Antibiotic use for empirical therapy in the critical care units in primary and secondary hospitals in Vietnam: a multicenter cross-sectional study

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Summary

Background The high rate of infections among patients admitted to critical care units (CCUs) is associated with high rate of antibiotic consumption, especially broad-spectrum antibiotics. This study is to describe the antibiotics use in CCUs in primary and secondary hospitals in Vietnam, a setting with high burden of antibiotic resistance.

Methods This was a 7-day observational study in 51 CCUs in hospitals from 5 provinces in Vietnam from March to July 2019. Patients aged ≥ 18 years admitted to the participating CCUs was enrolled consecutively. We collected data on patient’s demographics, initial diagnosis and antibiotic therapy within the first 24 hours. Antibiotic therapy was classified by the Anatomical Therapeutic Chemical (ATC) Index and the 2019 WHO Access, Watch, Reserve (AWaRe) groups.

Findings Out of 1747 enrolled patients, empirical antibiotic treatments were initiated in 1112 (63.6%) patients. The most frequently prescribed antibiotics were cefotaxime (22.3%), levofloxacin (19%) and ceftazidime (10.8%). Antibiotics were given in 31.5% of patients without diagnosis of infection. Watch and/or Reserve group antibiotic were given in 87.3% of patients and associated with patient’s age (aOR 1.01 per 1-year increment, 95%CI 1.00-1.02) and the presence of SIRS on admission (aOR 2.1, 95%CI 1.38-3.2).

Interpretation We observed a high frequency use and a substantial variation in patterns of empirical antibiotic use in the CCUs in Vietnam. It highlights the importance of continuous monitoring antibiotic consumption in CCUs.

Funding None.

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Keywords: antibiotic; antimicrobials; AWaRe; critical care; emergency; severe acute respiratory; infection, ICD-10; sepsis

Introduction

Severe acute respiratory infection (SARI) and sepsis are leading causes of mortality worldwide with more than 336 million episodes of SARI in 2106 and more than 19 million people with sepsis annually. Delay in the initiation of appropriate antibiotic therapy for suspected bacterial infections is associated with an increase in adverse outcomes including death. Selection of empiric antibiotics depends on patient’s characteristics, suspected site of infections, differential diagnosis, local microbial susceptibility data and antibiotic stewardship. Other consideration of empirical therapy may include the cost of treatment, availability of antibiotics, potential drug intolerances and toxicity.

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With a high burden of infectious diseases, critical care units had the highest consumption of antibiotics with an estimate of 71% of patients receiving any antibiotic. However, the rate of inappropriate antibiotic prescription in this setting may be up to one third. Beyond the benefit of early empiric antibiotic therapy to improve the outcome in patient with sepsis and septic shock, the use of broad-spectrum antibiotics is associated with adverse clinical effects, including destruction of the normal gut microbiota and development and selection of multidrug resistance organisms. The accurate diagnosis of infection in intensive care unit (ICU) is challenging and up to 43% of patients were treated inappropriately for infection. High selective pressure favouring resistant bacteria is exerted by the intensive care setting might increase antibiotic resistance. It is a transparent tool to track and measure the consumption of antibiotics at local, national and global level and easy use for monitoring the antibiotic use.

Vietnam has one of the highest potential of antibiotic drug resistance in Asia. During the period of 2013 to 2016, the resistance to third-generation cephalosporin in E. coli increased from 64% to 71%, the resistance to carbapenem in K. pneumonia increased from 23% to 24% and the proportion of methicillin-resistant Staphylococcus aureus (MRSA) increased from 46% to 73%. Because of the high rate of resistant bacteria, timeliness of empiric therapy is still important for critically ill patients and therefore, it is challenging to choose empiric antibiotics for severe life-threatening infections in CCUs. There is limited data on antibiotic initiation in CCUs in Vietnam. This study aims to describe the current situation of empirical antibiotic initiation in patients admitted to CCUs in Vietnam.

Methods

Study design and data collection
Viet Nam is composed of 63 provinces, including five centrally governed cities (Ha Noi, Ho Chi Minh City, Can Tho, Da Nang and Hai Phong). Administrative divisions of Viet Nam is consisted with province, district, and commune and each level has health care facilities according to their capacity (e.g. provincial hospital, district hospital, and commune health centre), in addition to national hospital in the central cities. This is the layer of reference system, e.g. a district hospital refer to a provincial hospital, and the national hospital. In this manuscript, ‘primary and secondary CCUs’ refers to CCUs in district or provincial hospitals.

