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Audit of antibiotic prescribing in two governmental teaching hospitals in Indonesia

*U. Hadi[1], D. O. Duerink[2], E. S. Lestari[3], N. J. Nagelkerke[4], M. Keuter[5], D. Huis in't Veld[5], E. Suwandojo[1], E. Rahardjo[6], P. van den Broek[2] and I. C. Gyssens[7,8,9] on behalf of the study group 'Antimicrobial Resistance in Indonesia: Prevalence and Prevention' (AMRIN)**

[1]Department of Internal Medicine, Dr Soetomo Hospital – School of Medicine, Airlangga University, SBY, Indonesia, [2]Department of Infectious Diseases, Leiden University Medical Centre, Leiden, The Netherlands, [3]Department of Clinical Microbiology, Dr Kariadi Hospital – School of Medicine, Diponegoro University, SMG, Indonesia, [4]Department of Community Medicine, United Arab Emirates University, Al Ain, UAE, [5]Department of Internal Medicine, Nijmegen University Centre for Infectious Diseases International Health (NUCI-IH), Radboud University Medical Centre, Nijmegen, The Netherlands, [6]Department of Anaesthesiology, Dr Soetomo Hospital – School of Medicine, Airlangga University, SBY, Indonesia, [7]Section of Infectious Diseases, Department of Medical Microbiology & Infectious Diseases and Department of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, [8]Department of Medical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital and [9]Department of Internal Medicine, Nijmegen University Centre for Infectious Diseases (NUCI), Radboud University Medical Centre, Nijmegen, The Netherlands

ABSTRACT

This article estimates the magnitude and quality of antibiotic prescribing in Indonesian hospitals and aims to identify demographic, socio-economic, disease-related and healthcare-related determinants of use. An audit on antibiotic use of patients hospitalized for 5 days or more was conducted in two teaching hospitals (A and B) in Java. Data were collected by review of records on the day of discharge. The method was validated through concurrent data collection in Hospital A. Multivariate logistic regression analysis was performed to determine variables to explain antibiotic prescribing. Prescriptions were assessed by three reviewers using standardized criteria. A high proportion (84%) of 999 patients (499 in Hospital A and 500 in Hospital B) received an antibiotic. Prescriptions could be categorized as therapeutic (53%) or prophylactic (15%), but for 32% the indication was unclear. Aminopenicillins accounted for 54%, and cephalosporins (mostly third generation) for 17%. The average level of antibiotic use amounted to 39 DDD/100 patient-days. Validation revealed that 30% of the volume could be underestimated due to incompleteness of the records. Predictors of antibiotic use were diagnosis of infection, stay in surgical or paediatric departments, low-cost nursing care, and urban residence. Only 21% of prescriptions were considered to be definitely appropriate; 15% were inappropriate regarding choice, dosage or duration, and 42% of prescriptions, many for surgical prophylaxis and fever without diagnosis of infection, were deemed to be unnecessary. Agreement among assessors was low (kappa coefficients 0.13–0.14). Despite methodological limitations, recommendations could be made to address the need for improving diagnosis, treatment and drug delivery processes in this setting.

Keywords Antibiotic policy, antibiotic use, Asia, prescribing practice, quality

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Corresponding author and reprint requests: U. Hadi, Department of Internal Medicine, Dr Soetomo Hospital – School of Medicine Airlangga University, Jl. Manyar Tirtomoyo II/21, Surabaya 60118, Indonesia
E-mail: usmanhadi@sby.centrin.net.id

*Members of the AMRIN study group are given in the Appendix.

INTRODUCTION

Antimicrobial resistance is increasing worldwide, in Gram-positive as well as Gram-negative bacteria [1,2]. Antibiotic use contributes to the emergence of antimicrobial resistance by selective pressure [3]. In developing countries, antibiotics are prescribed for 44–97% of patients in hospital, often unnecessarily or inappropriately [4–8]. Several socio-economic and behavioural factors are thought to contribute to the inappropriate use of antibiotics and, consequently, to the increased incidence of bacterial resistance in developing countries [9]. In Indonesia, pathogens have become resistant to many classes of antibiotics [10,11]. There are no reliable data concerning the quantity of antibiotic use and the appropriateness of prescriptions in Indonesian hospitals.

In Indonesia, hospital care is delivered by public and private providers. Public hospitals include large governmental teaching hospitals (Class A and Class B) and district hospitals. In Class A hospitals, all medical (sub)specialties are available. Public hospitals provide health services to everyone at heavily subsidised prices. Health insurance schemes are mandatory for government employees and health subsidies are available for the poor [12]. However, up to 86% of the population is not covered by any form of health insurance [12], and drugs for inpatients must be purchased from a (hospital) pharmacy and paid for in cash. The need to pay in cash also applies to all laboratory investigations.

The Antimicrobial Resistance in Indonesia: 'Prevalence and Prevention' (AMRIN) study was aimed at investigating antibiotic use and antimicrobial resistance inside and outside hospitals on the island of Java, Indonesia. Recent antibiotic use was the most important determinant of carriage of resistant *Escherichia coli* in the study population screened upon discharge from hospital [13], and high rates of resistance to ampicillin (73%), trimethoprim–sulphamethoxazole (56%) chloramphenicol (43%) and ciprofloxacin (22%) were found among these *E. coli* isolates [14]. In this article, we describe the magnitude and quality of antibiotic use of this patient group and we explore the contribution of demographic, socio-economic, healthcare-related and disease-related variables to antimicrobial prescribing. We hypothesized that, as well as being driven by diagnosis of infection, antibiotic consumption could also be determined by these variables.

