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MAJOR ARTICLE

Evaluating Antibiotic Misuse and Cost Analysis Among Hospitalized Dengue Virus–Infected Adults: Insights From a Retrospective Cohort Study

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Background. Dengue is a prevalent cause of acute febrile illness, predominantly in Asia, where it necessitates supportive care without the need for antibiotics. This study aimed to evaluate antibiotic usage and analyze hospitalization costs among adults infected with the dengue virus.

Methods. This retrospective cohort study was conducted at the Hospital for Tropical Diseases, Thailand, in 2022. Two independent reviewers assessed all adult cases with confirmed dengue from 2016 to 2021. Determinants of inappropriateness were analyzed using Poisson regression.

Results. The study included 249 participants with over half presenting with severe dengue or dengue with warning signs upon admission. The cumulative incidence of antibiotic use was 9.3% (95% CI, 8.23–10.47), predominantly involving empirical treatment strategies. Ceftriaxone and doxycycline were the most frequently prescribed antibiotics. Notably, patients who received empirical antibiotics showed no definite or presumed bacterial infections. Among those who received definite strategies, inappropriate durations, including both short treatments and the overuse of broad-spectrum antibiotics, were observed. A private ward admission was identified as a significant predictor of inappropriate use, with an incidence rate ratio of 4.15 (95% CI, 1.16–14.82) compared with intensive care unit admission. Direct medical costs did not differ significantly between appropriate and inappropriate uses.

Conclusions. The incidence of antibiotic use among dengue cases was moderate; however, inappropriate use by indication was observed. Antimicrobial stewardship strategies should be encouraged, particularly in patients with dengue with warning signs admitted to a general or private ward. Direct medical costs between appropriate and inappropriate use were comparable.

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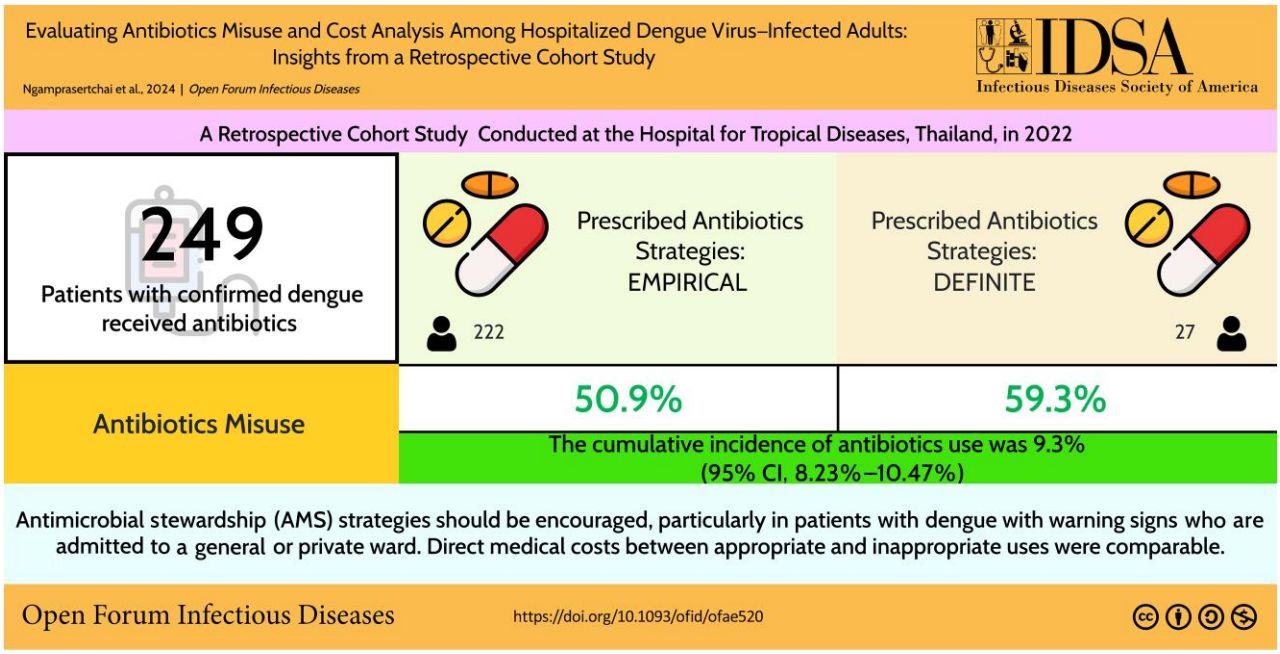
Graphical Abstract



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Keywords. antibiotic; antimicrobial agents; antimicrobial stewardship; dengue; inappropriate use.