We conducted a cross-sectional study in 2 centrally governed cities (Hanoi and Can Tho) and 3 provinces (Hanam, Thai Nguyen, Kontum) in 5 ecological regions in Vietnam from March to July 2019. In each province, we invited all CCUs in primary and secondary hospitals to participate in a 7-day prospective, observational cohort study in patients presented to critical care units. All patients admitted at the CCUs in selected hospitals for 7 days from the study initiation were included in this study. We collected the information of demographics, diagnosis, antibiotic prescriptions and data derived severity scores within 24 hours of admission and the outcomes at 7 days after the admission. Data was extracted from the medical charts. Doctors were not informed about the contents of the analysis and they managed their patients as they would normally.

Study definitions
The initial diagnosis on admission to the CCUs were defined by the International Statistical Classification of
Diseases and Related Health Problems 10th Revision (ICD-10): WHO Version 2019. The diagnosis was made by the treating doctors in both ICD code and free text descriptions as a routine practise. All diagnosis were further cleaned and verified by two study doctors (VQD and TTD) by comparison of the consistency between ICD-10 coding and free-text data of diagnosis and severity across the patients and study sites. Discrepancies between the code and free texts were resolved by consensus through two study doctors. Patients were further defined as having severe acute respiratory infections (SARI) if they had a registered ICD-10 diagnosis code of J00-J06 (acute upper respiratory infections), J09-J18 (influenza and pneumonia) and J20-J22 (other acute respiratory infections)17 or an ICD-10 diagnosis code of J44.1 (exacerbation of chronic obstructive pulmonary disease, COPD). Other infections were defined in individuals who did not meet the SARI definition but had at least one diagnosis of corresponding ICD-10 codes for the remaining miscellaneous infections.

We used the 2019 WHO AWaRe classification of antibiotics to describe the empirical antibiotic therapy in patients presenting to the CCUs.14 The Access group recommended for patients with multi-drug-resistant organisms. Systemic inflammatory response syndrome (SIRS) was defined in patients with at least two of the following criteria within 48 hours of admission to CCUs: body temperature $>$38.5$^\circ$C or $<$36.6$^\circ$C, tachycardia $>$90 beats/minute, tachypnoea $>$20 breaths/minute, leucocytosis $>$12,000/mm$^3$, $<$4,000/mm$^3$ or bandemia $\geq$10%.18 In the Sepsis-3, SIRS criteria was considered as a non-specific indicator of dysregulated, life-threatening host response but it may still remain useful for the identification of infection.19 Therefore, we used SIRS criteria to analyse the pattern of empirical antibiotic treatment. Because the lactate measurement is limited in primary and secondary hospitals in Vietnam, we defined septic shock in a patient with suspicion of infection and a systolic blood pressure less than 90 mmHg or a mean arterial pressure less than 65 mmHg or requiring administration of vasopressors or treating doctor’s clinical judgement.

The quick Sequential related Organ Failure Assessment (qSOFA) score was used to assess the severity of organ dysfunction in all patients. It consists of three components, assigning one point for each: respiratory rate $\geq$22 breaths per min, systolic blood pressure $\leq$100 mmHg, and Glasgow Coma Score (GCS) $<$15.18

Statistical analysis
Data were entered in Epidata (EpiData Association, Odense, Denmark) and analysed using IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. Standard descriptive statistics were calculated for categorical (in percentage) and continuous variables (in median and interquartile, IQR). Differences between CCUs in the primary and secondary hospitals were analysed with Pearson chi-square test or Fisher’s exact test for categorical variables when appropriated.

Logistic regression was used to identify variables that predict abilities of choosing Watch and Reserve group antibiotics. A previous study in Vietnam have shown that doctors tended to choose a broader spectrum for empirical treatment when the patients had more severe illness, older age and medical comorbidities.19 An in depth interviews of Vietnamese doctors has shown their considerations on white blood cells, age and underlying diseases when antibiotic prescribing for pneumonia.20 Therefore, we chose age, number of comorbidities, SIRS, level of hospital and diagnosis on admission for our multivariable logistic regression model. The VIF values for variables ranged from 1.074 to 1.184. None of the VIF values exceeds 5 and therefore we considered as no collinearity. Differences were considered statistically significant at p values $\leq$ 0.05.

Ethics
Eligible patients and/or their relatives were verbally informed about the study. The institutional review board (IRB) in the Hanoi Medical University approved the study (59/GCN-DDNCYSH-DHYHN). The IRB approved a waiver of consent based on the minimal risk to the participants.

