephalosporins in 2012 (16%) than in 2008 (11%) [5]. This may be explained by the change in antibiotic susceptibility between the two periods.

The antibiotic use DDD/1000 patient-days provides a rough indication that 91% of patients in hospitals were on antibiotic treatment. However, DDD/1000 patient-days is not an appropriate measure with which to study the impact of antimicrobial stewardship because DDD/1000 patient-days can be misrepresented by use of combination therapy or of higher dosages for certain indications or guided by therapeutic drug monitoring (not yet practiced in Viet Nam). This biases towards higher DDD/1000 patient-days and, thus, an overestimate of antibiotic use. As evidence of these biases in DDD/1000 patient-days measurements, a monthly point prevalence study conducted in ICUs within VINARES reported that the proportion of patients receiving antibiotics at survey time was 85% (2787/3287) and that 60% of patients were prescribed more than one antibiotic [15]. This result was higher compared with the point-prevalence conducted in 2008 (67% (5104/7571) of patients receiving antibiotics) [5]. Two possible explanations were that 16 of 36 participating sites of the previous study were district-level hospitals with an expected lower usage and that there has been an increase in use of antibiotics in hospitals over time. The global report of antibiotic consumption also stated an increase of 20–25 DDD/1000 patient-days in Viet Nam in the 2010–2015 period [16].

The number of days of antimicrobial therapy (DOT) can be used along with DDD/1000 patient-days to report antibiotic consumption practices in hospital, which offers more clinical relevance [17]. The DOT reports the administration of a single agent on a given day, regardless of the number of doses administered or dosage concentration [18], which avoids overestimation of usage. The DDD/1000 patient-days allows comparison of antibiotic use across countries and hospitals, while DOT could make conclusions about the relative use of one antibiotic compared with another [18]. The measurement of DOT might be difficult for most hospitals [17]. The measurement of antibiotic use by DDD/1000 patient-days and DOT/1000 patient-days was dissimilar because the administered dose is dissimilar from the DDD recommended by the WHO, according to a study on 130 hospitals in USA [18].

The current study reported similar levels of resistance among four Gram-negative bacteria — including *E. coli*, *K. pneumoniae, P. aeruginosa* and *Acinetobacter* spp. — compared with the GARP situation analysis [6]. Further studies to evaluate the changes in antibiotic consumption and the likely effect on resistance levels at hospitals are warranted to prioritise targets of intervention. In addition, linking microbiology and susceptibility data with clinical data should be aimed for in this surveillance network, to allow assessment of the origin of the infection (community vs. hospital-acquired) for better informing of evidence-based guidelines.

In the GARP situation analysis, an MRSA proportion of between 30–64% was reported [6]. An evaluation from 2008–2009 in three hospitals in Viet Nam revealed an MRSA proportion of 19% in 80 patients with *S. aureus* bacteraemia [19]; while the current study reported 61% of MRSA in blood and CSF specimens. Better and more comprehensive surveillance methodology may explain the higher proportions of MRSA bacteraemia. In VINARES, all MRSA tests were performed by oxacillin or cefoxitin disc diffusion test, which is a reliable proxy for detection of MRSA [20].

More than 50% of *S. pneumoniae* were non-susceptible to penicillin. This was also confirmed in a recent review by WHO [21], showing the result of penicillin non-susceptibility from 47–48% in two countries in the South-East Asia and 17–64% in 10 countries of Western Pacific region. However, the extent of the problem is uncertain, partly due to variations in how reduced susceptibility is being reported and large proportions of intermediate results. The SOAR study reported 48% (138/289) of penicillin-non-susceptibility among *S. pneumoniae* [22].

Carbapenems were still mostly active against the tested Enterobacteriaceae. Compared with 2009, there was a slight increase of resistance to imipenem among *E. coli* (from 2% to 6%) and *Klebsiella pneumoniae* (from 10% to 17%) [6]. Most imipenem-susceptibility tests for Enterobacteriaceae were performed by disk diffusion, but this may not be as reliable as broth microdilution or other methods [23]. *Klebsiella* spp. showed increased resistance to third-generation cephalosporins in comparison with a 2009 situation analysis study (from 40% to 66%). Fourth-generation cephalosporins also had less effect on these species. For *E. coli*, the current study showed similarly high resistance proportions to the conventional agents used for treatment, such as SXT and third-generation cephalosporins, in comparison with the 2009 situation analysis (from 60–80%) [6]. These data showed the persistent and increasing problem of Enterobacteriaceae resistance to third-generation cephalosporins in the hospital setting. Even though resistance to carbapenems in this report is still low, the levels tended to increase from the time of the 2009 situation analysis and are likely to continue increasing unless effective interventions are undertaken.

