ANTIMICROBIAL RESISTANCE AND ANTIBIOTIC USE IN LOW-INCOME AND DEVELOPING COUNTRIES

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ABSTRACT

The threat to human health posed by antimicrobial resistance of bacteria is a worldwide and ever growing problem related to the use of antibiotics as is demonstrated by numerous examples of which some are discussed in this review. Resistant bacteria emerge by the selective pressure of antibiotics. Information about antibiotic use in developing countries is limited. We found quantitative data about 15 low-income and developing countries, and data about the appropriateness of antibiotic use of 3 countries. Important determinants of antibiotic use playing a role in prescribers, dispensers and customers are lack of knowledge of antibiotics, economic incentives, and marketing influences. A prerequisite for an adequate fight against ever increasing rates of resistance is information about the quantity and quality of antibiotic use. Methods to measure quantity and quality are discussed. The prudent use of antibiotics should be promoted. WHO has set a number of targets to improve antibiotic use, among which are changing behaviour of prescibers by introduction of guidelines and education about preferred antimicrobial therapy.

Keywords: *Anti-bacterial agent, hospital, community, developing country, Indonesia*

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INTRODUCTION

The threat to human health posed by antimicrobial resistance of bacteria is a worldwide and ever growing problem. Well-known resistant bacteria currently causing problems in many countries all over the world are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), penicillin-resistant *pneumococci*, extended-spectrum betalactamase (ESBL) producing *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter baumannii*, and multiresistant *Mycobacterium tuberculosis* (Guzman-Blanco et al. 2000; Stevenson et al. 2005). The emergence of resistance is driven by the use of antibiotics and transmission of resistant bacteria in health care settings (Austin et al. 1999; Tenover & Hughes 1996; Tenover & McGowan 1996). Of these two, antibiotic use is discussed in this review. Examples demonstrating the relationship between antibiotic use and resistance are given, and the biological mechanism underlying this relationship is discussed. A review of the literature about antibiotic use in low-income and developing countries is given, and determinants of antibiotic prescribing in these countries are mentioned. The methodology of measuring the quantity and quality of antibiotic use is described, after which the review focuses on improvement of antibiotic use and strategies to increase adherence to guidelines for the management of infections.

RELATIONSHIP BETWEEN RESISTANCE AND ANTIBIOTIC USE

Many examples illustrate the relationship between antibiotic use and antimicrobial resistance. Few years after the introduction of benzylpenicillin in 1941, penicillin resistance was noted among *gonococci* and *staphylococci* (Dillon & Yeung 1989; Kirby 1944; Lowy 2003). Likewise, shortly after the introduction of betalactamase-resistant penicillines in 1959 the first MRSA were reported (Jevon 1961). Apart from these observations showing a relationship between time of emergence of resistance and preceding introduction of an antibiotic, planned studies of the relationship between antibiotic use and antimicrobial resistance have been done in several ways. Surveillance of antibiotic use and bacterial resistance over long periods of time enables detection of trends in resistance and relationship to antibiotic use.

Looking for risk factors by multivariate analysis in retrospective or prospective studies is another possibility to investigate the relationship between antibiotic use and antimicrobial resistance (White 2005). A recent example of surveillance of resistance and antibiotic use over time showed that the incidence of MRSA in Aberdeen in the period 1996-2000 was related to the use of several classes of antimicrobial drugs (Monnet et al. 2004A). The incidence of MRSA was independently determined by the incidence of MRSA in the preceding month as well as by the use of macrolides, third-generation cephalosporins, and fluoroquinolones. A rise in use of macrolides, third-generation cephalosporins or fluoroquinolones of 10 DDD/1000 patient-days, or 30 more patients treated, increased MRSA prevalence by a factor of 2.84 after 8 months, 4.99 after 12 months, and 4.40 after 11 months, respectively.

