From Division of International Health (IHCAR), Department of Public Health Sciences Karolinska Institutet, Stockholm, Sweden

ANTIBIOTIC USE AND RESISTANCE

ASSESSING AND IMPROVING UTILISATION AND PROVISION OF ANTIBIOTICS AND OTHER DRUGS IN VIETNAM

Mattias Larsson

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ABSTRACT

**Background:** In Vietnam there were shortages of drugs until the end of the 1980’s. In 1986 the "Doi Moi" economic reforms towards market economy were initiated. An expanding private health care sector emerged and the per capita drug consumption has increased dramatically.

**Aim:** To assess drug provision in the public and private sectors, antibiotic use and resistance in the community, as well as the effect of an intervention package aimed at improving case management in private pharmacies in Vietnam.

**Methods:** Drug utilization was assessed in 6 provinces using 2400 prescriptions, 1200 drugs, 200 interviews with doctors and 200 medical records (I). Community antibiotic use and bacterial resistance was assessed among 200 children 1-5 years of age in the rural Bavi district using a questionnaire and disc diffusion tests (II). Antibiotic prescribing was assessed in relation to serum levels of C-reactive protein among 100 children 1-6 years who received antibiotic treatment (III). A randomized control trial assessed the effect of an intervention package (enforcement of regulation, education and peer influence) on case management of childhood mild respiratory infection, male sexually transmitted disease and dispensing of prescription only drugs (antibiotics and steroids) in 60 private pharmacies in Hanoi. Knowledge was assessed through interviews with a structured questionnaire pre and post intervention and practice through simulated client method with five encounters per pharmacy after each intervention (IV, V & VI).

**Results:** Essential drugs were available in remote areas. The average number of drugs per prescription was high and injections were common (I). In Bavi 75% of the children had been treated with antibiotics within one month preceding the study, most commonly ampicillin, penicillin or amoxicillin. Of the carers deciding on treatment 67% consulted a drug seller, 22% a doctor and 11% decided themselves. Of the antibiotics 80% were purchased from private drug outlets. Of *S. pneumoniae* and *H. influenzae* 90% and 68% were resistant to at least one antibiotic, respectively (88% and 32% to tetracycline, 32% and 44% to trimethoprim/sulphonamide and 25% and 24% to chloramphenicol, respectively). There was a significant difference in ampicillin and penicillin resistance between the group of children previously treated with beta lactam antibiotics and the group of children not having received antibiotics (II). Elevated CRP concentrations (>10 mg/L) were detected in only 17% of the children who had received antibiotic prescription (III). Of the pharmacy staff 20% stated that they would dispense antibiotics for a child with cough, in practice 83% of the pharmacies did. Fifty-three percent stated that they would ask the patient questions related to breathing, in practice 10% did; Eighty one percent stated that antibiotics are not effective in short courses, in practice 47% dispensed for courses less than 5 days. Only 36% of the cases were handled according to guidelines (IV). Compliance with the prescription regulation was weak. Sixty percent said that they would not dispense steroids without prescription. In practice all but one pharmacy did (V). The intervention pharmacies improved significantly compared to the control pharmacies in all tracer conditions. For mild respiratory infections, antibiotic dispensing decreased and questions regarding rapid breathing increased. For sexually transmitted diseases, advice to go to the doctor and dispensing the correct symptomatic treatment increased. Dispensing of prednisolone and cephalexin decreased and prescription requests increased (VI).

**Conclusion:** Considering the common practice of self-medication with antibiotics through private pharmacies and high levels of antibiotic resistance there is a need to improve drug utilization and provision in Vietnam. Promoting Good Pharmacy Practice standards towards improving case management in private pharmacies is likely to have a major public health impact.
**Background:** Vietnam has been progressive in dealing with basic health problems and achieved a comparably low infant mortality rate and high life expectancy. In the late 1980’s there were shortages of drugs after a period of isolation from the international community and a costly post war reconstruction. In 1986 an economic reform, the “Doi Moi” renovation towards market economy, was initiated. Between 1986 and 1994 there was a three-fold increase in drug production, ten-fold increase in drug imports and a six-fold increase in per capita drug consumption. A rapidly expanding private health care sector has emerged now acting as an important source of primary health care.

**Main Objective:** To assess drug utilization in public and private sector, antibiotic use and resistance in the community as well as the effect of an intervention package to improve case management in private pharmacies in Vietnam.

**STUDY I** Pharmaceutical Sector in transition – A cross sectional study in Vietnam.

- To assess availability/affordability of drugs and rational use of essential drugs (ED) in Vietnam.

**STUDY II** Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community.

- To investigate antibiotic use and antibiotic susceptibility of respiratory tract pathogens in children 1 to 5 years of age.

**STUDY III** Assessing routine antibiotic prescribing in relation to C-reactive protein in capillary blood of children in rural Vietnam.

- To assess antibiotic use prescribing in relation to bacterial infection by measuring CRP.

**STUDY IV** Case management of Childhood ARI at Private pharmacies in Hanoi

- To assess the knowledge and practice regarding case management of ARI at private pharmacies.

**STUDY V** Private pharmacy staff in Hanoi dispensing steroids

- To assess the private pharmacy compliance to prescription regulation in relation to provision of Steroids.

**STUDY VI** Improving Private pharmacy practice: a multi intervention experiment in Hanoi.

- To evaluate the impact of an intervention package including Enforcement of regulation, Education and Peer Influence on private pharmacy practice.

4800 Client Encounters assessing case management of Childhood ARI, STD and dispensing of prescription only drugs

**Variables**

<table>
<thead>
<tr>
<th>Antibiotics dispensed</th>
<th>BL</th>
<th>PI</th>
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<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathing Questions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptable Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go to a doctor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question sexual activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advised condom use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP in diarrheal episode</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Pre cri 
| Pre prescription request |    |    |
| Prescri 
| Sto teriods dispensed |    |    |

**Antibiotic Resistance:** High levels of antibiotic resistance and multi-resistant strains among respiratory pathogens (%).

**Conclusion:**

- These findings identify priorities for action to improve the present situation in relation to rational use of drugs.

- Significantly - less prescription only drugs dispensed on request without prescription; - less antibiotics dispensed without indication; - improved Case management of ARI and STD

**Results**

- **Conclusion:** Considering the high proportion of irrational self-medication through private pharmacies and high levels of antibiotic resistance there is a need to improve drug utilization in Vietnam. Integration of private pharmacies in the health care sector through appropriate support with updated information and pharmacy treatment guidelines may contribute to contain antibiotic resistance, improve ARI and STD case management and avoid waste of resources.
LIST OF PUBLICATIONS

This thesis is based on the following papers:


The original papers are printed in this thesis with permission from the publishers.

The papers will be referred to by their roman numerals: I-VI.
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<th>Description</th>
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<tbody>
<tr>
<td>ARI</td>
<td>Acute Respiratory Infection</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>CHC</td>
<td>Community Health Centre</td>
</tr>
<tr>
<td>CRP</td>
<td>C - Reactive Protein</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Doses</td>
</tr>
<tr>
<td>ED</td>
<td>Essential Drug</td>
</tr>
<tr>
<td>GPP</td>
<td>Good Pharmacy Practice</td>
</tr>
<tr>
<td>HCMC</td>
<td>Ho Chi Minh City, Vietnam</td>
</tr>
<tr>
<td>IHCAR</td>
<td>Division of International Health at the Department of Public Health Sciences, Karolinska Institutet, Sweden</td>
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<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-the-counter</td>
</tr>
<tr>
<td>SCM</td>
<td>Simulated Client Method</td>
</tr>
<tr>
<td>Sida</td>
<td>Swedish International Development Cooperation Agency</td>
</tr>
<tr>
<td>STD</td>
<td>Sexually Transmitted Disease</td>
</tr>
<tr>
<td>STG</td>
<td>Standard treatment guidelines</td>
</tr>
<tr>
<td>TM</td>
<td>Traditional Medicine</td>
</tr>
<tr>
<td>UNDP</td>
<td>United Nations Development Program</td>
</tr>
<tr>
<td>USD</td>
<td>United States Dollar</td>
</tr>
<tr>
<td>VND</td>
<td>Vietnamese Dong</td>
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</table>
GENERAL OBJECTIVES

To assess and improve drug utilization and provision in Vietnam with a focus on antibiotic use and resistance in the community and interventions to improve private pharmacy case management.

SPECIFIC OBJECTIVES

I. To assess the availability, affordability and rational use of essential drugs (ED) in Vietnam (Study I).

I. To investigate antibiotic use and antibiotic susceptibility of respiratory tract pathogens in children 1 to 5 years of age in Bavi, Vietnam (Study II).

I. To assess antibiotic prescribing in relation to serum C-reactive protein (CRP) among children who received antibiotic treatment in the Bavi health care (Study III).

I. To describe the knowledge and practice regarding case management of mild acute respiratory infection in children at private pharmacies in Hanoi (Study IV).

I. To investigate the knowledge and practice of drug sellers in private pharmacies in relation to provision of prednisolone, a prescription-only drug (Study V).

I. To assess the effectiveness of an intervention package on drug provision in private pharmacies through a randomized control trial (Study VI).
INTRODUCTION

During the last century, health has improved worldwide, in terms of decreased infant mortality rate and increased life expectancy. However, in low-income countries, infectious diseases, that could be prevented if diagnosed and treated, still account for 45% of the mortality (WHO, 2001). Availability and affordability of drugs is crucial in order to achieve improved health among the poorest. Vietnam has been progressive in dealing with basic health problems, and has achieved a comparably low infant mortality rate and high life expectancy (World Bank, 2001). In the late 1980’s, there were shortages of drugs after a period of isolation from the international community and a costly post-war reconstruction. In 1986, an economic reform, the "Doi Moi” renovation towards market economy, was initiated. Between 1986 and 1994, there was a three-fold increase in drug production, ten-fold increase in drug imports and a six-fold increase in per capita drug consumption (Witter, 1996). A rapidly expanding private health care sector has emerged, now acting as an important source of primary health care.

Antibiotics are among the largest group of drugs used and have, in combination with immunization and improved hygiene, contributed to decreased mortality in infectious diseases (Col & O’Connor, 1987). In low-income countries, the high number of patients, lack of time, small resources and lack of laboratory tests make it difficult to clinically distinguish bacterial from viral infection (Kunin, 1993). Physicians often feel compelled to prescribe antibiotics to prevent treatment failure due to possible undetected, sub-clinical, or secondary bacterial infection (Hardon, 1987). Self-medication through pharmacies is a low-cost alternative compared to consultation with physicians as it obviates consultation fees and waiting times and has been widely reported in low-income countries (Kunin, 1983; Etkin et al., 1990; Paredes et al., 1996; Ross-Degnan et al., 1992; Tomson & Sterky 1986; Igun, 1987). However, the competence of pharmacy staff to diagnose and treat, or to know when to refer to a doctor, is often insufficient (Kamat & Nichter, 1998). Most of the antibiotics are used to treat respiratory infections, that - in up to 80% of the cases - have a viral aetiology (Tupasi et al., 1990a).

Antibiotics use suppresses the susceptible flora and selects for antibiotic resistant bacterial stains (Halloran & Struchiner, 1995). Increased bacterial resistance is endangering the therapeutic effectiveness of antibiotics, increasing the amount of treatment failures, and as a result, leading to longer and more severe illness episodes with higher costs and mortality rates (WHO, 2001). This is a world-wide problem, which is particularly serious in low-income countries, where many of the affordable antibiotics have become powerless due to resistance, and where the cost of newer, broad-spectrum antibiotics is a burden (O’Brien, 1992), especially for the poor, who cannot afford good medical care and expensive new antibiotics (WHO, 2001).

In high-income countries, self-medication with antibiotics is prevented by easy access to affordable health care and strict regulations regarding prescription-only drugs. However, in low-income countries enforcement of prescription regulation may exclude the poorest from accessibility of drugs, leading to increased vulnerability to infectious diseases. On the other hand, if drugs can be purchased without restrictions, the affordable antibiotics may soon be useless. To empower those who provide drugs, e.g. private pharmacy staff, to make simple diagnostic evaluations and detect danger signs and when relevant refer to physician in accordance with Good Pharmacy Practice (GPP) may be a useful strategy.
BACKGROUND

VIETNAM

Vietnam's history has been characterized by a long struggle for autonomy. Chinese domination, which lasted a millennium, was thrown off in the 9th century. External control was imposed once again in the mid-19th century, when Vietnam was occupied by the French.

French rule lasted until World War II, when the country was invaded by Japan. At the war’s end in 1945, the Viet Minh, which had led the resistance movement against the Japanese, founded the Democratic Republic of Vietnam, and declared the country's independence. The French Indochina War continued until France admitted defeat in 1954, and the Geneva Accords left Vietnam divided into a northern and a southern part.

In the north, an ambitious health care policy was adopted, stating the right of all citizens to health care and provision of free medical examinations and treatment. A highly structured and centralized health care service was developed. The local primary health care system was based on small community health centres “Tram Y Te”, financed by agricultural cooperatives. These were engaged to implement national public health programs such as vaccination campaigns. The health care system was heavily subsidized with all drugs and services supplied free of charge (Witter, 1996). This was done before the primary care ideology had been formulated in Alma Alta in 1978 (Valdelin et al., 1992; Guldner, 1995). In South Vietnam, a strong private health sector dominated until the reunification in 1975.

In 1964, the tension between the north and the American-sponsored south mounted, and war erupted. The effects of the American War 1965-1975 impaired the health system’s ability to provide basic health care, despite heavy subsidization by the North Vietnamese government. The drug production capacity was not capable to meet the inflated demand, which lead to constant shortages of essential drugs. The drugs produced in Vietnam and donated from the Eastern block were often of poor quality. The centralized distribution system prioritized the military forces. Those affected by the shortage were mostly civilians.

In 1973, the U.S. withdrew its troops, and on the 30th of April 1975, the American War ended, and the country was unified. Measures were taken to rapidly unify the economic
systems of the north and the south. Consequently, the centralized plan-economic system of
the north was also implemented in the south, and private enterprises, including health care
services, were closed. Although public health care expansion was rapidly initiated, full
coverage was never achieved due to economic constrains. The liberation of Cambodia from
the Pol Pot regime and the Chinese invasion placed even more constraints on the already
strained economy. The strong emphasis on job security and equal living standards at the
expense of promotion of individual efforts undermined people’s work incentives (UNDP,
2001). In early 1978, thousands of people began to escape from Vietnam in search of a more
prosperous life elsewhere (Bloom, 1998).

Despite the isolation from the international community, low economic growth rate of 0.4 %
per year between 1975 and 1980 and a costly post war reconstruction process, Vietnam
managed to sustain a fairly good educational and health care system. Health indicators such
as the infant mortality rate and the life expectancy rate improved, reaching better levels then
in most comparable countries (Chalker, 1995). In the late 1980’s, when the assistance from
the USSR declined, and inflation rates soared, the financial support to the health sector was
substantially reduced. As a consequence tremendous shortages of drugs appeared (Chalker,
1995).

The “Doi Moi” economic reforms

In 1986, the Vietnamese government initiated an economic reform program “Doi Moi”,
putting Vietnam on the road from plan economy to market economy. There was a return to
household-based farming in agriculture, a removal of restrictions on private sector activities
in commerce and industry, an end to price regulation and subsidizing of state-owned
companies, openness to foreign trade and decentralization of decision-making to managers
of state-owned enterprises (Chuc, 2002). The renovation increased choices and opportunities
to generate and increase incomes, and the poverty incidence has been reduced from over
70% in the mid 80’s to 37% in 1998 (UNDP, 2001).

The impact of the “Doi Moi” renovation policies on the health care sector was dramatic. The
agricultural work brigades, which had financed community health care, including drugs,
disappeared. The Peoples’ committees had to take over the responsibility for health care
funding. Due to lack of resources, the quality of health services, fell drastically. As the
commune health centres approached collapse, the government took over the responsibility
for salaries to employees. User fees for health services at public hospitals were introduced.
The system of free dispensing of drugs through the public health care system was abolished.
Revolving drug funds were introduced, where a batch of Essential drugs (EDs) is purchased
initially, and the capital earned from sales is reinvested in new drugs, (World Bank, 2001).
Private practice was allowed, including the establishment of private pharmacies. The
pharmaceutical industry and drug retail were liberalized. State-owned pharmaceutical
companies were given the freedom to make their own decisions, and could no longer rely on
state subsidies (World Bank, 2001). Pharmacists were allowed to open retail pharmacies,
and the pharmaceutical market shifted from publicly financed to private enterprise. The
reforms also had profound effects on household health-seeking behaviour, as out-of-pocket
spending for health care increased, as did the utilization of the private sector, including
private pharmacies. Health transactions between providers and consumers have evolved
from bureaucratic management and subsidized health care to free and virtually unregulated
market exchanges (Chalker, 1995).
THE VIETNAMESE HEALTH SITUATION

Vietnam has experienced an epidemiological transition with a major decline in the proportion of communicable diseases. In 1986, communicable diseases accounted for 52%, in 1997 for 27%, of total mortality. Few reliable estimates of pre-1989 infant mortality exist. However, various sources of existing data indicate a steep decline from about 160 per 1000 live births in 1960, to 44 in 1993. Maternal mortality has declined from 200 in the 1980's to 160 in the year 2000. (World Bank, 2001). These health indicators are better than in most comparable countries (Chalker, 1995).

Factors that may have contributed to these improvements include the steady annual rate of economic growth of 5-7%, the reduction of poverty, and an increase in the average food consumed per capita of 25%. Good vaccination coverage and dramatically decreased incidence of vaccine-preventable diseases also play an important role. The increased per capita consumption of drugs including antibiotics, enabling improved treatment of childhood diseases, may also have contributed to the decrease in the share of infectious diseases.

Despite the fact that a majority of the population has benefited from the economic growth a significant proportion of the population still lives in poverty, especially in remote mountainous areas in north and central Vietnam. About 35% of children under five are still undernourished (World Bank, 2001). This is an indication of the inequity in the distribution of economic growth with an increase of Gini index from 0.3 in 1984 to 0.41 by 2000 (UNDP, 2001).

**Acute respiratory infection (ARI)**

Acute respiratory infections (ARIs) are the leading cause of morbidity and mortality among children in low and middle-income countries, accounting for 3.5 million deaths worldwide during 1998 (Shann, 1995). Studies indicate, that up to 80% of the ARI episodes has a viral aetiology (Tupasi et al., 1990b; Muhe, 1994; Khan et al., 1993). Viral, lower respiratory-tract infections are in most cases self-limiting, and no treatment is necessary (van Woensel, 2003). The most common viral pathogens are respiratory syncytial virus (RSV), adenovirus, parainfluenza and Influenza A and B viruses. The most common bacterial pathogens are *H. Influenzae* and *S. Pneumoniae*, that cause a range of infections, most commonly pneumonia,
but also more severe diseases such as meningitis and sepsis (Muhe, 1994). Secondary bacterial infection is also common after viral infections, especially influenza and measles.

Since ARI can be caused by a variety of organisms, the ideal approach would be to find the causative agent in each case, so that appropriate treatment could be given. However, both viral and bacterial ARI present roughly the same clinical symptoms, making it difficult to clinically differentiate between bacterial and viral infection (Kunin, 1993). Bacterial cause can only be established through lung or pleural aspiration, an invasive procedure involving the risk of serious complications, or by blood cultures, which are only positive in a portion of cases (Muhe, 1994). In children, radiology is an unreliable method for determining the aetiology. Laboratory tests such as C-reactive protein (CRP) can be used to discriminate bacterial from viral aetiology (Babu et al., 1988; Peltola & Jaakkola, 1988; Hansson et al., 1995). However, this method is usually unavailable in low- and middle-income countries. While bacterial infections can kill, treating viral illness with antibiotics is not only ineffective, but contributes to the development of resistance as well (van Woensel, 2003).

In Vietnam, ARIs are still among the leading causes of morbidity. In 1998, there were nearly 450,000 hospitalized cases of pneumonia and acute bronchitis. It is also a major cause of mortality, accounting for 2195 hospital deaths in that year (MoH, 2000). In rural Vietnam, children under five years of age are reported to suffer four to seven episodes of respiratory diseases annually. The corresponding figure in urban areas is three to five episodes (Chinh & Hiep, 1995). In a study among preschool children in Hanoi, high carrier rates of H. Influenzae serotype B (HIB), causing epiglottises and meningitis, has been detected (Törnquist et al., 2000). HIB vaccination is not yet part of the Vietnamese vaccination schedule.

In 2000 pneumonia was the most common cause of hospital mortality. The distribution is however uneven throughout the country. In the northern highlands with a high percentage of indigenous people and low-income per capita hospital mortality due to pneumonia is high. In Ha Tay province there is a comparably low mortality, probably due to the proximity to Hanoi hospitals. The real difference might however be larger, as there might be a difference in how big percentage of the infection related mortality that occurs in hospitals. In the urban areas it was estimated that 90% of the pneumonia related mortality occurred at hospitals, for rural and remote areas 50% and 30%, respectively. The real pneumonia related mortality would be 15/100,000 in Lai Chau, 2.2 in Ninh Binh and as stated in Hanoi and HCMC (MoH, 1993-2000).

<table>
<thead>
<tr>
<th>Province</th>
<th>Mortality per 100,000</th>
<th>Area</th>
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<tbody>
<tr>
<td>Lai Chau</td>
<td>5.4</td>
<td>Northern highlands</td>
</tr>
<tr>
<td>Hoa Binh</td>
<td>4.2</td>
<td>Central coast</td>
</tr>
<tr>
<td>Khanh Hoa</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Hanoi</td>
<td>2.5</td>
<td>Major urban areas</td>
</tr>
<tr>
<td>HCMC</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Ninh Binh</td>
<td>1.1</td>
<td>Red river delta</td>
</tr>
<tr>
<td>Ha Tay</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Source: MoH, 1993 - 2000

Health care workers in low- and middle-income countries often have to make treatment decisions without laboratory tests. To help in making such decisions, WHO has developed assessment and treatment algorithms, based on clinical signs distinguishing pneumonia from other causes of ARI (Walsh & Warren, 1979). Several studies have concluded that fast breathing is a sensitive and specific indicator of pneumonia (Mulholland et al., 1992). A child aged 2 month to 2 years with a respiratory rate higher then 50 per minute, or aged over one year, and with a respiratory rate over 40 and a cough, is classified as suffering from pneumonia, and should receive antibiotic treatment. Danger signs for very severe disease include intercostal retractions, not being able to drink, convulsions, modified consciousness,
having stridor when calm, and suffering from severe malnutrition. Appropriate case management can avert most deaths of ARI, but only if families seek care promptly from a trained health worker (Muhe, 1994). From this perspective, it is important to educate both the community and first line health care workers to recognize these signs.

**Sexually transmitted diseases (STDs)**

Urethritis in men usually presents with urethral discharge and pain when urinating, is primarily caused by gonococcal and/or chlamydial infections (Crabbe et al., 2000). Gonorrhoea and other sexually transmitted diseases (STD) are important co-factors in the transmission and spread of HIV. Studies show that co-infection STDs such as gonorrhoea increase the risk of HIV transmission during a single act of intercourse by up to 50 times (Bond, 1992).

In Vietnam, there were 119,188 reported cases of sexually transmitted diseases (STDs) in 1998, of which 6859 were gonorrhoea, 3088 were syphilis, and 108,152 were chlamydia and other STDs, (AIDS Wkly., 2000). The first case of HIV infection was reported in 1990, and by the end of 2000, 33,747 positive HIV cases had been detected. Among the HIV positives, 5,120 had AIDS, accounting for 2,764 deaths (MOH, 2000). However, there seems to be a large number of undetected cases; by the end of 2000, it was estimated that between 135,000 and 160,000 had contracted HIV, and 14,000-21,000 people had developed AIDS (AIDS Wkly., 2000).

Condom use is the most effective method to reduce the spread of STDs and HIV (d'Cruz-Grote, 1996). Interviews with male STD patients in the Mekong Delta showed, that it is common to visit commercial sex workers, and that married men were as likely as single men to have casual partners. Furthermore, only 7% of men used condoms consistently, and 70% had never used them. Prevention programs for STD in Vietnam need to focus on improving condom use (Thuy et al., 1999).

Prompt and effective treatment of urethritis does not only prevent complications and sequelae, but also reduces the risk of HIV-transmission (Grosskurth et al., 1995; Holmes et al., 1999). The gold standard for diagnosis of STD includes gonococcal culture and chlamydia antigen detection. In clinical practice, direct microscopy and chlamydia culture is often used. However, for several reasons, it is not always feasible to achieve a correct diagnosis: (i) STDs are often socially stigmatized, and people with risk behaviour might refrain from seeking care; (ii) costs for medical consultation and correct diagnosis might cause absence and delay in the health-seeking behaviour; (iii) lack of diagnostic tools such as microscopy, especially in low- income countries, complicates making a correct diagnosis. Hence, from a public health perspective, it might be of interest to strive for making cheap treatment accessible, in combination with providing a minimum of harm to personal integrity. Symptomatic management of urethritis following WHO guidelines, recommends antibiotic therapy, including a ciprofloxacin 500 mg single oral dose, plus doxycycline 100 mg, twice daily orally for seven days (WHO, 1994). This treatment strategy has proven effective in curing gonococcal and chlamydial infection (Djajakusumah et al., 1998). It can be applied at all levels of health care, including private pharmacies, if the staff is educated how to ask differential diagnostic questions. In combination with advice regarding partner notification and condom use, this approach could have a major impact on STD/HIV/AIDS control and prevention (Djajakusumah et al., 1998).
DRUG AND HEALTH CARE UTILIZATION

In every country, drugs rank among the most cost-effective tools for the prevention, treatment and alleviation of disease (Falkenberg & Tomson, 2000; World Bank, 1993). Pharmaceuticals and vaccines account for between 5-20% of health-care spending in most high-income countries, and up to 50% in many low-income countries (Quick & Bremer, 1997; World Bank, 1993). In 2000, total global expenditure on pharmaceuticals amounted to about 373 billion USD (Torbett, 2001), on average approximately 62 USD per capita. However, drug expenditure varies widely, from a low of two USD per capita per year, in parts of Bangladesh and Sub-Saharan Africa, to a high of 412 USD in Japan (World Bank, 1993).

Drug use is influenced by the interaction between several actors including the health authorities, health care providers, pharmaceutical industry and the consumers. These actors are in turn influenced by the environment such as policies, socio-economic factors, demography, drug use traditions, education levels, health status, geography and culture (Dong, 2000).