Role of the funding source
The authors did not receive any funds for conducting this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We enrolled consecutively a total of 1747 adult patients admitted to 31 CCUs, including 36/51 (70.6%) CCUs in primary and 15/51 (29.4%) CCUs secondary hospitals in 5 provinces in Vietnam for a study period of 7 days in each study CCUs from March 2019 to July 2019. The demographics of patients was showed in Table 1. The most common diagnosis on admission were any diagnosis of infection (52.5%, 918/1747). Leading infectious causes of CCU admission were SARI (86.5%, 794/918), abdominal infections (5.2%, 48/918), cardiovascular diseases when antibiotic prescribing for pneumonia.20
infections (0.9%, 8/918) and other infection (2.72%, 25/918). Of 794 patients with SARI on admission, exacerbation of COPD was diagnosed in 35.3% (280/794).

Overall, 63.7% (1112/1747) patients received at least one antibiotic within 24 hours of admission. The overall rate of receiving antibiotics were 63.6% (1112/1747) (663/980, 67.6% and 449/767, 58.5% in patients admitted to CCUs in primary and secondary hospitals, respectively). The rate of antibiotic use in patients with SIRS and any diagnosis of infections were 76.0% (835/1098), 91.9% (828/901) respectively. At the day 7 after CCU admission, 34.0% patient remained hospitalised while 60.2% patients were discharged to home. The overall 7th day mortality rate was 4.7% (82/1747) among patients admitted to CCUs for all causes and was 3.7% (29/794) among patients with SARI. Among patients receiving at least one antibiotic, the proportion of patients receiving any microbiological culture (blood, sputum, urine or other sterile specimen) was 12.9% (144/1112) (31/663 or 4.7% in CCUs in primary hospitals and 121/449 or 26.9% in CCUs in secondary hospitals). The rate of pathogen identification in primary and secondary hospitals were 16.1% (39/243) and 42/121 (34.7%), respectively. No susceptibility results were further collected.

There were 31.5% (267/846) patients without diagnosis of infection in the medical notes received any antibiotic, while 6.8% (62/901) patients with diagnosis of any bacterial infection received no antibiotic within 48 hours of admission. There was a total of 72 different antibiotics used over all CCUs and (Table 3) represented

| Characteristics | All patients (n=1747) | CCUs in primary hospitals (n=980) | CCUs in secondary hospitals (n=767) | P value |
|-----------------|----------------------|---------------------------------|---------------------------------|--------|
| Age (median, IQR) (years) | 68 (55-81) | 68 (56-81) | 68 (53-80) | 0.422 |
| Male gender (%) | 988 (56.6%) | 531 (54.2%) | 457 (59.6%) | 0.024 |
| Onset to CCU admissions (median, IQR) (days) | 1 (0-3) | 1 (0-3) | 1 (0-3) | 0.004 |
| Number of comorbidity | 1177 (67.4%) | 681 (69.5%) | 496 (64.7%) | 0.044 |
| No comorbidity | 570 (32.6%) | 299 (30.5%) | 271 (35.3%) | 0.089 |
| One comorbidity | 700 (40.1%) | 401 (40.9%) | 299 (39.0%) | 0.175 |
| Two comorbidities | 389 (22.3%) | 237 (24.2%) | 152 (19.8%) | 0.008 |
| Three and more comorbidities | 88 (5.0%) | 43 (4.4%) | 45 (5.9%) | 0.001 |
| Medical history | | | | |
| Cardiovascular diseases | 689 (39.4%) | 404 (41.2%) | 285 (37.2%) | 0.084 |
| Chronic respiratory disease | 584 (33.4%) | 396 (40.4%) | 188 (24.5%) | <0.001 |
| Diabetes | 183 (10.5%) | 85 (8.7%) | 98 (12.8%) | 0.005 |
| Self reported alcoholism | 104 (6.0%) | 50 (5.1%) | 54 (7.0%) | 0.089 |
| Chronic liver diseases | 80 (4.6%) | 39 (4.0%) | 41 (5.3%) | 0.175 |
| Chronic kidney diseases | 71 (4.1%) | 29 (3.0%) | 42 (5.5%) | 0.008 |
| Malignancy | 59 (3.4%) | 18 (1.8%) | 41 (5.3%) | <0.001 |
| Diagnosis at admission | | | | |
| SARI | 749 (45.4%) | 515 (52.6%) | 279 (36.4%) | 0.001 |
| Non SARI infection | 124 (7.1%) | 42 (4.3%) | 82 (10.7%) | 0.004 |
| No infection | 829 (47.5%) | 423 (43.2%) | 406 (52.9%) | 0.005 |
| Systemic inflammatory response syndrome (SIRS) (%) | 1098 (62.9%) | 593 (60.5%) | 505 (65.8%) | 0.022 |
| Septic shock at admission | 124 (7.1%) | 38 (3.9%) | 86 (11.2%) | <0.001 |
| Quick SOFA score | | | | |
| Quick SOFA 0-1 | 1204 (68.9%) | 716 (73.1%) | 488 (63.6%) | <0.001 |
| Quick SOFA ≥2 | 543 (31.1%) | 264 (26.9%) | 279 (36.4%) | <0.001 |
| Empirical antibiotic treatment within 24 hours of admission | 21 (1.2%) | 3 (0.3%) | 18 (2.3%) | <0.001 |
| No antibiotic therapy | 635 (36.3%) | 317 (32.3%) | 318 (41.5%) | <0.001 |
| Single antibiotic therapy | 647 (37.0%) | 465 (47.4%) | 182 (23.7%) | <0.001 |
| Dual antibiotic therapy | 444 (25.4%) | 195 (19.9%) | 249 (32.5%) | <0.001 |
| Triple antibiotic therapy | 21 (1.2%) | 3 (0.3%) | 18 (2.3%) | <0.001 |
| 7-day mortality rate after admission | 82 (4.7%) | 29 (3.0%) | 53 (6.9%) | <0.001 |