In Finland, after restriction of macrolides for the treatment of respiratory tract and skin infections in outpatients, the consumption of macrolide antibiotics decreased from 2.40 DDD/1000 population per day in 1991 to 1.38 DDD/1000 population per day in 1992. This decrease was followed by a steady decrease in the frequency of erythromycin resistance among group A streptococcal isolates (Seppala 2006). Comparison of bacterial isolates obtained from patients of two haematology-oncology services with high and low fluoroquinolone consumption showed that fluoroquinolone resistance in *Escherichia coli* was significantly higher in the hospital with high consumption than the hospital with low consumption of fluoroquinolones (Kern et al. 2005). No such correlation was seen between fluoroquinolone use and fluoroquinolone resistance rates in *Pseudomonas aeruginosa* and *staphylococci*. This study showed that the impact of antibiotic consumption on the prevalence of resistance may differ between different pathogens. A Swedish study illustrates that the relationship between use of a specific antibiotic and prevalence of resistance against that antibiotic is not always straightforward. Whereas, increased use of quinolones in Sweden was followed some years later by increased ciprofloxacin and or norfloxacin resistance in most of the 12 hospitals investigated, cotrimoxazole resistance increased too despite a decreasing consumption of that antibiotic (Farra et al. 2002).

These few examples of many available, support the point that the emergence of antimicrobial resistance and the use of antimicrobial drugs are closely interlinked. Resistant bacteria emerge under the selective pressure of antibiotics, which are used to treat infections in humans in the community and in healthcare settings including nursing homes, short-stay departments, and hospitals. However, we should not forget that antibiotics are used also to treat animals, and are added to animal feed as growth promoters, which application contributes to the emergence of resistant bacteria. (Tenover & Hughes 1996).

BIOLOGICAL MECHANISM OF RESISTANCE

The concept of selective pressure refers to environmental conditions, which promote or inhibit the growth of bacteria with specific features. In the case of antimicrobial resistance, antibiotics permit the growth of resistant bacteria while inhibiting the growth of sensitive micro-organisms. The favoured bacteria have developed resistance through spontaneous mutation or by acquisition of genes coding for resistance, which can be located on a chromosome, plasmid, or transposon. Most resistance genes are carried on plasmids, which are extra chromosomal pieces of DNA. Plasmids can replicate within the bacterial cell but are limited in transfer between bacterial classes, i.e. not from gram-positive to gram-negative organisms. Transposons are pieces of DNA that have the ability to "jump" from plasmid to plasmid, chromosome to chromosome, or between plasmid and chromosome (transposition). Bacteria can exchange genetic information by transformation (the uptake of naked DNA), transduction (transfer of DNA by bacteriophage), and conjugation (cell-to-cell contact) (Tenover & Hughes 1996).

ANTIBIOTIC USE

A literature search of the English literature indexed in the PubMed and EMBASE databases was conducted for publications about antibiotic use in low-income and developing countries using the following MESH Terms: anti-bacterial agent/supply, developing country, pharmacology, therapeutic use, antibiotic prescription, utilization, Asia, Africa, South America, Caribbean region, Latin America. Low-income and developing countries were defined according to the World Bank's economic classifications (http://web.worldbank.org/data/countryclass/classgroups.htm (accessed 20 July 2006)).

Antibiotic use outside hospitals

Quantity

Eleven studies were found that reported about antibiotic use in non-hospitalized patients (Table 1). Eight of these studies retrieved information by reviewing medical records or prescriptions (Avci et al. 2006; Chukwuani et al. 2002; Moghadamnia et al 2002; Morikawa 2005;

Llanos-Zavalaga et al. 2002; Siddiqi et al. 2002; Stein et al. 1984; Teng et al. 2004). Three reports give information about antibiotic use by patients visiting a primary healthcare centre (Moghadamnia et al. 2002; Llanos-Zavalaga et al. 2002; Teng et al. 2004).The percentage of patients visiting a primary healthcare centre who were prescribed an antibiotic was 13.5% in Peru, 15% in Malaysia, however, much higher (61.9%) in Iran. Five publications reported about antibiotic use by patients who visited an outpatient clinic. (Avci et al. 2006; Chukwuani et al. 2002; Morikawa 2005; Siddiqi et al. 2002; Stein et al. 1984) In Zimbabwe (Stein et al. 1984), Nigeria (Chukwuani et al. 2002), Pakistan (Siddiqi et al. 2002), Afghanistan (Morikawa 2005), 47-57% of outpatients was treated with antibiotics. In Turkey this percentage was much lower, 2.8% (Avci et al. 2006). Two studies investigated the use of antibiotics by questioning people in the community about antibiotic use in a specified foregoing time period. In Vietnam 75% of children aged one to five years had used an antibiotic in the last month (Larsson et al. 2000).