The national authorities formulate the health care financing mechanism and the regulatory context for health care providers. Regulatory instruments are incentives that are used to effect price, distribution or quality and requirements that can lead to punishments if they are not met. In low-income countries the regulatory authorities often lack resources for effective regulatory implementation and enforcement (Hongoro & Kumaranyake, 2001; Stenson et al., 2001a). This leaves room for a virtually unregulated private sector to fill the gaps of an insufficient public health sector (Kamat & Nichter, 1998; Roemer, 1984; WHO, 2000; Lönnroth, 2000). However, with a good regulatory framework and policies as well as a planned implementation strategy there are possibilities to achieve substantial improvements (Stenson et al., 2000b; Syhakhang, 2002).

In low-income countries, there is often a lack of updated, reliable or unbiased sources of information. This poses a problem in the public sector and even more so in the private sector, where provider’s work more isolated from one another and have less access to and support from updated information, as well as relying to a higher degree on material, provided by the pharmaceutical industry (Brugha & Zwi, 1998). Other obstacles are high numbers of patients, lack of time, small resources and lack of diagnostic laboratory tests. In terms of infections, it may in many situations be difficult for the physician to distinguish a bacterial aetiology from a viral one without recourse to laboratory tests (Kunin, 1993). Physicians often feel compelled to prescribe antibiotics to prevent treatment failure due to possible undetected, sub-clinical or secondary bacterial infection (Kunin, 1993). Patient demand and social expectations are important factors influencing provider practice (Paredes et al., 1996). In particular doctors in private practice are dependent on satisfied patients; hence patient demand contributes to irrational drug and antibiotic prescribing (Lönnroth et al., 1998). It is also simplistically assumed that when providers are aware of the correct management they will adopt it. However, discrepancies between provider knowledge and practice are common (Brugha & Zwi, 1998). Paredes (1996) showed that although physicians knew the correct indication for antibiotics in cases of childhood diarrhea, they still prescribed antibiotics unnecessarily. It has also been shown that medical practitioners who work in both public and private sector behave differently depending on which sector they work in, dispensing ORS for diarrhea in the public sector and antibiotics in the private (Brugha & Zwi, 1998).
In the community there are several factors influencing drug use. Among these provider-patient interaction, patient characteristics such as age, gender, social class, education, beliefs, sources of information costs and distances (Tomson, 1990; Dong, 2000). Rarely patients fully comply with physicians recommendations including prescriptions regarding antibiotic therapy, leading to ineffective management, additional costs and the emergence of antibiotic resistance (Kardas, 2002). Members of the public often define treatment effectiveness quite differently from western-trained providers. The providers define effectiveness in terms of a therapy’s ability to cure a disease, whereas the patient defines and evaluates effectiveness related to their illness, whether they feel that the therapy allows them to cope more effectively with their families, jobs, neighbours, etc (Tomson, 1990). Craig (1997) showed that Vietnamese women as household decision-makers often have sophisticated system of indigenous understandings about when to take medicines and substantial product knowledge of antibiotics. Winkvist (1997) reported that Pakistani women from different social classes interpret health differently. Low-class rural women spoke of health in terms of physical strength, had a pragmatic attitude towards health care resources, using all types of health care until treated and, in relation to the doctor, were mostly concerned with the medical treatment. Low-class city women spoke of health in terms of mental strength, and middle-class women discussed it in terms of cultural competence, choosing health care providers depending on the type of illness, and being mainly concerned with being treated with respect. An Indian study showed that customers often expect immediate improvement from drugs purchased, where antibiotics are perceived as potent drugs with immediate effects on numerous conditions (Kamat & Nichter, 1998).

Western medicine is often interpreted and integrated into traditional belief systems (Tomson, 1990). In traditional Vietnamese medicine, the basic properties of illness are interpreted as “am” (Yang) and “duong” (Ying), and drugs are interpreted as “nong” (warm) and “lanh” (cold). The important feature of this is that there should be a balance between “duong” and “am”; if either of these dominates there will be a disturbance in the balance and that will cause disease. The aim of treatment is to restore the balance between “duong” and “am”. Drugs that are warm (nong) should be combined with drugs that have cold (lanh) properties, e.g. antibiotics are regarded as warm (nong) drugs and should be combined with a cold drug, most often vitamin C, which is regarded as cold (lanh) (Jamieson, 1993).

**Box 1.1. Traditional Vietnamese Medicine**

Traditional Vietnamese medicine is based on a cosmological worldview, involving maintaining a proper balance between “duong” (Yang) and “am” (Yang). Illness is explained as a disturbance in balance, and treatment based on restoring balance, both within a person and between the person and the external world. According to traditional folk thought, all things that can be passed into the body like food, drinks and drugs were believed to have an essential nature, be warm (nong) or cold (lanh). Warm foods were “duong” and cold “am”. Diet could thus disrupt or restore the harmony between “duong” and “am”. As the proper balance between “duong” and “am” produced health in the human body and between the human being and her environment, so too did proper relationships between categories and groups of people produce social harmony, happy and prosperous families, villages and nations. In society “am” is defined as a tendency towards male dominance, high redundancy, low entropy, complex and rigid hierarchy, competition and strict orthodoxy, focused on rules of based on social rules. “Duong” is defined by a tendency toward greater egalitarianism and flexibility, female participation, mechanisms to dampen competition and conflict, high entropy, low redundancy and more emphasis on feeling, empathy and spontaneity (Jamieson 1993).

**Drug utilization in Vietnam**

In Vietnam, it has been estimated that the liberalization of pharmaceutical production as part of the “Doi Moi” economic reforms led to a three-fold increase in drug production and a ten-fold increase in drug imports from 1987 to 1992 (Witter, 1996). From 1990 to 1997, drug expenditure increased from 1.5 USD per capita to 5.0 USD, including 1 USD from the public drug budget. Since 1994, the drug market showed signs of stability, and drugs have been available to cover the essential need of health care as well as public demand. In 2001,
drug expenditure per capita was 6 USD (DAV, 2002) and drug utilization has dominated health expenditure, accounting for about 90% of total household expenditure on health care (Chuc, 2002; GSO, 1994; GSO, 1999).

The economic renovation, “Doi Moi” has managed to successfully increase the availability of drugs and the possibilities to successfully treat communicable diseases have improved. However, it has not been accompanied by the information infrastructure that is needed to utilize this resource in an optimal way, leading to irrational use of drugs and waste of scarce resources (Chuc, 2002). The liberalized economy, rapid increase of pharmaceuticals available on the market and increased domestic demand has resulted in a situation where the private sector is increasingly taking over and where profits from drug sales has lead to a temptation to over-prescribe/dispense (Cederlöf & Tomson, 1995; Lönroth et al., 1999). In the current situation, people in general can buy most drugs, including prescription-only drugs, over the counter. This has led to a vast part of medical treatments by-passing the public healthcare sector, and people self-medicate, sometimes with the advice from the drug-seller as the only form of medical consultation (Chuc, 1999).

National drug policy and essential drug lists

National Drug Policies aim to ensure a sufficient supply of good quality drugs in order to respond to needs in health protection and to ensure the rational use of drugs in curative and preventive health care (SRV, 1996). To date, 72 countries have official drug policies. The Vietnamese National Drug Policy (VNDP) was developed with the support of Sida and the WHO. The process includes developing a drug law and a drug regulation system that is compatible with the challenges in the new drug market, as well as developing and implementing internationally accepted technical guidelines and standards in the pharmaceutical field (Lalvani et al., 1996; Chuc, 2002). The VNDP does not specifically mention self-medication, the role of pharmacists and GPP. However, considering the high utilization the objectives of ensuring good quality drugs to people and rational use of drugs cover these issues (Chuc, 2002). Pharmaceutical personnel are mentioned in the VNDP although pharmacy training has so far included little of GPP and rational use of drugs.

Essential drug lists serve as a guide for more than 120 countries and contain the names of the most effective and economic drugs in treating important health problems. The aim is to increase the availability of quality drugs as well as to encourage rational use. In general, more extensive drug lists are considered appropriate in settings with better-trained health workers, for example physicians, while community health workers may only be able to prescribe 20 drugs effectively. Successful attempts to increase the availability of antibiotics in a coordinated manner are dependent on creative private and public sector collaboration. The introduction of an essential drug list is most effective if it is accompanied by an introductory educational program, effective follow-up and mechanisms to ensure the supply of high-quality drugs (Hogerzeil, 1995). In Vietnam, the Ministry of Health has issued four Essential Drug Lists (EDL) in the years 1985, 1989, 1995 and 1999 with 223, 187, 255 and 306 essential drugs, respectively (Chuc, 2002). The updating process was evidence-based on e.g. the changing disease pattern in Vietnam, antibiotic resistance, adverse reactions and WHO guidelines.
THE VIETNAMESE HEALTH CARE SYSTEM

The public health care system has four levels, which are described briefly below:

i. At the central level, the Ministry of Health is the national authority responsible for health care in the whole country. It also directly controls the activities of central medical and pharmaceutical training institutions, academic institutions and national hospitals.

ii. At provincial level, there are 61 health bureaus, serving an average population of 1.2 million, directly coordinated by MOH as well as the provincial people’s committees. In each province, there is at least one general hospital and some specialized hospitals.

iii. At the district level there are health centres with public pharmacy and a district hospital serving a population of about 50,000 to 300,000 persons.

iv. At the community level there are community health centres "Tram y Te" with 3-5 health staff responsible for providing primary health care and implementing preventive health programs, e.g. mother and child health, family planning, and immunization programs to a population of between 2,000 and 10,000. Of the 10,511 communes, 98% have community health centres (MOH, 2000). Due to the under-utilization of the community health centres, the revenues from the public drug outlets that should be used to cover electricity, water supply and overhead costs, are small, affecting the availability and volume of various drugs (GSO, 1999).

Private health care plays an important role in most low- and middle-income countries, constituting more than half of the total health care expenditure (Bath, 1993; Bennet, 1997; Berman, 1996; World Bank 1993). In Vietnam, 80% of the health expenditure comes from private sources and about 50% of all health care delivery from private providers (Gerter & Litwack, 1998). The private health care has extremes, from the expensive high quality care provided for the affluent, to the low cost, poor quality care, provided by badly trained practitioners for the less affluent part of the population, often out of control of the authorities. (Lönnroth, 2000a). It is also heterogeneous, involving practitioners with different backgrounds, medical doctors, assistant doctors, nurses, midwives, pharmacists, traditional practitioners and also practitioners without formal competence.

A problem with private health care is an ignorance of externalities. Even if the provider does his/her best for the individual patient, this might not be the best for the whole population. Public health goals might be neglected and resources wasted, that could be better utilized elsewhere. One such example is antibiotic use, where – due to increased resistance - how individual patients are treated effects the possibility of future treatments for the whole population (World Bank, 1993; Lönnroth, 2000a). Due to these market failures, it is argued that private health care requires a substantial degree of control in order to contribute efficiently to public health goals (Lönnroth, 2000a). This may be achieved through well-formulated goals, policies, regulation, mechanisms for reinforcement and a competence support system for continuous education (Chen, 1994; Witter, 1996).

Figure 1:3. Proportion of private and public health care financing.

In Vietnam, private health care has rapidly expanded and now plays an increasingly important role (Guldner, 1995; Wolffers, 1995). A study by Gerter and Litvack (1998) showed that private pharmacies and private practitioners are used for 66% and 14% of all illness episodes, respectively. According to the national household survey in 1997-1998, on average, about two-thirds of those who are sick, self-medicate. The private sector, and especially the private pharmacies, is increasingly important as first line medical care providers.

**Private Pharmacies**

Since the HCMC and Hanoi Health Services allowed licensed pharmacists to open private pharmacies in 1987, the number of private pharmacies increased from none in 1986 to more than 6000 in 1996 (Phuong, 1997). Most private pharmacies are situated in urban areas, and in Hanoi represent 72% of the total drug supply (Binh & Tiep, 2002). Licenses for private pharmacies are mainly provided to pharmacists who have a university degree and 5 years of experience, except in the case of remote areas, where assistant pharmacists can apply for licenses. The licensed pharmacist must always be physically present in the pharmacy while it is open for business (MOH, 1994). However, there are private pharmacies without licensed pharmacists on the premises or which run during working hours although they have a license for non-working time only (Dinh, 2002; MOH, 2001; Chuc, 2002).

As private pharmacies often are the first and only contact with health delivery services, the pharmacy profession has increasingly been internationally recognized as having a strategic position in health promotion and for improving rational use of drugs (Tomson & Sterky, 1986; Kamat & Nichter, 1998; Cederlof & Tomson, 1995; WHO, 1994). This is especially true in many low- and middle-income countries, where the patients appear to consult the private pharmacies rather than the official health care system. However, the quality of case management may often be poor with irrational practices such as inappropriate treatment of major public health problems, and over-dispensing of drugs with a high profit margin such as antibiotics and steroids. Product knowledge is often derived from the marketing of pharmaceutical companies (Kamat & Nichter, 1998). A

<table>
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<tr>
<th>Provider</th>
<th>Poorest</th>
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<th>Third</th>
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<td>6</td>
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<td>6</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>5</td>
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<td>Other public providers</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
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<tr>
<td>All public providers</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td>12</td>
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<tr>
<td>Private clinics, doctors</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>14</td>
<td>18</td>
<td>15</td>
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<tr>
<td>Private pharmacies</td>
<td>62</td>
<td>63</td>
<td>59</td>
<td>56</td>
<td>52</td>
<td>57</td>
</tr>
<tr>
<td>Traditional healers</td>
<td>3</td>
<td>3</td>
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<td><strong>Total</strong></td>
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Source: GSO, 1999; Chuc, 2002.
case study showed that less than 1% of the private pharmacy customers have prescriptions, and 95% decide themselves which drug to buy, without consulting the pharmacist (Chuc & Tomson 1999). Prescription-only drugs such as corticosteroids and antibiotics are often dispensed without a prescription (Goel et al., 1996a; Kamat & Nichter, 1998). Antibiotics are among the most profitable drugs to dispense but are often dispensed in too short courses, depending on the clients’ ability to pay (Thamlilikitul, 1988; Bartoloni et al., 1998; Chuc & Tomson, 1999). This indicates that pharmacy staff knowledge is often insufficient and business considerations are a more important determinant of behaviour than health aspects (Wolfers, 1995; Chuc & Tomson, 1999; Halfvarsson et al., 1998; Thamlilikitul, 1991; Ross-Degnan et al., 1996). As the pharmaceutical market has boomed and taken over a big part of the primary health care during a period of less than 15 years, the regulatory system has not been able to keep up with the rapid change. Although the National Drug Policy was implemented in 1995, legal offences and penalties are often not clearly stated therein (Stenson et al., 2001b).

Olsson et al., (2002) studied the perceptions of Hanoi pharmacy personnel of their role and concluded that they encompassed three different views: (i) The counselor, whose main role is to serve the customers, supply medications, check prescriptions and guide customers in the use of medicines. (ii) The medical doctor's assistant, whose role is to follow instructions, given either directly or indirectly by the medical doctor. (iii) The businessman, selling pharmaceutical products, who usually does not care to give the customers any advice and where the sole motivation of the pharmacy personnel is to sell as much medicines as they can in the shortest possible time.

**Good Pharmacy Practice**

Standards for quality of pharmacy services, including supply, dispensing and prescribing, have been set out in the Good Pharmacy Practice (GPP) document established in 1993 by the International Pharmaceutical Federation (FIP, 1993). The World Health Organization adopted this document in its 1994 World Health Assembly resolution (WHO, 1994). The resolution recognizes the key role of pharmacists in public health and in the use of medicines. According to a WHO report in 1998, regarding the role of the pharmacist in self-care and self-medication (WHO, 1998), the pharmacist’s role is to be: (i) A communicator and listen to clients in order to understand the nature of their conditions, ask questions to obtain a medication history, give information about the drugs dispensed, give advice in cases where no drugs are needed; (ii) A quality drug supplier to ensure that procurement of drugs should be from the right sources, storage of drugs should keep good quality, dispensing should be correctly labelled; (iii) A trainer and supervisor and participate in continuing medical pharmaceutical education programs, supervise and train other categories of pharmacy staff and develop protocols for referral of clients to doctors when needed; (iv) A collaborator working together with the general public, other health care professionals and with "peers" i.e. colleagues in national professional organizations; (v) A health promoter, using the position as "front-line health worker" to, wherever appropriate, promote non-drug solutions to health problems.

**PROBLEM DRUGS**

The prescribing and dispensing of inappropriate drugs has been reported in a wide range of low-income countries. Antibiotics may be prescribed in 35-60% of clinical encounters, and constitute up to 50% of the national drug costs (Nizami et al., 1996), despite being appropriate in less than 20% of the cases (Hogerzeil et al., 1993; Trostle, 1996). Several
studies show that corticosteroids are commonly used irrationally for health problems like diarrhoea, fever, jaundice and lower back pain (Prakash et al., 1998; Ferraz et al., 1996).

**Corticosteroids**

Corticosteroids are an important group of drugs used mainly for two purposes: (i) replacement therapy in patients with adrenal gland deficiency (ii) immunosuppressive and anti-inflammatory therapy for a wide range of conditions such as hyper-sensitive allergic reactions, e.g. asthma and urticaria, collagen diseases such as SLE and rheumatoid arthritis, skin diseases, autoimmune diseases, post-transplantation therapy to prevent rejection of organs, haematological disorders such as haemolytic anaemia and purpura, inflammatory bowel disease such as Crohn’s disease and ulcerative colitis, as well as for tumour-associated cerebral oedema and nephritic syndrome. When indicated, they may be lifesaving, such as for patients with anaphylactic shock or life expanding as for patients with autoimmune diseases. However, there are serious adverse effects of steroid use such as immunosuppression and metabolic effects on water and electrolyte balance, muscle wasting, osteoporosis, hyper-glycaemia, hypertension-increased fatty tissue (moon face and buffalo hump), all part of Cushing’s syndrome (Rang et al., 1995; Davidsons, 1999). For most infectious diseases, steroid use is contraindicated, as steroids tend to disguise inflammatory symptoms giving a subjective feeling of improvement, while in fact the immunosuppressive effect decreases the ability of the infected person to fight the invasive organism, which can then proliferate faster, leading to more serious disease. In some infectious diseases it though has therapeutic role e.g. bacterial meningitis, arthritis and respiratory infections in patients with chronic obstructive pulmonary disease (Davidsons, 1999). Due to the severe adverse effects, most countries, including Vietnam, have chosen to restrict the availability of steroids through prescription-only regulations. A case study in Vietnam reported that combinations of antibiotics and corticosteroids were commonly dispensed in a private pharmacy without a prescription (Chuc & Tomson, 1999). In the private sector, corticosteroids are also used in combination therapy with antibiotics for fast relief of symptoms, as this is thought to correspond to the expectations of the patients as well as increasing compliance with therapy.

**Antibiotics**

Antibiotics have revolutionized the treatment of common bacterial infections and play a crucial role in reducing child mortality in low and middle-income countries. As infectious diseases account for 45% of the mortality in low-income countries (WHO, 2000), antibiotic therapy is often indicated. Since antibiotics were first introduced, their consumption has increased dramatically and, in most low-income countries, they constitute the single largest group of drugs purchased (Col & O’Connor, 1987). In 1997, the world market for antibiotics was 17 billion USD (Carbon & Bax, 1998).

There are no credible data available about the total expenditure for antibiotics in Vietnam. In the public sector, antibiotics account for 40-50% of the total drug costs, and in some hospitals as much as 74% (Ha, 1991). In 1993, antibiotics represented about 40% of the total amount of imported pharmaceutical material. Among the 100 highest selling pharmaceutical products in the Vietnamese market there were 21 antibiotics, constituting 29% of the total value (Chuc, 2002). Along with vaccines, oral re-hydration solutions and contraceptives, antibiotics represent the most important means to prevent mortality in low- and middle-income countries (Col & O’Connor, 1987). About 85-90% of the antibiotics are used in the community, and up to 80% are used to treat respiratory tract infections (Huoivinen & Cars, 1998). In high-income countries, 20–50% of antibiotic use is considered unnecessary, in low-
and middle-income countries perhaps even more (Wise et al., 1998; Chetley, 1996; Hart & Kariuki, 1998; Levy, 1998).

As antibiotics are targeted against microorganisms that can be cultured in laboratories, their effects can be studied in vitro. It is however much more difficult to study these effects in vivo, since bacterial infections are caused by bacteria with different properties, that can colonize different organs, producing a variety of anatomical and physiological conditions. In order to achieve the desired effect, the antibiotic must be transported to the site of infection (pharmacokinetics), and the concentrations there be sufficient to combat the infection (pharmacodynamics). In addition, as bioavailability varies in different individuals the same antibiotic dose may lead to different tissue concentrations (Norrby & Cars, 1997).

Antibiotics are either bacteriostatic, suppressing bacterial growth and proliferation, or bactericidal, killing the bacteria. Antibiotics defined as bacteriostatic are macrolides and chloramphenicol, which inhibit protein synthesis. Antibiotics defined as bactericidal are those affecting the cell-wall synthesis, such as beta-lactams (penicillins, cephalosporins, monobactams and carbapenems), and quinolones, that bind to DNA gyrase, disrupting life sustaining processes, as well as aminoglycosides and co-trimoxazole (Norrby & Cars, 1997). The rate of bacterial elimination is different for different antimicrobial substances. For aminoglycosides such as gentamycin it is fast; this drug is commonly used to treat severely ill patients, e.g. with sepsis. Some antibiotics like quinolones and aminoglycosides have a concentration-dependent elimination of bacteria, and so a high peak concentration is preferred. The elimination rate for beta lactams is slow and not concentration-dependent after the preferred serum concentration level has been reached. Hence, a stable concentration during a prolonged period is preferred (Norrby & Cars, 1997).

**ANTIBIOTIC RESISTANCE**

Antibiotics are one of the most important medical discoveries of our century; yet, their widespread misuse gradually diminishes their potency. The continuous erosion of the health impact of antibiotics by the rapid spread of antibiotic resistance is a world-wide problem, which is particularly serious in low-income countries, where alternative antibiotics are often not available or are too expensive (O’Brien, 1992). This is eroding the very basis for treatment success of infectious diseases, affecting the whole society as infections are becoming increasingly more difficult to treat. In many countries, the cost of newer antibiotics, developed to replace drugs that have become powerless due to resistance, is a burden. This leaves the health care services with many untreatable infections (WHO, 2001), a situation that has clinical, epidemiological, and economical consequences. An untreated or poorly treated infection increases the risk of death, prolongs illness, and increases the pool of infected people and the spread of resistant strains.

The are two main types of antibiotic resistance in bacteria, (a) intrinsic, whereby the bacteria are naturally resistant to an antibiotic due to inherent features, and (b) acquired, whereby resistant strains emerge in a previously sensitive population, usually after antibiotic exposure (Gentry, 1991).

Susceptibility to antibiotics is defined by MIC (Minimal Inhibitory Concentration) or MBC (Minimal Bactericidal Concentration). The MIC can be determined by different methods: (i) Agar dilution method with different concentrations of antibiotics are included in the agar, where bacteria are inoculated and incubated. The MIC value is the lowest concentration that
inhibits visible growth. (ii) Broth dilution method with antibiotics in different concentrations in the broth, bacteria’s are added and after incubation the transparency is measured. (iii) The E- test, an indirect MIC method using an impregnated strip with a concentration gradient of antibiotics that is added to an agar plate with the culture. MBC is determined by adding broth from the MIC to an agar plate, incubating, and determining the antibiotic concentration that has eliminated 99.9% of the organisms.

In most cases, direct MIC determinations are not suitable for clinical routine analysis. The most common method is therefore the antibiotic susceptibility disc diffusion test where a piece of paper impregnated with antibiotics is added on an agar plate inoculated with bacteria. After incubation, the inhibition zone around the antibiotic paper is measured, and this zone is inversely proportional to the MIC value of the isolate.

The SIR system is used to classify the susceptibility of the tested microorganisms. The isolates are defined as susceptible (S), intermediate resistant (I) or resistant (R). When an isolate is S for a specific antibiotic, that antibiotic can be used in the recommended dose. When I is noted, the bacteria have acquired a low degree of resistance or are intrinsically resistant, and the treatment effect is questionable, but the drug can still be used in high doses for certain infections. When R is the case, the bacteria are resistant and the antibiotic cannot be used. The exception is if there is a synergistic effect between antibiotics and they are used in combination (Olsson-Liljequist & Forsgren, 1997).

**Genetic mechanisms for resistance**

The three main mechanisms of acquired antibiotic resistance are (1) Inactivation of drug due to enzymatic degradation of antibacterial drugs, (2) alteration of bacterial structures that are antibiotic targets, and (3) changes in membrane permeability to antibiotics (Dever & Dermody, 1991), (table 1:4).

Antibiotic resistance genes can be either carried on the bacterial chromosome or on mobile genes such as plasmids, transposons and as integron-borne gene cassettes. Plasmids are autonomous, extrachromosomal, self-duplicating genetic elements that can confer antibiotic resistance, virulence and other metabolic capacities (Gentry, 1991). Genes encoded on plasmids are more mobile than chromosomal genes and can be transferred horizontally between bacteria of the same or different species. There are two main ways of transference: (a) Conjugation or DNA transfer occurs through cell-to-cell contact, within or between species, often in an environment with many microorganisms, as the commensal flora in the gastrointestinal tract, often considered as a storage site of resistance traits (Gentry, 1991; APUA, 1998). (b) Bacteriophage mediated transfer of gene elements, usually limited within one species.

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<tbody>
<tr>
<td>Beta-lactamase</td>
<td>Inhibit cell wall synthesis by blocking cross-linking of peptidoglycan</td>
<td>++</td>
<td>-</td>
<td>*</td>
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<tr>
<td>Penicillin &amp; Cephalosporin</td>
<td></td>
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<tr>
<td>Aminoglycosides &amp; Gentamicin</td>
<td>Inhibit ribosomal translation 30S subunit</td>
<td>++</td>
<td>-</td>
<td>*</td>
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<tr>
<td>Tetracyclines</td>
<td>Inhibit ribosomal translation 30S subunit</td>
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<td>+</td>
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<td>Chloramphenicol</td>
<td>Inhibit ribosomal translation 50S subunit</td>
<td>+</td>
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<td>Macrolides &amp; Erythromycin</td>
<td>Inhibit ribosomal translation 50S subunit</td>
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<td>Sulphamamide</td>
<td>Inhibition of Inhibition of folate--DNA synthesis</td>
<td>++</td>
<td></td>
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</tr>
<tr>
<td>Trimethoprim</td>
<td>Inhibition of Inhibition of folate--DNA synthesis</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>Inhibit DNA gyrase</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Inhibit DNA synthesis</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Transposons are mobile DNA sequences capable of being transferred from a donor DNA and integrated into a recipient; they cannot replicate independently and must be maintained within a plasmid or a chromosome (Gentry, 1991). Multiple resistance determinants are often
found to be clustered on the mobile genes. The horizontal spread of the element in the bacterial population is responsible for simultaneous transfer of several resistance determinants. By using one antibiotic, whose resistance is represented in the mobile element, the whole array of resistance genes may be selected for.