PATIENTS AND METHODS

Population and healthcare setting

The study was performed in two Class A governmental teaching hospitals. Dr Soetomo University Hospital in Surabaya (Hospital A, 1432 beds) and Dr Kariadi University Hospital in Semarang (Hospital B, 900 beds) report *c.* 60 000 and 26 000 admissions per year, respectively. Patients who were hospitalized in the departments of internal medicine, surgery, obstetrics and gynaecology (O&G) and paediatrics for 5 days or more were eligible for inclusion in the study on the day of discharge. Only general wards of medicine and surgery were included; specialized units (predominantly present in Hospital A), renal units and intensive care units were excluded. Patients were hospitalized in three different nursing classes ranging from I to III, class I being the most expensive. In nursing class I, patients were in a single room and antibiotics were prescribed by a senior doctor. In nursing class II, patients were in two-bed rooms, and in class III, 25–30 patients were hospitalized in a 25–30-bed ward; the treating physician was a resident under senior supervision. In Hospital A, antibiotic policy guidelines and protocols had been developed in 1992, but they had not been updated. In Hospital B, no documents concerning antibiotic policy were available.

Study design and inclusion procedure

Written informed consent was obtained from all participants and caretakers of children before enrolment. The medical ethics committees of the hospitals approved of the study protocol (ethical clearance Nos. Panke.KKE/2001 (Surabaya) and 11/EC/FK/RSDK/2001 (Semarang)). The patient selection procedure is shown in Fig. 1. Patients were selected on three fixed study days per week with a maximum of four patients per day per department. Inclusion was discontinued when the predetermined number of 125 patients per department was reached. When more than four patients were discharged on one study day, the patients with the longest duration of stay were selected. Inclusion started at 8 a.m.

Data collection

On the day of discharge, data from the medical and nursing records were noted in case report forms in both hospitals by the same team of physicians and a number of trained data collectors (medical students or junior physicians). The patients, or caretakers of children, were interviewed to obtain data on demographic and socio-economic variables. Data on antibiotic use were extracted from medical records. Data on prescriptions (type of antibiotic, dose, frequency, duration) were obtained from the physician's notes. Data on consumption were obtained from the nurses' notes in the same (standard format) record. Medication charts with the actual record of each dose were not available. Antibiotic consumption was defined as the actual times and number of days that the prescribed antibiotic was recorded as shown in these nursing records. Patients, physicians or nurses were not approached when information was missing.

Antimicrobial drug use was expressed as a percentage of patients with at least one administered dose and as defined daily doses (DDD)/100 patient-days. The latter was calculated from the consumption data using the Anatomical Therapeutic Chemical classification index from the WHO Collaborating Centre for Drugs Statistics Methodology 2003 (http://www.whocc.no/atcddd/; accessed 15 July 2006). We used the term 'prescription' to indicate each time an antibiotic was prescribed. Modifications in type of antibiotic, dose or route were considered to be new prescriptions [15].

