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Antibiotic usage and antimicrobial resistance in indonesia

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Chapter VIII

Summary and General Discussion

Summary and general discussion

Antibiotic therapy is the cornerstone of the treatment of infectious diseases. Its beneficial effects in patients with bacterial infections are beyond doubt. Unfortunately, the introduction of antibiotics was soon followed by the emergence of bacterial resistance, which seriously limited the beneficial effects. Resistance of bacteria against antimicrobial drugs has become an important health care problem. Infections with (multi-)resistant bacteria are associated with increased morbidity and mortality because empiric therapy is often inappropriate [1]. Second or even third-choice antibiotic therapy has to be given which often is less effective, may have more side-effects and often costs more than standard therapy.

Emergence of resistant bacteria is driven by the selective pressure that antimicrobial drugs exert on bacterial populations in patients. The other contributor to the occurrence of resistant bacteria in health care institutions is the transmission between patients, often made easy by poor adherence to hygienic measures. Considering these two drivers of antimicrobial resistance, the problem should be tackled on two fronts. The first is the promotion of the prudent use of antibiotics, the second the improvement of hospital hygiene.

The main goals of the studies described in this thesis were to measure the quantity and quality of antibiotic use in extramural and intramural health care in order to identify targets for improvement and to explore methods to stimulate the prudent use of antibiotics. Together with the results of the studies on the prevalence and mechanisms of antimicrobial resistance and infection control of the AMRIN study (Antimicrobial Resistance in Indonesia: Prevalence and Prevention), the data presented in this thesis will hopefully contribute to the scientifically based fight against bacterial resistance in Indonesia.

Antibiotic use in extramural health care

Antibiotic use in extramural health care was studied in patients who visited a primary health center (puskesmas) and patients upon admission to the hospital on the island of

Java (chapter III). The health centers involved were puskesmas Mojo and puskesmas Pucang in Surabaya, and the rural puskesmas Mijen in Semarang. The hospitals involved were Dr. Soetomo Hospital in Surabaya and Dr. Kariadi Hospital in Semarang. For comparison, family members accompanying patients at the time of admission were included in the survey to obtain an approximate measurement of antibiotic use in healthy individuals. Antibiotic use was determined by interviewers using a semi-structured questionnaire on antibiotic use in the previous month.

Summary of results

Of 2996 individuals interviewed, equally distributed over the three groups, 486 (16%) had taken an antibiotic. Relatives of patients admitted to the hospital had the lowest use of antibiotics (7%) compared to patients seeking help at a puskesmas (19%; odds ratio 2.0, 95% confidence interval (CI) 2.1 to 3.0) and patients upon admission to the hospital (22%; odds ratio 3.7, 95% CI 2.8 to 5.0). Almost all patients (99%) who used antibiotics reported health complaints, compared to 62% of the individuals who did not take antibiotics. Complaints indicating involvement of a specific organ system were reported by 954 individuals: respiratory tract symptoms 80%, gastro-intestinal symptoms 13%, dermal symptoms 5%, and urinary tract symptoms 2%.

The most frequently used agents were ampicillin and amoxicillin (71%). In second and third place came tetracyclines (9%) and trimethoprim-sulfamethoxazole (8%), respectively. The use of amphenicols was still surprisingly high in our study, almost 7% of the courses of treatment. The majority of antibiotics was prescribed by doctors: private practice 37%, puskesmas 29% and public hospital 13%. Six percent of the antibiotics were prescribed by nurses or midwives and 17% were taken without a prescription. Amoxicillin and ampicillin were taken for a mean duration of 3.7 days. Individuals who took antibiotics as self-medication used the drug for a shorter period than those who obtained antibiotics from private practitioners. Doctors in puskesmas prescribed antibiotics for 3 days, and therapy was continued for another 3 days when the patients came back for a control visit.