It has been shown that bacteria during times of stress increase their mutation rates. Such stress includes selective pressure of antibiotics, especially when the microbes are not instantly killed as when there are low concentrations, short time of exposure or slow killing ability (Martínez & Baquero 2000; Shapiro, 1999). Many bacterial populations harbour a proportion of cells with a mutator phenotype, that have a mutation rate that is increased from 10 to 50 up to 10,000 times, generally as a consequence of a defective methyl-directed mismatch repair system (Miller, 1996). The mutator phenotype allows bacteria to develop a large variability of alleles that can survive stressful environments during antibiotic treatment (Matic et al., 1997). Selection of mutator alleles by antibiotic therapy with different drugs can be the basis for the emergence of some phenotypes of multiple antibiotic resistance (). Transposable elements also increase the rate of mutation (Kidwell & Lisch, 2000). Findings also indicate that antibiotics, by stressing the microbes, increase inter-species gene transfers 10-10,000 fold (Krishnapillai, 1996). This adaptation to the environment makes sense from an evolutionary perspective. By increasing mutation rates and sharing resistance genes, bacteria generate and share survival information (Kidwell & Lisch, 2000).

**Antibiotic resistance in Vietnam**

Several studies have shown high resistance among the most common pathogens in Vietnam. The respiratory pathogens *S. Pneumoniae* and *H. Influenzae* show high resistance against co-trimoxazole, chloramphenicol, erythromycin, sulphonamides and macrolides (Ha 1991, Tornquist et al., 2000; Bogaert et al., 2002; Parry et al., 2000). Tornquist et al., (2000) show *S. Pneumoniae* penicillin resistance below 10%, other studies indicate higher penicillin resistance (Bogaert et al., 2002; Parry et al., 2000).

**RELATIONSHIP BETWEEN ANTIBIOTIC USE AND RESISTANCE**

Antibiotic use is thought to be the key driver of resistance (Granizo et al., 2000; Huovinen & Cars, 1997; Kristinsson, 1997). The theory behind this is that antibiotic usage by some people may increase the risk of colonization or infection with resistant organisms in people who have not received antibiotics (Lipsitch & Samore, 2002). For many pathogens, acquisition of one strain reduces a person's chances of acquiring other strains (Van der Waaïj & Nord, 2000; Shinefield et al., 1974; Lipsitch et al., 2000 ). Antibiotic treatment eradicates susceptible strains and thereby reduces the probability of transmitting susceptible strains. Similarly, with a higher colonization rate of resistant strains, the probability of transmitting resistant strains increases (Austin et al., 1997; Bonhoeffer et al., 1997; Blower et al., 1998; Lipsitch et al., 2000; Garber 1989). This mechanism of shifting the competitive balance in favour of resistant strains can increase the prevalence of resistant organisms in the community (Lipsitch & Samore, 2002). Thus the increase in transmission of resistant pathogens is a consequence of successful treatment of the infected host, resulting in the eradication of drug-susceptible pathogens that colonize or infect that host. As a consequence, the more effective a treatment is at eradicating drug-susceptible populations of these organisms, the more it will promote the spread of resistant ones (Blower et al., 1998).
Four mechanisms by which antibiotic treatment can create selection for resistance in a population have been outlined (Lipsitch & Samore 2002). (1) Treatment failure due to subpopulations of resistant bacteria in a host, infected with predominantly susceptible strains, resulting in outgrowth of the resistant subpopulation, which can then be transmitted to others. (2) Successful treatment of an infection caused by susceptible strains, reducing the ability of that host to transmit the infection to others, making those more likely to be infected by resistant pathogens than they would otherwise have been, and shifting the competitive balance toward resistant infections. (3) Treatment eradicates susceptible bacteria carried by the host, making that host more susceptible to colonization by new strains. If the newly acquired strain has a high probability of being resistant, this can significantly increase the treated individual’s risk of carrying a resistant strain, relative to an untreated one. (4) Treatment of an infection in an individual who is already colonized with resistant organisms may result in an increased load of those organisms, if competing flora are inhibited - leading to increased shedding of the resistant organism and possibly to increased individual risk of infection with the resistant organism (Lipsitch & Samore 2002).

Most studies that have investigated the relationship of antibiotic use and antibiotic resistance have been undertaken in hospital, multi-centre, or country settings (Lyytikainen et al., 1996; Fridkin et al., 1999; Mouton et al., 1990; Goettsch et al., 2000). For infections with penicillin-resistant S. pneumoniae, studies have demonstrated that at the individual level, previous use of beta-lactam antibiotics such as penicillin is an important risk factor (Nava et al., 1994; Deeks et al., 1999). Studies on carriage of penicillin-resistant S. pneumoniae in children have shown that sulfamethoxazole-trimethoprim (co-trimoxazole) and macrolides such as erythromycin have also been associated with selection of penicillin-resistant S. pneumoniae (Arason et al., 1996, Melander et al., 2000). Translated to the population level, sales of beta-lactam antibiotics, co-trimoxazole, or macrolides in a given geographic region may be proportional to microbial resistance to penicillin. This is also supported by the correlation between sales of beta-lactam antibiotics and macrolides, and corresponding S. pneumoniae resistance in 11 European countries (Bronzwaer et al., 2002).

**Does the dose matter?**

Is the relationship between antibiotic use and resistance fully linear or does the pattern of antibiotic use influence the development of resistance? On population level it might be argued that frequent use in short courses selects for resistance more effectively than fewer but longer courses. This can be theoretically described from two perspectives:

(i) From an epidemiological perspective the transmission of antibiotic resistance can be compared to herd immunity, that is when a certain level of vaccination is reached, also those who are not vaccinated will benefit, as the risk of transmission is decreased (Halloran & Struchiner, 1996). Similarly, when antibiotics are frequently used in a population, many people will have a suppressed susceptible flora, simultaneously giving a comparable advantage for resistant strains to colonize. On the other hand, when antibiotics are less frequently used, although the individual person using antibiotics will be as susceptible for colonization of resistant strains, the chances of acquiring resistant strains is lower. Even if the total amount of antibiotics used is similar, frequent use of antibiotics increases the chance of transmission, as a greater percentage of people are hosts, capable of transmitting the resistant strains.

(ii) From a genetic perspective low concentration of antibiotics allows the growth of low-grade antibiotic-resistant bacteria with mutations in a single gene. Once the antibiotic
concentration rises, the number of selectable mutants decreases. At certain antibiotic concentrations, combinations of mutations in more than one gene might be required to provide a resistant phenotype. With high antibiotic concentrations, there will be a sharp decrease of successful mutations. With pre-selection of low-grade antibiotic resistant bacteria, where a single mutation already has occurred, there are more clones that (a) are protected from the action of the antibiotic and thus selectable (b) that can through single mutations achieve a resistant phenotype. Hence, the presence of low-level antibiotic resistance determinants in bacteria, will increase the possibility of the emergence of a clinically relevant antibiotic resistance phenotype (Martinez & Baquero, 2000).

There is, however, a difference between a low concentration of antibiotics through frequent sub-clinical doses and shorter courses but with an adequate concentration. The recommended duration of antibiotic treatment has been questioned, and in a recent study published in the Lancet (MASCOT, 2002) where it was shown that a 3-day course of oral amoxicillin was as effective as a 5-day course. There was no significant difference in relapse rate. The authors argue that a 3-day course would have many benefits, including lower cost for therapy, reducing therapeutic expenditures in low-income countries, better compliance to the therapy as the dose regimens are shorter, and the costs for the families lower. This would also decrease the rate of resistance development, as fewer antibiotics are used, decreasing the total antibiotic pressure. This makes sense from both a genetic and an epidemiological perspective given that the 3-day course eliminates the pathogens as effectively as the 5-day course, as suggested by the study.

**IS IT POSSIBLE TO REVERSE RESISTANCE THROUGH RATIONAL ANTIBIOTIC USE?**

Will more prudent use of antibiotics reduce the occurrence, rate of spread and evolution of antibiotic resistance? This could be the case, if resistant strains have a selective disadvantage compared to their sensitive counterparts. In other words, do the resistant bacteria suffer a cost of resistance when the antibiotic is absent? There are two theoretical ways that resistance might be a disadvantage for the cell: (a) Mutations that confer resistance disrupt some normal physiological process in the cell, thereby causing side effects, (b) The bacteria must synthesize the additional nucleic acids and proteins. This imposes an energetic burden on the bacteria and is the most likely scenario in plasmid-mediated resistance (Lenski, 1998).

If this is the case, a strategy for containing the spread of resistance would be to suspend the use of a particular antibiotic, until resistant genotypes had declined to low frequencies (Bonhoeffer et al., 1997). The efficiency of this strategy would then be reversibly proportional to the cost of resistance for the bacteria, e.g. it would take 10 times as long to eliminate a population of bacteria, where the cost of resistance is 1% compared to a population where the cost is 10% (Lenski, 1997).

The biological costs of containing resistance can be measured in three ways: (a) experimentally, by estimating the relative growth, survival and clearance of susceptible and resistant bacteria in *vitro* and in *vivo*, (b) by prospectively measuring the rate of clearance of resistant bacteria and, (c) by retrospectively measuring changes in frequencies of hosts infected with resistant bacteria following known changes in antibiotic use (Andersson & Levin, 1999).
(a & b) There are experimental studies indicating that resistant genotypes are less fit than their sensitive counterparts in the absence of antibiotics, indicating a cost of resistance (Zund & Lebec, 1980; Jin & Gross, 1989). However, these studies have put antibiotic resistance genes into naive bacteria, which have no evolutionary history of association with the resistance genes (Lenski, 1997). An important question, therefore, is whether bacteria can overcome the cost of resistance by evolving adaptations that counteract the harmful side effects of resistance genes. In fact, several experiments have shown that the cost of antibiotic resistance may be substantially diminished, even eliminated, by evolutionary changes in bacteria over rather short periods of time (Lenski, 1997). This adaptation might be due to the increased mutation rate induced by the stress of antibiotic compounds, as earlier discussed (Martinez & Baquero, 2000). Once a mutation that causes an antibiotic resistance phenotype has occurred, the resistant bacterium must compete with the rest of the bacterial population, or other resistant mutants. The outcome of the competition process depends on the relative fitness of the resistant bacterium, defined as the efficiency of multiplication of the mutant cell compared with that of the total population. Not only the mutability but also the selective process will have a relevant effect on the final mutation rate values. As a consequence of this adaptation of bacteria to their resistance genes, it becomes increasingly difficult to eliminate resistant genotypes simply by suspending the use of antibiotics (Martinez & Baquero, 2000).

(c) There are examples to support the hypothesis that changing consumption of antibiotics can reduce the prevalence of antibiotic-resistant bacterial strains. In Iceland, the rapid increase of penicillin-resistant S. pneumoniae was met with propaganda against overuse of antimicrobials, which lead to reduction of antimicrobial use and subsequently a reduced incidence of penicillin-resistant pneumococci (Kristinsson, 1997). In Finland, consumption of macrolide antibiotics decreased from 2.40 DDD in 1991 to 1.38 in 1992, and this was followed by a steady decrease in the frequency of erythromycin resistance among group A streptococcal from 16.5 percent in 1992 to 8.6 percent in 1996 (Seppala et al., 1997).

From a theoretical point of view, it might be possible to reverse resistance. This would, however, require that use of the specific antibiotic is drastically reduced before the bacteria has adapted to the burden of carrying the resistance genes. This might have been the case in Iceland and Finland, where the policies were changed as a consequence of increased resistance detected by antibiotic surveillance. Is this generalizable to other settings? These examples are from high-income countries with a centralized health care system, an information and regulatory infrastructure that permit new policies to have an impact on the health care sector, strict prescription regulations and good compliance among prescribers and providers. No studies published internationally have been carried out in low and middle-income countries, despite the fact that these countries often serve as a reservoir of high levels of resistance that is easily spread globally through increased travel and trade (Lester et al., 1990).

**INTERVENTIONS TO IMPROVE CASE MANAGEMENT AND DRUG USE**

There are few randomized control trials that have shown impact of interventions in developing countries (Brugha & Zwi, 1998; Ross-Degnan, 1996). Most interventions have been targeted at physicians, mainly in the public health sector (Angunawela et al., 1991; Brugha & Zwi, 1998). Intervention approaches proven effective in low-income countries are: standard treatment guidelines; essential drugs lists; pharmacy and therapeutics committees; problem-based basic professional training; and targeted in-service training of health workers. Some other interventions, such as training of drug sellers, education based on group processes, and public education, need further testing but should be supported (Laing et al.,
Several simplistic approaches have been proven ineffective, such as disseminating prescribing information or clinical guidelines in written form only. In Vietnam, an intervention study in Hai Phong aimed at drug utilization at Community Health Stations, “Tram Y Te”, as well as public education through various media resulted in decreased irrational dispensing of antibiotics and injections, as well as improved dispensing of full antibiotic courses. Public knowledge regarding these issues also improved (Chalker, 2001). Stenson et al., (1997) concluded that interventions to optimize provider practice needs to be context-sensitive and based on an understanding of the range of factors which determine or influence provider behaviour. Success of regulation is often strongly influenced by the general socioeconomic context. All interventions, especially in the private health care sector, need to take the “business-profession” dilemma into account, i.e. that it might be harder to change provider or dispenser practices if such changes result in diminished revenue (Cederlöf & Tomson 1995; Stenson et al., 2001a).

Educational approaches aim to empower providers in their health service role by providing information. Among physicians, problem-based basic professional training, face-to-face education, peer groups, interactive group processes to review and apply information about appropriate use of medicines are all methods that have been proven effective for improving prescribing (Lundborg et al., 1999; Wahlström et al., 1997; Laing et al., 2001). Providing a combination of written material such as newsletters reinforced by education such as a group seminar has been shown to improve antibiotic prescribing (Angunawela et al., 1991). Santos et al., (1996) showed that a formal seminar had a greater impact than a small-group, face-to-face intervention in changing prescribing practices for diarrhea. In private pharmacies, brief one-on-one meetings, followed by small-group training sessions was effective in improving diarrhea treatment in Kenya and Indonesia (Ross-Degnan et al., 1996). As most antibiotics are used outside the control of physicians, improved pharmacy staff skills in identifying and managing common diseases might have a great impact on the rational use of antibiotics. These could be aimed at improving case management of the most common complaints, through questions recognizing early danger signs and, when indicated, referring to a physician or dispensing the appropriate drugs and advice. Educations aimed towards the community are of importance, as patient demand and social expectations are important factors influencing provider practice (Paredes et al., 1996).

Management strategies try to influence usage by improving decision-making processes and monetary incentives. At national level, National Drug Policies have the goal to make effective and safe drugs of good quality available and affordable for all, as well as promoting their rational use. Essential Drug Lists contain the basic medications required to treat prevalent diseases and help providers to choose cost-effective treatments. Standard treatment guidelines (STG) including comprehensive, evidence-based information regarding treatments and selection of drugs can be developed for each level of care, public and private, based on the local disease pattern, the resources available, the competence of prescribers and dispensers, and the results from available antibiotic resistance data (Grimshaw & Russell, 1993). They can be centrally produced on a national or regional level, as well as locally by drugs and therapeutics committees, established at hospitals or in regional health authorities and introduced with an intensive training program (Laing et al., 2001). By encouraging rational use of drugs and infection-control, this might prevent the transmission and spread of resistant organisms. In low-income countries, this strategy has been shown to improve case management of malaria (Ofori-Adjei & Arhinful 1996; Nabiswa et al., 1993) and quality of care at 8 public provincial hospitals in Laos (Wahlström et al., 2003).
Laws, regulations and enforcement mechanisms may have a large impact on provider practice, ensuring that a minimum quality of service is delivered (Brugha & Zwi, 1998; Goel et al., 1996; 1999; Quick et al., 1991). In most high-income countries, there are prescription laws that prevent self-medication with drugs that have adverse effects or socially undesirable externalities, such as steroids and antibiotics, and direct health care seeking towards the health care sector. In low-income countries, although regulations commonly exist, the regulatory authorities often lack resources for effective implementation and enforcement, limiting their ability to influence private sector activity (Hongoro & Kumararayake, 2001; Stenson et al., 2001a). According to the Vietnamese regulations, there are 10 over-the-counter (OTC) antibiotics for which a prescription is not needed (MoH, 1997). However, in practice all antibiotics as well as other drugs are sold OTC without a prescription request. An improved enforcement of regulations might decrease the irrational dispensing of prescription-only antibiotics, e.g. cephalosporin’s and quinolones, saving these drugs as second-line drugs for serious cases.

On the other hand, successful treatment of common diseases such as STDs often requires these drugs, e.g. Ciprofloxacin for Gonorrhea. As many patients are reluctant to seek physician’s assistance, due to cost, time consumption and loss of income as well as stigmata, especially for STDs, these infections might go untreated, increasing the further spread in society (Chalker et al., 2000). Having and enforcing a strict prescription policy, without providing adequate and affordable access to medical consultation and treatment, might be contra productive in reducing the morbidity from infectious diseases. There are few studies regarding regulatory interventions for the rational use of drugs and improved practice, particularly in private pharmacy settings in low and middle-income countries. One exception is Lao PDR, where a regulatory intervention was conducted to improve the quality of service in private pharmacies (Syhakhang, 2002; Stenson et al., 2001a).

Technical support such as diagnostic tests might also improve drug utilization. One such test is C-reactive protein (CRP) for the discrimination between bacterial and viral infections (Babu et al., 1989; Peltola & Jaakkola, 1988; Hansson et al., 1995). The use of CRP test in primary care has been shown to decrease unjustified antibiotic prescribing for ARI (Hopstaken et al., 2003) as well as being cost-effective, due to decreased laboratory utilization (Dahler-Eriksen et al., 1999).

Multi-faceted intervention strategies to promote evidence-based care in high-income countries have been shown to improve provider knowledge and practice (Brugha & Zwi, 1998). In low and middle-income countries, a wider range of factors needs to be considered, especially factors which contribute to discrepancies between provider knowledge and practice, such as patient demands (Paredes et al., et al., 1996). Involvement of the key stakeholders, including policy makers and private practitioners, is crucial. Interventions need to be inexpensive, practical, efficient, effective and sustainable over the medium to long term. Multi-faceted strategies may include locally adapted relevant education of providers, patients and communities, feasible mechanisms for ensuring and monitoring service quality as well as self-regulation by provider organizations or provider accreditation (Brugha & Zwi, 1998).

METHODS FOR ASSESSMENT OF PROVIDER BEHAVIOR

When aiming to assess provider behaviour there are several things to consider when choosing an assessment method: (i) The reliability – whether the method is reproducible at different times and with different observers - is important, as the effect often is monitored on
change of a few selected variables, the intervention is aimed to change, (ii) The validity of
the method, if it is appropriate for what is intended to be measured. E.g. after an educational
intervention, is the aim to assess the impact on theoretical knowledge or on improved
behaviour or both? (iii) The risk of observation bias has to be considered, as the observed
person might adjust his/her responses and behaviour in a more socially acceptable direction
(Madden et al., 1997).

It is important to know the specific context in which the study is conducted. There may be
context-specific confounders, due to different factors shaping provider behaviour such as
different levels of pharmaceutical and medical knowledge, economic incentives and
customer expectations (Cederlöf & Tomson, 1995). The economic incentives are a strong
force, especially in the competitive private sector. Customer expectations - or perhaps to an
even higher degree provider conceptions of customers’ expectations - have a great impact on
practice (Cederlöf & Tomson, 1995), as well as drug regulations and the extent to which they
are implemented (Hongoro & Kumaranayake, 2001; Stenson et al., 2001a).

There are several different and complementing assessment methods that can be considered:
Provider self reports, interviews through structured (closed response) and semi-structured
(open response) questionnaires, assessing mainly knowledge, verbal explanations assessing
competence, demonstration and observation at site, assessing performance as well as exit
interviews and simulated client method (SCM) assessing practice (Madden et al., 1997).

<table>
<thead>
<tr>
<th>Method</th>
<th>Reliability/ Reproducibility</th>
<th>Recall bias</th>
<th>Observation bias</th>
<th>Assess Practice</th>
<th>Assess Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reports</td>
<td>Poor</td>
<td>Yes</td>
<td>Yes</td>
<td>Poor</td>
<td>Yes</td>
</tr>
<tr>
<td>Structured questionnaires</td>
<td>Good</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
<td>Yes</td>
</tr>
<tr>
<td>Standardized case histories</td>
<td>Good</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Observation</td>
<td>Poor</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Exit interview technique</td>
<td>Poor</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>SCM</td>
<td>Good</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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</table>

Practice can be assessed by asking providers to describe their typical and most recent client
cases. However, self-reports are problematic due to poor recall, lack of relevant experiences
and observation bias towards the most socially desirable response (Madden et al., 1997).
Moreover, as the provider experiences differ, the reproducibility needed to use this indicator
as a reliable assessment method is lacking.

Still, reproducibility can be achieved by interviewing providers how they would manage
standardized case histories, e.g. using structured questionnaires with closed questions of true-
false or multiple choice character, or semi-structured questionnaires with open-ended
questions. The former assesses theoretical knowledge and the latter more practice-based
knowledge. As with self-reports, interviews have the disadvantage of observation bias
towards the most socially desirable response (Madden et al., 1997). However, the same
questionnaire can be used both pre and post intervention, and the interviewer can be trained
to act in a reproducible way. Hence structured and semi-structured questionnaires may
achieve a high reproducibility and reliability.

Another method is to observe the behaviour in a specific situation, e.g. a patient contact or a
dispensing situation. This method seeks to monitor behaviour. In this case, the provider
knows he is being assessed, and so there is a risk of observation bias. Withholding the information that he is being observed and playing the role of e.g. a colleague or a cleaner might reduce this confounder (Madden et al., 1997). However, in assessing interventions, the method has yet another drawback as the manner in which the customers present their cases cannot be controlled for, making the reproducibility and reliability low, decreasing the possibility to assess impact of e.g. an intervention in a generalized way.

Practice can also be assessed through exit-interview technique, when interviewers wait outside the providing facility and conduct interviews with exiting customers (Igun, 1987; Kloos et al., 1986; Lansang, 1990). This method gets around the problem with observation bias, as the assessed health worker does not know that he is being assessed. There are some other disadvantages, though. The account of the provider is second hand, as she/he is untrained and unprepared. The response might be biased due to time constraints or considerations related to issues of integrity. It is also difficult to compare different customer experiences, as their cases differ as do the ways in which they communicate about them (Madden et al., 1997). As with observation studies, it is not possible to assess impact of e.g. an intervention in a generalized way, as the manner in which the customer presents the case cannot be controlled for and reproduced.

The SCM has been used for over 20 years to study health-care provider behaviour in a first-hand way, while minimizing observation bias. It is a practical and consistent and reasonably economic way for studying health provider behaviour. It has become increasingly common globally (Madden et al., 1997; Ross-Degnan et al., 1996; Thamlikitkul, 1988; Tomson & Sterky, 1986; Tuladhar et al., 1998; Adu-Sarkodie et al., 2000; Garcia et al., 1998). It has proven useful in the study of physicians, drug retailers, and family planning services. In SCM, research assistants with fictitious case scenarios (or with stable conditions or a genuine interest in the services) visit providers and request their assistance. Providers are not aware that these clients are involved in research. Simulated clients later report on the events of their visit and these data are analyzed. As the client can be trained to act in a reproducible way, the health care provider can be assessed with a "fine calibrated instrument", achieving reliable results both pre and post intervention.

Among the methods described, from interviews through structured and semi-structured questionnaires to the SCM, the latter seems to be the most suitable method for assessing interventions to improve provider behaviour, as they are reproducible, providing a high level of reliability in the assessment. Several studies have shown that questionnaire response differs consistently from practice, measured by SCM (Thamlikitkul, 1991; Igun, 1994), indicating that the methods yield different information (Madden et al., 1997). The questionnaire captures provider knowledge to a higher extent but misses the impact of other incentives important for practice. On the other hand, the SCM captures practice but will not be able to separate the impact of knowledge, or lack of it, from other incentives. Hence, a combination of these methods might be the most desirable in assessing interventions.
METHODS

The methods used in this thesis are summarized in Table 2:1.

Table 2:1. Scientific design

<table>
<thead>
<tr>
<th>Study</th>
<th>Study areas</th>
<th>Design</th>
<th>Methods</th>
<th>Sample size</th>
<th>Data collection</th>
<th>Data Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cao Bang</td>
<td>Cross sectional</td>
<td>- Prescription analysis - Interviews with</td>
<td>40 health facilities , 40 private DO and 40</td>
<td>2400 prescriptions, 1200 names of drugs sold, 200</td>
<td>χ², t-test</td>
</tr>
<tr>
<td></td>
<td>Hanoi</td>
<td></td>
<td>medical records</td>
<td>public DO 20 remote health facilities.</td>
<td>interviews with doctors and 200 medical records.</td>
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<td></td>
<td>Thanh Hoa</td>
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<td>Lam Dong</td>
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<td>HCMC</td>
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<tr>
<td>II</td>
<td>Bavi, Ha Tay</td>
<td>Cross sectional</td>
<td>- Susceptibility test of respiratory bacteria</td>
<td>200 children, 1-5 years of age</td>
<td>-400 specimens from naso-pharynx and throat</td>
<td>χ², t-test</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Interviews with carers</td>
<td></td>
<td>-166 interviews</td>
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<tr>
<td>III</td>
<td>Bavi, Ha Tay</td>
<td>Case – Control</td>
<td>- CRP test - Interviews with carers</td>
<td>Study group: 100 children 1-6 years who were</td>
<td>- 135 capillary blood samples - 135 interviews</td>
<td>χ², exact-test</td>
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<tr>
<td></td>
<td></td>
<td>study</td>
<td></td>
<td>prescribed antibiotics. Control: 35 children</td>
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<td>t-test</td>
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<td></td>
<td>considered healthy</td>
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<tr>
<td>IV &amp; V</td>
<td>Hanoi</td>
<td>Cross sectional</td>
<td>- Interviews with pharmacy staff - SCM</td>
<td>- 60 randomly selected private pharmacies in</td>
<td>- 70 interviews with pharmacy staff - 297 SCM</td>
<td>χ², t-test</td>
</tr>
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<td></td>
<td>Hanoi.</td>
<td>encounters</td>
<td></td>
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<tr>
<td>VI</td>
<td>Hanoi</td>
<td>Randomized control</td>
<td>- SCM</td>
<td>- 58 randomly selected private pharmacies in</td>
<td>- 4800 SCM Encounters</td>
<td>Summary statistics and Wilcoxon signed rank test</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hanoi.</td>
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</tbody>
</table>

DO: Drug outlets; SCM: Simulated client method

STUDY AREAS

Vietnam can be divided into three different demographical areas: major cites, delta provinces and remote mountainous provinces. In study I, six out of Vietnam’s 53 provinces were selected to represent the Vietnamese pharmaceutical situation, 2 from each kind of demographical area, and of these one in the south and one in the north. Stratified sampling was used, based on demographic, financial and logistic conditions. Hanoi and Ho Chi Minh City (HCMC) were selected to represent major cites. Thanh Hoa and Khanh Hoa, representing delta provinces, and Cao Bang and Lam Dong, representing remote mountainous provinces, were selected at random. As seen from Table 2:2, there are great differences between the study areas in terms of resources and health where e.g. the GDP per capita is almost six times as high, and the infant mortality rate six times as low, in HCMC, compared to Cao Bang.