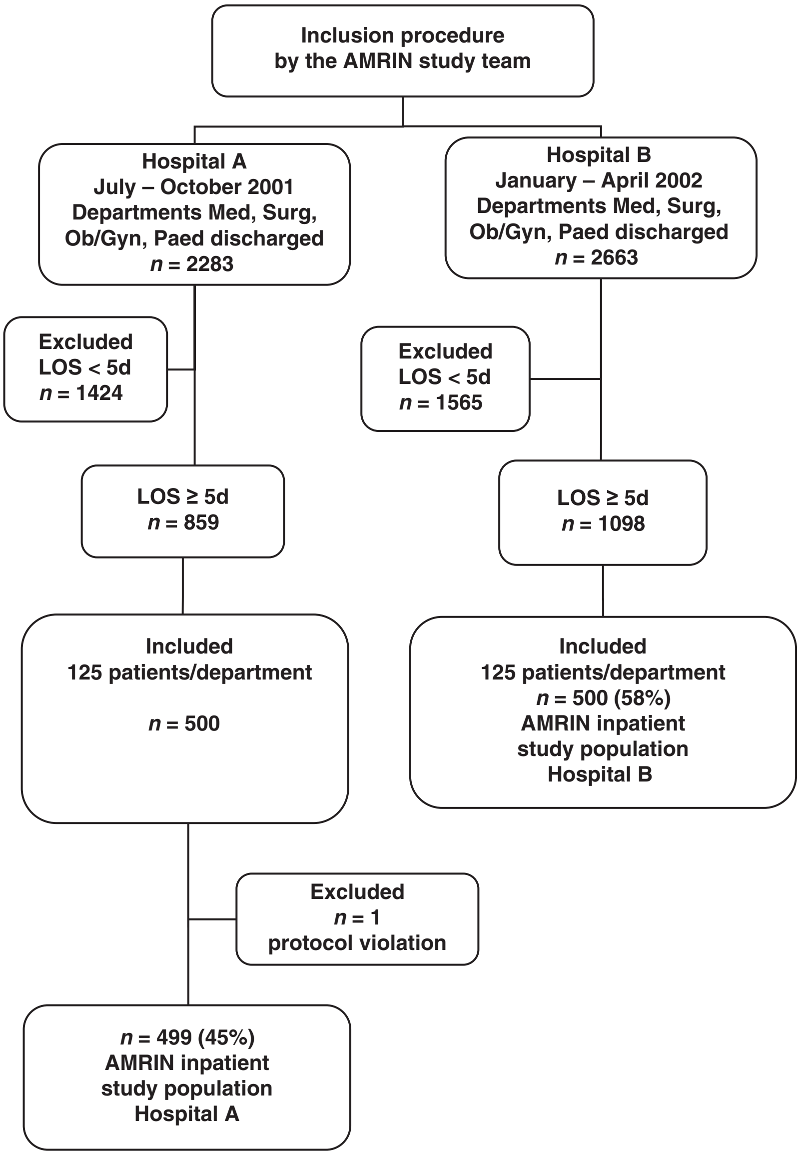

Fig. 1. Study design of the Antimicrobial Resistance in Indonesia: 'Prevalence and Prevention' (AMRIN) study. Med, medicine; Surg, surgery; Ob/Gyn, obstetrics and gynaecology; Paed, paediatrics; LOS, length of stay.

Validation of the quantitative data

The retrospective data collection was validated through concurrent data collection in Hospital A. Thus, a random sample of *c.* 40 patients was selected (ten in each department for whom antibiotics had been prescribed on the day of admission). An experienced pharmacist interviewed the patients and nurses to gain information concerning antibiotic use on the previous day. The pharmacist also checked the nurse's 'injection book', which was not part of the medical and nursing records, but did contain data on antibiotic administration. In cases of discrepancies between the patients' and nurses' interviews, the pharmacist made the final decision after obtaining consensus between the patient and nurse. In order to make blind comparisons, the medical and nursing records were not checked by the pharmacists. The nurses were not informed of the reason for the validation, and, to avoid influencing prescription behaviour, the treating physicians were not approached by the pharmacist. These data on antibiotic use were compared with the data extracted from the medical records on the day of discharge by the researchers. In total, 100 fully documented patient-days per department were compared.

Variables

Demographic variables included hospital, sex, age (over 18 years of age or 17 years and younger), living area (urban or rural) and ethnicity. Socio-economic variables included monthly family income level (below or above poverty line) [16], employment (paid work for an employer on a regular basis or having a regular income from a profession, e.g. farmer; housewives and students were not considered to be unemployed), education (primary school not completed vs. primary school education and higher), and health insurance. Department and nursing class were regarded as healthcare-related variables and diagnosis of infection was chosen as the disease-related variable.

Quality evaluation

The quality of antibiotic use was assessed according to the method of Gyssens *et al.* [15]. Twenty records of patients who used antibiotics were randomly selected from the 125 records of each department, totalling 160 records. Abstracts for review were made using the clinical information from the records. Prescriptions were considered therapeutic if (a) the medical record contained information that the antibiotic was prescribed for therapy, or (b) an infectious disease was diagnosed, or (c) clinical signs of infection, e.g. fever, were present on the day that antibiotic therapy was started. Antibiotics were classified as prophylactic if (a) the medical record stated that the antibiotic was prescribed for prophylaxis or (b) the antibiotic was given for only 1 day relative to the timing of a surgical intervention. In all other cases, prescriptions were termed as being of unknown indication.

Three clinicians, one from the relevant department, one from another department of the same hospital and one foreign expert on infectious diseases, independently reviewed every abstract form. The Indonesian reviewers were chosen on the basis of seniority and not on the basis of experience in antimicrobial therapy, as these experts were not available. The foreign expert had extensive experience with the evaluation method [17,18]. The Indonesian reviewers were trained by one of the Dutch investigators (ICG) during a 2-day course. Every prescription was evaluated with the help of a flow chart, and prescriptions were categorized as follows: definitely appropriate; not indicated; inappropriate regarding dose, interval or route; inappropriate regarding duration; inappropriate with respect to efficacy, toxicity, broadness of spectrum or costs; and insufficient information [15]. The assessments of the individual reviewers were summarized in a combined evaluation when at least two of the three reviewers evaluated the prescription as appropriate, not indicated or inappropriate. All other cases were classified as 'no agreement among reviewers'.

Statistical analysis

Individuals with experience of antibiotic use were compared to individuals without experience of antibiotic use. Proportions were compared among groups using the standard chi-square test using a p value of <0.05 as the level of significance. Univariate analysis was performed to determine the risk-factors for antibiotic use. Variables for which the p value was <0.05 in the univariate analysis were forced in a multivariate model. Forward stepwise logistic regression was used. ORs, significance and 95% CIs were calculated. SPSS for Windows version 11.5 was used for all analyses.

With regard to the quality evaluation, agreement between reviewers (pairwise) was assessed using Cohen kappa coefficients, which assume the value of 0 if there is only agreement by chance, and a value of 1 for perfect agreement.