In addition to being a patient visiting a puskesmas or being seen upon admission to the hospital, Javanese race was found to be an independent determinant for antibiotic use (odds ratio 2.4, 95% CI 1.3 to 1.5, compared to the Madurese). Adult age (odds ratio 0.49, 95% CI 0.38 to 0.62) and lack of health insurance (odds ratio 0.75, 95% CI 0.60 to 0.90) were independently associated with lesser use of antibiotics. Independent determinants for self-medication with antibiotics were adult age (odds ratio 6.8, 95% CI 2.7 to 17), male sex (odds ratio 2.3, 95% CI 1.3 to 4.1), urban resident (odds ratio 4.5, 95% CI 2.3 to 9.0), and lack of health insurance (odds ratio 2.4, 95% CI 1.3 to 4.6).

Discussion

Regarding the main goals of the research presented in this thesis, the study among patients seeking help from extramural health care providers showed that about one-fifth of the patients who visit a puskesmas or are admitted to the hospital had taken an antibiotic in the past month. This level of antibiotic use is in line with data reported from other low-income and developing countries. Thirteen to fifteen percent of the patients visiting public health care centers in Peru, Malaysia or Turkey took antibiotics [2-4]. A study from Iran reported a much higher level of 62% [5]. About half (47-57%) of the patients who were seen in an outpatient clinic in Zimbabwe, Nigeria, Pakistan or Afghanistan used antibiotics [6-9]. A community survey in Vietnam showed that 75% of the children investigated had taken an antibiotic in the previous month [10]. In Mexico 5% of the housewives interviewed reported that family members had taken an antibiotic in the previous two weeks [11].

We did not assess the quality of these antibiotic prescriptions, but there are some indications that the quality was not optimal. The majority of the antibiotics were prescribed for complaints suggesting respiratory tract infections or gastro-intestinal infections. Many of these infections are caused by viruses and many of the bacteria causing gastro-intestinal infections are resistant to the most frequently used antibiotics, ampicillin or amoxicillin [12]. This suggests that many of these antibiotics were unnecessary or inappropriate. Not much information is available about the quality of antibiotic prescriptions in low-income and developing countries. Two studies reported on

the quality of antibiotics prescribed for patients who visited an outpatient clinic. In Zimbabwe 12% of the prescriptions were assessed to be incorrect, in Peru 82% [2, 6]. Another part of the AMRIN project provided resistance data on *Escherichia coli* and *Staphylococcus aureus* in the same study populations.[13]. These figures show that resistance against the three most frequently used antibiotics in extramural health care was high. For *Escherichia coli*, the highest levels of resistance were found for ampicillin and cotrimoxazole. *Escherichia coli* isolates from family members were resistant to ampicillin and cotrimoxazole in 20% of the cases, from patients visiting a puskesmas in 24 and 31% , and from patients screened upon admission to the hospital in 40 and 50% of the cases, respectively. *Staphylococcus aureus* isolates were resistant to tetracycline, another antibiotic in the top three of the list of antibiotic consumption, in approximately 20% of the family members and patients visiting a puskesmas and 35% of the patients seen upon admission to the hospital. Detailed studies on the determinants of carriage of (multi)resistant *Escherichia coli* are summarized and discussed in the paragraph “Carriage of resistant *Escherichia coli*”.

In conclusion, there is an urgent need for improvement of antibiotic use in extramural health care. Several recommendations can be made.

- a. Since three-quarters of the antibiotics were prescribed by doctors, they should be the primary target for interventions to improve the prescription of antibiotics.
- b. Since about one-fifth of the antibiotics were taken by the patients as self-medication, interventions directed at the general public to promote restraint in the use of antibiotics should be undertaken to contribute to the prudent use of antibiotics.
- c. The quality of antibiotic use in extramural health care should become a major topic of research in Indonesia to provide a scientific basis for interventions to improve the prudent use of antibiotics.