In a household survey of 1659 families conducted in the outskirts of Mexico city, housewives were asked whether their family members had taken antibiotics during the previous two weeks. In this survey 5% of the subjects said that they had consumed at least one antimicrobial agent (Calva & Bojalil 1996). In the same study people buying medication in a pharmacy were asked about their purchases. Twenty-nine percent of the clients of the pharmacy had purchased an antibiotic, of which 57% was prescribed by a doctor. The rest was sold without a prescription. This percentage is much higher than that mentioned by the housewives who indicated that 9% of the antibiotics used was bought over the counter (OTC). In Vietnam the percentage of antibiotics obtained OTC was 78% (Larsson et al. 2000). Just one of the studies is based on sales data and expresses antibiotic use as DDD/1000 population-days. In Iran antibiotic use is 43.5 DDD/1000 population-days (Ansari 2001A) which is considerably above the levels of antibiotic use in the community in Europe (Goossens et al. 2005).

Quality

Two studies evaluated the quality of antibiotic use in non-hospitalized patients (Stein et al. 1984; Llanos-Zavalaga et al. 2002) (Table 2). In both studies prescriptions to outpatients were evaluated. The percentage of inappropriate prescriptions varied widely: in Zimbabwe 12.3% of prescriptions was inappropriate (Stein et al. 1984), and in Peru as much as 81.67% (Llanos-Zavalaga et al. 2002).

Antibiotic use inside hospitals

Quantity

Nine studies were found that give information about antibiotic use in hospitalized patients (Ansari 2001B; Chukwuani et al. 2002; de Castro et al. 2002; Hu et al. 2004; Hughes et al. 2005; Orrett 2001; Palcevski et al. 2004; Usluer et al. 2005; Wattal et al. 2005) (Table 3). Five of these studies obtained data by reviewing the medical records of admitted patients. (Ansari 2001; Chukwuani et al. 2002; de Castro et al. 2002; Hu et al. 2004; Orrett 2001) The percentage of patients who were treated with antibiotics during their stay in hospital varied from 44 in Trinidad & Tobago (Orrett 2001) to 96.7 in Nigeria (Chukwuani et al. 2002). Two cross-sectional studies performed in Malaysia and Turkey found a prevalence of antibiotic use of 44 and 30.6%, respectively. (Hughes et al. 2005; Usluer et al. 2005) Four studies quantified antibiotic use as DDD/100 patient-days. Antibotic use varied from 210.8 to 101.92 DDD/100 bed-days (Ansari 2001; de Castro et al. 2002; Wattal et al. 2005). In a paediatric clinic in Croatia antibiotic use was 28.96 DDD/100 patient-days (Palcevski et al. 2004).

Quality

Two studies evaluated the quality of antibiotic use in hospitalized patients (Aswapokee et al. 1990; Ayuthya et al. 2003) (Table 2). In one Thai study slightly less than 10% of patients had appropriate antibiotic therapy (Aswapokee et al. 1990). In another Thai study 13 years later 74.2% of prescriptions were appropriate (Ayuthya et al. 2003). In the last study only selected antibiotics with restricted use were assessed.

Antibiotic use in Indonesia

The literature search did not yield publications of Indonesia with general quantitative data about antibiotic use outside or inside hospitals. Some data about antibiotic use in specific patient groups are available. Patients presenting with mild upper respiratory tract infection received an antibiotic in 75-86% of the cases. Diarrhoea was treated with antibiotics in 73% of cases (Santoso et al. 1996). A study of physicians' prescribing behaviour for treatment of acute diarrhoea in young children in Jakarta showed that antibiotics were prescribed in 94% of cases, although most physicians believed that viral infections were a common cause of diarrhoea (Gani et al. 1991). Differences in the prescribing pattern according to the site of practice in private or government facilities were observed. The profits from expensive drugs compared to inexpensive drugs might have influenced the more frequent prescribing of more expensive antibiotics in the private facility. Furthermore, most practitioners who worked in government hospital or health centre, worked also in private sector making it difficult to assess how these two practice sites influenced physicians' behaviour in each of the settings (Gani et al. 1991).