Table 2:2. Demographic data for the study areas

<table>
<thead>
<tr>
<th>Major urban areas</th>
<th>Delta provinces</th>
<th>Mountainous provinces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanoi</td>
<td>HCMC</td>
<td>Hatay (Bavi)</td>
</tr>
<tr>
<td>Population</td>
<td>2844100</td>
<td>493600</td>
</tr>
<tr>
<td>Area (Km²)</td>
<td>972</td>
<td>2090</td>
</tr>
<tr>
<td>GDP per capita (PPP) (USD)</td>
<td>3588 5209 1006 946 1870 1023 892</td>
<td></td>
</tr>
<tr>
<td>Adult literacy rate (%)</td>
<td>97 94 91 91 91 91 62</td>
<td></td>
</tr>
<tr>
<td>Life expectancy male</td>
<td>73 71 66 66 68 69 56</td>
<td></td>
</tr>
<tr>
<td>Life expectancy female</td>
<td>78 79 76 74 74 75 66</td>
<td></td>
</tr>
<tr>
<td>Infant mortality (1999)</td>
<td>11 10 42 42 38 24 62</td>
<td></td>
</tr>
<tr>
<td>Doctor per 100,000 pop</td>
<td>58 66 28 29 34 45 42</td>
<td></td>
</tr>
<tr>
<td>Private pharmacies (nr)*</td>
<td>1033 1445 - 55 59 - -</td>
<td></td>
</tr>
</tbody>
</table>

**Bavi district in Hatay province (Study II & III)**

Study II and III were carried out in the Bavi district, Hatay province, 60 Km northwest of Hanoi. It is a north Vietnamese rural district including low-, middle- and high-land areas totalling about 410 square Km, with altitudes ranging from 20 to 1297 meters above the sea. The district is situated within the Red River delta area. The climate is monsoon tropical climate with a warmer and wetter season during May - October and a cooler drier season during the rest of the year. Bavi district includes 32 communes. The district had 241 812 inhabitants in 1999, about 91% belonging to the ethnic group of Kinh, the major ethnic group of Vietnam. Minority ethnic groups live in the mountains areas, most of them farmers. Agricultural production and livestock breeding are the main economic activities. Life expectancy at birth in Bavi is estimated at 78.8 years for females and 71.1 years for males (Thorson, 2003). In 1999, the median reported monthly income per household member was 61,000 Vietnamese Dong, or 4.4 USD. In the district there is one district hospital and 32 Community Health Stations (CHS), 3 private pharmacies (with license), a few private practitioners and, according to estimations, roughly 16 drug outlets. In this area, an epidemiological cohort study, the Epidemiological Field Laboratory in Bavi (Filabavi), is being conducted involving a random sample of 67 villages (out of 352 villages in total) with 11,089 households, including approximately 51,000 individuals, representing about 22% of the total population.

**Hanoi (I, IV, V & VI)**

Study I, IV, V and VI were carried out in Hanoi, the capital of Vietnam. Second only to HCMC in population and economic importance, Hanoi dominates the north and is the country's political centre. It is an important agricultural and manufacturing centre and the major transportation centre for the north, with roads and railway lines providing links to all other major Vietnamese cities. Hanoi is divided into four administrative districts: Hoan Kiem, Ba Dinh, Dong Da and Hai Ba Trung. There are 63 public hospitals and 118 commune health centres. The public pharmaceutical network in Hanoi includes more than 20 pharmaceutical factories producing drugs, more than 40 pharmaceutical companies functioning as wholesalers, 70 public pharmacies and 118 drug outlets at 118 rural commune health centres. Health care services in the private sector have mushroomed. There are 3 private hospitals including one joint venture, 2,043 private clinics, 1,727 private pharmacies, 60 pharmaceutical companies and 237 private drug outlets. The majority (70%) of the private health facilities are located in urban areas (Dinh, 2002; DAV, 2002; Chuc, 2002). In 1998, infectious diseases dominated the leading causes of morbidity in Hanoi, including acute bronchitis, pneumonia and dengue fever. Also, some non-communicable diseases like mental and behavioural disorders and hypertension were prevalent. The leading cause of mortality included pneumonia as well as tuberculosis and measles (MOH, 1998; Chuc, 2002).
PHARMACEUTICAL SECTOR IN VIETNAM (I)

The data were collected in 1994 during the course of a larger, on-going comparative National drug policy (NDP) research project, organized jointly by the WHO (EDM), Harvard School of Public Health and the Karolinska Institute (IHCAR). The methodology used in this project has been presented in detail previously (Brudon-Jakobowicz et al, 1994).

Sampling

Forty public district health facilities with drug outlets and forty private pharmacies in the two major cities and in the two delta provinces as well as twenty remote mountainous health facilities in the delta provinces and remote mountainous provinces were selected by proportional stratified sampling methodology (Table 2:3). In each area, a proportionate number in relation to the total number of pharmacies in each type of health facility were selected. In Hanoi e.g., there are 1033 private pharmacies. This number was divided by the total number of pharmacies in the study areas, 2592, and multiplied by the total number of pharmacies selected for the study, 40. Twenty remote health facilities, classified by the Vietnamese government in a national list of remote mountainous health facilities outside the main road system, were selected, 14 in the remote areas and 6 from the delta provinces.

Box 2:1. Private pharmacies vs. drug outlets

To operate a private pharmacy the licenser must be a pharmacist or assistant pharmacist with at least five years experience. For a private drug outlet the owner must be a pharmacist, an assistant pharmacist, elementary pharmacist or pharmacy technician with at least 2 years experience. In general, the drug outlets are smaller than the pharmacies. Of the private pharmacies 84% are located in urban areas and 56% in the two biggest cities HCMC and Hanoi. Of the private drug outlets 75% are located in rural areas. For public drug outlets located at community health centers the financing comes from the communal people committee. These are however increasingly being privatized (Chuc, 2002; MOH, 2001).

Table 2:3. Sampling design

<table>
<thead>
<tr>
<th>Major cities</th>
<th>Delta provinces</th>
<th>Remote provinces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanoi</td>
<td>HCMC</td>
<td>Thanh Hoa</td>
</tr>
<tr>
<td>Population</td>
<td>2641000</td>
<td>4989600</td>
</tr>
<tr>
<td>HF</td>
<td>6 (9)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Public DO</td>
<td>6 (21)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Private DO</td>
<td>15 (1033)</td>
<td>21 (1445)</td>
</tr>
<tr>
<td>Remote HF</td>
<td>-</td>
<td>6 (13)</td>
</tr>
<tr>
<td>HCMC= Ho Chi Minh City; HF= health facility; DO= drug outlet. Total number in brackets. In Thanh Hoa and Khanh Hoa 4 and 2 of the HF were categorized as remote HF, respectively.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indicators and data collection

The outcome indicators (Table 2:4) provide information on: availability of essential drugs, affordability of essential drugs and rational use of drugs. These outcome indicators are measured by a percentage or a figure based on information obtained through surveys.

Table 2:4. Outcome indicators

<table>
<thead>
<tr>
<th>Availability of essential drugs</th>
<th>Affordability of essential drugs</th>
<th>Rational use of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of drugs from a basket of drugs available in a sample of remote health facilities, out of total number of drugs in the same basket.</td>
<td>Average retail price of standard treatment of pneumonia, out of the average retail price of a basket of food.</td>
<td>Number of children under five with diarrhoea receiving antidiarrhoeal drugs, out of the total number of children under five with diarrhoea surveyed.</td>
</tr>
<tr>
<td>Number of drugs at the lowest price from a basket of drugs, out of total number of drugs in the same basket.</td>
<td>Value of a basket of drugs, out of the value of the same basket with the cheapest drugs.</td>
<td>Number of prescriptions with at least one injection, out of the total number of prescriptions surveyed.</td>
</tr>
<tr>
<td>Average number of drugs per prescription.</td>
<td>Number of children under five with diarrhoea receiving antidiarrhoeal drugs, out of the total number of children under five with diarrhoea surveyed.</td>
<td>Number of children under five with diarrhoea receiving antidiarrhoeal drugs, out of the total number of children under five with diarrhoea surveyed.</td>
</tr>
</tbody>
</table>
To assess the outcome indicators, the following information was collected: the first 30 prescriptions on the visiting day in public and private drug outlets; names of the 30 first-sold drugs in the private drug outlets; names of the 30 best-selling and cheapest drugs from each private drug outlet. Five interviews with randomly selected prescribers and five medical records of children under five with diarrhoea were collected in each of the district health facilities (Table 2:5). The collected information consisted of 2400 prescriptions, 1200 names of drugs sold, 200 interviews with doctors and 200 medical records. The values of forty treatment records (prescriptions) for pneumonia were collected from each health facility and the average price was calculated. Twenty bills from the remote mountainous health facilities were collected. In order to evaluate the average stock out time for the basket of 10 ED, twenty record books were collected.

A reference basket of 10 EDs was selected among the most used EDs of major public health importance in the country to investigate dispensing, prescribing, availability and accessibility of EDs (Table 2:6). The EDs were expected to be available at all times in adequate quantity and appropriate dosage forms.

### ANTIBIOTIC USE AND RESISTANCE IN BAVI (II)

#### Sampling

The study population consisted of children aged between 1-5 years selected from 225 households in five of Bavis 352 villages. The five villages were randomly selected from the 67 villages within the Filabavi study population. Villages more than one hour’s distance (about 30 Km) from Bavi hospital were excluded from the sampling. In collaboration with the village leaders, the children were selected through modified cluster sampling (Bennet et al., 1994). A few blocks in the villages were randomly selected, and then the interviewers and the personnel, collecting specimens, went from house to house, and selected the children within the selected age cohort, as well as interviewing the carers.

---

**Table 2:5. Data collection for the outcome indicators**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Drug outlets</th>
<th>Health facilities</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first 30 prescriptions on the visiting day</td>
<td>30</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>The 30 first sold drugs</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>The 5 cheapest drugs</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Interviews with randomly selected prescribers</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Medical records of children under five with diarrhoea</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Availability of 10 Essential drugs</td>
<td>-</td>
<td>-</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 2:6. Reference basket with 10 ED used for the surveys**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>Tab. 500 mg</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Tab. 200 mg</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Cap. 250 mg</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Tab. 150 mg</td>
</tr>
<tr>
<td>Ferrous salt</td>
<td>Tab. 60 mg</td>
</tr>
<tr>
<td>Levamisole</td>
<td>Tab. 150 mg</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Tab. 250 mg</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Tab. 100 mg</td>
</tr>
<tr>
<td>Phenoxylmethyl penicillin</td>
<td>Tab. 400000 UI</td>
</tr>
<tr>
<td>Sulfamethoxazole + Trimethoprim</td>
<td>Tab. 480 mg</td>
</tr>
</tbody>
</table>

**Picture 2:3:** The randomly selected villages in Bavi district and the number of children selected in each village: 1. Phu Chau (39), 2. Phu Phuong (36), 3. Tan Hong (42), 4. Van Thang (76) and; 5. Vat Lai (11).

---

29
Antibiotic consumption survey

Antibiotic consumption was assessed through interviews with a structured questionnaire with standardized questions to assess the type of antibiotic used, duration of treatment, where the antibiotics had been purchased and what type of treatment information the carers had retained. The questionnaire was developed in English, translated into Vietnamese and then retranslated into English to check that the sense was maintained. Four experienced local interviewers, working with the Filabavi continuous epidemiological survey, were trained for the questionnaire. All households of the children in the study population, from whom respiratory specimens were collected, were visited, and the carers were interviewed. Staff at Filabavi assisted in translation of the answers, and the data was entered into a computer, using Excel 97. The interviews took place simultaneously with the collection of respiratory specimens.

Antibiotic resistance survey

Collection of specimens: Four microbiologists from Hanoi Medical School were trained to collect naso-pharynx specimens and the culture procedure was discussed and revised according to local conditions. Instruction pamphlets and data entry forms for the susceptibility test were produced and tested. Nasopharyngeal specimens were collected in the households, using a swab with a thin flexible wire shaft and cotton tip, and throat specimens with a swab with a wood shaft and cotton tip. The swabs were immediately placed in isolated tubes with Charcoal transport medium and transported to the Department of Microbiology, Hanoi Medical School, within 12 hours.

Table 2:7. Culture method and antibiotic susceptibility test:

<table>
<thead>
<tr>
<th>Target bacteria</th>
<th>H. influenzae</th>
<th>M. catarrhalis</th>
<th>S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Translucent colonies on the chocolate agar.</td>
<td>Non-pigmented oxidase producing cohesive colonies on the chocolate agar plate.</td>
<td>Typical, non-mucoid or mucoid, optochin sensitive colonies on either medium</td>
</tr>
<tr>
<td>Agar</td>
<td>IsoSensitest agar supplemented with haemoglobin 1% and Isovitalex 1%. Inoculum 10^5-10^6 cfu/ml</td>
<td>IsoSensitest medium supplemented with 5% defibrinated horse blood.</td>
<td>S. pneumoniae ATCC 49619</td>
</tr>
</tbody>
</table>

The plates were incubated at 37°C for 16-20 h in 5% CO_2. The MIC limits for the susceptibility categories, S, I, and R, were those recommended by SRGA. The antibiotic susceptibility was determined using the disk diffusion method standardized according to the Swedish Reference Group for Antibiotics (SRGA, http://www.srga.org) (Olsson-Liljequist & Forsgren, 1997; Bauer et al., 1966; Ericsson & Sherris, 1971). Zone diameter breakpoints were adjusted according to control strains (Kronvall et al., 1988).
ANTIBIOTIC PRESCRIBING IN RELATION TO CRP IN CHILDREN (III)

CRP is one of the major acute phase proteins. The serum concentration of CRP is highest in severe bacterial infections with tissue damage. Serum CRP concentration over 40 mg/L is reported to have a sensitivity of 63% to 79% and specificity of 81% to 90% for the diagnosis of bacterial infections in children (Isaacman & Burke, 2002; Putto et al., 1986).

Study population

The study was conducted at Bavi hospital, in the same district, where study II was conducted. A total of 110 children in the study and 35 in the control group were tested for CRP concentrations in capillary blood. Ten of the tests were rejected, and in total, 100 children were included in the study group. Three study groups and one control group were used (Table 2:8).

Table 2:8. Study groups.

<table>
<thead>
<tr>
<th>Bavi District Hospital</th>
<th>Community health centre</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 79 children age 1-6 years were selected among children seeking health care. <strong>Inclusion criteria:</strong> Receiving antibiotic prescription after examination by a physician.</td>
<td>3. 21 children age 1-6 year subject to a health control were selected. <strong>Inclusion criteria:</strong> Receiving antibiotic prescription after being examined by a doctor. <strong>Exclusion criteria:</strong> Consumed antibiotics within one week prior to the health control.</td>
<td>4. 35 healthy children (age 1 to 6 years), who visited the community health centre for a health control, were selected. <strong>Inclusion criteria:</strong> Children considered as healthy, i.e. showed no sign of infection, during examination by a physician. <strong>Exclusion criteria:</strong> Healthy children who had consumed antibiotics within one week prior to the health control.</td>
</tr>
<tr>
<td>1. Children who were pre-medicated with antibiotics (64)</td>
<td>2. Children not pre-treated with antibiotics (15)</td>
<td></td>
</tr>
</tbody>
</table>

Data collection

Nurses were instructed to take capillary blood samples with a lancet from the fingertip. The blood was collected in a capillary tube and was immediately diluted and lysed in an Eppendorf tube and analyzed in an in vitro test for rapid determination of CRP in human whole blood with NycoCard CRP test system.

Reading and interpretation of results was done by both instrumental and visual readings. Instrumental reading was done, using NycoCard READER MK II measuring range 10-200 mg/L. Visual readings were done by comparing the colour intensity to a reference colour chart. The five zones of the reference colour chart corresponded to the following CRP concentrations in the blood sample: <10 mg/L, 10 - 25 mg/L, 25 -50 mg/L, 50 - 100 mg/L and 100 - 200 mg/L.

Each patient’s carer was interviewed, using a standardized questionnaire, including confounding factors that could interfere with the CRP results; age of the patient, family members’ smoking (passive smoking), duration of disease, if the child had consumed drugs one week preceding the study, and in that case, what type of drugs (antibiotics, steroids, or other drugs). Information regarding diagnosis and drugs prescribed by the physician during examination was also obtained. Staff at Fílabavi assisted in translating the answers, and the data was entered into a computer, using Excel 97.

All participating hospital staff were informed about the study. The doctors informed the carers about the study and testing procedure. It was underlined that participation in the study was voluntary, both for the health personnel and the patients.
PRIVATE PHARMACY PRACTICE IN HANOI (IV, V & VI)

These surveys were part of the European Union supported “Towards Good Pharmacy Practice in Thailand and Vietnam”, a randomized controlled trial with urban private pharmacies as study units. The research was divided into three phases: A) a baseline study assessing knowledge and practice regarding case management of childhood ARI, STD and dispensing of prescription- only drugs, cephalexin and prednisolone. B) The intervention phase with three different interventions applied sequentially: 1. Enforcement of regulation; 2. Education; 3. Peer Influence and C) the evaluation phase.

Study population

From 789 private pharmacies registered in the urban area of Hanoi, hospital pharmacies and wholesalers were excluded. A list of 641 pharmacies remained, and from those, 68 pharmacies were randomly selected. To avoid contamination, pharmacies within 150 metres from the selected pharmacy were excluded. The pharmacies were matched into 34 pairs, according to the following matching criteria: (identified by district inspectors): (i) Turnover: high, medium or low; (ii) Whether or not the pharmacist was the license holder and; (iii) Whether or not the pharmacy was close to a hospital. One pharmacy in each pair was randomly allocated to the intervention group and the other formed to the control group. During the study, five pharmacies dropped out or refused to take part in the last intervention. The five paired pharmacies were excluded. In total, 58 pharmacies (29 pairs) participated in the three interventions.

The sample size 68 out of 641 pharmacies (approximately 10%) was chosen to detect a difference in degree of 20% between the intervention and control group, using the t-test with a significance level of 5% and a power of 90%. This sample size was also assumed to be applicable for the Wilcoxon signed rank test used in the final analysis (VI).
**Tracer conditions**
A “tracer condition” is an indicator to assess the case management or the impact of interventions. It should build on a common complaint or disease, easily recognized and diagnosed (Kessner et al., 1974). Four tracer conditions building on identified public health problems were selected and the ideal questions, treatment, and advice were characterized (Table 2:9): (i) management of a simple upper respiratory tract infection (ARI) in a child less than 5 years old with cough for 3 days. Difficulty or breathing is an important differential diagnostic question to assess weather the condition is serious and demands medical attention; (ii) management of an STD (urethral discharge) in an adult man. STD needs to be diagnosed and treated correctly and referral to doctor is preferable; (iii) requesting some capsules of antibiotic (cephalexin) without a prescription and (iv) requesting some tablets of steroid (prednisolone) without a prescription. All of the scenarios, except the steroid request, had a potential relation to antibiotic use. The specific drugs selected as tracers (prednisolone and cephalexin) are prescription-only drugs that enable monitoring of the pharmacies' compliance with the drug dispensing regulations.

**Table 2.9.** The scenarios used for simulated clients.

<table>
<thead>
<tr>
<th>Tracer Condition</th>
<th>Presentation at the pharmacy</th>
<th>Information in response to questioning.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI</td>
<td>I have a (3,4,5) year old (daughter or son) who is coughing since two days. What should I buy?</td>
<td>Child's condition: somewhat tired, no high fever, no headache; no history of nasal allergy; no breathing problem, eating and drinking normally; the coughing is not very frequent and the child has no pain in the throat. Throat and nose: The child has clear, transparent nasal discharge. The symptoms presented should, interpreted correctly, indicate a mild ARI.</td>
</tr>
<tr>
<td>STD</td>
<td>My friend has a pain when peeing and have pus coming from their urethra for the last 3-4 days. Can you tell me how to assist him?</td>
<td>No symptoms before. Mild fever. Pain when urinating. Pus had a milky appearance the first days then turned more yellow and creamy. Small skin lesions. Intercourse with a few different girlfriends. Don't know if they have symptoms. Haven't seen a doctor. Willing to accept any suggestion</td>
</tr>
<tr>
<td>Steroid request</td>
<td>My back is aching. Could I have 2, 3, 4 or 5 tablets of Prednisolone please</td>
<td>Moderate lower back pain for one week. has been aching before, used Paracetamol, but it didn't help much. No other medical problem. Repetitive movements Recommended to get some Prednisolone.</td>
</tr>
<tr>
<td>Antibiotic request</td>
<td>Could I have 2, 3, 4 or 5 tablets of Cephalexin</td>
<td>Somewhat tired, no fever, no headache, no history of nasal allergy, no breathing problem. 1-2 coughings per hour the last 2 days, no throat pain. Clear, transparent sputum. No drugs have been taken.</td>
</tr>
</tbody>
</table>

**Practice assessed through SCM**
Trained research assistants presented histories of the tracer conditions at the pharmacies, posing as patients or parents, asking the drug outlet staff for advice and treatment. The use of this method to investigate health provider behaviour has become increasingly common globally (Bartolini, 1998; Goel, 1996; Madden, 1997; Tomson & Sterky, 1986, Thamlikiktul, 1988).

Forty volunteers between 25 and 45 years of age were chosen to attend a two-week training course. The training consisted of three parts: (i) the theory of the SCM; (ii) the content of each condition and; (iii) role-play and real life visits to private pharmacies where a professional drama teacher taught the clients to act according to the scenario described in Table 2:9 in a natural and reproducible manner. Out of the 38 trained clients, 20 were selected as clients.

Females were selected as clients in four of the five conditions, males for the STD condition. For every SCM round, each simulated client encountered all the pharmacies, presented the scenario, bought the drugs recommended by the pharmacy staff, and completed record
sheets, no later than 15 minutes after leaving the pharmacy. The clients did not know which pharmacies belonged to the intervention groups or which to the control groups.

Four supervisors, one for each condition, assigned pharmacies for the SCM clients, took care of the incoming drugs and protocols, and monitored the process of SCM. During the baseline study, 297 client encounters were conducted per scenario (IV, V). In total, 1700 SCM encounters were performed (VI).

**Knowledge assessed with the questionnaire (IV, V)**

In Study VI and V, knowledge was studied through means of interviews at pharmacies using a pre-tested questionnaire, assessing pharmacy staff knowledge and attitudes. The questionnaire was developed in English, translated into Vietnamese and then retranslated into English to check if the sense was maintained. The principle of the questionnaire was to find out what the respondent would say that they would actually have done, given a customer requesting assistance for childhood uncomplicated ARI, STD and request for a prescription-only drug without a prescription. Therefore, the questionnaire contained open questions such as “How would you deal with someone who came to you suffering from a urethral discharge?” Four interviewers were trained to use the questionnaire. In the baseline study, 60 pharmacies were visited, and all staff working at the pharmacy at the time of the visit were interviewed. A supervisor coded the answers, which were entered into Epi Info 6. The interviews took place after all the simulated client visits had been completed.

**The intervention package (VI)**

An intervention package including 1. Legal enforcement (LE); 2. Education (ED) and 3. Peer influence (PI) was developed. Each intervention was implemented during 3 months, with 4 months’ post-intervention monitoring of provider practice, using SCM. The intervention package was developed in cooperation with pharmacists who have worked in private pharmacies as well as with the Health Authorities and the Pharmacy Association in Hanoi.

**Enforcement of regulation intervention**

The Regulatory Enforcement Intervention was performed in collaboration with the Hanoi Health Bureau and focused on the regulations of prescription-only drugs. Particular attention was paid to drugs related to tracer conditions (antibiotics, with emphasis on cephalexin and pefloxacine/peflacine, and steroids including prednisolone). Four inspectors from the Hanoi Health Bureau were trained to cover these areas of inspection. The inspectors visited the intervention pharmacies twice, in pairs, with in an interval of one month. During the first visit, in addition to normal inspection procedures, they delivered the regulations regarding prescription-only drugs and then explained them in detail. The examples they gave included pointing out to the pharmacy staff that they should only sell cephalexin and prednisolone with a prescription. During the second visit, these messages were repeated. This was different from the normal inspection, that takes place a maximum of twice a year and focuses on administrative issues, e.g. noting if the licensed

<table>
<thead>
<tr>
<th>Box 2:2. The regulation on prescription-only drugs was issued on April 3, 1995. The following drugs are prescription-only drugs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Narcotic drugs</td>
</tr>
<tr>
<td>2. Toxicological drugs, except anti-malarial drugs and contraceptive drugs Diazepam (5mg can be sold a maximum of 10 tablets without a prescription)</td>
</tr>
<tr>
<td>3. Transfusion products</td>
</tr>
<tr>
<td>4. Injection products, except: Vitamins or combinations of vitamins; Atrophiu sulphate0,25mg/ml; Natri camphosulphonate 0.20g/2ml and;strychnine sulphate 1mg/1ml</td>
</tr>
<tr>
<td>5. Oral antibiotics, except: Amoxycillin, Ampicillin, Chloramphenicol, Erythromycin, Phenoxymethyl penicillin (penicillin V), Tetracycline, Sulfameth and Cotrimoxazole</td>
</tr>
</tbody>
</table>
A pharmacist is present or if the pharmacy staff wears a white coat when selling drugs (Chuc, 2002).