Table 1: Characteristics of patients admitted to the critical care units.
for essential antibiotics by WHO Model List of Essential Medicines. Among patients received at least one antibiotic, the most common prescribed antibiotics classes were the 3rd generation cephalosporins, fluoroquinolones and penicillins with beta lactamase inhibitors (Table 2). Table 3 stratified available antibiotic by chemical substance.

The proportion of any Access group, Watch group, Reserve group and non-recommended antibiotics were 24.1% (268/1112), 87.3% (971/1112), 0.54% (6/1112) and 5.0% (56/1112), respectively (Table 2 and Fig 1). All 6 patients who received Reserve group antibiotics in secondary hospital CCUs had the diagnosis of SARI (4 patients) and septic shock (1 patient).

Among the 1112 patients who received any antibiotics, 647 (37.0%) were treated with mono therapy, 444 (25.4%) received dual therapy and 21 (1.2%) received triple therapy (Table 1). The rates of antibiotic combination treatment (dual and triple therapy) were lower in CCUs in primary hospitals vs secondary hospitals (198/980, 20.2% vs 267/767, 34.8%, p < 0.001), higher in patients with SARI vs other infections (319/866, 40.1% vs 53/124, 42.7%, p < 0.001), and higher in patients with qSOFA ≥ 2 vs qSOFA < 2 (205/543, 37.8% vs 260/1204, 21.6%, p < 0.001). The antibiotic regimens were showed in the Table 4.

Independent factors associated with using Watch and/or Reserve groups were patient’s age (aOR 1.01 per 1-year increment, 95%CI 1.00-1.02) and SIRS (aOR 2.1, 95%CI 1.38-3.2) (Table 5).

Discussion

To the best of our knowledge, our study represents the first effort to describe the initially empirical antibiotic therapy in CCUs in Vietnam, a country with a high burden of antibiotic drug resistant.

Our study was completed 5 months before the COVID-19 that was reported in Vietnam in January 2020 and was declared as a global pandemic by WHO in March 2020.21 The high proportion of SARI cases in CCUs in our study had shown an existing burden on the healthcare system in Vietnam and the current issues of SARI case management had indicated a possibility of overwhelming demands of intensive care services if more SARI related cases would have occurred. At the global level, lower respiratory infections ranked the second as a causes of disease burden (in disability-adjusted life year, DALY) and ranked the fourth as a cause of deaths.22 The percentage of SARI among CCUs admission in our study were much higher than other studies in high income countries. In high income settings, sepsis was presented in 11-28% on admissions to ICUs in which respiratory infections was still the most common cause of sepsis (28-68%).23-25 In a study of sepsis in Southeast Asia (including Vietnam), acute respiratory infection was the most frequent diagnosis in adult patients with sepsis (53%).26 At the time of this study, there were no reported outbreaks of respiratory infections in the country. However, of note, the circulation of influenza was known as year-round in the country;
### Table 3: Frequency of antibiotic use as empirical therapy within 24 hours of CCUs admission.