RESULTS

During the two study periods, 4946 patients were discharged, of whom 1957 (40%) had been hospitalized for 5 days or more. Among these 1957 patients, 999 (51%) were included (Fig. 1). One patient from the O&G department in Hospital A was included twice. The demographic characteristics are shown in Table 1. No major differences were found except for the variables living area and health insurance (both p <0.001). Overall, almost three-quarters of the patients had no health insurance. Over 40% of patients who were 18 years or older were unemployed, while over 90% of them had an education level of at least primary school. One-third of the population was younger than 18 years, reflecting the typical age distribution of inpatients in a developing country. The majority of patients were hospitalized in nursing class III facilities. In Hospital A, the inclusion of 3% of nursing class I patients matched the usual proportion of patients in this class. In

Table 1. Demographic characteristics of included patients in Hospitals A and B

	Hospital A	Hospital B	Total	p value
Total	499	500	999 (100)	
Male	212 (43)	222 (44)	434 (43)	0.57
Age in years, median (range)	27 (0–81)	26 (0–88)	26 (0–88)	0.34
Adults ≥18 years old	334 (67)	337 (67)	671 (67)	0.89
Urban area	370 (74)	262 (52)	632 (63)	0.00
Javanese ethnicity	450 (90)	488 (97)	938 (94)	0.00
Low income	246 (49)	213 (43)	459 (46)	0.04
Unemployed, ≥18 years	145 (43)	138 (41)	283 (42)	0.53
Without education, ≥18 years	24 (7)	34 (10)	58 (8)	0.22
Without health insurance	385 (77)	317 (63)	702 (70)	0.00
Nursing class				0.01[a]
Class I	14 (3)	0 (0)	14 (1.4)	
Class II	75 (15)	125 (25)	200 (20)	
Class III	410 (82)	375 (75)	785 (79)	
Length of stay in days, median (range)	9 (5–162)	8 (5–99)	9 (5–162)	0.67

[a]Nursing classes I and II combined.
Values are given as *n* (%).

Hospital B, inclusion of nursing class I patients was not allowed. The mean (11.8 vs. 8.3 days) and median (9 vs. 6 days) duration of stay of included patients was higher than that of non-included patients, indicating that the consumption data primarily reflected antibiotic use in patients with prolonged hospital stay.

Diagnoses on discharge

The most frequent diagnosis upon discharge was infection; 278 cases (28%). In Hospital A, the number of infections was double that in Hospital B (193 vs. 85, $p < 0.001$). The most common infections were gastroenteritis with diarrhoea (43 cases) and pneumonia (39 cases). Significant differences were noted in the diagnoses of dengue fever (14 in Hospital A and 23 in Hospital B, p 0.09), and typhoid fever (21 in Hospital A and four in Hospital B, p 0.00). The diagnosis of infection was mostly based on clinical symptoms, as only minimal laboratory investigations were performed. Other frequent indications for admission were delivery (17%) and malignancy (14% in Hospital A and 9% in Hospital B).

Quantitative antibiotic use

An antibiotic was given to 834 of 999 (84%) patients hospitalized for 5 days or more. In the departments of surgery and paediatrics, almost all patients staying for 5 days or more used antibiotics (90%), while in the O&G and internal medicine wards, respectively, 87% and 67% of patients used antibiotics. Fifty-three per cent of 2058 prescriptions were categorised as therapy, 15% as prophylaxis and 32% as unknown indication. Overall, antibiotic use was 39 DDD/100 patient-days, and it was 50% higher in Hospital A than in Hospital B (Table 2).

Sixty-two per cent of antibiotics were administered intravenously. Penicillins (primarily ampicillin and amoxicillin) accounted for 54% of the total volume expressed in DDD/100 patient-days. The highest use of penicillins, 64.3 DDD/100 patient-days, was found in the O&G department. Cephalosporins were ranked second, comprising 17% of the total amount prescribed, 94% of which was administered intravenously. The most frequently prescribed cephalosporin was cefotaxime, followed by ceftriaxone. All but 20 of 487 of cephalosporins prescribed belonged to the third generation; four were first-generation, nine were second-generation and seven were fourth-generation. Most cephalosporins were administered in the department of surgery; 16.4 DDD/100 patient-days. Quinolones (ciprofloxacin) were ranked third; 85% was administered orally. This class was mostly used in the department of internal medicine; 16.6 DDD/100 patient-days. The mean prescribed daily dose of most antibiotics was in the order of magnitude of the DDD. For cephalosporins and amphenicols, the prescribed daily dose was *c.* 50% of the DDD.

Validation of the quantitative data

The results of the validation study showed important differences between the retrospective data from the nursing record and the concurrent daily data collected by the pharmacist. The

Table 2. In-hospital consumption of antibiotics of patients discharged from Hospitals A and B

	Hospital A			Hospital B			Total		
Antibiotic (ATC code)	Number of patients	Number of prescriptions	DDD/100 patient-days (%)	Number of patients	Number of prescriptions	DDD/100 patient-days (%)	Number of patients	Number of prescriptions	DDD/100 patient-days (%)
Amphenicols (J01BA)	18	25	0.79 (2)	49	62	1.27 (4)	67	87	1.03 (2)
β-Lactam antibacterials, penicillins (J01C)	278	490	25.86 (55)	277	470	16.14 (52)	555	960	21.05 (54)
Cephalosporins and related substances (J01DA)	143	199	8.16 (17)	179	288	5.32 (17)	322	487	6.75 (17)
Trimethoprim–sulphameth oxazole (J01EE01)	26	26	0.55 (1)	30	30	0.25 (1)	56	56	0.40 (1)
Aminoglycosides (J01G)	62	71	2.13 (5)	85	91	2.53 (8)	147	162	2.33 (6)
Quinolones (J01MA)	41	44	3.96 (8)	89	93	2.73 (9)	130	137	3.35 (9)
Metronidazole (J01XD01)	47	58	4.43 (9)	47	53	2.18 (7)	94	111	3.32 (9)
Other antibiotics	26	49	1.36 (3)	8	9	0.41 (1)	34	58	0.89 (2)
Total antibiotics		962	47.24		1096	30.83		2058	39.02

Other antibiotics included: tetracyclines, macrolides and lincosamides, meropenem, and fosfomycin.
ATC, Anatomical Therapeutic Chemical; DDD, defined daily doses.

collection by the pharmacist yielded 1101 doses, whereas only 775 administered doses were retrieved from the nursing records of the same calendar days for these patients. Three hundred and eighty-three (35%) doses were not written in the record, and 57 of 775 (7%) doses prescribed in the physician's notes of the medical records were reported by patients as not taken or by nurses as not administered. Thirty-eight (67%) of these doses were metronidazole, cefotaxime, ceftriaxone, ciprofloxacin or clindamycin, i.e. the more costly or less commonly prescribed antibiotics. Overall, the retrospective record review upon discharge revealed an underestimation of 326 antibiotic doses, indicating that the actual antibiotic use by the patients was probably about 30% higher.