DETERMINANTS OF ANTIBIOTIC PRESCRIBING

Determinants of antibiotic prescribing by health providers, dispensing of antibiotics, and community antibiotic use in low-income countries were recently summarized by Radyowijjati and Haak (Radyowijati and Haak 2003) (Table 4). From this review it appears that lack of knowledge about proper treatment of infectious diseases, economic motivations, and marketing of antibiotics are important determinants for prescribers, dispensers and patients. Some determinants influence prescribers and dispensers, such as the drive to meet patient demands and inappropriate examples by colleagues. Furthermore, prescribers are influenced by lack of laboratory results, and fear to miss a diagnosis and withheld therapy. Lack of regulation and enforcement of rules, and uncertainty about position in the health care system are determinants for delivery of antibiotics by dispensers. For customers inappropriate sources of information and folk beliefs about infectious diseases and antibiotic drugs determine antibiotic use, besides the determinants that are important for all the players in the field of antibiotic use. Many of the determinants mentioned are present in Indonesia, making it likely that antibiotic use will be high and often inappropriate.

MEASURING ANTIBIOTIC USE

A prerequisite for an adequate fight against ever increasing rates of resistance is information about the quantity and quality (appropriateness) of antibiotic use. Methods to obtain reliable data about the use of antibiotics are discussed in the next paragraphs.

Quantity of antibiotic use

Methodology

The quantity of antibiotic use in the community can be measured by interviews on antibiotic use during a past period (Calva & Bojalil 1996; Larsson et al. 2000). The weakness of this method is that people sometimes have forgotten what kind of drugs they took and how much. Another approach is to obtain data about antibiotic sales from several sources, e.g. the Institute Medical Statistics (IMS), Health Global Services. This private company gathers data from different sources including manufactures, wholesalers, pharmacies, prescribing doctors, and hospitals (Ansari 2001A; Goossens et al. 2005; Ho et al. 2004; Palcevski et al. 2004; Wattal et al. 2005).

In the setting of hospitalized patients and outpatients medical records are frequently used as source of information about antibiotic use. Medical records are usually screened for antibiotics after discharge of the patient. The problem with this retrospective assessment of antibiotic use is that often the use of antibiotics is not completely recorded in the medical records. Prospective measurement in the hospital is possible by regular follow-up of patients from admission until discharge. Patients, nurses, and doctors can be questioned about antibiotic use and/or medical and nursing records can be reviewed.

Unit of measurement

The quantity of antibiotic use in the community can be expressed by calculating the percentage of persons that used an antibiotic, or as the amount of antibiotics used expressed as Defined Daily Doses (DDD) per 1000 population per day which is an established measurement parameter (Monnet et al. 2004B). The DDD of a drug is the assumed average maintenance dose per day for a drug used for its main indication in adults. The ATC (Anatomical Therapeutic Chemical) classification system and the DDDs provide a fixed unit of measurement independent of price and formula enabling the researcher to asses trends in drug consumption and to perform comparisons between population groups. DDD are assigned by the World Health Organization Collaborating Centre for Drugs Statistics Methodology (http://www.whocc.no/atcddd/ (accessed July 15th, 2005)). Calculation of antibiotic DDDs is facilitated by the Antibiotic Consumption Calculator (ABCcalc) tool of the European Study Group on Antibiotic Policies (ESGAP) downloadable from the internet free of charge on: http://www.escmid.org/ (go to Science & Education, study group, ESGAP, Scientific issues) (accessed July 15th, 2006).

Quantification of antibiotic use in hospitals as DDD/100 patient-days is common practice. However, the number of DDD/100 patient-days does not fully address the selective pressure for resistance and is sensitive to changes in numbers of admissions and length of stay over time (Filius et al. 2005). A study of trends in antibiotic use in Dutch acute care hospitals in 1997-2001, showed that antibiotic use significantly increased from 47.2 to 54.7 DDD/100 patient-days whereas expressed in DDD/100 admissions it remained constant.

From these data is concluded that on average patients used the same number of DDD but were admitted to the hospital for a shorter period of time, resulting in an intensification of antibiotic therapy per patient-day. This study shows that for understanding trends in antibiotic use over time or comparison between hospitals or countries, data should not only be presented in DDD/100 patient-days. Information about the mean number of patient-days, the mean number of admissions, and the mean length of stay is mandatory (Filius et al. 2005; Verbrugh and de Neeling 2005).