| Antibiotics by ACT | All patients (n=1112) | CCUs in primary hospitals (n=663) | CCUs in secondary hospitals (n=449) | p values |
|--------------------|-----------------------|----------------------------------|-------------------------------------|---------|
| J01DD01_cefotaxime | 248 (22.3%)           | 178 (26.8%)                      | 70 (15.6%)                         | <0.001  |
| J01MA12_levofoxacin| 211 (19.0%)           | 73 (11.0%)                       | 138 (30.7%)                       | <0.001  |
| J01DD02_cefazidime | 120 (10.8%)           | 104 (15.7%)                      | 16 (3.6%)                          | <0.001  |
| J01DD04_ceftaxime  | 113 (10.2%)           | 62 (9.4%)                        | 51 (11.4%)                         | 0.785   |
| J01DD12_cefopenozone| 104 (9.4%)            | 24 (3.6%)                        | 80 (17.8%)                         | <0.001  |
| J01DC02_cefoxime   | 100 (9.0%)            | 96 (14.5%)                       | 4 (0.9%)                           | <0.001  |
| J01MA02_ciprofoxacin| 96 (8.6%)            | 49 (7.4%)                        | 47 (10.5%)                        | 0.305   |
| J01CR01_ampicillin and beta-lactamase inhibitor| 89 (8.0%)| 55 (8.3%)| 34 (7.6%)| 0.266 |
| J01DD07_ceftazidime| 52 (4.7%)            | 51 (7.7%)                        | 1 (0.2%)                           | <0.001  |
| J01GB03_gentamicin | 50 (4.5%)            | 50 (7.5%)                        | 0 (0.0%)                           | <0.001  |
| J01CR02_amoxicillin and beta-lactamase inhibitor| 42 (3.8%)| 35 (5.3%)| 7 (1.6%)| <0.001 |
| J01DH51_imipenem and cilastatin| 41 (3.7%)| 0 (0.0%)| 41 (9.1%)| <0.001 |
| J01GB06_amikacin  | 41 (3.7%)            | 4 (0.6%)                         | 37 (8.2%)                          | <0.001  |
| J01MA14_moxifloxacin| 40 (3.6%)            | 22 (3.3%)                        | 18 (4.0%)                          | 0.888   |
| J01CR05_piperacillin and beta-lactamase inhibitor| 34 (3.1%)| 0 (0.0%)| 34 (7.6%)| <0.001 |
| J01XD01_mometronidazo| 34 (3.1%)| 15 (2.3%)| 19 (4.2%)| 0.155 |
| J01DD06_cefopenozone and beta-lactamase inhibitor| 28 (2.5%)| 10 (0.2%)| 27 (6.0%)| <0.001 |
| J01HD02_meropenem  | 26 (2.3%)            | 1 (0.2%)                         | 25 (5.6%)                          | <0.001  |
| J01DC01_cefoxin    | 14 (1.3%)            | 0 (0.0%)                         | 14 (3.1%)                          | <0.001  |
| J01GB01_tobramycin| 12 (1.1%)            | 11 (1.7%)                        | 1 (0.2%)                           | 0.013   |
| J01XD02_tindazolo  | 10 (0.9%)            | 0 (0.0%)                         | 10 (2.2%)                          | <0.001  |
| J01DE01_cefpime    | 9 (0.8%)             | 0 (0.0%)                         | 9 (2.0%)                           | 0.001   |
| J01XA01_vancocynyc| 8 (0.7%)             | 0 (0.0%)                         | 8 (1.8%)                           | 0.001   |
| J01XA02_teicoplanin| 6 (0.5%)             | 0 (0.0%)                         | 6 (1.3%)                           | 0.006   |
| J01DD08_cefoxime   | 6 (0.5%)             | 3 (0.5%)                         | 3 (0.7%)                           | 1.000   |
| J01EE01_sulfamethoxazole and trimethoprim| 5 (0.4%)| 1 (0.2%)| 4 (0.9%)| 0.175 |
| J01CA04_amoxicillin| 5 (0.4%)             | 4 (0.6%)                         | 1 (0.2%)                           | 0.393   |
| J01FA10_aziromycin  | 5 (0.4%)             | 5 (0.8%)                         | 0 (0.0%)                           | 0.071   |
| J01CA12_piperacillin| 4 (0.4%)             | 0 (0.0%)                         | 4 (0.9%)                           | 0.037   |