Dengue affects hundreds of countries worldwide, and 3.6 million people in most tropical and subtropical regions are at risk [1, 2]. The World Health Organization (WHO) reported that cases increased from >2.4 million in 2010 to 5.2 million in 2019, including a more recent outbreak in Europe after the coronavirus disease 2019 (COVID-19) pandemic due to unrestricted traveling [2, 3]. Dengue is caused by the dengue virus and mainly requires supportive treatment rather than antibiotics; therefore, several antiviral treatment and vector control modalities have been proposed. In addition, dengue is a common cause of acute febrile illnesses in nonmalarial endemic regions [4, 5], which is diagnostically challenging at the initial presentation, leading to unnecessary antibiotic use [6]. Rapid diagnostic tests (RDTs) or some biomarkers, such as C-reactive protein or procalcitonin, may limit antibiotic use by distinguishing bacterial and dengue infection [7, 8]. Antibiotic use in dengue would be appropriate if bacterial coinfection exists; however, the incidence of bacterial coinfection in dengue is low [4, 9].

Antimicrobial resistance (AMR) has emerged as a serious global public health threat following antibiotic overuse or misuse [10]. There is no definite study on the causal relationship between the inappropriate use of antibiotics and subsequent AMR emergence in dengue [6]. Adrizain et al. noted that the consequences of broad-spectrum antibiotics were the same in patients with and without dengue [11]. Increasing AMR rates require urgent attention and intervention by utilizing the antimicrobial stewardship (AMS) program to reduce inappropriate antibiotic prescriptions, particularly in viral infections such as dengue [12]. AMS refers to a coordinated program that promotes the appropriate use of antimicrobials to improve treatment outcomes and decrease the spread of AMR [13]. An example of AMS pertains to the right choice, duration, dose, and route of antibiotic administration for a patient with confirmed or suspected infection [14].

AMS is needed in tropical infections and general infectious diseases as there are high antibiotic prescription rates in malaria or dengue, which actually require no antibiotic treatment [15–17]. RDTs should limit antibiotic use; however, high antibiotic prescription rates were observed among RDT-positive cases [7, 18–20]. This study aimed to assess antibiotic use in adults with confirmed dengue virus infection admitted to the Hospital for Tropical Diseases in order to promote AMS in tropical diseases. Additionally, all cases underwent a cost analysis and were stratified by appropriateness to demonstrate the economic burden before wide AMS implementation in the hospital.

METHODS

This retrospective cohort study was conducted from May 2022 to March 2023 to analyze all patients with confirmed dengue infection admitted to the Hospital for Tropical Diseases Bangkok from 2016 to 2021. The Hospital for Tropical

Diseases is a public, 250-bed, university-based hospital that encounters ~500 dengue cases per year. Patients retrieved using International Classification of Diseases, 10th Revision, codes from the hospital database were screened. Only adults age ≥18 years with confirmed dengue by NS1Ag, immunoglobulin M serology, or molecular study at the time of admission who had 1 or more episodes of antibiotic prescription were included in the analyses. Dengue severity was determined at 2 time points; first, at the time of admission. Second, at the time antibiotics were given. They were classified based on the WHO 2009 classification of dengue with or without warning signs [21, 22]. The medical records were independently reviewed by 1 general practitioner and another infectious disease physician to evaluate the appropriate use of antibiotics. A third reviewer, an infectious disease physician, was consulted when there were discrepancies. Only the initial episode of antibiotic prescription was considered for analysis, as subsequent episodes were confounded by nosocomial infections. In addition, the episode of antibiotic prescription had to be subsequent to a known dengue diagnosis. This is because the evaluation did not account for the settings of empirical antibiotic prescription during the initial stage when the cause of the febrile illness was unidentified.