Quality of antibiotic use

Methodology

Quality of antibiotic use can be assessed retrospectively by reviewing the medical records or relevant data extracted from the medical records. The appropriateness of individual prescriptions is evaluated using a flow chart (Figure 1) (Gyssens et al. 1992). The flow chart allows a standardized, general and complete assessment of the quality of an antibiotic prescription on many aspects of importance for an antibiotic. The method of the flow chart can be used in a review process by experts, but also by comparing use with a guideline on treatment of infectious diseases (van Kasteren et al. 2003; Mol et al. 2005). A problem with assessment by reviewers is, that there never will be full agreement between them (Gyssens et al. 1996). Assessment of adherence to guidelines does not guarantee better agreement. Mol et al. (2005) found that agreements between observers with regard to adherence of the prescriptions to guideline recommendations varied according to the different criteria applied. It was moderate concerning drug of choice (kappa=0.59), fair for duration of treatment (kappa=0.36), moderate for dosage (kappa=0.48), and fair for route of administration (kappa=0.37)

Unit of measurements

Quality of antibiotic use can be expressed as percentages of adequate or inadequate, appropriate or inappropriate prescriptions. By using a standardized flow-chart as shown in figure 1 a more detailed assessment is possible giving percentages of prescriptions correct regarding indication, choice, dose, and duration.

IMPROVING ANTIBIOTIC USE

To reduce the problem of antimicrobial resistance, action should be taken along two tracks: promotion of prudent use of antibiotics and prevention of the spread of resistant bacteria. Promotion of prudent use of antibiotics is discussed here. The principles of prudent use of antibiotics, and targets for improvement as defined by WHO are discussed. Improving antibiotic use must be achieved by changing the prescribing behaviour of doctors. Interventions to influence this behaviour are reviewed with special attention for the use of guidelines.

Prudent use of antibiotics

Prudent use of antibiotics is characterized by using narrow spectrum antibiotics on strict indication, adequately dosed, and not longer than necessary. Initial therapy may have a broad spectrum but should be adapted as soon as results of microbiological tests are known. A prudent antimicrobial policy is characterized by restriction of the number of effective antibiotics available as first choice treatment. Restriction of antibiotics, i.e. limiting the use of certain antibiotics or classes of antibiotics, can be achieved by applying strict guidelines with a limited number of antibiotics or by categorizing antibiotics in groups as non-restricted, restricted to senior clinicians, or to a group of expert consultants (Gyssens 1999).

Strict indication for antibiotic therapy begins with strict diagnosis of infections using clinical information and results of additional diagnostic investigations. Antibiotics should not be described for viral infections or self-limited diseases. The prescriber should have a specified goal for the antibiotic therapy like shortening the period of illness, preventing death or complications. Preferably, well conducted clinical trials should have shown that these goals are achievable indeed. Antibiotic prophylaxis in surgery is generally not indicated for clean operations.

The choice of an antibiotic is based on the documented or expected causative micro-organism(s). Knowledge about the prevalence of pathogens causing infections and their usual sensitivity pattern is indispensable for this purpose. The antibiotic with the narrowest spectrum is preferred because it has the least selective pressure for resistance. Starting therapy with broad spectrum antibiotics can be justified but in most cases for no longer than 48 hours until diagnostic tests have revealed the causative pathogen. Every empirically started therapy should be evaluated after 48 hours to see whether antibiotics should be continued or tailored to the laboratory results. Broadening the spectrum of antibiotic treatment is an accepted indication for combination of antibiotics. Other reasons for combination therapy are synergism (e.g. enterococcal endocarditis), and prevention of emergence of resistance (e.g. tuberculosis). Apart from these indications use of antibiotic combinations is unjustified. The dosage of antibiotics should be adequate according to the pharmacokinetic and pharmacodynamic features of the drug.

For many infections the optimal duration of treatment is not known. Duration of treatment is often based on tradition. (Gyssens 2001) For surgical prophylaxis the duration is at most 24 hours. In most cases only one dose given circa 30 min. before the incision suffices. A study of the treatment of community-acquired pneumonia by El Moussaoui et al. (2006) showed that 3 days amoxicillin treatment was not inferior compared with 8 days. Another study demonstrated the efficacy of short-course therapy (8 vs 15 days) for ventilator-associated pneumonia. Mortality was similar and there was a significant reduction in the emergence of resistance (Richards 2005). There is need for many more studies to determine the optimal duration of antibiotic therapy for a number of infections.