| J01DB05_cefadroxil  | 4 (0.4%)             | 0 (0.0%)                         | 4 (0.9%)                           | 0.037   |
| J01FF01_clindamycin| 4 (0.4%)             | 0 (0.0%)                         | 4 (0.9%)                           | 0.037   |
| J01CA01_ampicillin  | 4 (0.4%)             | 3 (0.5%)                         | 1 (0.2%)                           | 0.636   |
| J01DC03_cefamandole| 4 (0.4%)             | 4 (0.6%)                         | 0 (0.0%)                           | 0.136   |
| J01XB01_colistin   | 3 (0.3%)             | 0 (0.0%)                         | 3 (0.7%)                           | 0.084   |
| J01FA09_clarithromycin| 3 (0.3%)| 1 (0.2%)| 2 (0.4%)| 0.585 |
| J01DB12_cefezole   | 3 (0.3%)             | 2 (0.3%)                         | 1 (0.2%)                           | 1.000   |
| J01XX08_linezolid  | 2 (0.2%)             | 0 (0.0%)                         | 2 (0.4%)                           | 0.193   |
| J01DB01_cefalexin  | 2 (0.2%)             | 1 (0.2%)                         | 1 (0.2%)                           | 1.000   |
| J01MA01_ciprofloxacin| 2 (0.2%)| 1 (0.2%)| 1 (0.2%)| 1.000 |
| J01MB02_naldics acid| 2 (0.2%)| 1 (0.2%)| 1 (0.2%)| 1.000 |
| J01BD04_cefazolin  | 2 (0.2%)             | 2 (0.3%)                         | 0 (0.0%)                           | 0.507   |
| J01DC09_cefmetazole| 1 (0.1%)             | 0 (0.0%)                         | 1 (0.2%)                           | 0.439   |
| J01DE02_cefpirome   | 1 (0.1%)             | 0 (0.0%)                         | 1 (0.2%)                           | 0.439   |
| J01MA09_sparfloxacin| 1 (0.1%)             | 0 (0.0%)                         | 1 (0.2%)                           | 0.439   |
| J01XX01_fosfomycin  | 1 (0.1%)             | 0 (0.0%)                         | 1 (0.2%)                           | 0.439   |
| J01CE01_benzylpenicilicin| 1 (0.1%)| 1 (0.2%)| 0 (0.0%)| 1.000 |
| J01DB03_cefotolin  | 1 (0.1%)             | 1 (0.2%)                         | 0 (0.0%)                           | 1.000   |
| J01DC04_cefaclor   | 1 (0.1%)             | 1 (0.2%)                         | 0 (0.0%)                           | 1.000   |
| J01DD13_cefprodoxime| 1 (0.1%)             | 1 (0.2%)                         | 0 (0.0%)                           | 1.000   |
| J01GB07_netilmicin | 1 (0.1%)             | 1 (0.2%)                         | 0 (0.0%)                           | 1.000   |
potentially with peaks in June to August and in December to January in northern Vietnam. In Vietnamese guideline on antibiotic use in 2015, antibiotics recommended for moderate pneumonia were amoxicillin plus clarithromycin or benzylpenicillin plus clarithromycin or β-Lactam (cefotaxime, ceftriaxone) or ampicillin-sulbactam plus macrolide or fluoroquinolone. For severe pneumonia, it was recommended to start amoxicillin/clavulanic acid plus clarithromycin or benzylpenicillin plus quinolone or a third cephalosporin plus clarithromycin. We found a quite variations of antibiotic prescriptions by in CCUs. The reasons may be attributed to the lack of timely updates, not supported by local susceptibility data, and not reflecting doctors’ behaviours or comments in the national guideline. Consequently, in a survey in 1280 health professionals in Vietnam, empirical antibiotic selection was decided by infection source and diseases severity. The large numbers and complexity of available antibiotics may create challenges for clinicians and pharmacists in choice of empirical therapy. Additionally, the lack of confirmatory laboratory capacity, such as bacterial cultures and PCR for viral etiologies, is still an obstacle to the implementation of antimicrobial stewardship programme in in resource constraint countries.