Table 1. Proposed Definitions and Scenarios of Inappropriate Antibiotic Use

Inappropriate Antibiotic Use	Scenarios
Indications	• Failure to stop empiric antibiotics (if given) once a diagnosis of dengue is confirmed. • Antibiotics prescribed after established dengue diagnosis in patients with no suspicion of bacterial coinfection.
Choice of antibiotics	• Patients are treated with antibiotics that do not cover the suspected bacteria causing infection. • Patients received broad-spectrum antibiotics without evidence of microbiological resistance.
Duration	• Incorrect duration of intended treatment. Too short: antibiotic stopped despite ongoing infection. Too long: antibiotic continued despite resolved infection.
Dosage	• Incorrect dose of antibiotics. • Higher or lower appropriate dosage based on kidney functions.
Route	• Incorrect route of antibiotics.

Operational Definitions

There were 2 main strategies for antibiotic prescription: empirical and definite. Empirical antibiotic prescription was defined as antibiotics given for presumed bacterial infections by the doctor-in-charge before confirmed bacterial infection. Definite antibiotic prescription was the administration of antibiotics for known or confirmed bacterial infections. We assessed the probability of bacterial infection and classified it as nondefinite, presumed, or definite bacterial infection after extensive medical record review in combination with microbiology results. Nondefinite bacterial infection was defined as the absence of clinical assumption or confirmed microbiological results, while presumed bacterial infection was a clinical assumption or judgment by the doctor-in-charge. Definite bacterial infections were confirmed both microbiologically and clinically by the doctor-in-charge. Thereafter, we evaluated the appropriateness of antibiotic prescriptions stratified by strategies. This definition of appropriateness has been used in various settings; however, there is no reference standard [23]. Most evaluations have relied on expert review; therefore, we developed our criteria for evaluating appropriateness based on previous evidence [11, 23–26]. Inappropriateness was defined as antibiotics improperly prescribed in all the following aspects: indications, choices, duration, dosage, and route of administration (Table 1). Our hospital operates 2 systems for hospitalized patients: a general ward, which offers full reimbursement of medical treatment costs and accommodates 10–12 patients per room, and a private ward, where reimbursement of medical treatment costs is partial and contingent upon medical insurance, providing private accommodation with 1 bed per single room.

Ethics Statement

This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The studies involving human participants were reviewed and approved by the Institutional Review Board (or Ethics Committee) of the Faculty of Tropical Medicine, Mahidol University (COA: MUTM 2022–024–01). The study was registered at the Thai Clinical Trials Registry (TCTR20220410001).

Statistical Analyses and Sample Size Calculation

The sample size for estimating incidence was calculated. According to previous studies, the incidence of inappropriate antibiotic use among in-patients ranged between 20% and 50% [24, 27, 28]. Therefore, we estimated that the incidence would be ~20%. The target sample size was 246 subjects, with an alpha error of 5% and an acceptable error of 5%. Demographic data, microbiological results, antibiotic prescriptions, antibiotic assessment, and cost analyses were presented using descriptive statistics (mean and SD, median and interquartile range [IQR], or percentage, as appropriate). The nonparametric statistical test (the Mann-Whitney *U* test) was used to determine whether there is a significant difference between the direct medical cost among groups. The incidence of inappropriate antibiotic use and corresponding 95% CI were estimated. The incidence was calculated as the proportion of participants with confirmed dengue who were considered to receive inappropriate antibiotic prescriptions out of all those who received antibiotics. Univariable and multivariable Poisson

regression analyses were used to determine the factors associated with inappropriate antibiotic use. Significant factors in the univariable analyses ($P < .15$) were selected for multivariable analyses to determine adjusted incidence rate ratios (aIRRs). All costs were converted to USD using the official exchange rate of the World Bank for the Thai Baht (35.06 THB = 1 USD in 2022). Data were analyzed using Stata/MP 17 (StataCorp, College Station, TX, USA). *P* values were 2-sided and considered statistically significant if they were <.05.