Determinants of antibiotic use

Multivariate analysis of possible determinants for antibiotic use in hospitalized patients identified four independent variables (Table 3). The most important determinant for antibiotic use was the department from which the patient was discharged. The likelihood of receiving an antibiotic while hospitalised in the departments of surgery, O&G or paediatrics was four to five times that in the department of internal medicine. Having an infection was the second most important determinant of antibiotic use. Variables that independently determined antibiotic use were living in an urban area and being nursed in a class III bed facility.

Quality of antibiotic prescriptions

Overall, 160 medical records containing 1153 antibiotic prescriptions were reviewed (Table 4). In only 2% of cases did two or more reviewers state that the medical record did not provide enough information for an assessment of the (non-) indication or inappropriateness of antibiotics. Approximately 60% of prescriptions were classified as incorrect, either unjustified (not indicated) or inappropriate, by at least two of the three reviewers. Combined assessment resulted in 21% of definitely appropriate prescriptions, 28% in Hospital A and 16% in Hospital B ($p < 0.001$). Fifteen per cent of the prescriptions were classified as inappropriate regarding choice, dosage or duration of therapy.

Table 3. Determinants of antibiotic use in patients discharged from Hospitals A and B

	Antibiotic Yes n = 834	Antibiotic No n = 165	OR (95% CI)	
	n (%)	n (%)	Univariate	Multivariate
Hospital A	412 (49)	87 (53)	0.88 (0.63–1.22)	NS
Male	365 (44)	69 (42)	1.08 (0.77–1.52)	NS
Adult	547 (66)	124 (75)	0.63 (0.43–0.92)	NS
Urban residence	542 (65)	90 (55)	1.55 (1.09–2.20)	1.86 (1.29–2.67)
Javanese ethnicity	780 (94)	158 (96)	0.64 (0.29–1.43)	NS
Low income	378 (45)	81 (49)	0.86 (0.62–1.20)	NS
Unemployed, ≥18 years	237 (43)	78 (37)	1.30 (0.85–1.98)	
Primary school not completed, ≥18 years	48 (9)	10(8)	1.10 (0.52–2.39)	
No insurance	594 (71)	108 (66)	1.31 (0.92–1.86)	NS
Nursing class				
Class III	665 (80)	120 (73)	Reference	Reference
Class I + II	169 (20)	45 (27)	0.68 (0.46–0.99)	0.64 (0.43–0.96)
Department				
Internal medicine	168 (20)	82 (50)	Reference	Reference
Surgery	224 (27)	26 (16)	4.21 (2.59–6.83)	4.87 (2.95–8.04)
Obstetrics/gynaecology	217 (26)	32 (19)	3.31 (2.10–5.22)	3.41 (2.15–5.41)
Paediatrics	225 (27)	25 (15.2)	4.39 (2.69–7.17)	4.47 (2.73–7.34)
Diagnosis				
No infection	592 (71)	129 (78)	Reference	Reference
Infection	242 (29)	36 (22)	1.47 (0.98–2.18)	2.53 (1.58–4.07)

NS, not significant, adult ≥18 years old.

Table 4. Combined quality assessment of antibiotic prescriptions (n = 1153) by three reviewers

Department	Definitely appropriate	Inappropriate	Unjustified, no indication	No agreement among reviewers
Hospital A				
Internal medicine	49 (46)	7 (7)	20 (19)	30 (28)
Paediatrics	33 (24)	48 (35)	25 (18)	33 (24)
Obstetrics/gynaecology	27 (25)	13 (12)	53 (49)	16 (14)
Surgery	38 (22)	22 (13)	80 (47)	31 (18)
Subtotal Hospital A	147 (28)	90 (17)	178 (34)	110 (21)
Hospital B				
Internal medicine	25 (17)	20 (13)	71 (47)	35 (23)
Paediatrics	34 (22)	17 (11)	73 (47)	32 (21)
Obstetrics/gynaecology	13 (10)	14 (11)	71 (56)	28 (22)
Surgery	26 (13)	27 (14)	88 (45)	54 (28)
Subtotal Hospital B	98 (16)	78 (12)	303 (48)	149 (24)
Total	245 (21)	168 (15)	481 (42)	259 (22)

Values are given as n (%).

Most importantly, 34% of prescriptions in Hospital A and 48% in Hospital B were judged to be not indicated ($p < 0.001$). Antibiotic prophylaxis was administered unnecessarily for clean surgery. Antibiotics were started days before the operation and continued orally for several days post-operatively (categorized as 'for unknown indication' according to the study definition). Antibiotic therapy was often initiated for 'sepsis' in the absence of objective clinical diagnostic criteria or documented microbiological evidence (culture report) of infection. Although the Indonesian reviewers allocated approximately the same number of prescriptions in the various assessment categories (Fig. 2), mutual agreement was low (kappa coefficient 0.13) because prescriptions were allocated to different categories. The foreign expert's judgement differed strongly from that of the Indonesian reviewers (kappa coefficients 0.13 and 0.14), particularly regarding the classification of prescriptions as definitely appropriate (Category I) and not indicated (Category V) (Fig. 2).