In a previous study, the percentages of antibiotic purchased in Access, Watch and Reverse groups in health care facilities in Viet Nam, were 47.2%, 52.4% and 0.1% respectively. The most commonly used antibiotics in CCUs in provincial and district general hospitals were cephalosporins, penicillins, aminoglycosides and imidazole, while they were the third generation cephalosporins, fluoroquinolones, and carbapenems in the CCUs setting. The high frequency of Watch and Reserve group antibiotics (87.3% and 0.54% respectively) in our study indicated the strategy of early administration of broad-spectrum antibiotic in CCUs, and therefore, the surveillance on antibiotic consumption and patterns of prescription is particularly important to ensure a rational antibiotic use.

Our study had some limitations. Firstly, we did not collect data to distinguish between antibiotic treatments and perioperative antibiotic prophylaxis. However, we considered the proportion of prescription for perioperative antibiotic prophylaxis was small because of the low rate of surgery within 24 hours of admission in our study participants (27/1747 or 1.5%). Secondly, because of the short-period observational study design, there may be some bias in evaluation of causes of admission. Additionally, the majority of initial diagnosis of infection were clinically made, partly related to the lack of rapid diagnostics whilst the empirical antibiotic prescribing decisions were influenced by doctors’ experiences and by level of hospitals. It makes the interpretation of empirical antibiotic choice difficult and must be related to the current burden of antibiotic resistant pathogens in community and in a particular CCU. Thirdly, due to the limitations of study design, data collection and low frequency of microbiological culture, we were unable to evaluate the necessity and appropriate-ness of antibiotic treatment in our study patients. Further studies are required to evaluate the compliance...
Antibiotic regimens

|                           | All patients (n=1112) | Patients with SARI (n=749) | Patients with other infection (n=96) | Patients without infection (n=267) |
|---------------------------|-----------------------|----------------------------|--------------------------------------|-----------------------------------|
| Mono antibiotic therapy   | 647 (58.2%)           | 430 (57.4%)                | 43 (44.9%)                           | 174 (65.2%)                       |
| J01DD_Third generation cephalosporins | 408 (63.1%)           | 290 (67.4%)                | 22 (51.2%)                           | 96 (55.2%)                        |
| J01CR_Combinations of penicillins, incl. beta lactamase inhibitors | 85 (13.1%)            | 60 (14.0%)                 | 4 (9.3%)                             | 21 (12.1%)                        |
| J01DC_Second generation cephalosporins | 77 (11.9%)            | 55 (12.8%)                 | 2 (4.7%)                             | 20 (11.5%)                        |
| J01MA_Fluoroquinolones    | 42 (6.5%)             | 17 (4.0%)                  | 9 (20.9%)                            | 16 (9.2%)                         |
| J01DB_First generation cephalosporins | 8 (1.2%)            | 2 (0.5%)                   | 3 (7.0%)                             | 3 (1.7%)                          |
| J01XD_Imidazole derivatives | 8 (1.2%)             | 0 (0.0%)                   | 1 (2.3%)                             | 7 (4.0%)                          |
| J01CA_Penicillins with extended spectrum | 6 (0.9%)             | 0 (0.0%)                   | 1 (2.3%)                             | 5 (2.9%)                          |
| Other mono therapy        | 13 (2.0%)             | 6 (1.4%)                   | 1 (2.3%)                             | 6 (3.4%)                          |
| Dual antibiotic therapy   | 444 (39.9%)           | 310 (41.4%)                | 48 (50.0%)                           | 86 (32.2%)                        |
| J01DD_Third generation cephalosporins and J01MA_Fluoroquinolones | 163 (36.7%)           | 115 (37.1%)                | 15 (31.3%)                           | 33 (38.4%)                        |
| J01DC_Second generation cephalosporins and J01MA_Fluoroquinolones | 28 (6.3%)            | 24 (7.7%)                  | 1 (2.1%)                             | 3 (3.5%)                          |
| J01DD_Second generation cephalosporins and J01XD_Imidazole derivatives | 23 (5.2%)            | 4 (1.3%)                   | 10 (20.8%)                           | 9 (10.5%)                         |
| J01CR_Combinations of penicillins, incl. beta lactamase inhibitors and J01MA_Fluoroquinolones | 54 (12.2%) | 41 (13.2%) | 4 (8.3%) | 9 (10.5%) |
| J01DH_Carbapenems and J01MA_Fluoroquinolones | 36 (8.1%) | 19 (6.1%) | 7 (14.6%) | 10 (11.6%) |
| J01DC_Second generation cephalosporins and J01MA_Fluoroquinolones | 28 (6.3%) | 24 (7.7%) | 1 (2.1%) | 3 (3.5%) |
| J01DD_Second generation cephalosporins and J01XD_Imidazole derivatives | 23 (5.2%) | 4 (1.3%) | 10 (20.8%) | 9 (10.5%) |
| J01CR_Combinations of penicillins, incl. beta lactamase inhibitors and J01GB_Other aminoglycosides | 16 (3.6%) | 16 (5.2%) | 0 (0.0%) | 0 (0.0%) |
| J01DH_Carbapenems and J01GB_Other aminoglycosides | 8 (1.8%) | 7 (2.3%) | 0 (0.0%) | 1 (1.2%) |
| J01DE_Fourth generation cephalosporins and J01MA_Fluoroquinolones | 5 (1.1%) | 3 (1.0%) | 1 (2.1%) | 1 (1.2%) |
| Other dual therapy        | 54 (12.2%)           | 33 (10.6%)                 | 10 (20.8%)                           | 16 (18.6%)                        |
| Triple and quadruple antibiotic therapy | 21 (1.9%) | 9 (1.2%) | 5 (2.5%) | 7 (2.6%) |
| J01DD_Second generation cephalosporins, J01MA_Fluoroquinolones and other | 6 (28.6%) | 1 (11.1%) | 1 (20.0%) | 4 (57.1%) |
| J01DH_Carbapenems, J01MA_Fluoroquinolones and other | 5 (23.8%) | 2 (22.2%) | 1 (20.0%) | 2 (28.6%) |
| Carbapenems and 2 others | 5 (23.8%) | 2 (22.2%) | 3 (60.0%) | 0 (0.0%) |
| J01CR_Combinations of penicillins, incl. beta lactamase inhibitors, J01MA_Fluoroquinolones and other | 3 (14.3%) | 2 (22.2%) | 0 (0.0%) | 1 (14.3%) |
| Others                    | 2 (9.5%)             | 2 (22.2%)                  | 0 (0.0%)                             | 0 (0.0%)                          |