**Educational intervention**

The aim of the intervention was to educate staff in the intervention pharmacies on key issues identified in the baseline to improve case management and chose therapeutically appropriate treatment options. It focused on Questions, Advice and Treatment (QAT) strategies for the 4 tracer conditions: case management of ARI, STD and the use of oral steroids and short course of antibiotics.

Pharmacy treatment guidelines including case management flow charts for ARI and STD (Figure 2:3) for the four tracer conditions were developed by the research team in collaboration with the Hanoi Health Bureau, the Hanoi Pharmacy Association, experts on STDs (the Vice Director of Dermato-venereology Centre of Hanoi), ARIs (a member of the ARI National Programme) and pharmacology (the Director of Pharmacology, Department of Hanoi Medical University).

For ARI and STD case management, the guidelines were developed based on those at the national level (MOH, 1997b; MOH, 1999) and adjusted for the pharmacy setting. For example, for urethral discharge in a man, the National Guideline recommended ceftriazone or spectinomycin for gonorrhoea. These are drugs which need to be injected, and are not available at the pharmacy level. Ceftriazone in particular was not popular at that time and a group of STD experts recommended ciprofloxacin and pefloxacin instead. Guidelines were developed on how to deal with cephalixin and prednisolone requests.

Two senior Vietnamese research team members and two clinicians were trained to implement the intervention. Each intervention pharmacy received two face-to-face educational sessions at the pharmacy. The sessions lasted for 45 minutes, and included both verbal and written information. One session was regarding case management of ARI and short course of antibiotics, the other regarding STD and the use of oral steroids each. Both sessions included information regarding the questions, advice and treatment strategy, emphasizing the value of asking questions to come to a proper diagnosis and correct treatment, to give appropriate advice and to refer if necessary; the role of the pharmacy in primary health care and the importance of GPP (FIP, 1993; WHO, 1994).
Peer Influence Intervention

The aim of the peer influence strategy was to improve local quality assurance work, self-education, self-monitoring and control of drug dispensing among private pharmacy drug sellers (Lassen & Kristensen, 1992). The intervention was developed and contextualised in collaboration with Hanoi Private Pharmacists Association and visiting experts from the collaborating institutions, HSPI and LSHTM. Central issues as team building process, defining criteria for choice of topics, performance, strategy planning, implementing change as well as reviewing and evaluating progress were discussed. Some predicted problems or barriers to change were also discussed. The pharmacies were invited by personal visits from the research group and a representative of Private Pharmacy Association. A letter issued by Hanoi health bureau was shown that briefly presented the objectives of GPP and Peer Review methodology. One pharmacy did not agree to attend, three pharmacies agreed but did not attend.

Hanoi was divided into 5 areas or groups. As there are 30 intervention pharmacies, each group had 5-6 pharmacies represented. In each group, a key person was chosen. A training course with the key persons in each group and one with all pharmacies was held, where the aims and methods of peer influence were presented. Training was given on how to manage the peer groups, how to lead the discussions as well as how to monitor and evaluate progress.

During the first meeting with all participating pharmacy staff, the aims and methods of peer influence were presented. The goals of the peer review were decided on a mutual agreement basis. As suggested by the leading group it was decided that the peer meetings should focus on a few priority problems: case management of respiratory tract infections and STD as well as ways to deal with drugs requests. These objectives were discussed within the group with participatory guidance from a representative of the research group.

During the preceding three-month period, each pharmacy group held five meetings. In the first group meeting each group decided what they wanted to do within the scope of the intervention and evaluated how to apply QAT in their specific setting. During the four preceding meetings, each pharmacy staff member presented one or more client encounters that were discussed among the group members.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

In study I, II and III, the results were coded and entered into a computer using Microsoft Excel and Epi-nfo. Statistical analysis was performed with $\chi^2$ and a 2-tail t-test where p<0.05 was considered as significant. In study III fisher's exact test for small samples was used. The unit of analysis for the statistical comparisons were in study I, the drug outlets and the health facilities, in study II and III the children. In the case-control study (III), there were three study groups: children pre-treated at the hospital, children not pre-treated at the hospital, and children not pre-treated and examined at the community health centre. These groups were compared with each other, and with the control group of healthy children, examined at the community health centre.

For the Study IV, V and VI, all the data forms from simulated clients were kept at the College of Pharmacy in Hanoi. The pharmacies were coded by numbers. One College of Pharmacy staff member was in charge of entering the data. She did not know which pharmacy belonged to the control group or to the intervention group. When entering the pharmacy code, the computer automatically valued “1” for intervention and “0” for control pharmacies. To control the reliability of the entered data, 5% of all forms were checked.
The results were coded and entered into a computer using “Microsoft Access” 1998 and the Statistical Package for Social Sciences for Window Software (SPSS) version 9.0 (a software for data processing and statistical analysis). The pharmacies were the unit of analysis for SCM and questionnaire data as well as for comparisons between SCM and questionnaire data. Analysis of SCM data was also done at the level of individual SCM client encounters at the pharmacies. Statistical analysis was performed with $\chi^2$, Wilcoxon and a 2-tail t-test to determine group differences.

<table>
<thead>
<tr>
<th>Methods Used</th>
<th>Study</th>
<th>Unit of analysis</th>
<th>Data management</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interviews with structured questionnaire</td>
<td>I</td>
<td>Administrative data</td>
<td>Data entered in Epi info and analyst using excel</td>
<td>To test for significance (p&lt;0.05) $\chi^2$ and t-test were used.</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Children</td>
<td>Data entered and analyst using Excel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV, V</td>
<td>Pharmacies/encounters</td>
<td>Data entered in Epi-info, then transferred to Access and analyst with SPSS</td>
<td></td>
</tr>
<tr>
<td>Prescription analysis</td>
<td>I</td>
<td>Pharmacies/encounters</td>
<td>Data entered in Epi info and analyst using excel</td>
<td>Fishers exact test for small samples * Summary statistics and Wilcoxon rank test</td>
</tr>
<tr>
<td>Susceptibility test</td>
<td>II</td>
<td>Isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>III</td>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCM</td>
<td>IV, V, VI*</td>
<td>Pharmacies/encounters</td>
<td>Data entered in Epi-info, then transferred to Access and analyst with SPSS</td>
<td></td>
</tr>
</tbody>
</table>

In study VI, the changes in behaviour among intervention and control pharmacies were tested using summary statistics (Matthews et al., 1990). The main question was the difference in trend between the intervention and control pharmacies. Here, the regression coefficient, i.e. the slope, from a linear regression of each pharmacy, was selected as a suitable summary statistic. The dependent variable was e.g. antibiotics dispensed, measured with SCM. The four rounds of SCM were used as independent variables. The individual effect was then separated from the cohort effect, and the dependence within pharmacies taken into consideration. Since the pharmacies are paired and the distribution of the slopes are unknown but continuous, the distribution-free, Wilcoxon signed ranked test for paired observations was used. If the test shows a difference, the trend of the two groups differs over time/SCM. One pair of pharmacies was excluded from the longitudinal analysis, due to that one just having been visited during two SCMs, and no summary statistics could be estimated. In total, 29 pairs (58 private pharmacies) were used for the statistics.
RESULTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| I | **Pharmaceutical Sector in transition – A cross sectional study in Vietnam.**  
*Availability of Drugs*  
Of the essential drugs assessed 80% were available in remote health facilities. Of the surveyed drugs 53% were sold at the lowest price. Drugs dispensed were 2.6 times more expensive than the cheapest alternative. |
| **Rational Use of Drugs**  
| Public | Private |  
| Average number of drugs per prescription | 3.8 | 3.6 |  
| Drugs prescribed on the ED list | 40% | 36% |  
| Number of prescriptions with at least one injection | 32% | 17% | |

| II | **Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community.**  
*Antibiotic Use*  
A majority of the children (82%) had according to the carers at least one symptom of acute respiratory tract infection (ARI) during the 4 weeks preceding the study. Of all children 75% were reported treated with antibiotics during the four weeks preceding the study (91% of the children with any symptom).  
| **Antibiotic Resistance:**  
High levels of antibiotic resistance and multi-resistant strains in respiratory pathogens (%).  
| **Bacteria** | R | I |  
| H influenzae | 8 | - |  
| S pneumoniae | 6 | - |  
| Amoxicillin | 18 | 6 | - |  
| Chloramphenicol | 24 | 0 | 25 | 3 |  
| Ciprofloxacin | 6 | 6 | 80 |  
| Erythromycin | 4 | 49 | 23 | 3 |  
| Gentamicin | 0 | 0 | 95 |  
| Loracarbef | 2 | 0 | - |  
| Penicillin V | 24 | 60 | 7 | 5 |  
| Tetracycline | 32 | 32 | 88 | 2 |  
| T/S | 44 | 3 | 32 | 12 |  
| Vancomycin | - | - | 2 | 2 |  
| | Most antibiotics were obtained without consulting a doctor. When deciding on treatment 67% consulted a drug seller in private pharmacies, 22% a doctor and 11% decided themselves. Of the antibiotics 80% percent were purchased from private pharmacies, 18% from community health stations and 2% from a national hospital pharmacy. |
| | There was a significant difference in amoxicillin and penicillin resistance between the group of children previously treated with beta-lactam antibiotics and the group of children not having received antibiotics. |

| III | **Antibiotic prescribing in relation to C-reactive protein in capillary blood of children in rural Vietnam.**  
*CRP:* A majority of children who received an antibiotic prescription based on clinical examination did not have an elevated CRP (>10 mg/L), detected in 17% of the study population where 2% had CRP above 25 mg/L, one 36 mg/L and the other 140 mg/L. In the control group none had elevated CRP.  
| **Pre-treatment:**  
Among the children tested at the Bavi District hospital 88% had been pre-treated with antibiotics and 11% with corticosteroids. Not pre-treated children examined in the Bavi hospital had significantly higher frequency of elevated CRP compared to not pre-treated children at the community health centre.  
| **Prescribing:**  
The average number of drugs per patient was 3.1 where 77% received vitamins and 15% corticosteroids in combination with antibiotics. Among 43 antibiotics registered amoxicillin, amoxicillin and chloramphenicol were the most commonly prescribed. |

| IV | **Case management of Childhood ARI at Private pharmacies**  
*Knowledge:* 20% of the pharmacy staff stated that they would dispense antibiotics; 81% stated that antibiotics are not effective in short courses and 53% stated that they would ask the ARI patient questions related to breathing.  
| **Practice:**  
83% of the pharmacies dispensed antibiotics. 47% in courses less than 5 days, 10% asked questions related to breathing. 36% of the cases were managed according to national guidelines. |

| V | **Private pharmacy staff in Hanoi dispensing steroids**  
*Knowledge:* Sixty percent of the pharmacy staff interviewed said that they would not dispense corticosteroids without prescription and 60% could mention some adverse effects.  
| **Practice:**  
All but one pharmacy dispensed corticosteroids without prescription in 76% of the encounters. Questions and advice given to the clients were associated with significantly lower dispensing of corticosteroids. |

| VI | **Improving Private pharmacy practice: a multi-intervention experiment in Hanoi.**  
The intervention pharmacies improved significantly compared to the control pharmacies (P <.05) in all tracer conditions.  
| **ARI** | **STD** | **Drug Request** |
| **BL** | **PI** | **BL** | **PI** | **BL** | **PI** |
| **Antibiotics** | I | 45 | 30 | 42 | I | 22 | 37 | C | 95 | 56 | C | 94 | 89 |
| **Breathing Questions** | I | 11 | 30 | 7 | I | 22 | 30 | C | 24 | 37 | C | 0 | 2 |
| **Acceptable Drugs** | I | 4 | 48 | 29 | I | 1 | 7 | C | 1 | 4 | C | 73 | 58 |

For ARI, antibiotic dispensing decreased (P <.02), questions regarding rapid breathing increased (P <.01). For STD, advice to go to the doctor and dispensing the correct symptomatic treatment increased (P <.01). Dispensing of prednisolone and cephalexin decreased (P <.01) and prescription requests increased (P <.01).
The average number of drugs per prescription was 3.8 in the public sector and 3.6 in the private one. It was found that 17% of prescriptions from private pharmacies and 31% from public pharmacies contained one injection or more.

To assess the availability of EDs, the number of drugs from the basket of 10 drugs (Table 3) available in 20 remote health facilities was investigated. It was found that on average, 80% of the representative EDs were available on the day of the survey.

To assess the affordability in both the public and private sectors regarding the treatment of one of the most common diseases, pneumonia, the average retail price of a standard treatment of pneumonia provided by the National Institute for Tuberculosis and Lung Disease was compared with the average retail price of a basket of food, sufficient to feed one person one day (2100 kcal), provided by the Institute for Nutrition. It was found that the standard treatment obtained in either private or public pharmacies was roughly two-fold more expensive than the basket of food. To assess the price difference between private and public sectors, 2400 prescriptions were collected from public and private pharmacies. It was found that the average expenditure per prescription was 3.3 US$ in private pharmacies and 2.3 US$ in public drug outlets.

### ANTIBIOTIC USE AND HEALTH SEEKING IN BAVI (II)

A total of 166 carers of the study population of 200 children were interviewed. The age of the carers ranged from 19 to 75 years with an average of 33 years (SD:10), median 30 years. The households had on average 1.2 (SD:0.4) children 1-5 years of age. The average age was 3 years (SD:1.2).

Eighty two percent of the children had, according to the carers, at least one symptom of acute respiratory tract infection (ARI) during four weeks preceding the study.

When deciding which antibiotic to use, 67% consulted a seller in a pharmacy, 11% decided themselves, and 22% followed the doctor’s prescription. Eighty percent of the antibiotics were purchased from drug sellers in private pharmacies.
including registered private drug stores as well as drug outlets (small shops and peddlers), 18% from community health stations and 2% from a national hospital pharmacy. Of all children, 75% were reported treated with antibiotics during the four weeks preceding the study (91% of the children with any symptom).

The children were on average treated with 1.3 different kinds of antibiotics (SD: 0.6), 17% had been treated with 2 or more different kinds of antibiotics, of these, 28 had been treated with 2 antibiotics, the most common being ampicillin in combination with: amoxycillin (8); penicillin (5); erythromycin (3) or tetracycline (2). Antibiotics alone or in combination were used on average 3.9 days (SD:2.1), median 3 days, ampicillin 3.3 days (SD:1.8), median 3 days and penicillin 2.6 days (SD:0.7), median 2.5 days. Sixteen carers did not remember which antibiotic they used to treat their children. When treating their children with antibiotics, 87% of the carers said that they paid attention to the information regarding daily dosage, 52% to information regarding how to take the drug (for example together with water), 12% to the total dosage, 8% to contraindications and 3% to the expiry date of the drug. One carer mentioned antibiotic resistance.

**ANTIBIOTIC RESISTANCE IN BAVI (II)**

*S. pneumoniae* was isolated in 106 specimens, where 87 and 19 specimens were found in the nasopharynx and throat, respectively. In six cases, strains were found in both the nasopharynx and the throat specimens from the same child. Hence, 100 of the children harboured *S. pneumoniae*, resulting in a carrier rate of 50%. The carrier rate for *H. influenzae* was 39% (78 specimens), and two strains (3%) were serotype b. The carrier rates for *M. catarrhalis* and *S. pyogenes* were 17% (34 specimens) and 1% (2 specimens), respectively. A total of 163 isolates from 145 children were susceptibility tested. Of the 78 *H. influenzae* strains collected, 74 were susceptibility tested, and of the 34 *M. catarrhalis* strains collected, 27 were susceptibility tested. Of the 106 *S. pneumoniae* strains, 62 were susceptibility tested (57 children). Due to low laboratory capacity locally at a critical stage 44 *S. pneumoniae* isolates were not susceptibility tested. It is not possible to judge whether this gives a bias due to selection. In 74% of the 145 children resistant pathogens were found.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naso-pharynx specimen</td>
<td><em>H. influenzae</em></td>
<td>200</td>
</tr>
<tr>
<td></td>
<td><em>M. catarrhalis</em></td>
<td>34</td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
<td>87</td>
</tr>
<tr>
<td>Throat specimen</td>
<td><em>S. pneumoniae</em></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td><em>S. pyogenes</em></td>
<td>2</td>
</tr>
</tbody>
</table>

Note that one child may test positive for more than one pathogen.

**Figure 3:** Antibiotic consumption among the children in Bavi. Eighty-two percent of the 200 children had symptoms of ARI four weeks preceding the study (left pie chart). Seventy-five % of the children had used antibiotics within four weeks preceding the study (right pie chart). As some antibiotics were used in combination, the percentages add up to more than 100%.

**Table 3:** Bacterial findings Respiratory pathogens recovered from the study population. Numbers and percentages indicate children with positive cultures.
A total of 400 naso-pharynx and throat specimens were collected from 200 children from 166 households. The households had on average 1.2 (SD:0.4) children 1-5 years of age, 31 households (19%) had 2 children and 2 households (1%) 3 children. Of the children, 98 (49%) were boys and 102 girls (51%), and the average age was 3 years (SD:1.2).

**S. pneumoniae resistance:** A total of 56 strains, 90%, of the susceptibility tested strains showed resistance to one or more antibiotics, 29 to more than 2 or more (47%) and 19 to 3 or more (31%). The vast majority (88%) of the S. pneumoniae strains were tetracycline resistant. **Multi-resistance:** As shown in table 3:5, a total of 19 strains (31%) were multi-resistant. Of these, one strain was resistant to 6 of the antibiotics tested, four to 4 and fourteen to 3. Seventeen of the 19 multi-resistant S. pneumoniae strains were resistant to both tetracycline and trimethoprim/sulphonamide. Eight of these strains are also resistant to chloramphenicol, nine to erythromycin, and three strains to both chloramphenicol and erythromycin.

**H. influenzae resistance:** A total of 50 strains, 68% of the susceptibility tested strains, showed resistance to one or more antibiotics, 28 to 2 or more (38%) and 19 to 3 or more (26%). The high intermediate resistance to penicillin V only leaves 15% susceptible. Of the two serotype b strains, one was resistant to 5 antibiotics; ampicillin, chloramphenicol, penicillin V tetracycline and trimetoprim/sulphonamide. **Multi-resistance:** As shown in table 3:7, 26% of the H. influenzae strains were multi-resistant, defined as resistant to three or more antibiotics. Of these, one strain was resistant to 7 of the antibiotics tested, one to 6, ten to 5, two to 4 and five to 3. Nine of the multidrug-resistant strains, 12% of all susceptibility tested H. influenzae, were resistant to the combination chloramphenicol, tetracycline, trimethoprim/sulphonamide, penicillin V and ampicillin. Beta-lactamase test was performed on 38 strains (51%) and, of these, 15 (41%) were beta lactamase producers.

### Table 3:5. Antibiotic resistance for *S. Pneumoniae*

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>S.pneumoniae n=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>R  I</td>
</tr>
<tr>
<td>Trimethoprim/Sulfonamide</td>
<td>R  R  R  R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>R  R  R  R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R  R  R  R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R  R  R  R  R  R  R</td>
</tr>
</tbody>
</table>

| Antibiotic resistant (R) and intermediate susceptible (I) strains |

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>19</td>
</tr>
<tr>
<td>Trimethoprim/sulphonamide</td>
<td>17</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>13</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>4</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>1</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3:6. Multi - resistance for *S. Pneumoniae*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>16</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>15</td>
</tr>
<tr>
<td>Trimethoprim/sulphonamide</td>
<td>12</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>12</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>7</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 3:7. Antibiotic resistance for *H. influenzae*

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>H. influenzae n=74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>R  I</td>
</tr>
<tr>
<td>Trimethoprim/Sulfonamide</td>
<td>R  R  R  R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>R  R  R  R  R  R  R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R  R  R  R  R  R  R</td>
</tr>
</tbody>
</table>

| Antibiotic resistant (R) and intermediate susceptible (I) strains |

<table>
<thead>
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</tr>
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<tbody>
<tr>
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<td>Ciprofloxacin</td>
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| Antibiotic resistant (R) and intermediate susceptible (I) strains |

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</tr>
<tr>
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<td>3</td>
</tr>
</tbody>
</table>

The columns indicate different resistance patterns with R representing resistance to a specific antibiotic. The figures in the last row indicate the number of strains with the specific antibiotic resistance pattern.
M. catarrhalis resistance: A total of 20, 74%, of the susceptibility tested strains showed resistance to one or more antibiotics, 15 to 2 or more (56%) and 5 to 3 or more (19%). The average number of antibiotics, to which M. catarrhalis was found to be resistant (susceptible strains excluded), was 2.1 (SD: 0.9), median 2. More than half of the M. catarrhalis strains were trimethoprim/sulphonamide and penicillin resistant, 59% and 54%, respectively. Further, 19%, 15% and 13% of the strains were ampicillin, chloramphenicol and tetracycline resistant, respectively. Multi-resistance: Two strains (8%) were resistant to 4 antibiotics, both of which were resistant to the combination chloramphenicol, tetracycline, penicillin V and trimethoprim/sulphonamide. Three strains (12%) were resistant to 3 antibiotics, of which all were resistant to the combination of ampicillin, penicillin V and trimethoprim/sulphonamide.

Correlation between use and resistance
In 74% of the 145 children resistant pathogens were found. When the occurrence of antibiotic resistance in bacteria was compared in children with and without prior antibiotic therapy, there was a significant difference related to beta-lactam antibiotic use. Prior treatment with ampicillin or/and penicillin gave a possible higher risk of ampicillin or/and penicillin resistance with an odds ratio of 2.3 (p <0.05).

ANTIBIOTIC PRESCRIBING IN RELATION TO C-REACTIVE PROTEIN (III).
One hundred children, 46 girls and 54 boys, were surveyed for CRP in the study groups. There were no significant differences in age between sexes within the groups. There was a significant difference between the age of children not pre-treated in the hospital, and the age of children in the control group.

Diagnosis
The most common diagnosis was acute respiratory infection (54) followed by asthma (7), tonsillitis (4) and diarrhoea (4) (Table 3:10). Of the children with ARI, 11 (20%) had elevated CRP (≥10 mg/L) and one had a CRP of 140 mg/l.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hospital Pre-treated with Antibiotics</th>
<th>CRP ≥10 mg/L</th>
<th>Hospital Not pre-treated with antibiotics</th>
<th>CRP ≥10 mg/L</th>
<th>CHC Not pre-treated with antibiotics</th>
<th>CRP ≥10 mg/L</th>
<th>All Patients</th>
<th>CRP ≥10 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI / Pneumonia</td>
<td>44</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>54</td>
<td>11</td>
</tr>
<tr>
<td>Asthma</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>-</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Sore throat</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Entritis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Unclear</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>11</td>
<td>15</td>
<td>5</td>
<td>21</td>
<td>1</td>
<td>100</td>
<td>17</td>
</tr>
</tbody>
</table>

* Other diseases include rheumatic fever, whooping cough, conjunctivitis, furunkulus (CRPs 10 mg/L), schema and latitut. One patient CRP 140 mg/L. One patient CRP 36 mg/L. CHC: Community Health Centre.
**Pre-medication**

Data regarding antibiotic consumption within one week preceding the visit to the district hospital was obtained from carers of 73 among the 79 children tested in Bavi district hospital. Of these, 64 children (88%) were pre-treated with antibiotics. Steroids in combination with antibiotics had been given to 9 (12%), and of these, 6 were diagnosed with ARI / pneumonia, and 3 with asthma. There was no significant difference in the frequency of elevated CRP in children pre-treated with steroids compared to those not pre-treated. Other drugs reported being used by 40 of the children included paracetamol (27), vitamins (8), salbutamol (8), ephedrine (6), Oresol (6), atropine (1) and theophylline (1).

**CRP results**

Seventeen (17%) of the children had elevated CRP levels (≥10 mg/L). Of these, 2 children had CRP >25 mg/L, one had 36 mg/L and the other 140 mg/L (Table 3:12). The frequency of elevated CRP levels was significantly (p<0.05) higher among both pre-treated and not pre-treated children in the hospital compared to the control group, where none had elevated CRP levels. There was no significant difference in the frequency of elevated CRP levels between the community health centre group and the control group. There was a significant difference between not pre-treated in the hospital - where 30% had elevated CRP levels - and children in the community health centre, where 5% had elevated CRP levels. Among the children with symptoms lasting less than 72 hours at the hospital, the not pre-treated group had a significantly higher frequency of elevated CRP levels compared to the pre-treated group.

**Table 3:12. CRP levels for the 100 children who were prescribed antibiotics and for the control group.**

<table>
<thead>
<tr>
<th>CRP (mg/L):</th>
<th>Pre-treated in the Hospital</th>
<th>Not pre-treated in the Hospital</th>
<th>CHC</th>
<th>All Children</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>53 (83%)</td>
<td>10 (66%)</td>
<td>20 (95%)</td>
<td>83</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>10-25</td>
<td>10 (15%)</td>
<td>4 (27%)</td>
<td>1 (5%)</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>25-50</td>
<td>-</td>
<td>1 (7%)</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>50-100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>100-200</td>
<td>1 (2%)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>&gt;200</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total (%CRP &gt;10 mg/L)</td>
<td>64 (17%)</td>
<td>15 (33%)</td>
<td>21 (5%)</td>
<td>100 (17%)</td>
<td>35 (0%)</td>
</tr>
</tbody>
</table>

CHC: Children examined at the Community Health Centre not pre-treated with antibiotics within one week prior to the health examination. Control: 35 children considered healthy during health examination that had not used antibiotics one week prior to the study. 1 Abt hospital significantly (P<0.05) higher compared to Control. 2 No Abt Hosp significantly (P<0.05) higher compared to Control. 3 No Abt Hosp significantly (P<0.05) higher compared to CHC.

**Drugs prescribed**

Information regarding the prescribed antibiotics given to the patients was obtained from 42 out of 100 children (Table 3:13). Of all the 100 patients, 82% were prescribed additional drugs. The average number of drugs per prescription was 3.1. Vitamins were prescribed to 77% of the patients, Vitamin C (52%), B1 (54%), B12 (3%), E (5%) and K (1%). Steroids were prescribed to 15% of the study population, and of these 7 were diagnosed with ARI, 6 with asthma, one with rheumatic fever, and one was undiagnosed. Salbutamol was prescribed to 20, of which 14 where diagnosed with ARI, 5 with asthma, and 1 with bronchitis.