RESULTS

Confirmed Dengue Cases Characteristics

Of 2676 hospitalized patients with confirmed dengue infection between 2019 and 2021 who were screened, 249 who received antibiotics were included in the analysis. The overall incidence of antibiotic use was 9.3%; the incidence varied yearly from 2016 to 2019 (Supplementary Figure 1). The majority of participants were healthy middle-aged Thai with a median hospitalization duration (IQR) of 5 (4–6) days. Regarding disease severity on admission or at the time of antibiotic prescription, the majority had dengue with warning signs (49.4% or 48.6%, respectively) according to the WHO 2009 classifications. Of the study participants, 48 (19.3%) were transferred or admitted to the intensive care unit (ICU) for intensive monitoring. Additionally, 233 (93.6%) demonstrated favorable treatment outcomes (Supplementary Table 1). Three common sites of confirmed bacterial infections were the bloodstream (40.7%), lungs (33.3%), and urinary tract (25.9%). In addition, cephalosporins (mainly ceftriaxone) were the most prescribed antibiotics (57.8%), followed by doxycycline (Figure 1*A* and *B*).

Antibiotics Assessment and Determinants

In cases where definite antibiotic strategies were used, the majority of patients had confirmed bacterial infections, while a smaller proportion had presumed bacterial infections. However, among the empirical antibiotic strategies employed, 93 cases (39.2%) had no definite bacterial infections (Figure 2*A*). Within the group receiving definite antibiotic strategies, 16 cases (53.3%) were treated appropriately. In contrast, among those receiving empirical antibiotics, appropriateness was observed in 109 patients (46.0%). The inappropriate use of antibiotics by indication was substantial among empirical strategies, whereas it was non-notable in definite strategies. Inappropriate use by duration, particularly treatments that were too short, was common, followed by improper antibiotic choices among definitive strategies (Figure 2*A* and *B*).

Dengue-infected patients admitted to general or private wards had a significantly higher incidence of inappropriate antibiotic prescription than those who were admitted to the ICU throughout their stay after adjustment for confounding in the multivariable analyses (aIRR, 4.13; 95% CI, 1.16–14.70; or aIRR, 4.15; 95% CI, 1.16–14.82; respectively). Disease severity on admission was a significant determinant of inappropriate antibiotic use in univariable analyses but was not after adjustments for confounders (Table 2).

The Antibiotic Cost Analysis

The median direct medical cost for individuals hospitalized with confirmed dengue infection (IQR) was US$185.4 (US $85.6–$320.9) and US$168.3 (US$94.8–$321.3) for appropriate and inappropriate antibiotic use, respectively. The antibiotic cost was significantly higher for appropriate use than for inappropriate use ($P = .005$). There was no significant difference in direct medical cost between the groups in terms of admission, medical supplements, laboratory testing, or hospital services (Supplementary Table 2).

DISCUSSION

This study demonstrated the incidence, characteristics, and cost of antibiotic use among adults with confirmed dengue. The incidence of antibiotic prescription in this study was 9.3% and varied yearly between 6.9% and 17% from 2016 to 2021. However, from 2020 onward, the data did not truly reflect the annual dengue cases because people were reluctant to visit the hospital because of the COVID-19 pandemic. The previous literature showed that the prevalence of antibiotic use in dengue was ~3%–74.6% [7, 11, 16, 17, 29]. Rammohan et al. found that antibiotic use was 12.7% according to a strict antibiotic policy followed at the RajaRajeswari Medical College and Hospital [29], similar to the antibiotic prescription rate in our hospital. Doctors in private and general wards were observed to prescribe antibiotics inappropriately more frequently than those in other settings. These wards should be prioritized for the implementation of AMS programs, as they were significant determinants of inappropriate use. Additionally, the duration of antibiotic administration should be considered in antimicrobial stewardship assessments. Our study revealed that inappropriate durations were more frequently observed in definite treatment strategies compared with empirical treatment strategies.