Table 4: Empirical antibiotic regimens within 24 hours of admission to CCUs by the Anatomical Therapeutic Chemical (ATC) Index.

|                           | Adjusted OR (95% CI) | P value |
|---------------------------|----------------------|---------|
| Age (years) (1-yr. increment) | 1.01 (1.00-1.02)     | 0.014   |
| Number of comorbidities   |                      |         |
| No comorbidity            | 1                    |         |
| 1 comorbidity             | 0.66 (0.42-1.04)     | 0.076   |
| At least 2 comorbidities  | 1.28 (0.74-2.22)     | 0.384   |
| quick Sequential Organ Failure Assessment (qSOFA) |                      |         |
| qS OFA 0-1                | 1                    |         |
| qSOFA 2-3                 | 0.80 (0.53-1.22)     | 0.299   |
| Systemic Inflammatory Response Syndrome (SIRS) |                      |         |
| Without SIRS on admission | 1                    |         |
| With SIRS on admission    | 2.10 (1.38-3.20)     | 0.001   |
| Diagnosis on admission    |                      |         |
| No diagnosis of any type of infection | 1 |         |
| Non-respiratory infection | 1.39 (0.69-2.81)     | 0.363   |
| SARI                      | 1.50 (0.99-2.29)     | 0.058   |
| Level of hospitals        |                      |         |
| Primary hospitals         | 1                    |         |
| Secondary hospitals       | 1.50 (1.00-2.23)     | 0.05    |

Table 5: Logistic regression analysis of factors associated with empirical therapy of Watch and Reverse group antibiotics on admission.
with antimicrobial treatment guidelines for empirical antibiotic selection and rational antibiotic use in relation to diagnosis and microbiological findings in Vietnam. In conclusion, there was an over prescription of broad spectrum antibiotic and high frequency of antibiotic combination for all causes of admission to CCUs in primary and secondary hospitals in Vietnam. It is crucial to implement the surveillance of antibiotic use in CCUs and establish a protocol the empirical antibiotic treatment to improve overall SARI patients’ outcome.

Contributors
VQD, SO supervised the project implementation, including designing the study and analysing the data. VQD, TTD reviewed and classified diagnosis on admission. SO, VQH, KBG and VQD collected data and monitor the study. VQD, TTD has consolidated and drafted the first report. All authors involved to the acquisition and interpretation of data. All authors contributed to and approved the final report.

Data sharing statement
All data requests will be considered by the corresponding author for approval.

Declaration of Competing Interest
We declare no competing interest.

Acknowledgments
We are very grateful to the patients and staff at the selected hospitals in Ha Noi, Thai Nguyen, Ha Nam, Kon Tum and Can Tho. We would like to thank Dr. Kenji Kubo from Japanese Red Cross Wakayama Medical Center for his comments on the first draft of this paper. The authors thank the staff from the Centre for Assessment and Quality Assurance, Hanoi Medical University for their assistance in data collection. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Funding
None.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi: 10.1016/j.lanwpc.2021.100306.

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