Antibiotic use among hospitalized patients

Antibiotic use in hospitals was studied in the Dr. Soetomo Hospital in Surabaya and Dr. Kariadi Hospital in Semarang, both large teaching hospitals on the island of Java, Indonesia (chapter IV). Patients who had been admitted for at least five days to the

Departments of Internal Medicine, Surgery, Gynecology & Obstetrics, or Pediatrics were included. Data on antibiotic use were obtained by retrospective analysis of patient records on the day of discharge. To validate the accuracy of this method of data collection, retrospective antibiotic use figures were compared with prospectively collected data on antibiotic use. The quality of antibiotic prescriptions was assessed by reviewers who used a validated scoring system for assessment of antibiotic therapies.

Summary of results

An antibiotic was prescribed for 84% of the patients hospitalized for at least five days. In the Departments of Surgery and Pediatrics 90% of the patients staying for 5 or more days used antibiotics, while in the Gynecology & Obstetrics and Internal Medicine Departments 87 and 67% of the patients, respectively used antibiotics. Fifty-three percent out of 2058 prescriptions were classified as therapy, 15% as prophylaxis, and 32% as unknown indication. Antibiotic use quantified as defined daily doses (DDD)/100 patient-days was 47.24 in Surabaya and 30.85 in Semarang. Penicillins (primarily ampicillin and amoxicillin) accounted for 54% of the total volume of antibiotics expressed as DDD/100 patient-days. The highest use of penicillins, 63.3 DDD/100 patient-days was found for the Department of Gynecology & Obstetrics. Cephalosporins were ranked second, comprising 17% of the total amount prescribed. The most frequently prescribed cephalosporin was cefotaxime followed by ceftriaxone. All but 20 out of 487 prescriptions for cephalosporins belonged to the third generation; four were of the first, nine of the second and seven of the fourth generation. Most cephalosporins were administered in the Department of Surgery, 16.4 DDD/100 patient-days. Quinolones ranked third among the antibiotics prescribed for hospitalized patients. Quinolones were used mainly in the Department of Internal Medicine, 16.6 DDD/100 patient days, and in 85% of the cases were given orally.

The validation study showed that the retrospective review of medical records upon discharge of patients from hospital leads to an underestimation of antibiotic use of about 30%. The amounts of antibiotics given above should be corrected for this under-reporting due to missing data in medical records.

The most important determinant for antibiotic use was the department from which the patient was discharged. Compared to patients cared for in the Department of Internal Medicine, the odds of being prescribed an antibiotic in the Surgery department were 4.9 (95% CI 3.0-8.0), in Paediatrics 4.5 (95% CI 2.7-7.3) and in Gynaecology & Obstetrics 3.4 (95% CI 2.1-5.4). Having an infection was the second most important determinant of antibiotic use (odds ratio 2.3, 95% CI 1.4-3.7). Socio-economical variables that independently determined antibiotic use among hospitalized patients were living in an urban area (odds ratio 1.9, 95% CI 1.3-2.7), and being nursed in a class III bed (odds ratio 1.6, 95% CI 1.04-2.35),

The quality of antibiotic use was assessed by two Indonesian and one foreign reviewer. Almost 60% of the assessed prescriptions were classified as incorrect, either unjustified (42%) or inappropriate (15%), by at least two of the three reviewers. Inappropriate prescriptions could be attributed to choice, dosage or duration of therapy. Unjustified means that the medical records did not contain information justifying the use of antibiotics. In Semarang more prescriptions were judged to be not indicated than in Surabaya, 48% and 34%, respectively ($p < 0.001$). Twenty-one percent of the prescriptions were considered correct, 28% in Surabaya and 16% in Semarang ($p < 0.001$). The foreign expert's judgment differed markedly from the Indonesian reviewers (kappa coefficients 0.13 and 0.14), particularly regarding the classification of prescriptions into definitely appropriate and not indicated.

Discussion

Our study on antibiotic use in two hospitals showed that a high percentage of the patients who were admitted for at least five days were treated with antibiotics. This was not much different from those reported for other low-income and developing countries. Based on a similar method of inspection of medical records antibiotic use was 97% in Nigeria, 78% in China and 64% in Trinidad for Gynecology & Obstetrics and 71% for Pediatrics [7, 14, 15]. Malaysian and Turkish studies reported lower levels, 44% and 31%, respectively, but these figures were based on cross-sectional studies [16, 17].