WHO targets

In the Global Strategy for Containment of Antimicrobial Resistance WHO indicates that the battle against antimicrobial resistance should be fought on many fronts: patients and the general community, prescribers and dispensers, hospitals, national governments and health systems, use of antimicrobials in food-producing animals, drug and vaccine development, pharmaceutical promotion, and international aspects of containing antimicrobial resistance (WHO 2001). Here, we mention in more detail the recommendations for interventions among prescribers and dispensers, and hospitals (tables 5 and 6). Education, development and implementation of guidelines, auditing of antibiotic use, adequate facility for microbiology, and effective infection control and therapeutic committees are the key elements from the WHO recommendations

Changing behaviour

To improve the use of antibiotics a major change in behaviour of prescribers of antibiotics is needed. Changing behaviour is possible, but not easy, and requires comprehensive approaches at different levels: individual doctors, teams of healthcare deliverers, hospital management, and national institutions (Grol & Grimshaw 2003). Several activities have proved very useful and effective in promoting rational drug use. Standard treatment guidelines, essential drug list, pharmacy and therapeutic committees, problem-based basic professional training, and targeted in-service education should be recommended as strategies to change behaviour of healthcare professionals. (Laing et al. 2001).

Clinical guidelines

The introduction of new or revised guidelines is a commonly used method to influence the behaviour of doctors. Physicians often acquire their antimicrobial prescribing habits from the practice of their colleagues, the recommendations of antibiotic handbooks, and from information provided by representatives of the pharmaceutical industry. Information from these sources may vary widely and conflict with what is considered best practice at an institution. Guidelines, when developed and introduced in a correct way, can tackle these problems (MacDougall and Polk 2005). Guidelines are systematically developed statements to help practitioners and patients to make decisions in specific clinical circumstances. They essentially define best practice (Campbell et al. 2003). "Appraisal of Guideline Research and Evaluation (AGREE)" is a valuable checklist to evaluate and to design the quality of a guidelines (AGREE 2001). In developing a guideline attention should be paid to a great number of factors determining the impact of a guideline: validity, reliability and reproducibility, clinical applicability, clinical flexibility, clarity, scheduled review, development team, implementation, dissemination and evaluation.

CONCLUSION

Increasing antimicrobial resistance presents a major threat to public health and causes great concern world wide. The problem calls for action at a local and global level, also in low-income and developing countries because they are no exception, although information about levels of resistance and antibiotic use from these countries are limited. Countries should develop programmes to measure resistance rates and quantity and quality of antibiotic use. The AMRIN study, which developed such a programme for hospitals in Indonesia, can serve as an example for other low-income and developing countries (AMRIN study group, 2005). Data about the quantity and especially quality of antibiotic use should guide the development of interventions to improve the prudent use of antibiotics, e.g. implementation of guidelines for the treatment of common infectious diseases. However, not only efforts to change the behaviour of prescribers of antibiotics are needed. Hospital directors and governments should attend to good laboratory facilities, well-functioning antibiotic therapy committees and infection control committees, and microbiological and infectious disease consultation facilities, which all are indispensable for an adequate fight against resistant bacteria.

Table 1. Quantity of antibiotic use in non-hospitalized patients

Author	Country	Time of data collection	Method	Population	% of population using antibiotic	DDD/ 1000 population-days	Prescriber
Stein et al. 1984	Zimbabwe	Not reported	Review medical records	Outpatients	54.3	-	Nurse
Calva and Bojalil 1996	Mexico	1989 -1990	Interview of housewives about drug use in preceding 2 weeks	Families in peri-urban area	5	-	Doctor 81% OTC 19%
				Customers of pharmacy	29	-	Doctor 57% OTC 43%
Larsson et al. 2000	Vietnam	1999	Questionnaire antibiotic use preceding month	Children 1-5 years old	75	-	Doctor 22% OTC 78%
Ansari 2001A	Iran	1997-1998	Review whole-sale database	General population	-	43.5	Not reported
Chukwuani et al. 2002	Nigeria	1999	Review prescriptions	Outpatients	50.3	-	Doctor
Siddiqi et al. 2002	Pakistan	1998	Observation of prescription and dispensing practices	Outpatients	57	-	Doctor and nurse
Llanos-zavalaga et al. 2002 (Abstract)	Peru	2001	Review prescriptions	Primary care clinic	13.5	-	Doctor
Moghadamnia et al. 2002	Iran	2000	Review prescriptions	Primary care clinic	61.9	-	Doctor
Teng et al. 2004	Malaysia	2002	Review prescriptions	Primary care clinic	15	-	Doctor
Morikawa 2005	Afghanistan	2002	Review medical records	Outpatients	47	-	Not reported
Avci et al. 2006	Turkey	2004	Review prescriptions	Outpatients	2.48	-	Not reported