**Table 3:13. Type of antibiotics prescribed by the doctors during the consultation (n=42).**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>ARI</th>
<th>Sore throat/tonsillitis</th>
<th>Bronchitis</th>
<th>Other*</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Penicillin &amp; Gentamicin</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biseptol</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin &amp; Gentamicin</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>21</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td>43</td>
</tr>
</tbody>
</table>

*Other disease includes Asthma, Conjunctivitis, Food poisoning, Furuncle, Scrapes, Stomatities and no diagnosis
PRIVATE PHARMACY PRACTICE IN HANOI (IV, V, VI)

Private Pharmacy Profile (IV & V)
Questionnaire interviews were conducted in the 60 intervention and control pharmacies. In five pharmacies two staff were present and both were then interviewed. A total of 70 pharmacy-staff members were interviewed. A pharmacist was present in half of the 60 private pharmacies encountered during the questionnaire survey and most of the pharmacy staff had some basic pharmaceutical training.

ARI case management (IV)
Questions were asked in 90% of the 297 encounters. In the questionnaire, 53% stated that they would ask questions regarding difficulties of breathing. In practice, these questions were asked in only 11% of the encounters.

In 98% of the 297 encounters, drugs were dispensed. Two or more drugs were dispensed in 24% of the encounters. Only 36% of the encounters were managed in line with the existing guidelines. In the questionnaire, 20% of the 70 pharmacy staff said that they would dispense antibiotics. In practice, 83% of the pharmacies dispensed antibiotics in 42% of the encounters, revealing a discrepancy between knowledge and practice. Traditional Medicines such as Bo Phe and Ho Tre Em (registered and accepted for dispensing) accounted for 32% of the dispensed drugs.

<table>
<thead>
<tr>
<th>Knowledge</th>
<th>Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult breathing</td>
<td>53%</td>
</tr>
<tr>
<td>Fever</td>
<td>7%</td>
</tr>
<tr>
<td>Drugs consumed</td>
<td>2%</td>
</tr>
<tr>
<td>Allergy</td>
<td>4%</td>
</tr>
<tr>
<td>Cough</td>
<td>84%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>18%</td>
</tr>
</tbody>
</table>

There was a significant difference (p<0.001, t-test) in cost between the encounters where antibiotics were dispensed, average cost 11180 Vietnamese Dong (VND) corresponding to 0.9 United States Dollar (USD) and the encounters where no antibiotics were dispensed, average cost 4, 913 VND (0.4 USD). The average cost per encounter was 7593 VND (0.6 USD).
Advice was given in 25% of the 297 encounters. The most common advice was drug related and correlated significantly with dispensing of antibiotics. Advice related to Symptoms was only given in 4% of the encounters, the most common were “to recognize danger symptoms” and “to send a child with persistent fever to a doctor”.

**Steroids dispensed on request (V)**

In the questionnaire, 60% stated that they would not sell cortico-steroids; of these 60% justified this by saying that it was against the regulation.

In practice, all but one pharmacy (98%) dispensed cortico-steroids in at least one encounter. In total, corticosteroids were dispensed in 79% of the encounters. Prescription was only requested in 1% of the encounters.

Questions were asked in 43% of the encounters, on average 1.1 question per encounter. Questions relating to significantly less dispensing (p<0.01) were: back-pain; previous steroid use; alternative treatment with another analgesic drug; who had advised you to buy and; why do you want to take prednisolone. Questions relating to significantly more dispensing (p<0.05) were: stomach problems, just wanting the requested amount of tablets.

Advice was given in 57% of all the encounters with an average of 1.47 advice per encounter. Advice related to significantly less dispensing (p<0.01) were: not to use corticosteroids; use other drugs; visit a doctor; take before meals; and to use massage. Advices related to significantly more dispensing (p<0.05) were: information about side effects and recommended to take the drug at least 5-7 days.

Adverse effects were mentioned by 60% in the questionnaire. However, in only 3% of the SCM encounters, the SCM clients were informed about adverse effects.

**STD case management (VI)**

Out of the planned 300 SCM encounters, 297 were recorded. The most frequent question asked (23%) was about whether sexual intercourse had taken place recently. This is an important question for determining if there is a possible STD. In 21% of the encounters, the simulated client was advised to visit a doctor. Only 3% of the drug dispensing was in accordance with the national guidelines for symptomatic STD treatment, and none were given for an adequate number of days and in adequate daily doses for chlamydia.
Prescription-only antibiotics dispensed on request (VI)

Two hundred and ninety eight encounters, where clients requested a first-generation prescription-only cephalosporin (cephalexin) were conducted. In 95% of the encounters, the pharmacies complied with the request, and cephalexin was dispensed. In none of the encounters, the pharmacy staff asked for a prescription.

Pharmacy knowledge versus practice (IV & V)

There was a significant difference (p<0.01) between stated dispensing of antibiotics and steroids (20% and 40%, respectively) compared to the actual dispensing (83% and 98% of the pharmacies in 42% and 79% of the encounters, respectively). Pharmacies stating they would not sell dispensed significantly (p<0.001) less (36% and 73%) compared to the pharmacies stating that they would sell (87% and 60%). All pharmacies that justified not dispensing steroids with it being against the regulation did in practice dispense steroids in at least one encounter. No staff stated that they would sell traditional medicine, but in practice 32% of the drugs dispensed were traditional medicine.

IMPACT OF THE INTERVENTION (VI)

All selected tracer variables except advice to use condom for STD improved significantly (p<0.05) in the intervention pharmacies after the after the intervention package compared to the control group.

ARI Case Management

Questions regarding breathing increased in the intervention pharmacies (from 11% to 30%) and decreased in the control pharmacies (from 10% to 7%) with a significant difference in trends (p=0.01), (Table 3:20). Dispensing of antibiotics decreased in the intervention pharmacies (from 45% to 30%) while it increased in the control pharmacies (from 39% to 42%) with a significant difference in trends (p=0.02).

STD Case Management

Advice regarding consultation with a physician increased in the intervention pharmacies (from 22% to 37%) compared to the control pharmacies (from 20% to 18%). A significant difference in trends (p=0.01) was shown. Correct syndromic treatment increased in both the intervention (from 3% to 30%) and the control pharmacies (from 4% to 19%). However, to a greater degree in the intervention pharmacies with a significant difference in trends compared to the control pharmacies (p=0.01). Advice given to use a condom during intercourse and asking about sexual activities showed no
significant difference in trends between the intervention and the control pharmacies (table 3:21).

### Table 3:18. STD case management. Mean (%) and standard deviation (SD) of encounters. Summary statistics and test of difference between the intervention (I) and control (C) groups across the study time and Trend-line graphs with the means (%) plotted out.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean % (SD)</th>
<th>Summary Statistics</th>
<th>Trend-line graphs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>RE</td>
<td>ED</td>
</tr>
<tr>
<td>Advised the client to go to a doctor</td>
<td>I: 22 (42)</td>
<td>1 (10)</td>
<td>38 (49)</td>
</tr>
<tr>
<td></td>
<td>C: 20 (40)</td>
<td>3 (16)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>Question regarding sexual activity</td>
<td>I: 22 (24)</td>
<td>16 (26)</td>
<td>12 (17)</td>
</tr>
<tr>
<td></td>
<td>C: 24 (24)</td>
<td>21 (24)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Advised condom use</td>
<td>I: 1 (12)</td>
<td>1 (10)</td>
<td>6 (25)</td>
</tr>
<tr>
<td></td>
<td>C: 1 (9)</td>
<td>0 (0)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Correct symptomatic treatment</td>
<td>I: 3 (17)</td>
<td>7 (26)</td>
<td>21 (41)</td>
</tr>
<tr>
<td></td>
<td>C: 4 (19)</td>
<td>9 (29)</td>
<td>15 (36)</td>
</tr>
</tbody>
</table>

BL: Baseline; RE: Regulatory enforcement; ED: Education; PI: Peer influence. Summary statistics mean: Mean of trends over all pharmacies in (I) or (C) group and p-value for difference in trend between the groups. (-): Trends of intervention group; (--): Trend of control group.

### Prescription-only drug request (prednisolone and cephalexin).

Steroid request: Steroids dispensed decreased both in the intervention (from 78% to 17%) and control pharmacies (from 73% to 58%) with a significant difference in trends (p=0.001). Prescription requests increased (from 1% to 18%) in the intervention compared to the control pharmacies (from 1% to 4%) with a significant difference in trends (p=0.002), (table 3:22).

### Table 3:19. Drug Request. Mean (%) and standard deviation (SD) of encounters. Summary statistics and test of difference between the intervention (I) and control (C) groups across the study time and Trend-line graphs with the means (%) plotted out.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean % (SD)</th>
<th>Summary Statistics</th>
<th>Trend-line graphs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>RE</td>
<td>ED</td>
</tr>
<tr>
<td>Prescription request (Steroid)</td>
<td>I: 1 (12)</td>
<td>2 (14)</td>
<td>20 (40)</td>
</tr>
<tr>
<td></td>
<td>C: 1 (8)</td>
<td>1 (12)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Steroids dispensed</td>
<td>I: 78 (42)</td>
<td>65 (48)</td>
<td>29 (46)</td>
</tr>
<tr>
<td></td>
<td>C: 73 (44)</td>
<td>69 (46)</td>
<td>64 (48)</td>
</tr>
<tr>
<td>No drugs, NSAID or TM dispensed</td>
<td>I: 20 (22)</td>
<td>33 (27)</td>
<td>66 (39)</td>
</tr>
<tr>
<td></td>
<td>C: 26 (29)</td>
<td>27 (29)</td>
<td>31 (31)</td>
</tr>
</tbody>
</table>

BL: Baseline; RE: Regulatory enforcement; ED: Education; PI: Peer influence. Summary statistics mean: Mean of trends over all pharmacies in (I) or (C) group and p-value for difference in trend between the groups. (-): Trends of intervention group; (--): Trend of control group; NSAID: Non Steroid Anti Inflammatory Drugs; TM: Traditional Medicines

Cephalexin request: Dispensing of cephalexin decreased more in the intervention pharmacies (from 95% to 56%) compared to control pharmacies (94% to 89%) with a significant difference in trends (p=0.002). Prescription requests increased in the intervention pharmacies (from 0% to 21%) compared to control pharmacies (from 0% to 2%) with a significant difference in trends (p=0.009) (table 3:22).

47
<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean % (SD)</th>
<th>Summary Statistics</th>
<th>Trend-line graphs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean*10^-2</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(S.E*10^-2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-tailed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dispensed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>95 (23)</td>
<td>56 (50)</td>
<td>6.7 (1.9)</td>
</tr>
<tr>
<td></td>
<td>91 (29)</td>
<td>89 (31)</td>
<td>1.1 (0.7)</td>
</tr>
<tr>
<td></td>
<td>60 (49)</td>
<td>79 (41)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>56 (50)</td>
<td>89 (31)</td>
<td>0.009</td>
</tr>
<tr>
<td>C</td>
<td>95 (22)</td>
<td>56 (50)</td>
<td>6.7 (1.9)</td>
</tr>
<tr>
<td>Prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>request</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Cephalexin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0)</td>
<td>21 (41)</td>
<td>6.7 (1.9)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>1.1 (0.7)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>5 (22)</td>
<td>0.009</td>
</tr>
<tr>
<td>C</td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>1.1 (0.7)</td>
</tr>
</tbody>
</table>

BL: Baseline; RE: Regulatory enforcement; ED: Education; PI: Peer influence. Summary statistics mean: Mean of trends over all pharmacies in (I) or (C) group and p-value for difference in trend between the groups. (I): Trends of intervention group; (C): Trend of control group.

Cost for the intervention The cost trends for all four conditions in both the control and intervention groups showed an increase. As the increase was similar in the intervention and control pharmacies there were no significant difference in trends. However, in the STD condition, the cost in the intervention pharmacies increased more than in the control pharmacies with a significant difference (p<0.01) in trends.
DISCUSSION

In Bavi community, 75% of the children had been treated with antibiotics four weeks preceding the study (II), and at the hospital, 88% of the surveyed children had been treated with antibiotics prior to consultation (III). Frequent antibiotic use selects for resistant bacterial strains, suppresses the susceptible flora, and gives resistant strains a comparable advantage to colonize (Lipsitch & Samore, 2002). This increases the risk of colonization or infection with resistant organisms also in people who have not used antibiotics (Lipsitch & Samore, 2002). Four out of five children in the community carried resistant respiratory pathogens (II). Similar results have been found in Hanoi, HCMC and Hue (Törnquist et al., 2000; Parry et al., 2000).

Most antibiotics were used for minor respiratory symptoms such as cough and sore throat (II) as also shown in several other studies (Huovinen & Cars, 1998; Kumar, 1997; Lansang et al., 1990; Perez-Cuevas et al., 1996; Wise et al., 1998; Van Duong et al., 1997). Of the ARI episodes, up to 80% have a viral etiology, where antibiotics are ineffective (Khan et al., 1993; Tupasi et al., 1990). Hence, reducing unjustified antibiotic use for ARI could be an effective way towards containing antibiotic resistance (Schrag et al., 2000). However, appropriate use of antibiotics when indicated is vital, as for pneumonia that is one of the major causes to childhood mortality (Black et al., 2003). This underlines the importance of provider competence to make basic diagnostics including identifying and referring serious cases to physicians, treating according to evidence-based guidelines and questioning drug requests that might be irrational, as set out in the GPP document (FIP, 1993; WHO, 1994).

In Hanoi, private pharmacy case management of ARI, STD and drug requests were poor (IV, V & VI). Few asked about difficulty of breathing, an important differential diagnostic question for detection of pneumonia (IMCI, 2003), although half had recognized its importance during interview. Most pharmacies dispensed antibiotics, although few had stated that they would do so (IV). Similar results have been found in Thailand (Thamlikiktul, 1988). Most pharmacies dispensed prescription- only drugs without prescription (V, VI), although the majority knew about the prescription regulation (V). Few clients with urethral discharge were referred to physicians, although most had stated that they would do so. Almost all were incorrectly treated and virtually none advised condom use (VI). Similar findings have been shown in Peru (Garcia et al., 1998).

Also in the public sector, there seems to be an over-utilization of drugs, including antibiotics as indicated by the high number of drugs and injections per prescription (I). Only 17% of patients, that received an antibiotic prescription, had elevated CRP, indicating bacterial infection (III). In low-income country settings, the high number of patients, lack of time, small resources and lack of laboratory tests makes it difficult to clinically distinguish bacterial from viral infection, and physicians may feel compelled to prescribe antimicrobials to prevent treatment failure due to possible undetected, sub-clinical or secondary bacterial infection (Tomson, 1990; Kunin, 1993; Hardon, 1987).

The most commonly used antibiotics were the beta-lactams ampicillin, amoxicillin and penicillin (II, III & IV). Oral ampicillin has low absorption bioavailability, and more than 50% of the dose taken remains in the intestine, where it is capable of selecting resistance in gram-negative Enterobacteriaceae (Moe et al. 1977), an important reservoir for antimicrobial resistance genes (Levy et al. 1988). These resistance traits may spread to respiratory tract pathogens through plasmid transfer of beta-lactamases (Huycke et al., 1992; Mea-Wan et al., 1998). This may contribute to the beta-lactam resistance levels
observed (II). This is supported by the significant difference in ampicillin and penicillin resistance between the group of children previously treated with beta-lactam antibiotics and the group of children not receiving antibiotics (II). This association between use and resistance has also been documented in other studies (Nasrin et al., 1999; Tsolia et al., 1999).

In Hanoi, an intervention including enforcement of regulation, education and peer review improved case management in private pharmacies. Of importance were the increase in questions regarding breathing, as they might enable detection of severe ARI cases, and furthermore the decreased antibiotic dispensing, and the improved symptomatic treatment for gonorrhoea and chlamydia (VI). Few studies of interventions in private pharmacies with such a robust design have been reported (Goel et al., 1996; Ross-Degnan et al., 1996). With improved case management competence, private pharmacies could fill the role as communicator, collaborator and front-line health care party where certain serious cases could be identified and referred to a physician, and less serious cases treated according to evidence-based guidelines (WHO, 1998).

To achieve a sustainable change towards more rational use of drugs, other measures are also needed, including interventions on the “demand side”, to inform and empower consumers in relation to rational use of drugs, as they are the ultimate decision-makers in the use of medicines (Hongoro & Kumaranayake, 2000; ICIUM, 1997).

METHODOLOGICAL CONSIDERATIONS

Design, study areas and sampling

Study I was a cross-sectional study. As such, it represents the situation in 1994. Since then, there have been further changes, e.g. the National Drug Policy and regulations regarding prescription-only drugs have been implemented (MOH, 1997). To achieve a representative sample for the pharmaceutical sector in the whole of Vietnam, stratified sampling was used, based on demographic, financial and logistic conditions. The regions are very heterogeneous in relation to the development of the pharmaceutical sector. Some provinces, such as Thanh Hoa and Cao Bang, are poor with a BNP per capita around 900 USD, and Hanoi & HCMC are comparatively rich with a BNP per capita of 3600 and 5200 USD, respectively (UNDP, 2001). Although the provinces are supposed to represent the three major types of regions (delta, mountainous and urban in both the north and the south), there might be regional differences not captured by the choice of these provinces.

Study II and III were conducted in Bavi, Hatay province, about 60 Km outside Hanoi. The reason for choosing this setting was access to good logistics and demographical data through the Epidemiological Field Laboratory in Bavi (Filabavi). It is also similar to many other Vietnamese districts in terms of socio-economic condition and health status (Thorson, 2003). During the time of the sampling in March (II), the weather in North Vietnam is misty and characterized by drizzling rain, which might have contributed to the high number of children with symptoms of ARI detected. The health-seeking behaviour with 80% self-medication through private pharmacies as well as the drugs reported, mainly ampicillin and amoxicillin, is in line with other studies in Vietnam (Van Duong et al., 1997; Chuc & Tomson, 1999).

To control for the confounding effect of the high frequency of antibiotic self-medication prior to the consultation at Bavi hospital, the design of study III was altered. Children who
had consumed antibiotics within one week prior to the consultation were excluded in the Community Health Centre. This made the study design complicated, as there were three study groups, children pre-treated with antibiotics at the Bavi hospital, not pre-treated at the Bavi hospital and not pre-treated at the community health centre. The reason for the much smaller control group was the difficulty of finding healthy children for capillary sampling.

Study IV, V and VI were conducted in Hanoi. The reason for choosing Hanoi was the rapid expansion of private pharmacies and the concern regarding their dominance in outpatient care. The randomized controlled trial (RCT) is the cornerstone of clinical medicine to assess effectiveness of interventions (Grimshaw et al., 2001). By using random sampling of the private pharmacies, confounding factors in the environment were assumed to be similar for intervention and control pharmacies. To ensure a similar composition of the intervention and control groups, the pharmacies were paired. The high standard deviation in most variables during the baseline indicated that the pharmacies were heterogeneous. By random allocation of the pairs into the control and intervention groups, the possible effect of this was controlled for, as indicated by the fact that most baseline variables were similar in the intervention and the control group (Diwan et al., 1992). It is thus assumed that the differences found between the intervention and control groups can be attributed to the interventions. Four pharmacies dropped out and one refused to participate. Consequently, the 5 pairs of pharmacies were excluded. However, a potential dropout of pharmacies was predicted, when the sample size was decided upon. Contamination between intervention and control pharmacies cannot be excluded because there is a small average distance between private pharmacies in Hanoi (0.42 km) (Binh & Tiep, 2002). This is also indicated by the improved STD case management in both intervention and control pharmacies (VI).

**Structured interviews**

Structured interviews with questionnaire were conducted in study II, III, IV and V. In all of these, a face-to-face interview technique was used. The presence of the interviewers encouraged the participation and involvement of the respondents, and questions could be clarified during the interview.

The effect on the interview of possible interviewer bias - i.e. that the respondents modify their answers according to what they think the interview want to hear (Yeneneh et al., 1993; Krause et al., 1998) - has not been studied. Data may be affected by characteristics of the interviewers as well as affected by the interactions of the interviewer/respondent characteristics. Interviewers with different backgrounds and of different ages conducted the questionnaire interviews. In study II, interviewers were selected from the Filabavi continuous survey. As they had a good context knowledge and experience of interviewing, their capacity was utilized in the design of the questionnaire, which also served as a training opportunity.

Observation bias and the Hawthorne effect, which could be caused due to the subject knowing that they are being studied, might have influenced the results of the study. Respondents may feel their answers are not confidential and answer in a certain way because they think they are being checked (Sarantakos, 1998). Among pharmacy staff, the difference between knowledge and practice supports this assumption (IV & V). However, as random sampling was used, it can be assumed that there was no difference between the intervention and the control groups in terms of the Hawthorne effect.

The length of the recall period has been shown to be an important factor influencing the quality of data (Kupec et al., 1999). A four-week recall period has commonly been used to
measure health status and use of health services (Coppo et al., 1992; Henderson et al., 1994; Asenko-Okyyere et al., 1997; Kupek et al., 1999). However, some researchers have suggested that that a two-week recall is more appropriate for measurement of acute diseases (Kroeger, 1983; Tipping & Segall, 1996; Felming & Charlton, 1998). The reliability and validity of a respondent’s recall is also influenced by the importance of the event. In Study II a four-week recall period was used, based on experiences from other studies conducted in Vietnam (GSO, 1994; Tipping & Segall, 1996). It has been demonstrated that carers in Vietnam can account quite well for their children’s treatment in case of disease (Halfvarsson et al., 2000), possibly due to the high literacy rate, helping the interviewees to remember and answer correctly about symptoms or diseases, health-seeking behaviour, drugs used, etc. (Coppo et al., 1992; Hederson et al., 1994; Toan, 2001). The interviewers were instructed to ask for evidence such as packages or tablets of drugs mentioned, and they also brought some drug samples along to facilitate recognition by the carers. However, no strategy was used to verify the results obtained through the questionnaire, e.g. via a urine test (Catalano et al., 1990). Hence, the results must be considered indicative. In Study III, a one-week recall time was used to control for antibiotic and steroid use as confounders affecting the measured CRP level (Babu et al., 1989).

SCM

To prevent the clients’ individual behaviour from affecting the pharmacy staff, all clients were trained to act in a reproducible way, and they were not informed about which pharmacies were intervention or control ones. The scenarios, including who should be present at pharmacies for each of the tracer conditions, were discussed between the research team, the Hanoi Health Bureau and the Hanoi Pharmacy Association in order to maximize the similarity of a “simulated” and a “real” client. To avoid the attention and recognition of pharmacy staff members, five different clients per condition visited each pharmacy. Recognition of the clients by the pharmacy staff is unlikely, as each client only encountered each pharmacy once every seventh month, neither was such recognition reported by the clients. This situation was different from that in an intervention study conducted in Lao PDR, where the researchers/assistant researchers could easily be noticed as being strangers in the rural setting (Stenson et al., 2001b; Syhakhang, 2002).

For the ARI and drug request conditions, females were engaged as simulated clients. This selection was based on the fact that, in Vietnam, women are usually the caregivers in the family (Chuc, 2002). For a mild ARI, the clients visiting the pharmacies were acting as child caregivers, since the child was too young to attend to the pharmacies alone. For the STD case management, the scenario was a male friend with urethral discharge. It was assumed by involved experts that an STD patient would not come to a pharmacy and tell the drug-sellers that he himself was suffering from an STD. He would rather say that he had a friend who was suffering from the condition, or send a friend. Hence five males were engaged as clients.

After the third SCM round, it was found that some clients did not perform their tasks accurately, e.g. one client asked another to take over his work. To avoid stigmatizing those clients, all clients were replaced in the fourth and last SCM round. The new clients received about the same training, including role-playing exercises. This change made the interpretation of the longitudinal trends less robust. However, as it was a randomized control trial, where the simulated clients didn’t know which pharmacies belonged to the intervention or control group, any inaccurate performance would effect both groups similarly, decrease the group difference and the measured effect of interventions. In the last round of SCM, questions regarding sexual activity increased in both the intervention and
control pharmacies, compared to the two previous SCM rounds. This effect might partly be due to the fact that the clients in the last round of SCM were younger than those used in the preceding SCMs.

**Indicators**

The idea of the NDP indicators was to briefly assess the pharmaceutical sector, including the existence of laws and regulations, structures and rational use of drugs. This was part of a multi-centre study using indicators developed by WHO to assess the pharmaceutical sector for national drug policy development and implementation (Brudon-Jacobivicz et al., 1994). There are publications, where indicators are used to monitor drug use in health facilities (Tomson, 1990; Hogerzeil et al., 1993; Syhakhang, 2002). The outcome indicators allow rapid assessments of the general pharmaceutical situation in Vietnam, intended to highlight problems with regard to availability, affordability and rational use of drugs. The indicator to assess availability of drugs, if ten essential drugs were available in twenty remote health facilities, may not be generalized to the whole country, as the remote health facilities received a subsidy responding to 1 US$ per inhabitant per year for drug purchase (Do, 1998). Using the average number of drugs per prescription as an indicator builds on the assumption, that the main problem with drug use relates to over-prescribing; prescribing being considered more rational, if the indicators receive a lower score (Kanji et al., 1992). Two or more drugs per prescription are considered to indicate a problem in prescription practices, as defined by WHO (Rainhorn et al., 1994). However, as the diagnosis and patient history was not recorded, it is not possible to assess the rationality at the individual patient level. The data obtained will only indicate problems, but in order to assess them in detail, further studies are needed.

**Susceptibility test**

The collection of naso-pharyngeal specimens was done using swabs. In order to get a representative sample the swab has to be inserted through the nose to naso-pharynx. The microbiologists engaged to collect the naso-pharynx specimen had prior experience and were trained until satisfactory results were obtained. If substandard specimens had been collected that would have affected the carrier rates negatively. The carrier rates were 44% and 39% for *S. pneumoniae* and *H. influenzae*, respectively. This is as expected and in line with other studies (Parry et al., 2000), and thus the collection procedure seems to have been of a good standard. The swabs were stored in charcoal media and after each day of sampling in Bavi transported to the laboratory at Hanoi Medical University, all within 24 hours.