P. aeruginosa was still susceptible to ceftazidime, ciprofloxacin and imipenem, with a resistance rate around 30%. The 2009 situation analysis showed similar rates of around 40% resistance to ceftazidime and ciprofloxacin [6]. Data from VINARES are more likely to be representative, given the improved and quality assessed microbiological and reporting practices. *P. aeruginosa* was among the three most common aetiologies of hospital-acquired infections in ICUs in Viet Nam in the same period [15]. This point prevalence survey showed higher resistance proportions of *P. aeruginosa* to carbapenems (55.7%) compared with the current surveillance results, reflecting the larger burden of resistance in the ICU settings.

In the current study, *Acinetobacter* spp. also showed 70% resistance to imipenem, while the proportion reported in the 2009 situation analysis was 40% [6]. High carbapenem resistance in these organisms raised great concern for treatment alternatives, as colistin is usually the last resort and an increase in colistin resistance is likely to happen. Colistin resistance was only assessed at one hospital in the network, and 0.6% of 333 tested isolates showed resistance using Etest/VITEK (which are not the recommended standard). Higher levels of carbapenems (85%) and colistin (1.3 [n = 78] and 31.6% [n = 38]) resistance were reported from two hospitals (of the three provincial and university hospitals participating in VINARES) in southern Viet Nam in another study from 2012–2014 [24].

VINARES reported higher AMC resistance *H. influenzae* compared with SOAR (39% and 2.6%, respectively). This could be the result of increasing rate over time, or due to a large overlap between participating hospitals. Most importantly, SOAR samples were from outpatients whereas the current ones were from samples sent to the micro laboratories. As microbiology is underutilised in Viet Nam (and other LMICs) this probably represents a population with more advanced infections or a more extensive history of pre-treatment and, thus, selection of resistance pathogens. This is very illustrative of how the current AMR surveillance overestimates resistance because of this underuse and lack of clinical metadata and denominators.

Antimicrobial sensitivity testing was not conducted for all reported isolates and this could have introduced bias in the

reported resistant proportions. Three explanations can be given: first, some ASTs are only indicated based on the results of another (e.g. in *S. aureus* vancomycin was only tested for MRSA); second, ASTs may have only been indicated when the isolates were suspected to be the aetiological pathogen causing clinical manifestations; and third, ASTs may have been ordered because of failure in empirical treatment.

For future efforts to conduct antimicrobial resistance surveillance and to provide more useful data for guiding local clinical treatment and public health research, it is important for clinical microbiology laboratories to be strengthened and better utilised. Currently, the number of samples coming to the laboratory is low in comparison with the number of admitted patients. It is likely that the more severe patients, transferred patients, patients failing primary treatment, and patients with hospital-acquired infections are overrepresented among patients from whom samples are sent to the laboratory. Clear clinical diagnostic and treatment guidelines, with consistent microbiological testing on suspicion of infectious aetiology, could partially overcome this bias. Clinical data should also be considered to be part of the surveillance data. This could include clinical syndrome, date of admission, transfer status, and antibiotic use while sampled.

5. Conclusion

This project demonstrates an initiative with a large network of hospitals to monitor AMR in Viet Nam. Resistance proportions to common antibiotics in 16 hospitals were remarkably high, and most have increased since the 2009 situation analysis. Policy development for pharmacies both in hospitals and the community requires a structured solution to address this problem. AMR surveillance could be improved by enhancing capacity of clinical microbiologists through advanced training and upgrading WHONET program with more control of data entry and a pre-defined global configuration. Clinical data should be included in the reports from the hospitals in future. External quality assurance is also recommended for all testing performed in the laboratory.

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Competing interests

None declared.

Ethical approval

Not required.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2019.06.002.

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