OTC = over the counter

Table 2. Quality of antibiotic use in non-hospitalized and hospitalized patients

Author	Country	Time of data collection	Data sources	Assessment	Population	Prescriptions appropriate (%)	Prescriptions inappropriate (%)
Non-hospitalized patients							
Stein et al. 1984	Zimbabwe	Not reported	Medical records	Reviewers	Outpatients	57.5	12.3
Llanos-zavalaga et al. 2002 (Abstract)	Peru	2001	Not reported	Reviewers	Outpatients	-	81.67
Hospitalized patients							
Aswapokee et al. 1990	Thailand	1985	Medical records	Guideline (Kunin criteria)	Teaching hospital	9.8 (of patients)	91.2 (of patients)
Ayuthya et al. 2003	Thailand	2000	Medical records	Infectious diseases specialist	Teaching hospital	74.2	25.8

Table 3 Quantity of antibiotic use in hospitalized patients

Author	Country	Time of data collection	Method	Population	% of population using antibiotic	DDD/ 100 patient-days
Ansari 2001B	Iran	1997	Review medical records	Teaching hospital	-	101.92
Orrett 2001	Trinidad & Tobago	1997	Review medical records	Teaching hospital	Total 44 Orthopaedics 79.4 Paediatrics 70.8 Obstetrics & Gynaecology 64	-
De Castro et al. 2002	Brazil	1990-1996	Review medical records	Tertiary hospital	-	1990: 83.8 1996: 124.58
Chukwuani et al. 2002	Nigeria	1999	Review medical records	General hospital	96.7	-
Hu et al. 2004	China	1997	Review medical records	University hospital	77.8	-
Palcevski et al. 2004	Croatia	2000	Database of hospital pharmacy	Children 0-15 years old	-	28.96
Wattal et al. 2005	India	2001	Consumption data from hospital bulletin	Tertiary hospital	-	210.8
Hughes et al. 2005	Malaysia	1999	Cross sectional study	Tertiary hospital	44	
Usluer et al. 2005	Turkey	2002	Cross sectional study	Tertiary hospital	30.6	

Table 4. Determinants of antimicrobial use in developing world*

Determinant	Prescriber	Dispenser	Customer, patients, or community members
Lack of knowledge on antibiotics and therapeutics	X	X	X
Lack of trust in or delayed laboratory results	X		
Desire to meet patient demand	X	X	
Fear of clinical failure, desire to stay on safe side	X	(X)	
Economic incentives/considerations	X	X	X
Unstable or inadequate drug supply	X		
Inappropriate peer norm / poor modeling by seniors or local physicians	X	X	
Marketing influences	X	X	(X)
Folk beliefs and traditions on antibiotic use	X	(X)	X
Lack of regulation and enforcement		X	
Unclear role as health care providers		X	
Use of trained and untrained sources of advice			X
Gender preferences			X
Lack of access to appropriate health care			(X)
Diagnostic uncertainty	(X)		
Inadequate supervision	(X)	(X)	
Inadequate infection control	(X)		
Limited communication skill	(X)	(X)	

* Compiled from Radyowijati & Haak 2003
X: determinant present, references available;
(X): determinant present, no references available

Table 5. WHO recommendations to improve antibiotic use targeted to prescribers and dispensers

Recommendation for intervention
Education on: 1. the importance of appropriate antimicrobial use and containment of antimicrobial resistance 2. disease prevention and infection control issues 3. accurate diagnosis and management of common infections 4. instruction of patients on antimicrobial use and the importance of adherence to prescribed treatment 5. factors that may strongly influence prescribing habits, such as economic incentives, promotional activities and inducements by the pharmaceutical industry
Management, guidelines and formularies 1. supervision and support of clinical practices, especially diagnostic and treatment strategies 2. auditing of prescribing and dispensing practices 3. utilization of peer group or external standard comparisons to provide feedback and endorsement of appropriate antimicrobial prescribing 4. encouragement of development and use of guidelines and treatment algorithms 5. empowerment of formulary managers to limit antimicrobial use to the prescription of an appropriate range of selected antimicrobials
Regulation Linkage of professional registration requirements for prescribers and dispensers to requirements for training and continuing education

Table 6. WHO recommendations to improve antibiotic use targeted to hospitals.