Although the percentage of patients treated with antibiotics during hospitalization was high, the amount of antibiotics, expressed as DDD per 100 patient-days, was in the

middle of the range for European hospitals [16]. Although the quantity of antibiotics was substantially higher after correction for underreporting, inclusion of children and counting both admission and discharge days as full days, i.e. 62 instead of 39 DDD/100 patient-days, it remained within the interquartile range of European hospitals.

In one-third of the cases it was unclear from the information in the medical records whether the prescription was for therapy or prophylaxis. Reviewers judged that there was no indication for 42% of the antibiotic prescriptions. Data about quality assessment of antibiotic use inside hospitals in low-income and developing countries are scarce. A study published in 1985 from Thailand showed that 90% of the prescriptions were inappropriate, i.e. not according to the guidelines [19]. A more recent study from Thailand showed that 26% of the prescriptions of a selected group of antibiotics were inappropriate [20].

The AMRIN study also reported high rates of carriage of (multi)resistant *Escherichia coli* in patients on the day of discharge from the hospital [12]. The rate of resistance was 73% for ampicillin, 55% for cotrimoxazole, 43% for chloramphenicol 22% for ciprofloxacin, 18% for gentamicin and 13% for cefotaxime. Compared with the presence of resistant *Escherichia coli* on the day of admission there is a marked increase in resistance, due, undoubtedly, to the selective pressure of antibiotic use in the hospitals. However, resistance rates did not always correlate directly with antibiotic consumption in the hospital. Ampicillin and amoxicillin were the most frequently used antibiotics and the resistance rate for ampicillin was the highest. On the other hand, although cephalosporin use ranked second, the rate of cefotaxime resistance was the lowest of all antibiotics tested. Detailed studies on the determinants of carriage of (multi)resistant *Escherichia coli* after a stay in hospital are summarized and discussed in the paragraph “Carriage of resistant *Escherichia coli*.”

Our study revealed two problems regarding the methods applied: the limited accuracy of the measurement of the quantity of antibiotics administered by retrospective reviewing of medical records, and the wide divergence of assessment of the quality of antibiotic prescriptions by reviewers.

The medical records were incomplete as far as the administration of the prescribed antibiotics is concerned. Prescriptions by the doctors were noted down in most cases but

the accounts of the administration were inaccurate. A prospective approach as applied for the validation would be more accurate but it is time-consuming and for that reason not well-suited for large studies. Medical record keeping might be improved by the introduction of an antibiotic record form or the electronic prescription of drugs, including antibiotics, and registration of administration. Studies using retrospective analysis of medical records should validate their findings for a subset of prescriptions by prospective collection of data.

The low agreement between reviewers assessing the quality of antibiotic prescriptions using a standardized method for assessment is not typical of our study alone. A problem with assessment by multiple reviewers is that there will never be full agreement between them [21]. Compared to similar studies in developed countries, the agreement in our study was lower. In an intervention study in a Dutch university hospital, kappa coefficients between two reviewers for therapy before and after intervention were 0.37 and 0.30, respectively [21]. The lower agreement in our study might be caused by differences in knowledge and experience among the reviewers. For example, in our study no Indonesian infectious diseases specialists were available for review. An alternative for assessment of quality by reviewers is the use of quality indicators derived from the available evidence and consensus of an expert panel, in a carefully planned procedure [22].

In conclusion, there is a need for the improvement of antibiotic use in hospitals.

For improvement in hospitals, several recommendations can be made.

- a. The antibiotic committee should take the initiative for development of guidelines.
- b. Clinicians should be instructed to follow these local guidelines strictly.
- c. Microbiologists should provide results of cultures and sensitivity tests as soon as possible and discuss the results with the doctor in charge.
- d. Pharmacists should monitor and evaluate antibiotic use according to the guidelines and the hospital formulary.
- e. Nurses should record all antibiotic administrations correctly by using a medication chart.
- f. The management of the hospital should facilitate the upgrading of microbiology laboratories to actual standards

- g. Microbiology laboratory services should be available for 24 hours per day.