DISCUSSION

This audit in two Indonesian governmental hospitals showed that a high proportion (84%) of inpatients was treated with antibiotics. The proportion of patients treated with antibiotics was similar in both hospitals, despite the fact that in Hospital A the number of patients diagnosed with an infection was double that in Hospital B. In surgical and paediatric wards, almost all patients were using antibiotics during their stay. As compared to reviews in teaching hospitals reported in the literature, this figure is in the very high range. Studies in low-income and developing countries have reported that 44–97% of admitted patients are treated with antibiotics [4–8]. In general wards of Western hospitals, 21–30% of patients were given antibiotics [17]. In a recent point-prevalence survey of five European university hospitals, only 14–32% of patients were given antibiotics [19]. In contrast to this high proportion of patients treated with antibiotics, a consumption of 39 DDD/100 patient-days was calculated. This is a very low figure as compared to other studies that used this unit of measurement in teaching hospitals in developing [5,6] and Western [17,18] countries. There are several explanations for this relatively low consumption figure in the present study. A validation study in Hospital A revealed that 30% of the volume could be underestimated due to incompleteness of nursing records. Unlike in Western hospitals, there was no actual record of each dose being administered on a medication chart. Second, children comprised one-third of the study population for which the consumption was calculated in DDD. No specific DDD are available for children. A third possible explanation is that the dosages for cephalosporins and amphenicols prescribed to adults were lower than the DDD for these antibiotics. A fourth reason may be that, in this study, the day of admission and the day of discharge were both counted as days of exposure. When the antibiotic use data are adjusted for the inclusion of children, admission and discharge days are counted as 1 day of exposure, and the 30% rate of underestimation is taken into account, antibiotic consumption is 62 DDD/100 patient-days. Even after this correction, the volume of antibiotic use in the Indonesian hospitals in this study was low as compared to published data. For example, in a Brazilian tertiary hospital, antibiotic use was 84 DDD/100 patient-days in 1990 and increased to 125 in 1996 [6]. In a teaching hospital in Iran, antibiotic consumption amounted to 102 DDD/100 patient-days [5]. Consumption was also lower than in a report from the internal medicine department of a Dutch university hospital, where antibiotic use increased from 60 to 73 DDD/100 patient-days after an intervention [18].

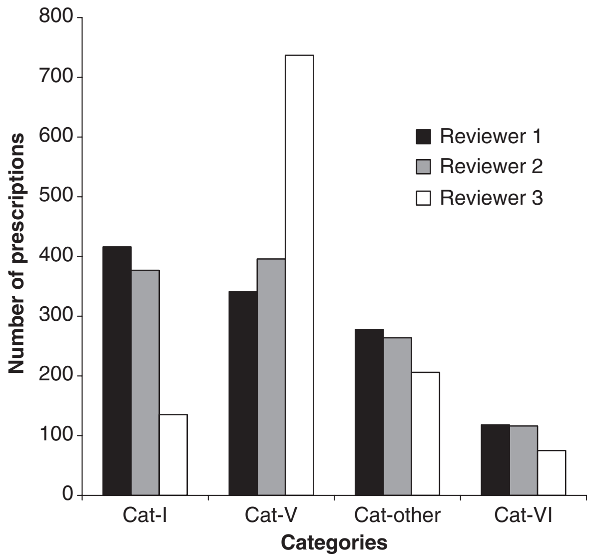

Fig. 2. Quality assessment of antimicrobial drug prescriptions ($n = 1153$) by three reviewers. Reviewer 1 was a senior physician from the relevant department, reviewer 2 was from another department, and reviewer 3 was an infectious diseases expert from The Netherlands. Cat-I, category I, definitely appropriate; Cat-V, category V, unjustified, no indication; Cat-other, inappropriate for several reasons; Cat-VI, unevaluable due to insufficient information.

In this study, one important determinant of use, besides the clinical diagnosis of infection, was hospitalization in a surgical department, either O&G or general surgery. In these departments, many doses of oral aminopenicillins, given post-operatively until discharge to patients without signs of infection, were identified as unnecessary prophylaxis in the quality evaluation. Another healthcare-related variable, nursing class III, that determined antibiotic use could also be interpreted as socio-economic (poor patient population), although the socio-economic variables of low income and lack of health insurance were not independent determinants of antibiotic use in hospital. Interestingly, nursing class was not a significant indicator of hospital-acquired infection in the same period in these hospitals [20]. This finding may point to a difference in the prescribing behaviour of the junior physicians in charge of the class III wards, as compared to that of senior physicians in charge of class I rooms. The only positive demographic determinant, living in an urban area, may point towards a higher demand for antibiotics on the part of patients who are city dwellers. The choice of antibiotics in the two hospitals was as strikingly similar as the high proportion of patients treated with antibiotics. Low-cost amoxycillin, ampicillin and amphenicols accounted for more than half of the prescriptions. In the absence of updated guidelines, economic and other, unidentified determinants of prescribing in developing countries, such as fear of bad clinical outcomes and conformance with peers [21], could be responsible for this uniform prescribing behaviour.