Our study showed that 38.3% had no presumed or definite bacterial infections among those prescribed empirical antibiotics, which we considered inappropriate use as there were no indications in most cases. Inappropriate use by indication was the common misuse among the empirical antibiotic group, like in the Adrizain et al. study [11]. Ceftriaxone and doxycycline were substantially prescribed antibiotics, as noted in previous studies [11, 30]. This is because both antibiotics are not restricted, allowing all doctors to prescribe them without prior authorization. Additionally, some doctors in charge are concerned with tropical coinfections, such as rickettsial infections. However, few cases of coinfections requiring antibiotic treatment were noted in the studies [4]. Although AMR due to doxycycline

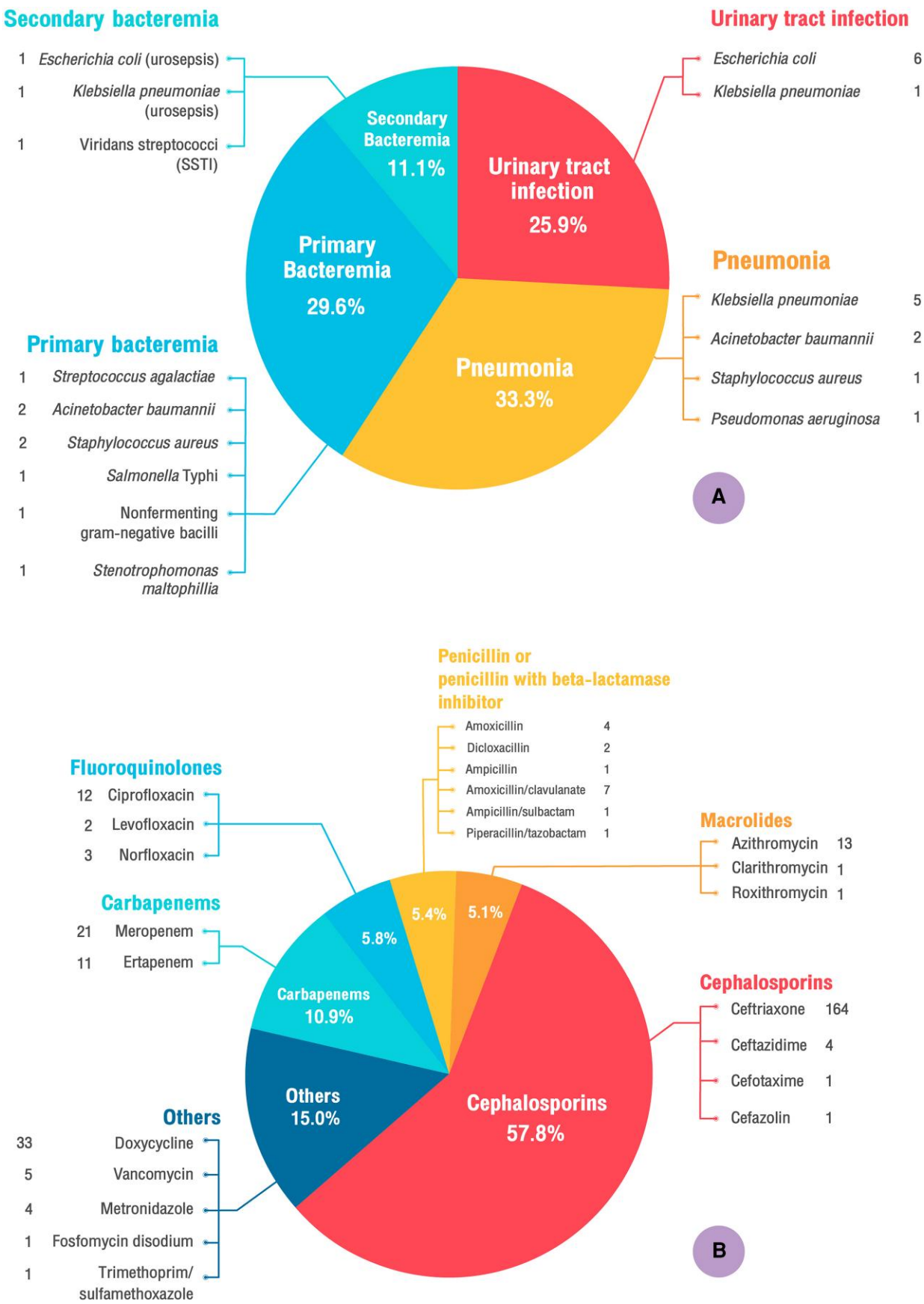

Figure 1. Microbiologically confirmed infections stratified by infection site (*A*). Proportion of prescribed antibiotics by type (*B*). Abbreviation: SSTI, skin and soft tissue infection.

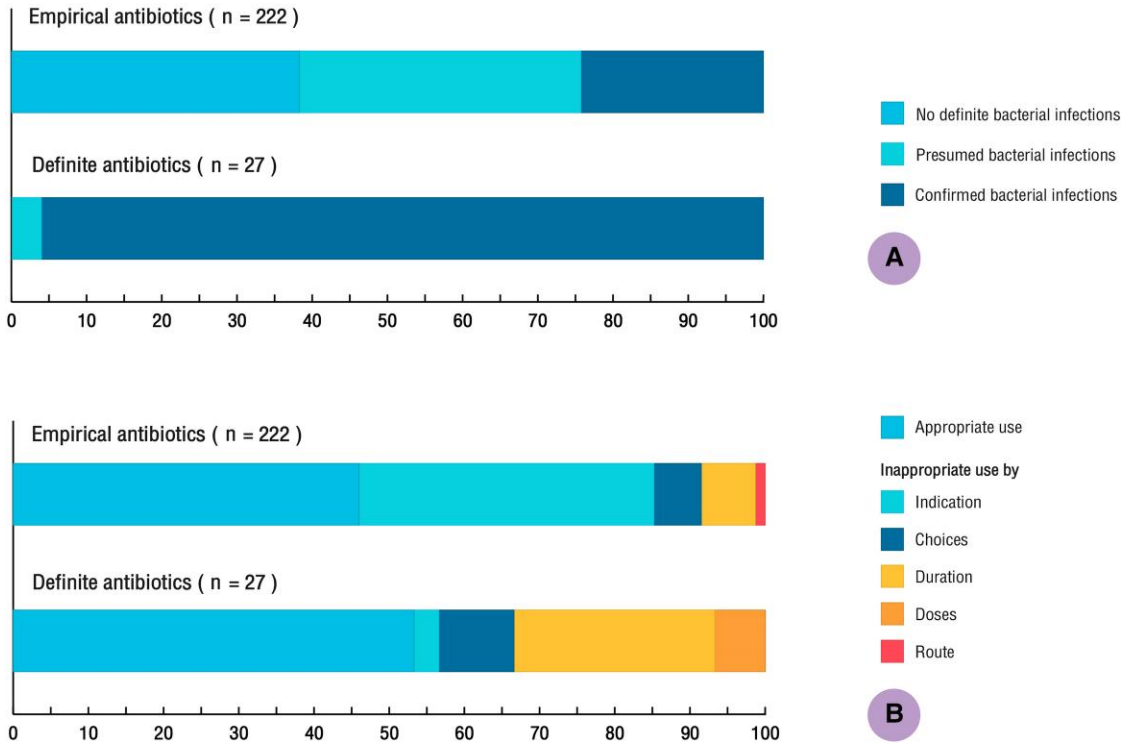

Figure 2. Results of bacterial infection evaluation by prescribed antibiotic strategies (*A*). Antibiotic assessment and rationale by prescribed antibiotic strategies (*B*). Percentages are represented on the x-axis.