Pharmacological quality of antibiotics

To investigate whether Indonesian antibiotics meet standard pharmacological quality criteria, samples of antibiotics were purchased from pharmacies, kiosks and drugstores or shinses around Dr. Soetomo Hospital, Pucang puskesmas and Mojo puskesmas in Surabaya (chapter V). The antibiotics were bought by Indonesian volunteers acting as patients using a prescription or just requesting a specific drug. Samples of the five most frequently used antibiotics were collected: amoxicillin, chloramphenicol, tetracycline, cotrimoxazole and ciprofloxacin.

Summary of results

One hundred and four antibiotic samples were randomly collected: 71% from pharmacies, 28% from kiosks and one sample from a drug store. Shinses did not sell antibiotics. Twenty-six (25%) samples were obtained with and 78 (75%) without a prescription. All amoxicillin and ciprofloxacin samples were generic preparations. Twenty-two percent of chloramphenicol, 15% of cotrimoxazole and 60% of tetracycline samples were brand name products. The acquisition costs were significantly lower for generic than brand name products and in pharmacies compared to kiosks.

According to the criteria of the British Pharmacopeia of 2005, a quarter of amoxicillin tablets and one fifth of tetracycline capsules contained slightly less antibiotic than required. Fifty percent of cotrimoxazole tablets contained considerably lower amounts of trimethoprim than required. There was no relationship between substandard quality and supplier, whether the capsules or tablets were packed in a blister or unpacked, or whether it concerned generic or brand name products. A significant relationship was found between one of the 14 manufacturers and substandard quality. This manufacturer produced half of the substandard samples.

Discussion

Substandard quality of antimicrobial drugs is a serious threat for patients. Statements that about 20% of drug products in Indonesia are counterfeit, do suppose that substandard

quality is a real problem in Indonesia [23, 24]. Although one-fifth of the antibiotic samples tested by us were substandard according to the criteria of the British Pharmacopeia 2005, there is no indication that substandard amoxicillin, chloramphenicol, tetracycline, cotrimoxazole or ciprofloxacin drugs are marketed deliberately. In most cases the aberrations from the standard were minor, probably not seriously hampering the anti-infective effect of the drugs. The most erratic results were found for the trimethoprim content of cotrimoxazole tablets. Because of the important differences between storage conditions in pharmacies and kiosks we assume that substandard quality could be related to the kind of supplier. In pharmacies drugs are stored in air-conditioned rooms. In kiosks they are exposed to the daily high temperatures in Indonesia which can be even higher when the drugs are exposed directly to the sun. Nevertheless, we found no differences in quality between suppliers. On the contrary, we found that substandard quality is to a great extent a manufacturing problem.

Selling antibiotics without a prescription is forbidden in Indonesia. However, it was no problem to obtain antibiotics in pharmacies or kiosks over the counter. Kiosks play an important role as unofficial suppliers of antimicrobial drugs. They are easily accessible. Kiosk owners buy their antibiotics over the counter from pharmacies. This makes it understandable why the drugs in kiosks are more expensive than in pharmacies. The kiosk owner needs his profit and probably more so because what he is doing, is illegal. Several recommendations can be based on our findings.

- a. The government should take measures to improve the production of antimicrobial drugs and should check the quality of the drug products regularly.
- b. In the interest of the prudent use of antibiotics, the rule that antibiotics are only obtainable with a prescription should be strictly enforced.
- c. A campaign should inform the Indonesian public that antibiotics are precious drugs that never should be used without a prescription from a doctor, and that antibiotics from pharmacies are cheaper than those from kiosks

Carriage of resistant *Escherichia coli*.

As part of the AMRIN project, nasal and rectal swabs of the individuals studied were cultured for the presence of *Staphylococcus aureus* and *Escherichia coli*, respectively.