The primary measurement in the disc diffusion test is the inhibition zone diameter, which is measured and converted into susceptibility interpretations according to zone breakpoints for the S, I and R categories (Kronvall et al., 2003). The zone breakpoints are given by different reference authorities like the National Committee for Clinical Laboratory Standards (NCCLS), the British Society for Antimicrobial Chemotherapy (BSAC) (Phillips at al. 1991) and Deutsche Industrie and the Norm-Medizinische Mikrobiologie (DIN) (DIN 1989). In this study, we used the recommendations by Swedish Reference Group for Antibiotics (SRGA) (Olsson-Liljequist & Forsgren, 1997). There are several problems encountered when trying to compare antibiotic susceptibility results in resistance surveillance, as there are differences between recommended zone breakpoints as well as differences in the standardisations of methodology (Kronvall, 2003). Thus these results should mainly be compared with studies using the same methodology.
The idea with using the CRP test was to get an additional measurement, in order to assess the prevalence of bacterial infections among children that had been prescribed antibiotics. There were several problems, however:

(i) Antibiotic use is a potential confounder that might alter the serum CRP concentration (Babu et al., 1989). To be able to control for this, it was asked for in the questionnaire. However, 88% of the children examined in the Bavi hospital had been using antibiotics prior to consultation. This was regarded as such a strong confounder that the study design was changed in the second part of the study and children with prior use within one week were excluded.

(ii) There was an unexpected low frequency of elevated CRP despite prior clinical diagnosis. Hence, the reliability of the CRP-testing procedure was investigated. The test-kits were stored at 8°C as recommended by the manufacturer and were only exposed to higher temperatures during transportation and use. The measuring procedure was performed according to the attached instructions (NycoCard CRP test system). A possibly confounding factor could be that the CRP tests were performed in a humid tropical climate with a temperature around 30°C (maximum recommended temperature). To evaluate the impact of this fact, the CRP of blood samples was measured directly at room temperature (30°C), as well as after cooling the blood sample in a refrigerator to below 20°C and then measuring the CRP level. The same results within the accepted 15% difference span were obtained with both methods. In the current setting, it is considered unlikely that the high room temperature has influenced the results. The local nurses who collected capillary blood from the children were thoroughly trained in capillary sampling technique, and their performance was monitored throughout the study.

The results in this study are difficult to interpret, as only one case diagnosed with ARI had CRP over 40 mg/L, shown to be a reliable positive predictor for a diagnosis of pneumonia, and that low serum CRP concentration does not exclude bacterial aetiology of respiratory infection (Babu et al., 1989; Korppi & Kroger, 1993). However, a low CRP level in a patient without fulminate symptoms suggests that antibiotic treatment is not indicated for the moment, and that some of these patients have to be re-evaluated about 8 – 24 hours later, to decide if antibiotic treatment is indicated (Table 4:1).

### Private pharmacies and self-medication

Self-medication has been defined as “the selection and use of medicines by individuals to treat self-recognized illnesses” (WHO, 1998). As the majority of the carers reported that they consulted the pharmacy staff and most of the antibiotics dispensed were OTC drugs, it could be argued that the drugs were legally dispensed, and that the condition was discussed with the pharmacy staff and not self-recognized in Bavi (II). Three categories were used to classify the health-seeking behaviour of the carers: consulted a physician, consulted the pharmacy staff, and decided themselves what to buy. However, in Bavi there were only three registered private pharmacies at the time of the study. Hence most of the antibiotics were probably purchased from small private shops with unqualified personnel similar to what has been found in Lao PDR and India (Stenson et al., 2001; Syhakhang 2002; Kamat

<table>
<thead>
<tr>
<th>Duration of disease</th>
<th>CRP (young children)</th>
<th>Suspected genesis of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 day</td>
<td>&lt; 10 mg/L</td>
<td>A second CRP within 8 – 24 hours</td>
</tr>
<tr>
<td>1-7 days</td>
<td>&lt; 10 mg/L, 10-25 mg/L</td>
<td>Viral, A second CRP within 8 – 24 hours</td>
</tr>
<tr>
<td>&gt; 7 days</td>
<td>&lt; 10 mg/L, &gt; 25 mg/L</td>
<td>Viral or low virulent bacterial, Bacterial</td>
</tr>
</tbody>
</table>
The ability to correctly diagnose and treat was probably worse than the poor case management found among the pharmacies in Hanoi, where most pharmacy staff had some basic pharmacy training (IV & V). Based on this reasoning, the concept of self-medication is in study II interpreted as covering all medications not prescribed by a physician.

**The intervention**

Intentionally, the interventions were applied in a sequence; hence the effect of the whole intervention package was assessed, as the study design does not permit separation of the effects of the different interventions. Although not allowed by the study design some observations can be made in relation to the possible effect of each intervention. Few improvements could be attributed to the enforcement of regulation intervention: possibly a slight increase in prescription request for cephalexin, but not for prednisolone, and a decrease in antibiotics dispensed for ARI. Late effects can however not be excluded, as the interventions were implemented sequentially in the same group of pharmacies. After the educational intervention, several variables improved for each condition, including questions regarding breathing, antibiotics dispensed, referral, STD treatment, prescription request and prescription-only drugs dispensed. Pure effects of the peer influence intervention are hard to assess, as the PI intervention was implemented as the last intervention. However, most tracers kept improving, except for antibiotics dispensed for childhood ARI, which was down to 15% after the EI intervention, but then increased to 30%, after the PI intervention. To assess the individual effect of each intervention, another design has to be used, whereby each intervention is separately implemented in an intervention group of randomly selected pharmacies, and compared to a control group.

The assessment of the practice took place one month after the interventions. There was no follow up to assess the sustainability of the intervention effect after the study period. Tuladhar et al. (1998) showed that the effect of an intervention diminishes with time. One of the researchers, Chuc (2002), visited 29 intervention pharmacies 2 years after the last survey and asked the drug sellers if they remembered the content of the interventions, and whether they still kept the regulations on prescription-only drugs and the printed documents regarding the four conditions. Out of 29 pharmacies, five had either closed or had changed license holders. Of the 24 interviewees, 46% remembered the main contents of the interventions. None were able to find the documents, including the pharmacy treatment guidelines.

**Statistical analysis**

In study II, the correlation between use and resistance was assessed, using both odds ratio and chi-square analysis. A more appropriate method would have been to use confidence intervals in combination with odds ratio (Altman, 1991). This was, however, not acknowledged by the author until after publication of the results.

In study IV and V, the pharmacy was the unit of analysis. However, frequently the data was analyzed based on the encounters. It might be argued that by using encounters as the unit of analysis, the power was inflated, as the number of encounters was roughly five times as many as the number of pharmacies (in each SCM round each pharmacy was encountered five times). The encounters conducted in one pharmacy cannot be regarded as independent samples, as the same pharmacy-staff member might have served the client. To control for this, t-test for dependent samples was used.
In the statistical analysis of study VI, linearity of the trend curves was assumed. On an aggregated level, the linearity can be questioned, e.g. the mean values for antibiotic dispensing for ARI dropped from 42% to 15% in the intervention pharmacies after the educational intervention, but then increased 30% after the peer review. However, the applied linear model for each separate pharmacy can be seen to summarize the total trend over all the four SCM rounds in a reasonable way.

**Ethical considerations**

Taking naso-pharynx, throat (II) and capillary (III) samples is harmless although slightly uncomfortable for the children. The carers were thoroughly informed about the study and its aim and of the sample procedures, both verbally and in writing, and before sampling, they gave their consent. The interviewees were informed in advance and agreed to participate (II, III, IV & V).

Most of the ethical questions raised by the SCM (IV, V & VI) stem from its central feature – the blindness of the subjects (Madden et al., 1997; Ross-Degnan et al., 1996; Tomson & Sterky, 1986). One might raise a question about the ethics of performing an act, using benevolent deception (Bok, 1974) to gather information from pharmacy staff. However, the study was done in collaboration with the Hanoi Health Bureau and the Hanoi Pharmacy Association. The leaders of these organizations knew about the study design in advance and furthermore participated in the planning. After the study, the representatives from the study pharmacies were informed of the study design, its methods and the results. It should be pointed out that the potential harm of low-quality pharmacy service, including frequent irrational provision of drugs by the private pharmacies, was considered to be an increasing problem by the national health authorities. Moreover, one should consider the major difficulties involved in obtaining the necessary information on actual practice by using other methods in these contexts, and the obvious advantages of data obtained from real practice. Using only the questionnaire would have grossly overestimated the rationality of private pharmacy practice, whereas the SCM provided a more realistic picture.

**SELF-MEDICATION**

A majority of the surveyed children in Bavi (75%) were treated with antibiotics one month preceding the study (II). This figure corresponds to 9 treatments per year or approximately 39 defined daily doses (DDD) of antibiotics per year (ten 3.9-day courses of antibiotics per year). In Sweden, children in the same age group received 9.9 DDD of antibiotics per year (Apteket AB, 1998). Most of the antibiotics were obtained through consultation with pharmacy staff or the carers deciding for themselves; only 22% were prescribed by a physician. These findings are also supported by the finding at the Bavi hospital, where 88% of the children had been treated with antibiotics within one week prior to examination (III). Self-medication with antibiotics and has been widely reported in low-income countries (Kunin 1983; Etkin et al. 1990; Paredes et al. et al. 1996; Ross-Degnan et al. 1992; Tomson & Sterky, 1986). However, to the knowledge of the author, few studies have shown such high rates of antibiotic use through self-medication. A study in China showed that 51% of children had self-medicated at six or more occasions during a year (Bi et al., 2000). In an ongoing project in Peru and Bolivia, 20% to 35% of the children had used antibiotics within a two-week period, and about half of this use represented self-medication (Kristiansson et al., 2003).
There are several possible reasons for the high frequency of the practice of self-medication: lack of access to health care, poverty, and the stigma associated with having illness, cultural preferences and beliefs (Radyowijati & Haak 2002). In Vietnam, historically, there is a high degree of self-reliance in health care, and traditional concepts of health and disease influence many aspects of health management (Törnquist et al., 2000). Vietnamese women are often the household decision-makers and have a sophisticated system of indigenous understandings about when to take medicines (Craig, 2000). Self medication is a common form of first-line treatment, as one interviewed mother in Hanoi stated: "If my child is sick I first go to the pharmacy for advice; if she does not improve by the drugs advised from the pharmacy I go to the doctor". Furthermore, she stated that: "If I have been to the doctor once and my child gets the same symptoms again, I just buy the same drugs as prescribed the previous time" (ongoing research). This pragmatic attitude, using all types of health care until cured and learning from experience, has previously been reported from Pakistan (Winkvist, 1997). Vietnamese carers also have substantial product knowledge of antibiotics (Craig, 2000).

Households may delay and minimise health-care seeking due to the high costs associated with services provided by physicians (Segall et al., 2002). A pneumonia treatment might consume up to one third of a family’s monthly disposable income (Khe et al., 2002). The same treatment obtained through a pharmacy, private or public, was just roughly equivalent to two days of food (I). Up to 10% of Vietnamese households face impoverishment through high medical costs (Xu et al., 2003). There are possibilities for poor patients to obtain free hospital care though formal applications. This is, however, used restrictively, and is available to only 2-3% of the population (Toan, 2001). The health care system is under-financed and has to relay on direct fees, contributing to 14% of the official health care expenditure (World Bank, 2001). The out- of- pocket expenditure for health care is high (80%), compared e.g. to USA (18%) (Everard, 2002). The salary for practitioners within the public sector is low (about 50-100 USD monthly) and the majority have a private practice on the side (Lönroth et al., 1998). Patients know this as well and expect to pay a bit extra directly to the doctor in addition to user fees, diagnostic tests and drugs. This adds to the already high out - of - pocket expenditure for health care.

The accessibility of health care differs throughout the country with an excess of doctors in the urban areas and a lack of health care personnel in the rural and remote areas where the prospect of earning a bit extra on private consultations is poor (World Bank, 2001). There was a high availability (I) and aggressive marketing of drugs, including antibiotics, by both domestic and international companies (Finer, 1999). In addition there is a lack of clear diversification of provider roles. In the urban areas physicians with private clinics acts as pharmacies that in addition to diagnosing and treating also dispense drugs (Lönroth, 2000a). Pharmacies both in urban but especially in rural areas also diagnose and treat in addition to dispensing drugs (II, IV, V, VI). This has also been shown in other low-income countries (Kamat & Nichter, 1998).

PRIVATE PHARMACY CASE MANAGEMENT

People use private pharmacies as their first contact with the health care system. In Bavi, four out of five antibiotic treatments represented self-medication through private pharmacies. This has also been reported from other low-income countries (Bruhga & Zwi, 1998; WHO, 2001; Gerter & Litvack, 1998). This means that private pharmacies have an important role in containing the development of antibiotic resistance by dispensing antibiotics as correctly as possible.
As the proportion of self-medication increases, the pharmacy staff role changes from dispensing towards diagnosing and treating. According to the GPP concept, the pharmacists’ first concern must be the welfare of the patients (FIP, 1993). To fulfil this task, knowledge regarding the common diseases that they often meet in their practice, is needed. Communication skills and knowledge about how to ask clients relevant questions is important in order to give them the appropriate advice and dispense drugs correctly. In Hanoi, the private pharmacy staff’s knowledge of and compliance with the principles of GPP was poor. The majority of pharmacy staff treated STDs without knowing how, only 3% dispensed a correct symptomatic STD treatment in accordance with the national guidelines (VI). Similar lack of correct symptomatic treatment has also been found in Peru and Nepal (Garcia et al., 1998; Tuladhar et al., 1998). Few questions were asked, many of these being wrong, little information was given to the customers, and drugs were dispensed as commercial commodities (IV, V, VI). Poor pharmacy service has also been described from other low-income countries (Stenson et al., 2001b; Syhakhang, 2002; Kamat & Nichter, 1998; Ross-Degnan et al., 1996).

It is noticeable that the reported behaviour according to the questionnaire was consistently different compared to practice in a socially desirable direction. This has earlier been shown with ORS treatment for diarrhoea in Kenya (Ross-Denegan et al., 1996). The difference between stated behaviour and actual practice is often attributed to observation bias (Madden et al., 1997) and underlines the importance to assess not only knowledge but also practice. Although superior to practice, knowledge was still poor. Only half of the interviewed pharmacy staff stated that they would ask a question about breathing, and 40% stated that they would sell prescription- only steroids without a prescription (IV & VI). Lack of appropriate knowledge might be one reason for this. In Vietnam, continuous education among practitioners is often non-existent or depends heavily on information from the representatives of the pharmaceutical companies which tends to be biased (Lönnroth, 2000a).

**ARI case management**

Respiratory infections were common among children in Bavi. Of the surveyed children, 82% had, according to their carers, at least one respiratory symptom within four weeks preceding the study (II). This indicates about 10 episodes of ARI annually, in agreement with studies from other low-income countries (Vathanophas et al., 1990; Selwyn 1990). Other studies indicate four to seven episodes of respiratory diseases among children under five in Vietnam (Chinh & Hiep, 1995). Many studies have shown that 85-90% of antibiotics are used in the community, and up to 80% of these are used to treat respiratory tract infections (Huovinen & Cars, 1998; Kumar, 1997; Lansang et al., 1990; Perez-Cuevas et al., 1996; Wise et al., 1998). Considering that most respiratory infections have a viral aetiology (Khan et al., 1993; Tupasi et al., 1990), there is reason to assume that a vast majority of these treatments were unnecessary. However, when indicated, antibiotic treatment is vital, 40% of the 2.1 million children who annually die in respiratory infections have not been treated with antibiotics (Black et al., 2003). Hence, the ability to recognize danger signs is important.

In Hanoi, only 10% of the pharmacy staff asked questions about difficulties of breathing, although half had stated that they would do so (IV). The approach of integrated management of childhood illness (IMCI) in classifying the severity of acute respiratory infections is to observe the child or ask the caretaker for two key signs of pneumonia, tachypnea and chest retraction (IMCI, 2003). By using this approach, pharmacy staff...
could be able to decide whether the child needs to be referred to a doctor or can be treated
with symptomatic therapy. However, in Bavi, 60% of the carers reported rapid breathing
during interview (II). Such high prevalence of rapid breathing is unlikely (Khan et al.,
1993; Tupasi et al., 1990) and underlines the difficulty of evaluating self-reported
symptoms (Muhe, 1994).

Antibiotics were dispensed by 83% of the pharmacies in 42% of the encounters, although
the case scenario used indicated a child with a common cold, where antibiotics are not
indicated. This has also been demonstrated in other studies (Ross-Degnan et al., 1996; Goel
et al., 1996). In the questionnaire, 80% of the pharmacy staff stated they would not
dispense antibiotics. Recommended drugs for mild ARI were anti-cough medicines
except for products containing antihistamines or opium and traditional medicines (MOH,
1998b). In only 36% of the encounters, drugs in line with the existing guidelines were
dispensed. One of the reasons for dispensing antibiotics might be economical, as
indicated by the significant difference in cost between the encounters in which antibiotics
were dispensed, (USD 0.9) and not (USD 0.4). Of the interviewees, 81% stated that an
inadequate course of antibiotics is ineffective, and 76% said that it promotes resistance.
However, half of the antibiotics were dispensed in insufficient doses corresponding to the
findings in Bavi (II) as well as several other studies (Chalker, 2001; Lam et al., 1997;
Halvarsson et al., 2000).

**Request for prescription-only steroids and antibiotics**

The ability of the pharmacy staff to deal with drug requests is important. In Bavi, 18% of
the carers reported that they decided the treatment themselves and just bought the drugs at
the pharmacy (II). It has been found that pharmacy customers in up to 95% of the
encounters request specific drugs, and that the pharmacies dispense, often without any
questions (Tomson & Sterky, 1986; Chuc & Tomson, 1999; Lam, 1997; Kamat & Nichter,
1998; Ferraz et al., 1996).

In Hanoi, prescription-only drugs, prednisolone and cephalexin, were commonly dispensed
in 76 % and 96% of the encounters, respectively. Prescription requests were only recorded
in 1% of the encounters for steroids and in none for cephalexin (V, VI). By the time of the
study a decree regulating prescribing had been in effect for two years, stating that all
corticosteroids and antibiotics except 8 OTC antibiotics (amoxicillin, ampicillin,
chloramphenicol, erytromycine, penicillin V, tetracycline, sulphonamides and
cotrimoxasole) were prescription-only drugs (MoH, 1995). The common dispensing of
prescription-only drugs shows that the regulations regarding prescriptions are generally not
respected.

The effectiveness of regulation is strongly influenced by the socioeconomic context
(Stenson et al., 1997; Syhakhang, 2002). As the number of pharmacies has grown
dramatically in Vietnam competition has increased and profit margins decreased (Wolffers,
1995). Pharmacy staff may feel compelled to focus more on profit than on their
professional role (Cederlof & Tomson, 1995; Brugha & Zwi 1998, Paredes et al., 1996). In
Vietnam, the control needed to implement regulations has been lacking, due to weak and
not clearly defined sanctions for violations as well as few incentives for officials and
inspectors to focus on the issue (Tran, 2001; Chuc, 2002; Lalvani et al., 1996; MOH,
2002). This has also been described in other low-income countries (Hongoro &
Kumaranyake, 2000, Brugha & Zwi 1998). In Lao PDR, the regulatory system was not
able to deal with the existence of dangerous, fake or substandard drugs (Stenson et al.,
In Vietnam an enforcement system including sanctions is being developed (DAV, 2002, MOH, 2001; Chuc, 2002).

Information about adverse effects was only given in 4% of the encounters, although it was mentioned by 60% in the questionnaire (V). It has been shown that some physicians deny hazardous drug effects, even though they have acknowledged adverse effects during interview (Paredes et al., 1996). The importance of awareness regarding adverse drug reactions is emphasized by the fact that adverse drug reactions now may account for up to 10% of the admissions of patients to internal medicine wards at a cost of hundreds of millions of US dollars annually (Sjöqvist, 2000). The extent of disease due to adverse drugs reactions in Vietnam is not known, but might - considering the ubiquitousness of self-medication - be extensive.

**PRESCRIBING PRACTICES**

Of the carers in Bavi, only 22% reported that they consulted a physician (II). However, physicians may influence antibiotic use, legitimizing popular choices of antibiotics, and their previous prescribing can be an important factor in determining self-medication (Radyowijati & Haak, 2002).

The average number of drugs per prescription was high in the 2400 prescriptions obtained from 80 private and public pharmacies (I) as well as in Bavi hospital (III). This corresponds to findings from other low-income countries (Tomson, 1990; Hogerzeil et al., 1993). Two or more drugs per prescription are considered to indicate a problem in the prescription practices as defined by WHO (Rainhorn et al., 1994). In 10 other developing countries, the average number of drugs per prescription for general outpatient encounters ranged from 1.3 to 2. However, Indonesia and Nigeria showed as many drugs per prescription as in Vietnam, 3.3 and 3.8, respectively (Hogerzeil et al., 1993).

The reason for poly-pharmacy is multi-factorial. In a low-income country context, proper diagnosis may often be difficult due to a lack both of time to make a good examination and of resources such as laboratory tests or radiology (Igun, 1994). In this situation, it may be tempting for physicians to try to treat all possible aetiology in order to prevent treatment failure. Lack of updated literature and biased sources of information such as literature from pharmaceutical companies is another factor influencing prescriber practice (Brugha & Zwi 1998). In Vietnam, continuous education among practitioners is often absent or depends heavily on information from the representatives of the pharmaceutical companies (Lönnroth 2000b, Chuc, 2002). Other factors are: economic incentives such as selling drugs during consultation or provision from affiliated drug stores; patient expectation to get several drugs prescribed and; combination therapy of e.g. corticosteroids, antihistamines and antibiotics in order to get symptom relief and satisfied patients (Brugha & Zwi 1998).

The high rate of injections per prescription (I) was worrying, considering the risk for local infections as well as for transmission of HIV- and B- hepatitis viruses in badly sterilised material (MOH, 1996). High rate of injections has also been reported from other low-income countries (Birungi et al., 1994). In Uganda, Sudan, and Nigeria the share of injectable drugs ranged from 36-48% (Hogerzeil et al., 1993). According to the prescribers interviewed, this was due to the fact that many patients, especially in mountainous areas, expected injections of vitamins. About one third of the public drug outlets were in the
mountainous area Thanh Hoa, and this contributed to the high frequency of injections found in the survey.

Antidiarrheal drugs were prescribed to 10% of children under the age of 5 with diarrhoea (I). This was low, compared to surveys undertaken in other countries. In Uganda, 60% received antidiarrheal drugs (Hogerzeil et al., 1993). In Vietnam, there have been intensive campaigns to improve diarrhoeal case management, and the case fatality rate due to diarrhoea has dropped from making it the leading cause of mortality in public hospitals during the 1980ties to, in 1995, it not even being included on the list of the 10 leading causes of mortality. In 1998, diarrhoea led to 250.000 hospital cases, despite a large decline during the last decade (Statistical yearbook, 2000). Improvement of safe water supplies, improved general nutrition status of children, greater use of dehydration therapy and less antidiarrheal use as well as better health education among parents on how to deal with diarrhoea have all contributed to this (World Bank 2001).

**Antibiotic prescribing in relation to CRP concentrations**

Only 17% of the children who received an antibiotic prescription had an elevated CRP over 10 mg/L, and of these, only 2% had a CRP level over 25 mg/L (III). More than half (55%) of the children tested were diagnosed with ARI. Of these, 20% had CRP over 10 mg/L and one had 140 mg/L. Low serum CRP concentration does not exclude bacterial aetiology of respiratory infection (Korppi & Kroger 1993). However, a serum CRP concentration over 35-40 mg/L has been shown to be a reliable positive predictor for diagnosis of pneumonia in children and rules out viral infection as the sole aetiology (Babu et al., 1989; Korppi & Kroger 1993). Using this latter interpretation, the results indicate that only one out of 55 patients diagnosed with ARI actually had bacterial pneumonia, and that 11 had slightly elevated CRP, indicating possible bacterial or mixed bacterial and viral aetiology. However, it has to be taken into consideration that the majority of the children diagnosed with ARI had been treated with antibiotics prior to the examination and this could have biased the results (Babu, 1989). The prevalence of atypical pathogens such as Mycoplasma pneumoniae and Chlamydia pneumoniae was not known. Studies indicate that these are important causes of community-acquired pneumonia, (Lieberman 1999; Marrie 1998) but cause only a limited increase in serum CRP concentration (Pauksen et al., 1994; Kragsbjerg et al., 1995). Although not confirmative, the findings might indicate over-prescribing of antibiotics in the Bavi health care system. These results have to be viewed with a degree of caution, as the clinical signs on which the diagnosis are based where not assessed.

**TYPES OF ANTIBIOTICS USED AND DISPENSED**

The dispensing pattern of antibiotics from private pharmacies in Hanoi (IV) is similar to the antibiotic use pattern in Bavi (II). The most commonly reported antibiotics used were ampicillin, followed by penicillin and amoxicillin (I). Amoxycillin was dispensed slightly more then ampicillin (IV). Erythromycin and the prescription-only antibiotic cephalaxin were also commonly dispensed. Similar patterns have also been seen in other studies from Vietnam (Lam et al., 1997; Van Duong et al., 1997; Chuc & Tomson, 1999).

The most commonly used antibiotics, ampicillin and penicillin, were reported to be used on average in 3.2 and 2.5 days, respectively (II). About half of the antibiotics were dispensed at insufficient doses (IV). Too short antibiotic treatment courses may fail to cure the condition and also promote the development of resistance (Lipsitch & Levin, 1997). However, this is disputed. A study has shown that a 3-day course of oral amoxicillin is as
effective as a 5-day course in treating pneumonia (MASCOT, 2002). The advantages of shorter courses are that they are cheaper and easier for the patient to take, potentially increasing compliance and reducing dose-dependent side effects (MASCOT, 2002). The majority of carers, 87%, said that they paid attention to the information regarding daily dosage. However, only 12% paid attention to the total dose (II). The bactericidal effect of beta-lactam antibiotics depends on the amount of time the serum concentration is above the minimum inhibitory concentration, and this depends on dose frequency during the day (Craig, 1998). Sub-optimal daily dosage and low concentration of antibiotics allows the growth of low-grade antibiotic-resistant strains, that will increase the possibility of the emergence of a clinically relevant antibiotic resistance phenotype (Martinez & Baquero, 2000).