The quality evaluation confirmed over-prescription in surgical and O&G departments and identified major room for improvement in surgical prophylaxis, which is a frequently encountered problem area in Western university hospitals also [17–19], and identified major room for improvement in surgical prophylaxis. Assessment reports of antibiotic prescriptions in hospitals in low-income or developing countries are scarce. Two studies that assessed the quality of prescribing in a teaching hospital in Thailand reported 92% of prescriptions as being incorrect in 1985 [22] and 26% of prescriptions as being incorrect in 2000 [23]. As compared with reports from a Dutch university hospital before an intervention in 1992, the quality of antibiotic prescribing in the two Indonesian hospitals was not particularly low. Using the same audit methodology, 15% of the prescriptions were assessed as appropriate, 39% as unjustified and 46% as inappropriate at the baseline before an intervention [17].

In this study, agreement among reviewers was lower than in the studies in a Dutch university hospital, in which the foreign expert was one of the reviewers [17,18]. Disagreement with the Indonesian reviewers was probably due to the completely different frame of reference. Stein *et al.* described similar assessor disagreements during their survey in Zimbabwe, illustrating the difficulties encountered when applying accepted guidelines for antibiotic use to developing countries [24]. More puzzling was the strong disagreement among the Indonesian reviewers. A possible explanation is that, in the absence of specific training in infectious diseases, they had no agreed standards against which to judge prescribing behaviour, and they had very different backgrounds as surgeons, gynaecologists, paediatricians or internists; also, local medical culture, e.g. peer influence, may have played a role [21]. The limited agreement among reviewers could probably be increased by longer and better training in evidence-based clinical practice to improve expertise, although this would not result in full agreement [17]. Assessment of adherence to guidelines, rather than reviewers' opinions, does not guarantee high kappa coefficients [25].

There are several limitations of this study. First, the study was designed to concurrently detect nasal and rectal carriage of resistant bacteria in the study population [13]. This required the inclusion of patients admitted for 5 days or more prior to discharge. Therefore, the consumption figures are not fully comparable with other reports. Nevertheless, this information can be considered very relevant, because the group of long-stay patients was the most vulnerable, considering that antibiotic use is related to the acquisition of multidrug-resistant bacteria and their infectious consequences. Also, a possible role of case-mix in explaining the striking difference in consumption between the current study populations and those of Western countries cannot be entirely excluded. Second, the data collection concerning antibiotic use relied on retrospective review of medical records on the day of discharge. Although this method is commonly used in developing countries [4–8], the level of use could not be measured accurately in this study, due to the absence of accurate medication charts and the poor quality of medication record-keeping in the hospitals. The irregular and delayed dispensing of antibiotics in the hospitals appeared to be influenced by the fact that most hospitalized patients were obliged to pay cash for the prescribed drugs at a (hospital) pharmacy, rather than an unstable supply of drugs to the healthcare facility. Concurrent review with daily interviews, as during the validation, would render the collection more accurate, but was considered not to be feasible for 1000 patients. In contrast, measurement of the proportion of patients that received antibiotics, deduced from physicians' notes, was accurate. Similarly, the clinical information from the medical records was sufficient for quality assessment. In the Dutch university hospital, up to 10% of prescriptions could not be evaluated [17,18], mostly because of the complexity of the cases. Third, the data were collected during different seasons, resulting in a different case-mix. However, the uniformity of the data collection method, using the same trained data collectors in both hospitals, is an important asset of the study. Finally, the findings cannot be generalized for Indonesia. Hospitals A and B are probably representative of other governmental teaching hospitals, but not of the many private hospitals that deliver healthcare to a wealthy proportion of the Indonesian population. It is of note that, in Indonesia, senior physicians in public hospitals can offer private services after office hours and practise in both types of institution [12]. We cannot exclude the possibility that antibiotic use in private hospitals differs substantially from that in governmental hospitals due to socio-economic and cultural factors.

In conclusion, the drug utilization method for quantitative and qualitative assessment developed in Western hospitals may need to be adapted for the Indonesian hospital setting. Some methodological issues could be resolved by conducting concurrent point-prevalence measurements of observed use and by employing more experienced assessors. However, this audit revealed the need for strong commitment on the part of the medical community to major improvements in medical diagnoses and medication record-keeping, in the training of those who review the process of prescribing, and in the clinical and diagnostic practice guidelines for surgical prophylaxis and sepsis. Feedback of results set the stage for acceptance of recommendations for hospital-wide practice and future interventions, including reorganization of the drug distribution policy of hospital pharmacies, introduction of appropriate medication charts, and better use of microbiological diagnostic facilities.