Resistance against a number of antimicrobial agents was determined by disk diffusion [13]. This offered the opportunity to look for the relationship between antibiotic use and carriage of resistant strains. Next to antibiotic use, demographic, socio-economic, disease-related and health care-related determinants were analyzed for association with carriage of resistant strains. The determinants of rectal carriage of resistant *Escherichia coli* are reported in this thesis (chapter VI), determinants for nasal carriage of resistant *Staphylococcus aureus* are reported elsewhere [25].

Summary of results

Patients included at admission, their relatives and patients seen when visiting a puskesmas were analyzed as one group, the so-called community group. Patients included on the day of discharge were analyzed as a separate group.

Community

In the community group 2996 individuals were enrolled. In 2494 cases information about carriage of *Escherichia coli* and all demographic, socio-economic, disease-related and healthcare-related variables were available. Forty-three percents of the population carried resistant *Escherichia coli*. Ampicillin resistance was observed in 851 (34%) isolates, trimethoprim/sulfamethoxazole resistance in 716 (29%) isolates and chloramphenicol resistance in 369 isolates (15%).

Logistic regression analysis showed that antibiotic use was the most important determinant for carriage of resistant *Escherichia coli* (odds ratio 1.8, 95% CI 1.5-2.3).

Direct associations were observed between the use of β -lactam antibiotics and ampicillin resistance (odds ratio 1.8, 95% CI 1.2-1.7) and between sulphonamide use and resistance to trimethoprim/sulfamethoxazole (odds ratio 7.5, 95% CI 2.0-28.0). Adults were less likely to carry resistant *Escherichia coli* than children (odds ratio for any kind of resistance 0.4, 95% CI 0.3-0.5, and ampicillin resistance 0.6, 95% CI 0.4-0.9). Socio-economic variables were not associated with carriage of resistant *Escherichia coli*.

Hospital admission was associated with carriage of resistant *Escherichia coli* (odds ratio compared with healthy relatives 2.4, 95% CI 2.0-3.0 for any kind of resistance, and 2.7,

95% CI 1.9-4.0 for ampicillin resistance). Diarrhea was associated with carriage of *Escherichia coli* resistant to any of the tested antibiotics (odds ratio 1.9, 95% CI 1.3-2.7).

Hospitalized patients

From the two participating hospitals 999 patients were included on the day of discharge after a stay of at least 5 days in the hospital. From 781 patients *Escherichia coli* had been isolated and all data were available for analysis. Eighty-one percent of the hospitalized patients carried *Escherichia coli* resistant to one or more antibiotics. Resistance to a single antibiotic was found for fewer than 100 isolates. Ampicillin resistance was seen most frequently (570 isolates, 73%), followed by trimethoprim/sulfamethoxazole resistance in 434 isolates (56%), chloramphenicol resistance in 334 isolates (43%), ciprofloxacin resistance in 173 isolates (22%) and gentamicin resistance in 141 isolates (18%). As expected, the use of antibiotics was associated with carriage of resistant *Escherichia coli* (odds ratio 2.5, 95% CI 1.6-3.9). Most patients (67%) took more than one antibiotic during their stay in the hospital. In the subgroup of patients who had taken only one antibiotic, cephalosporin use was associated with the least carriage of *Escherichia coli* resistant to any of the tested antibiotics (odds ratio 0.2, 95% CI 0.1-0.5). Single use of other antibiotics was not associated with the carriage of resistant *Escherichia coli*. Of the socio-economic and demographic variables only one variable was selected as a determinant. Having no health insurance was associated with less carriage of resistant *Escherichia coli* (odds ratio 0.6, 95% CI 0.4-0.9). Patients discharged from the hospital in Semarang were more likely to carry resistant *Escherichia coli* than patients discharged from the hospital in Surabaya (odds ratio 2.2, 95% CI 1.5-3.3). Likewise, patients discharged from the pediatric departments carried more resistant *Escherichia coli* than patients discharged from internal medicine departments (odds ratio 4.3, 95% CI 1.7-10.7).

