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## Antibiotic usage and antimicrobial resistance in indonesia

Hadi, U.

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# Chapter I

Introduction

Outline of the thesis

## **Introduction**

Antimicrobial resistance of bacteria is a worldwide and ever-growing problem, directly linked to the use of antimicrobial drugs [1-5]. Resistant bacteria emerge under the selective pressure of antibiotics [6]. In hospitals, where large-scale usage of antibiotics is common, bacteria frequently become resistant to several antibiotics which causes serious problems for the treatment of patients with infections by these microorganisms [7, 8].

Well-known (multi)-resistant bacteria causing problems in many countries all over the world are methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, penicillin-resistant pneumococci, extended-spectrum betalactamase-producing *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter baumannii*, and multiresistant *Mycobacterium tuberculosis*.

Prevention of antimicrobial resistance is part of the responsibility of every health care worker. To reduce the problem of antimicrobial resistance dual action should be undertaken: promotion of the prudent use of antibiotics and prevention of the spread of resistant bacteria by hygienic measures [5]. Physicians are primarily responsible for the rational use of antibiotics. Together with all other health care workers who have contact with patients, they should apply the rules for infection control and hospital hygiene carefully.

Between September 2000 and May 2005 the AMRIN (Antimicrobial Resistance in Indonesia: Prevalence and Prevention) study was performed in the cities of Surabaya and Semarang on the island of Java, Indonesia, to address the problem of antimicrobial resistance in extramural and intramural health care.

The AMRIN study was a collaborative study of the University of Airlangga, Dr Soetomo Hospital in Surabaya, the Diponegoro University, Dr Kariadi Hospital in Semarang and three Dutch university centres, Leiden University Medical Centre, Erasmus University Medical Centre Rotterdam and Radboud University Medical Centre Nijmegen. The study was supported financially by a SPIN (Scientific cooperation programme Netherlands – Indonesia) grant from the Dutch Royal Academy of Arts and Sciences.

The AMRIN study investigated the following questions:

1. What is the prevalence and genetic basis of antibiotic resistance among bacteria in the Indonesian population inside and outside hospitals?
2. What is the level and quality of antibiotic usage in the Indonesian population inside and outside hospitals?
3. What is the correlation between antibiotic usage and the development of antimicrobial resistance?
4. Does the introduction of guidelines for antimicrobial usage, e.g. prophylaxis, improve the use of antimicrobial drugs in Indonesian hospitals?
5. Which time-proven measures for the prevention of the spread of bacteria and nosocomial infections are implemented in Indonesian hospitals?
6. Which preventive measures should be given priority in order to optimize infection control in Indonesian hospitals and does introduction of preventive measures improve infection control?

The AMRIN study was carried out in two phases. The first phase, in which the present situation of antimicrobial resistance, antibiotic use and infection control was surveyed, lasted from September 2000 to January 2003. Nose and rectal swabs for bacterial cultures, and information about antibiotic use were collected from three different groups of patients, i.e. patients visiting a public health centre (puskesmas), patients upon admission to the hospital and patients discharged after a stay of at least five days in the hospital. For the purpose of comparison similar microbiological cultures and information were collected from healthy family members who accompanied patients at the time of admission to the hospital. Susceptibility tests were performed on *Staphylococcus aureus* isolates from nasal swabs and *Escherichia coli* isolates from rectal swabs. Antibiotic use was quantified and the quality of use during hospitalization was assessed. Halfway through the study, in January 2003, a meeting was held at Solo on the island of Java, Indonesia, to discuss the preliminary results of the first phase and to choose targets for intervention studies during the second phase of the study, which lasted from February 2003 to May 2005. Intervention studies were performed to promote the prudent use of

antibiotics among patients with fever upon admission to the hospital, to improve antimicrobial prophylaxis for surgery, and to increase adherence to standard precautions.

The AMRIN study aimed at the development of a scientifically based, efficient, and standardized program for the assessment of antimicrobial resistance, antibiotic usage patterns, infection control measures and execution of interventions in Indonesian hospitals. The AMRIN study ended with a meeting in Bandung (May 2005), organized by the Indonesian Ministry of Health.

The present thesis reports on the studies on antibiotic use in extramural and intramural health care that address research questions two, three and four of the AMRIN study.

### **Outline of the thesis**

In chapter II a review of the literature on the use of antimicrobial drugs in low-income and developing countries is given. The relationship between antimicrobial resistance and antibiotic use, the biological mechanisms of resistance, antibiotic usage data, determinants of the prescription of antibiotics, the methodology to measure quantity and quality of antibiotic use, and strategies to promote the prudent use of antibiotics are discussed.

The survey of the level and diversity of antibiotic use in extramural health care is described in chapter III. Two groups of patients were interviewed: visitors of public health centres (puskesmas) and patients upon admission to the hospital. For comparison, as an approximation of antibiotic use in healthy individuals, family members who accompanied patients at the time of admission were included in this study. An analysis of demographic, socioeconomic and health care-related determinants of antibiotic use was performed.

Antibiotic use in the intramural health care setting was studied by evaluating antibiotic prescriptions for patients who had been admitted for at least five days to the hospital. The amount and type of antibiotics used were determined and the quality of antibiotic use was assessed by reviewers. Demographic and socioeconomic determinants for antibiotic use were investigated. The results are reported in chapter IV.

To determine the pharmaceutical quality of commonly used antibacterial drugs, drug samples purchased from different suppliers were analyzed by high performance liquid chromatography. Possible determinants of quality such as kind of supplier, manufacturer and registration as a generic or branded name product were explored. (Chapter V). Chapter VI describes risk factors for carriage of resistant *Escherichia coli* in all four study populations, i.e. visitors of puskesmas, patients upon admission to the hospital, family members accompanying these patients, and patients who had been admitted for at least five days to the hospital. In addition to recent antibiotic use, other relevant demographic, socioeconomic, health care-related and disease-related variables were analyzed for possible association with carriage of resistant *Escherichia coli* isolated from rectal swabs.

An intervention study to improve the prudent use of antibiotics in patients with fever upon admission was carried out in the Department of Internal Medicine of Dr. Soetomo Hospital in Surabaya. The multifaceted intervention included the development of a consensus guideline, the official proclamation of the guidelines by the head of the department, teaching and refresher sessions for residents, the introduction of blood cultures and evaluation of initial antibiotic therapy after three days using the results of the blood cultures. The results of this study are described in chapter VII.

In chapter VIII the results of these studies are summarized and discussed.

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