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REFERENCES

1. Beekmann SE, Heilmann KP, Richter SS. Antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and group A beta-haemolytic streptococci in 2002–2003. *Int J Antimicrob Agents* 2005; **25**: 148–156.
2. Erb A, Stürmer T, Brenner H. Prevalence of antibiotic resistance in *Escherichia coli*: overview of geographical, temporal, and methodological variations. *Eur J Clin Microbiol Infect Dis* 2007; **26**: 83–90.
3. Bronzwaer SLAM, Cars O, Buchholz U *et al*. A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerg Infect Dis* 2002; **8**: 278–282.
4. Orrett FA. Antimicrobial prescribing patterns at a rural hospital in Trinidad: evidence for intervention measures. *Afr J Med Sci* 2001; **30**: 161–164.
5. Ansari F. Use of systemic anti-infective agents in Iran during 1997–1998. *Eur J Clin Pharmacol* 2001; **57**: 547–551.
6. De Castro MS, Pilger D, Ferreira MB, Kopittke L. Trends in antimicrobial utilization in a university hospital, 1990–1996. *Rev Saude Publica* 2002; **36**: 553–558.
7. Chukwuani CM, Onifade M, Sumonu K. Survey of drug practices and antibiotic prescribing at a general hospital in Nigeria. *Pharm World Sci* 2002; **24**: 188–195.
8. Hu S, Liu X, Peng Y. Assessment of antibiotic prescription in hospitalized patients at a Chinese university hospital. *J Infect* 2004; **48**: 117–118.
9. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerg Infect Dis* 1999; **5**: 18–27.
10. Tjaniadi P, Lesmana M, Subekti D *et al*. Antimicrobial resistance of bacterial pathogens associated with diarrheal patients in Indonesia. *Am J Trop Med Hyg* 2003; **68**: 666–670.
11. Ieven M, Van Looveren M, Sudigdoadi S *et al*. Antimicrobial susceptibilities of *Neisseria gonorrhoeae* strains isolated in Java, Indonesia. *Sex Transm Dis* 2003; **30**: 25–30.
12. Hidayat B, Thabrany H, Dong H, Sauerborn R. The effects of mandatory health insurance on equity in access to outpatient care in Indonesia. *Health Policy Plan* 2004; **19**: 322–335.

13. Duerink DO, Lestari ES, Hadi U *et al.* Determinants of carriage of resistant *Escherichia coli* in the Indonesian population inside and outside hospitals. *J Antimicrob Chemother* 2007; **60**: 377–384.
14. Lestari ES, Severin JA, Filius PMG *et al.* Antimicrobial resistance among commensal isolates of *Escherichia coli* and *Staphylococcus aureus* in the Indonesian population inside and outside hospitals. *Eur J Clin Microbiol Infect Dis* 2008; **27**: 45–51.
15. Gyssens IC, Van den Broek PJ, Kullberg BJ, Hekster YA, Van der Meer JWM. Optimizing antimicrobial therapy. A method for antimicrobial drug evaluation. *J Antimicrob Chemother* 1992; **30**: 724–727.
16. BPS-Statistics Indonesia BAPPENAS and UNDP. *The economics of democracy. Financing human development in Indonesia*. Jakarta, Indonesia: BPS-Statistics Indonesia BAPPENAS and UNDP, 2004.
17. Gyssens IC, Geerligs IEJ, Dony JMJ *et al.* Optimising antimicrobial drug use in surgery: an intervention study in a Dutch university hospital. *J Antimicrob Chemother* 1996; **38**: 1001–1012.
18. Gyssens IC, Blok WL, Van den Broek PJ, Hekster YA, Van der Meer JWM. Implementation of an educational program and an antibiotic order form to optimize quality of antimicrobial drug use in a department of internal medicine. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 904–912.
19. Vlahovic-Palcevski V, Dumpis U, Mitt P *et al.* Benchmarking antimicrobial drug use at university hospitals in five European countries. *Clin Microb Infect* 2007; **13**: 277–283.
20. Duerink DO, Roeshadi D, Wahjono H *et al.* Surveillance of healthcare-associated infections in Indonesian hospitals. *J Hosp Infect* 2006; **62**: 219–229.
21. Radyowijati A, Haak H. Improving antibiotic use in low-income countries: an overview of evidence on determinants. *Soc Sci Med* 2003; **57**: 733–744.
22. Aswapokee N, Vaithayapichet S, Heller RF. Pattern of antibiotic use in medical wards of a university hospital, Bangkok, Thailand. *Rev Infect Dis* 1990; **12**: 136–141.
23. Ayuthya SK, Matangkasombut OP, Sirinavin SM, Malathum K, Sathapatayavongs B. Utilization of restricted antibiotics in a university hospital in Thailand. *Southeast Asian J Trop Med Public Health* 2003; **34**: 179–186.
24. Stein CM, Todd WTA, Parirenyatwa D, Chakonda J, Dizwani AGM. A survey of antibiotic use in Harare primary care clinics. *J Antimicrob Chemother* 1984; **14**: 149–156.
25. Mol PGM, Wierenga JE, NannanPanday PV *et al.* Improving compliance with hospital antibiotic guidelines: a time-series intervention analysis. *J Antimicrob Chemother* 2005; **55**: 550–557.

APPENDIX

Dr Soetomo Hospital – School of Medicine Airlangga University Surabaya, Indonesia:

W. Gardjito; E. P. Kolopaking; K. Wirjoatmodjo; D. Roeshadi; E. Suwandojo; H. Parathon; U. Hadi; N. Zairina; E. Isbandiati; K. Deborah; K. Kuntaman; N. M. Mertaniasih; M. Purwanta.

Dr Kariadi Hospital – School of Medicine Diponegoro University Semarang, Indonesia:

A. Soejoenoes; B. Riyanto; H. Wahjono; M. Adhisaputro; B. Triwara; J. Syoeib; E. S. Lestari; B. Wibowo; M. A. U. Sofro; H. Farida; M.M.D.E.A.H. Hapsari; T. L. Nugraha.

Leiden University Medical Centre, Leiden, The Netherlands:

P. J. van den Broek; D. O. Duerink.

Erasmus University Medical Centre, Rotterdam, The Netherlands:

H. A. Verbrugh; I. C. Gyssens.

Radboud University Medical Centre, Nijmegen, The Netherlands:

M. Keuter.