Discussion

Not surprisingly, antibiotic use was the most prominent determinant of carriage of multi(resistant) *Escherichia coli* outside as well inside hospitals. This confirms that

antibiotic use is one of the causes of antimicrobial resistance and that the promotion of the prudent use of antibiotics should get more attention in Indonesia.

Children have higher rates of resistant *Escherichia coli* than adults. Inside hospitals this is reflected in a higher rate of carriage of resistant *Escherichia coli* in pediatric wards than in internal medicine wards. We have observed that antibiotic consumption is higher in pediatric wards than in internal medicine wards (chapter IV). However, age being an independent determinant, it is likely that this difference is not explained merely by the difference in antibiotic use. Other factors may contribute to this matter: e.g. insufficient adherence of the nurses to nosocomial infection control in the hospital.

The carriage of resistant *Escherichia coli* is higher among hospitalized patients than in individuals who have contact with extramural healthcare or are family members. Since antibiotic consumption is the most important determinant of the carriage of resistant bacteria, this difference reflects the high rate of empiric antibiotic therapy inside (85%) vs outside hospital (16-25 %).

Among hospitalized patients in Semarang, the carriage of resistant *Escherichia coli* was higher than that in Surabaya. Since the proportion of patients treated with antibiotics was similar in the two hospitals, other factors may determine the difference. For example the fact that antibiotic therapy in Surabaya was correct more often than in Semarang, 28% versus 16%, respectively.

Optimizing the use of antibiotics

The study of the administration of antibiotics to hospitalized patients (chapter IV), identified as one of the targets for promotion of prudent use of antibiotics, the use of antibiotics in patients admitted with fever to the Department of Internal Medicine.

Shortcomings were that the diagnosis sepsis was made too often without applying strict and generally accepted criteria for this diagnosis, blood cultures, if done, were performed days after starting antibiotic therapy, and empiric therapy started upon admission was not re-evaluated after two to three days. A study was developed consisting of six interventions: the development of a consensus guideline, an official declaration of the guideline by the head of the department, the distribution of a guideline booklet, performing blood cultures free of charge, teaching sessions and refresher courses (chapter

VII). Beginning sixteen weeks before the first activity, i.e. the development of a consensus guideline, and lasting until eight weeks after the last activity, i.e. the refresher courses, patients with fever upon admission were included in the study. The outcome was measured by (1) the percentage of patients with fever started on antibiotic therapy, (2) amount of antibiotics used expressed as defined daily doses (DDD)/100 patient-days, (3) percentage of correct prescriptions and prescriptions without any indication as assessed by independent reviewers, (4) percentage of treatments in accordance with guidelines, (5) percentage of patients for whom blood cultures were taken before starting antimicrobial therapy, (6) percentage of treatments appropriately stopped upon re-evaluation of the patients at 72 hours, and (7) mortality.

Summary of results

The multi-faceted intervention study had mixed results. Improvement was seen in the percentage of patients treated with antibiotics upon admission (absolute decrease of 17%), amount of antibiotics used during the first five days of admission (decrease from 99.8 to 73 DDD/100 patient-days), and the percentage of patients with sepsis and dengue fever treated in accordance with the guideline (absolute increase of 23 and 30%, respectively). However, the percentage of correct prescriptions and prescriptions without any indication, as assessed by the reviewers, did not improve. The intervention study failed to introduce blood cultures before the start of empirical antibiotic therapy and re-evaluation of this therapy after three days. Blood cultures were performed for a high percentage of the patients, however almost none of these blood cultures occurred before the start of antimicrobial therapy. Results of the blood cultures were not available at the moment the empiric therapy had to be re-evaluated, as a result of which very important information for the re-evaluation was lacking. The result was that the re-evaluation was not carried out for any of the patients.

Discussion

To promote the prudent use of antibiotics WHO identified a multitude of targets: community, patients, prescribers, pharmacists, hospitals, national governments, cattle breeders, pharmaceutical companies, and international health care organizations (chapter

II). Our intervention study was aimed at prescribers and hospitals. WHO recommendations to improve antibiotic use by prescribers include interventions in the form of education, measures regarding management, guidelines and formularies, and regulation. At the hospital level WHO recommends intervention in the fields of management and diagnostic laboratories [26]. Apart from regulations, we took action on all the other targets mentioned.