Table 2. Factors Associated With the Inappropriate Use of Antibiotics in Hospitalized Patients With Confirmed Dengue Infection: Univariable and Multivariable Poisson Regression Analyses

Factors	Antibiotics Assessment		Univariable Analyses, IRR (95% CI)	Multivariable Analyses, aIRR (95% CI)
	Inappropriate Use, No. (%)	Appropriate Use, No. (%)		
Prescribed antibiotic strategies				…
Empirical	113 (50.9)	109 (49.1)	1.25 (0.67–2.32)	
Definite	16 (59.3)	11 (40.7)	1	
Recent hospitalization				…
Yes	12 (57.1)	9 (42.9)	1.16 (0.64–2.11)	
Comorbidities				…
Yes	17 (42.5)	23 (57.5)	0.83 (0.50–1.38)	
Ward during admission				
General entire	56 (53.3)	49 (46.7)	4.27 (1.34–13.63)	4.13 (1.16–14.70)
Private entire	52 (54.2)	44 (45.8)	4.30 (1.35–13.88)	4.15 (1.16–14.82)
Transferred to ICU	13 (54.2)	11 (45.8)	4.30 (1.23–15.21)	4.11 (1.14–14.81)
ICU throughout	3 (54.2)	21 (87.5)	1	1
Disease severity on admission				
Without warning signs	48 (48.0)	52 (52)	1.78 (0.81–3.94)	1.0 (0.39–2.58)
With warning signs	69 (56.1)	54 (43.9)	2.08 (0.95–4.53)	1.23 (0.50–3.0)
Severe	7 (26.9)	19 (73.1)	1 ($P < .15$)	1
Disease severity at the time of antibiotic administration				…
Without warning signs	40 (44.9)	49 (55.1)	1.25 (0.68–2.30)	
With warning signs	70 (57.9)	51 (42.2)	1.61 (0.91–2.86)	
Severe	14 (35.9)	25 (64.1)	1	

Abbreviations: aIRR, adjusted incidence rate ratio; ICU, intensive care unit; IRR, incidence rate ratio.

is not well established, doxycycline has been reported to cause vaginal flora suppression and *Clostridioides difficile* diarrhea [6]. The prescription of restricted antibiotics and the implementation of effective AMS should be introduced for all admissions, addressing not only bacterial infections but also viral infections, such as dengue. Appropriate antibiotic use was more common in the definite strategies than in the empirical ones. However, too-short administration and the notable use of broad-spectrum antibiotics were observed. Feedback, knowledge-sharing, and multidisciplinary team reinforcement should be applied to all levels of medical personnel and prioritized in general and private wards and for dengue with warning signs.

Although our hospital is a university-based institution within the government system, the cost analysis may be of economic interest to stakeholders, particularly in the context of the private ward where reimbursement is partial. We observed economic losses associated with the inappropriate use of antibiotics, primarily in terms of cost. This was largely due to the high proportion of inappropriate indications, which confounded the cost comparison between the 2 groups. Generally, the cost associated with empirical strategies was lower than that for definite treatments, attributed to the shorter duration of antibiotic administration. We suggest that conducting a prospective cohort study or expanding the research to include private hospitals could yield a more comparable analysis of costs.

To our knowledge, only a few studies have evaluated the appropriateness of antibiotic use in tropical diseases such as dengue. However, there are some limitations to this study. First, the COVID-19 pandemic may have interrupted or modified the epidemiological data during 2020–2021. Second, direct nonmedical costs, indirect costs, and the societal impact of inappropriate antibiotic use were not included in the analyses. Studies after the COVID-19 pandemic, conducted in private hospitals, or including other cost types are encouraged to determine significant differences in appropriateness. Lastly, the direct medical cost comparison should be interpreted with caution due to potential confounding factors inherent in the retrospective cohort design of the study. Further subgroup analyses are warranted to explore interactions, such as the duration and cost of antibiotics.

CONCLUSIONS

The incidence of antibiotic use among dengue cases was moderate; however, inappropriate use based on indications was predominantly observed. Physicians should reassess presumed diagnoses of concurrent bacterial infections before the empirical administration of antibiotics in confirmed dengue cases. Furthermore, the implementation of AMS is recommended, especially for patients with dengue presenting with warning signs and those admitted to general or private wards. Direct medical costs between appropriate and inappropriate uses were comparable.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. The studies involving human participants were reviewed and approved by the Institutional Review Board (or Ethics Committee) of the Faculty of Tropical Medicine, Mahidol University (COA: MUTM 2022–024–01).

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