Recommendation for intervention
Hospitals management
1. establishment of infection control programmes, with the responsibility for effective management of antimicrobial resistance in the hospitals
2. establishment of effective hospital therapeutics committees with the responsibility for overseeing antimicrobial use in hospitals
3. development and regularly updating of guidelines for antimicrobial treatment and prophylaxis, and hospital antimicrobial formularies
4. monitoring of antimicrobial usage, including the quantity and patterns of use, and feedback of results to prescribers
Diagnostic laboratories
1. ensuring access to microbiology laboratory services
2. ensuring performance and quality assurance of appropriate diagnostic tests, microbial identification, antimicrobial susceptibility tests of key pathogens, and timely and relevant reporting of results
3. ensuring that laboratory data are recorded, preferably on a database, and are used to produce clinically and epidemiologically useful surveillance reports to resistance patterns among common pathogens and infections in timely manner with feedback to prescribers and to the infection control programme
Interactions with the pharmaceutical industry
Supervision of pharmaceutical company promotional activities within the hospital environment

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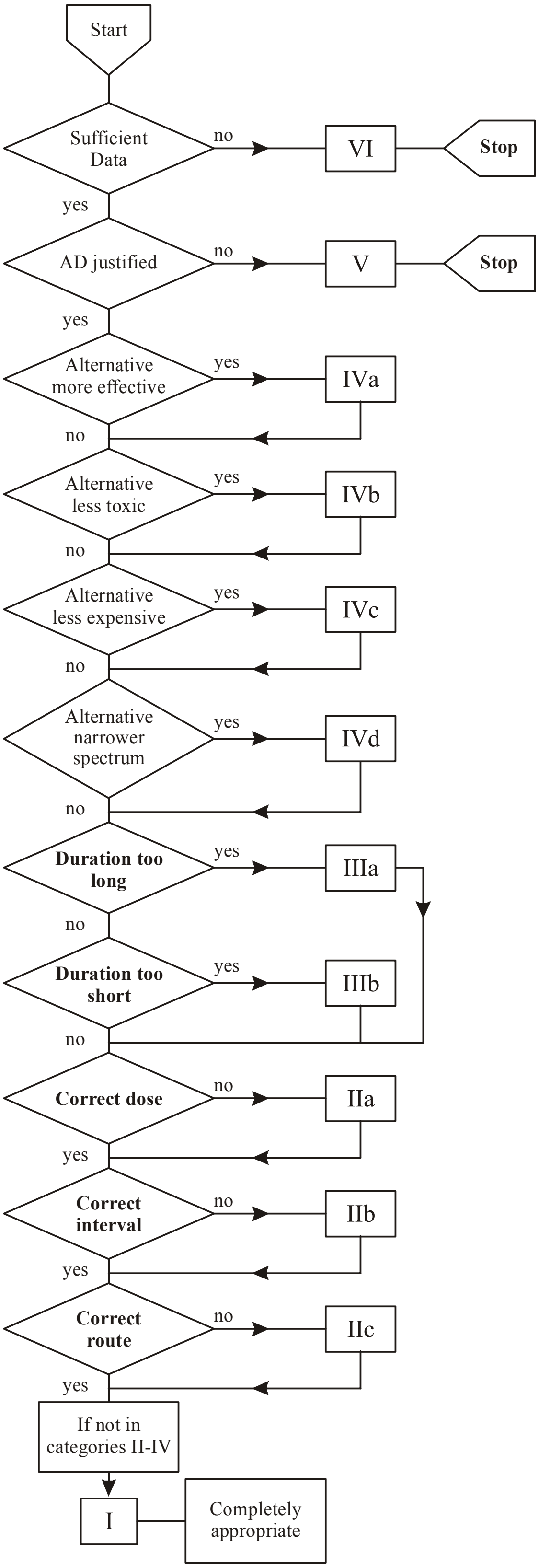

Figure 1. Flow chart for quality-of-use evaluation of antimicrobial drug prescription

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