The decrease in the quantity of antibiotic use achieved by the interventions is modest, although in the order of magnitude often achieved by this type of studies [27]. Our study was developed as a multifaceted study, although the opinion that this is the most effective design for intervention studies has been challenged by Grimshaw et al. [27]. In a meta-analysis of intervention studies they did not find a correlation between the number of interventions and the magnitude of the effects. The question is whether time-consuming and labor-intense interventions, as in our study, are efficient. Alternative approaches should be considered and explored in future investigations. For example, whether making use of the authority of senior doctors and health care officials or governmental regulations is more efficient in improving antibiotic use than an approach focusing on the motivation and rationality of individual prescribers.

A problem that should be solved by hospital management and governmental interventions is the lack of adequate microbiological diagnostic laboratories. Without a well-functioning discipline of medical microbiology, improvement of antibiotic use will not be achieved. The interventions we tried to improve microbiological diagnostics failed on two counts: the clinicians and the microbiologists. The clinician should take blood cultures before starting antimicrobial therapy and the microbiologist should contact the clinician promptly when a blood culture becomes positive, but neither happened. The cooperation between clinician and microbiologist which was the aim of the study was not achieved.

We do the following recommendations to improve the cooperation between clinicians and microbiologists.

- a. The organization of regular (weekly) meetings of clinicians and microbiologists to discuss current cases of infectious diseases in the hospital.

- b. Routine evaluation of adherence to clinical guidelines by clinicians and feedback of the results.
- c. Enhancement of the involvement of the clinical microbiologist in patient care, i.e. by the introduction of a 24-hour service for advice on the diagnostics and treatment of patients with infectious diseases.
- d. Promotion of active reporting of culture results by the microbiologist to the clinician as soon as (preliminary) results are available.
- e. Education of clinicians about the optimal use of microbiological tests, i.e. taking blood cultures before giving antibiotics, taking blood samples for culture by nurses directly after ordered by the doctor.

Epilogue

The investigations presented in this thesis are part of the AMRIN study that addressed antimicrobial resistance, antibiotic usage and infection control in Indonesia. They are the first studies that give insight into the quantity of antibiotic use inside and outside hospitals and about the quality of antibiotic use in hospitals in Indonesia. So far, only limited information on antibiotic use has been published concerning specific patient groups with mild upper respiratory tract infections or acute diarrhoea, as is reviewed in chapter II.

The AMRIN study showed that antimicrobial resistance has become a public health threat in Indonesia. The role and responsibility of health care providers regarding the resistance problem was made clear. Urgent action is needed.

One of the aims of the AMRIN study was to develop an efficient, standardized programme for the assessment of antimicrobial resistance, the quantity and quality of antibiotic usage, and infection control measures in Indonesian hospitals. This program should be applicable in every Indonesian hospital. The self-assessment tool was published under the auspices of the Directorate General of Medical Care of the ministry of Health, Republic of Indonesia and presented during a conference in Bandung in 2005

[28]. The Indonesian partners of the AMRIN project received a grant to counsel hospitals that started to plan activities to suppress the development of antimicrobial resistance. In this way AMRIN became a national programme to control antimicrobial resistance in Indonesia.

Application of the AMRIN self-assessment programme in more hospitals offers new possibilities to stimulate the fight against antimicrobial resistance by improvement of quality of care in health care institutions. The AMRIN self-assessment program can develop into a benchmark system for Indonesian hospitals regarding antimicrobial resistance, antibiotic use, and infection control. Amounts of antibiotics used, levels of antimicrobial resistance, and prevalence rates of health care-associated infection as measured by the AMRIN self-assessment program, can be used as performance indicators to compare hospitals or wards within hospitals. For this purpose these indicators should be validated and corrected for variables that significantly influence the indicators but cannot be influenced by the health care workers. Future research is needed to support this development.

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