The common use of antibiotic in short courses might be due to both economic constraints as well as influence of concepts from traditional Vietnamese medicine. Drugs that have warm (nong) properties should be combined with drugs that have cold (lanh) properties, e.g. antibiotics are regarded as warm drugs that should be combined with a cold drug, most often vitamin C which is regarded as cold (lanh) (Jamieson, 1993). This may partly explain the common poly-pharmacy, where 50% of the children had been treated with vitamins and syrups in addition to antibiotics. The belief is that by taking too much of "nong" drugs, the body might be overheated, causing diarrhoea and rashes. These are also the most common adverse reaction of many antibiotics, enforcing the "lanh - nong" idea. Due to the perceived adverse effects, the treatments with “nong” drugs like antibiotics should be as short as possible, and people tend to stop as soon as they feel better. The common short-course treatment is not only a financial problem; it is also based on the wrong conceptions regarding the properties of antibiotics. It is believed that when warm drugs are used in excess or without restoring the balance with cold drugs, adverse effects as diarrhoea, rashes as well as pimples occur. Diarrhoea and rashes are also common adverse effects of most antibiotics. As a consequence of this many thinks that by taking just "lanh" drugs the skin might improve and pimples may be prevented. Vitamin-C injections are commonly used (I) because it is believed that it gives beautiful skin and removes pimples (Ongoing research, preliminary finings). The high proportion of traditional medicine provided indicates that traditional medicine is popular among consumers as well as among private pharmacy providers. To investigating the safety, quality and efficacy of traditional therapies and defining their role within the health care system, has been recommended by the WHO in accordance with recent World Health Assembly resolutions.

**ANTIBIOTIC RESISTANCE IN BAVI**

Of the 145 children where respiratory pathogens could be isolated, 74% carried at least one resistant respiratory pathogen. As this study was community-based, and no children in the study population were excluded, the results are assumed to mirror the regular rate of resistant pathogens in the community. Surveys in Hanoi, Hue and Ho Chi Minh City showed similar results (Törnquist et al., 2000; Parry et al., 2000). The carriage rate of *S. pneumoniae* was 44%, higher than a study conducted in HCMC where the carriage rate was 35% (Lee et al., 2001), however, similar to another HCMC study where rural and urban carriage rate was 45% and 44%, respectively (Parry et al., 2000). Data are sparse regarding carriage rate of *H. influenzae* in Vietnam. A study conducted on children admitted to a Beijing hospital showed a carriage rate of 36% (Hu et al., 2002). The carriage of *H. influenzae* type b, causing meningitis and epiglottises, was 3%, similar to the Beijing study (2%) (Hu et al., 2002).
**S. pneumoniae**

*S. pneumoniae* is one of the major causes of respiratory tract infections and invasive diseases in children all over the world. About 1 million children under 5 years of age annually die of pneumococcal disease (Bogaert et al., 2002). Almost one third of the *S. pneumoniae* strains were multidrug-resistant (II). Of these, all were tetracycline resistant and 90% expressed full resistance against trimethoprim/sulphamethoxazol. These strains also express full resistance to chloramphenicol (47%) or erythromycin (65%) or both (18%). This is similar to findings from Australia and Greece where 19% and 11%, respectively, of the *S. pneumoniae* isolates were found to be resistant to this combination of antibiotics (Nasrin et al., 1999; Tsolia et al., 1999).

In our study multi-drug resistance was often associated with susceptibility to penicillin. Only 4 of the 19 strains resistant to more than 3 antibiotics were resistant to penicillin. This has also been shown by Nasrin et al., (1999) and Tsolia et al., (1999), though in most studies, multi-drug resistance in *S. pneumoniae* is associated with penicillin resistance (Schito at al. 1997; Corso et al., 1998; Appelbaum 1996). In Hanoi, Bogaert et al., (2002) showed even higher resistance rates in isolates from children with upper respiratory tract infections in 3 hospitals, where 75% were resistant to three or more classes of antibiotics; 52% of the strains were resistant and intermediate resistant to penicillin, 87% to co-trimoxazole, 76% to tetracycline, 73% to erythromycin and 39% to cefotaxime. The difference between the figures in this study compared to our results might be due to: (i) The isolates being collected in a hospital setting compared to in our study where the isolates were collected in the community; (ii) The isolates coming from children in an urban environment that is more crowded, the children having better access to drugs, compared to in our study where the isolates came from children in a rural area. As shown, self-medication is common, and a lot of these children might have been treated prior to the hospital visit, as in Bavi, where 88% of the children had self-medicated prior to hospital visit (III). Most of the self-medication is with beta-lactams, especially ampicillin, selecting for penicillin and multi-resistant strains (II). This is supported by Parry et al., (2002) who showed that carriage of penicillin-resistant *S. pneumoniae* was associated with referral from another hospital rather than being admitted directly from home and having received antibiotic therapy before admission, seven % of patients admitted directly from home had a penicillin-resistant *S. pneumoniae* infection compared with 52% of those referred from another hospital. In support of an urban rural difference, Parry et al., (2000) found a much higher carriage rate of penicillin-resistant *S. pneumonia* in HCMC than in nearby rural areas, 35% vs. 2%, and resistance to ceftriaxone, erythromycin, chloramphenicol, and trimethoprim-sulfamethoxazole was also more common in urban children than in rural. However, tetracycline resistance was most common in rural children, 78% in rural south Vietnam (Parry et al., 2000) compared to 88% in Bavi (II). Parry et al. (2002) also found that the proportion of patients with a penicillin- non-susceptible pneumococci infection was 36% (4 of 11) for those transferred from a hospital outside HCMC compared with 70% (7 of 10) for those transferred from a hospital in HCMC (P = 0.1).

**H. influenzae**

Among the *H. influenzae* strains, 26% were resistant to three or more antibiotics. Similar studies in Europe and United States indicate that less than 5% are resistant to multiple antibiotics (Bajanca-Lavado et al., 1996; Doern et al., 1999). Of these, about half were resistant to the combination of chloramphenicol, tetracycline, trimethoprim/sulphamamide, penicillin V and ampicillin. This is higher than in Taiwan, where 5.4% of the *H. influenzae* were found resistant to this combination of antibiotics (Lin et al., 1999). Compared to *H. influenzae* resistance reported from outpatients in Beijing, the ampicillin, chloramphenicol
and tetracycline resistance was higher in Vietnam. However, sulphamethoxazole/trimethoprim was lower then in China (Hu et al., 2002). This might reflect the a difference in pattern of antibiotic use.

Multi-drug resistant \(H. influenzae\) strains harbour plasmids with circular sizes of 38 to 52 mega-daltons (Campos et al., 1989). These plasmids may be transferred to recipient \(H. influenzae\) by conjugation or transformation (Lin et al., 1999). The reported high use of beta-lactam antibiotics, mainly ampicillin (II, III & IV), might select for the whole plasmid and promote resistance for trimethoprim/sulfonamide, tetracycline and chloramphenicol.

Trimethoprim/sulphonamide was, according to the Vietnamese treatment guidelines of 1999, the first-line drug to treat respiratory infections (MOH, 1999). As seen from the results, almost half of the isolates were resistant. The effectiveness of penicillin V and ampicillin might also be reduced, as 74% and 24% of the isolates were resistant or intermediate resistant. Moreover, chloramphenicol, the first-hand drug for meningitis, might not be effective, as 24% of the isolates were resistant, and, as shown in study III, this drug seems to be commonly used. Cephalosporins such as Loracarbef can still be used, but these are much more expensive and may not be affordable for the poorest.

**Relationship between antibiotic use and resistance**

The most commonly used antibiotics were the beta-lactams ampicillin and amoxicillin (II, III, IV). Oral ampicillin has low absorption bioavailability and more than 50% of the dose taken remains in the intestine, where it is capable of selecting resistance in gram-negative Enterobacteriaceae (Moe et al., 1977), an important reservoir for antibiotic resistance genes (Apua, 1998). These resistance traits may spread to respiratory tract pathogens through plasmid transfer of beta-lactamases (Huycke et al., 1992; Mea-Wan et al., 1998). The high use of oral ampicillin may contribute to the beta-lactam resistance levels observed. This is supported by the significant difference in ampicillin and penicillin resistance between the group of children previously treated with beta-lactam antibiotics and the group of children not receiving antibiotics found in this study. This supports the hypothesis that there is a correlation between antibiotic use in a given location and the corresponding prevalence of resistance. This association between use and resistance has also been documented in other studies (Nasrin et al., 1999; Tsolia et al., 1999). For infections with penicillin-resistant \(S. pneumoniae\), studies have demonstrated that, at the individual level, previous use of beta-lactam antibiotics such as penicillin is an important risk factor (Nava et al. 1994, Deeks et al., 1999). Studies on carriage of penicillin-resistant \(S. pneumoniae\) in children have shown that sulfamethoxazole-trimethoprim (co-trimoxazole) and macrolides such as erythromycin have also been associated with selection of penicillin-resistant \(S. pneumoniae\) (Arason et al., 1996; Melander et al., 2000). Translated to the population level, sales of beta-lactam antibiotics, co-trimoxazole, or macrolides in a given geographic region may be proportional to microbial resistance to penicillin.

As seen from the Bavi results and from Hanoi (Bogaret et al., 2002) as well as from southern Vietnam (Perry et al., 2000) there seems to be a great difference in the prevalence of penicillin-resistant \(S. pneumoniae\) in rural and urban areas. This difference might be due to a difference in antibiotic use patterns. However, as seen from the stated use of antibiotics in our study, the resistance pattern of \(S. pneumoniae\) is not directly reflected in the reported use of antibiotics. Most of the antibiotic consumption reported in Bavi, referred to beta-lactam antibiotics. However, the resistance, including intermediately resistant strains was
only 11%, which is higher compared to rural southern Vietnam, 2%, but much lower compared to HCMC and Hanoi (35% vs. 52%) (Parry et al., 2000, Bogaret et al., 2002). Tetracycline resistance was high (88%). but, only 4% of the study population were reported to have used tetracycline one month prior to the study. The reason for this might be that antibiotic use patterns change more rapidly in urban areas, and then slowly spread to rural areas. As stated in the background, antibiotic resistance, once it has emerged, might be difficult to reverse (Levin et al., 1997). During the 1970’s and 80’s, tetracyclines were one of the few antibiotics available in Vietnam and so were commonly used. Although little is known about previous consumption patterns of antibiotics in Bavi, it might be hypothesized that tetracycline use persisted longer in Bavi than in Hanoi or HCMC, where beta-lactams such as ampicillin became popular earlier. This might have preserved a higher tetracycline resistance among *S. pneumoniae* isolates in Bavi, as even a low consumption level might theoretically preserve a high level of bacterial resistance (Levin et al., 1997).

**Impact of the resistance situation**

The high prevalence of multidrug-resistant pathogens serves as an important predictor of treatment failure in communities where susceptibility testing is unavailable (Levy, 1986). The findings also raised doubts about the effectiveness of the 1999 standard treatment guidelines for ARI in Vietnam. According to the Vietnamese Ministry of Health’s “Antibiotic Treatment Guideline for Infectious Diseases” (MOH, 1999) the recommended first hand treatment for pneumonia is trimethoprim/ sulphamethoxazol. Almost half of the *H. influenzae* and one third of *S. pneumoniae* isolates were highly resistant against trimethoprim/ sulphamethoxazol. Use of trimethoprim/ sulphamethoxazol may therefore be ineffective, though it should be noted, that *in vitro* resistance does not always correlate with clinical outcome (Mulholland et al., 1995). As *H. influenzae* now appears to be highly resistant against chloramphenicol, penicillin and ampicillin, the traditional strategy of initiating treatment of serious and invasive infections such as meningitis with a combination of these drugs might no longer be effective in Vietnam.

At community health stations, the first-hand drug for treatment of pneumonia, trimethoprim/ sulphamethoxazol (Cotrimoxazol), has to a large extent been abandoned as - according to local doctors – it has an unsatisfactory treatment effect (personal communication). This might be related to the high resistance among common pathogens; 32% of the *S. pneumoniae* showed trimethoprim/ sulphamethoxazol resistance in Bavi. Amoxycillin and to some extent ampicillin have replaced trimethoprim/ sulphamethoxazol as the most commonly used first-line drugs. As the *S. pneumoniae* resistance to amoxycillin still is low, at least in rural areas (Parry et al., 2000), this may still in most cases be an effective treatment.

However, in most cases penicillin V should be as efficient, as the community resistance in Vietnam is still fairly low. Eleven percent of *S. pneumoniae* in Bavi were resistant and intermediate resistant, and similar rates have been found in clinical isolates (Törnquist et al., 2000). Pneumococcal pneumonia may still be treated successfully with benzyl penicillin or ampicillin, as shown in other studies (Choi & Lee, 1998; Deeks et al., 1999). However, as demonstrated by Parry et al., (2000) there might be a difference in the treatment effect due to the difference of penicillin-resistant *S. pneumoniae* prevalence in rural and urban areas. As other broad-spectrum beta-lactam antibiotics such as amoxycillin are also driving the resistance of penicillin V but not the reverse, it might be more rational to use penicillin V to a higher extent as first-hand treatment, leaving amoxicillin and ampicillin as secondary drugs for cases with treatment failure on penicillin V.
As indicated from the high prevalence of penicillin resistance among children with ARI in both Hanoi and HCMC hospitals (Bogaert et al., 2002; Parry et al., 2002), there might be a pre-selection of penicillin-resistant strains due to the common practice of self-medication with beta-lactam drugs, rendering these drugs unsafe to use as symptomatic treatment of severe infections such as pneumonia, meningitis and sepsis in hospitals. Due to the high resistance rates, chloramphenicol or erythromycin may not be recommended as an alternative treatment. Cephalosporin’s can probably still be used with good effect as seen by the low Loracarbef resistance in our study as well as by Parry et al. (2000) and Bogaert et al. (2002). Cephalexin accounted for 15% of the antibiotics dispensed to clients for treating a child with cough (IV). Increased use of cephalosporins might, however, also select for resistant strains, especially if not restricted to hospital setting. As seen in Bogaert et al., (2002) 39% of *S. pneumoniae* isolates from children with upper respiratory symptoms in Hanoi were intermediate resistant to cefotaxime.

The possibility to take specimen for culture and antibiotic resistance screening is not commonly available except at the bigger centres and then for the most severely ill patients. As a consequence the treatment is often symptomatic. The increased resistance among common pathogens resulting in treatment failures has been countered with an empirical treatment strategy where the doctors continuously re-evaluate the treatment response and change antibiotic accordingly. As one mother stated: "My child had throat pain, I took her to the doctor 4 times, she did not improve and each time the doctor changed antibiotics, the last time injections were given, she then improved" (non published focus group discussion). The resistance has affected the treatment strategies used in Vietnam. The new and more expensive cephalosporins are still used with good effect, these are though not affordable for all and those with limited available resources are forced to choose treatments, which are less effective.

**IMPACT OF THE INTERVENTION**

Two approaches were used to introduce the educational material, face-to-face education and peer review feedback. In some studies face-to-face education has been shown to be effective in influencing the practice of the pharmacy staff (Adu-Sarkodie et al., 2000; Ross-Degnan et al., 1996). Peer influence builds on the concept of group responsibility for self-education and monitoring. It has been proven effective for the improvement of practice in high-income countries (Brugha & Zwi 1998; Lundborg et al., 1999). An innovative feature was the question, advice and treatment strategy. This was used as an outline for the pharmacy treatment guidelines, to assess the intervention and to monitor GPP. The idea with the education process was a development from external education where educators come from external sources outside the recipients, to self-education where the educators are among the recipients i.e., peer education (Chuc, 2002). The messages were based on the identified problems in the private pharmacies in relation to ARI, STD and dispensing of prescription-only drugs and the common dispensing of antibiotics. The basic content of the messages focused on rational use of drugs and was constant throughout the different interventions, but increased in quantity and complexity. In addition the educational and peer influence interventions focused on case management. The philosophy of the intervention package was to have a few repeated messages and to implement the interventions in a logical sequential order.
**ARI case management**

Questions regarding breathing increased in the intervention pharmacies compared to the control pharmacies, from 10% to 30% vs. 10% to 7%. The importance of asking about breathing was emphasized in the educational intervention and repeated in the peer influence intervention. With improved ability to ask about breathing children with pneumonia that needs referral to a physician may be identified to a higher extent (WHO, 2001). Considering that 2.1 million children each year dies from pneumonia (Black et al., 2003) and that private pharmacies often is the first instance of health service (II) better case management might have a large impact on child survival.

The dispensing of antibiotics decreased in the intervention pharmacies compared to control pharmacies, from 45% to 30% vs. 39 to 42. Considering the documented frequent use of antibiotics for ARI (II, IV), improved rational use of antibiotics is of major importance for the containment of antibiotic resistance (Lipsitch & Samore, 2002). There was no decrease in total cost for the clients indicating that the pharmacies managed to maintain profit although fewer antibiotics were dispensed. Although this was a very positive improvement there is still room for further improvement as in 1/3 of the encounters antibiotics were still dispensed.

**STD case management**

In response to a case history of urethral discharge, indicating chlamydia or gonorrhoea, advice to see a physician increased significantly in the intervention compared to the control group, from 22% to 37% vs. 20% to 18%. This is positive as correct examination and diagnose of STDs needs knowledge and equipment not usually available at private pharmacies. However, patients with symptoms of STD are commonly hesitant to consult a physician, as the disease is stigmatizing and the patients might feel embarrassed. Visiting a pharmacy is more anonymous, often quicker and less expensive (Benjarattanaporn, 1997).

Correct symptomatic treatment in the intervention pharmacies improved significantly compared with the control pharmacies, from 3% to 30% vs. 4% to 19%. STD treatment is relatively expensive; thus there are in addition to medical also economic incentives for the pharmacies to follow the treatment guidelines. The improvement is similar as described in Ghana and Zambia (Faxelid, 1997; Adu-Sarkodie et al., 2000). Prompt and correct treatment is a proven method of reducing the spread of HIV (Gilson et al., 1997). However, overuse of quinolone should also be avoided considering the emerging resistance. A study in HCMC found that 12% of gonococcal isolates had an intermediate ciprofloxacin resistance (Thuc, 1999). To contain transmission of STDs including HIV it is of mutual interest for the public health care system and private pharmacies to recognize symptoms of gonorrhoea and chlamydia and dispense correct drugs to clients who are not willing to see a physician (Gilson et al., 1997; Chalker et al., 2000). The educational intervention made clear to the pharmacy staff that the appropriate drugs for this condition were prescription-only drugs, but they were not actively discouraged from dispensing these without a prescription. This strategy was agreed upon with the Hanoi Health Bureau in the interests of public health. In the educational and peer influence interventions, the pharmacy staff was taught to ask about sexual activity and symptoms of chlamydia and gonorrhoea. An increase of correct symptomatic treatment was also detected in the control pharmacies. As the Hanoi Health Bureau issued no official information to pharmacies regarding STDs during the intervention period it might be assumed that information could have spread from intervention to control pharmacies.
Very few drug sellers advised the clients to use a condom after the interventions although this was emphasized during both the educational and peer influence intervention. The reason for this result may be that in Hanoi, more than 70% of pharmacy staff members were female while the clients were male. It may be a sensitive issue to advise a client of the opposite sex to use a condom (Chuc, 2002). Studies in Nepal and Ghana have also shown low impact of interventions in relation to advice to use and dispensing of condoms (Tuladhar et al., 1998; Adu-Sarkodie et al., 2000). Condom use is an important focus for future preventive interventions in relation to health information on these diseases to reduce the spread of STDs including HIV, and to promote a more open attitude.

**Request for prescription-only steroids and antibiotics**

After the interventions, prescription requests increased in the intervention pharmacies from almost none to around 20%. Dispensing of prescription-only drugs decreased significantly in the intervention pharmacies compared to control. The reasons for the major improvements might be both that the messages were repeated in the sequential interventions and the simplicity of the messages. Other studies have shown the effectiveness of simple, frequently repeated messages (Brugha & Zwi, 1998). Cephalexin and prednisolone are relatively cheap drugs that can be substituted with OTC drugs without any loss of profit. In the intervention pharmacies dispensing of non-steroid anti-inflammatory drugs and traditional medicines increased threefold as prednisolone sales decreased. Cephalexin was substituted with OTC antibiotics, traditional medicines or paracetamol. Similarly, it has been shown that when the dispensing of antibiotics decreased, the dispensing of antidiarrhoeals increased (Ross-Degnan et al., 1996). This underlines the importance to design interventions so that profit can be maintained or increased.

**Limitations of the intervention**

Although there were positive changes after the intervention the impact was still limited. For ARI more than half did not ask about breathing and antibiotics were still dispensed for common colds. For STD there was no significant increase in questions regarding sexual activity, few advised the use of condom, only 37% referred to physician and the majority of the STDs were still not managed in correct way. For drug request the majority still dispensed cephalexin. One reason might be that the persons that were encountered by the simulated clients not always were the same pharmacy-staff that received the intervention. It can also be questioned if vertical projects focusing on only one part of the health care system are enough to generate substantial and sustainable improvements. To achieve a sustainable change towards more rational use of drugs other measures may be needed including interventions on the “demand side”, to inform and empower consumers in relation to rational use of drugs as the ultimate decision-makers in the use of medicines (Hongoro & Kumananayake, 2000).
REFLECTIONS

This thesis has described how self-medication with antibiotics through private pharmacies is a common phenomenon, as well as high levels of antibiotic resistance. However, in many parts of the world, a major public health problem is the lack of availability and/or accessibility of drugs. In as many as 40% of the cases leading to death in pneumonia, the deceased have not received appropriate medical attention or antibiotic treatment (Black et al., 2003). Major challenges for the future include how to ensure the availability, accessibility, quality and rational use of antibiotics for all in need, while simultaneously containing antibiotic resistance.

One of the major difficulties in relation to antibiotic use and resistance, is the inherent conflict between the individual’s health priorities and those of society and public health. From the individual’s perspective, self-medication with antibiotics might reduce the severity of the disease, prevent secondary bacterial infection, and in some occasions alter the natural progression of the disease (Kunin & Liu, 2002). The common practice of self-medication with antibiotics in low-income countries might even be a largely unrecognized contributing factor to the global decrease in child mortality due to infectious diseases. However, from a public health perspective, the common practice of self-medication with antibiotics is a ticking bomb. In a milieu, where 75% of the children have been using antibiotics during the period of one month (II) resistant strains are effectively selected for, and colonizing strains have a high probability of being resistant (Halloran & Struchiner, 1991). This is jeopardizing the effectiveness of antibiotics, leading to treatment failures and in the long run to increased morbidity and mortality in infectious diseases, in the absence of replacement by newly developed antibiotics.

Resistance also implies an equity problem, where poor families due to economic constraints have less access to efficient antibiotic medication for severe diseases. Meningitis is an example, where the first-line treatment in Vietnam is ceftazidine or chloramphenicol. Resistance to chloramphenicol is high (II), so from a clinical point of view, ceftazidine would be preferred. But, ceftazidine is ten times as expensive, and so chloramphenicol is being used with the risk of treatment failure.

The implications - for improving rational use of drugs - of improved management in private pharmacies, as shown in this thesis for ARI and STD as well as steroid and antibiotic requests (VI) are obvious, considering private pharmacy prevalence, popularity and the inherent business-profession dilemma. Promoting GPP standards, and integrating private pharmacies, as a reliable part of the health care system, is likely to have a major public health impact. In addition, empowering consumers to make informed choices, based on the recognition of danger signs for severe diseases and rational use of drugs, must also be taken into account (Hongoro & Kumaranayake, 2000).
CONCLUSIONS AND RECOMMENDATIONS

The majority of children in the community were reported to have self-medicated with antibiotics during the past month, and high rates of antibiotic resistance in respiratory pathogens were found. The main source of self-medicated antibiotics was private pharmacies and a majority of the children surveyed at the Bavi hospital had used antibiotics prior to the consultation.

- Investigations addressing the effects of self-medication with antibiotics on community morbidity and mortality as well as consequences for resistance are recommended.

- The relationship between use and resistance, and whether improvements in antibiotic utilization can be linked to changes in resistance patterns needs to be increasingly investigated, in order to safeguard the therapeutic effect of antibiotics.

The average number of drugs per prescription was high, and injections were common. Few of the children, who were prescribed antibiotics, had elevated CRP levels. Management of ARI and STD as well as of prescription-only drugs in private pharmacies were shown to be of low quality. It was possible to improve private pharmacy practice in line with GPP through a multi-component intervention.

- These findings underline the need for interventions aiming to improve public sector prescribing practice, as well as private pharmacy provision practice in Vietnam.

- Further studies on how interventions can be developed in order to facilitate private pharmacy participation as an integrated part of the health care system are suggested.

- Standard treatment guidelines and pharmacy treatment guidelines, as described in this thesis, need to be developed in relation to updated information regarding the current resistance situation.

Finally, this thesis describes discrepancies between knowledge and practice among private pharmacy-staff.

- Assessment methods addressing knowledge as well as practice are recommended for evaluation of interventions and monitoring of GPP.
ACKNOWLEDGEMENTS

The studies and findings presented in this report are the result of a great effort made by many people at IHCAR and the Department of Laboratory Sciences at Karolinska Institutet in Stockholm, Sweden, as well as at the Health Strategy and Policy Institute (HSPI), College of Pharmacy, and Hanoi Medical University in Hanoi, Vietnam during the period when the studies were conducted as well as when the papers and the thesis framework were produced.

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REFERENCES


Bonzwaer, S. L., Cars, O., Buchholz, U., Molstad, S., Goettsch, W., Veldhuijzen, I. K.,
Comparison between parental report and results of microbiologic agar assay for presence of antibiotic in urine of Argentinian children with acute lower respiratory tract infection. *Reviews of infectious diseases*, 12: (suppl. 8) 998-1000.


APPENDICIES

APPENDIX 1: QUESTIONNAIRE FOR THE HOUSEHOLD SURVEY IN BAVI

1. The age of the interviewee: .............................
2. Relation to the child  Mother  Father  Other: ......................
3. Occupation: .............................................

4. Level of education: Uneducated  Primary school (Age 6-11)  Secondary school (Age 11-15)  High school (Age 15-18)  Post high school

5a How many children do You have?
   Sons: .................  Daughters: .............

5b. How many children from the 1 to 5 years of age (born between March 94 to March 98) do you have?
   Sons: .................  Daughters: .............

6. Please indicate if your child has/has had any of the following symptoms during the previous four weeks: Cough  Fever  Runny nose  Runny ear/ears  Rapid/ difficult breathing  Other
   (please specify): ........................................

7a If your child has/has had any of the symptoms in question 6, did/do you give your child drugs?
   a) No  Yes

7b. If yes, please indicate what kind of drugs you used/use?
   a) Antibiotics  Specify kind: ........................................  Tonics  Other drugs
      Specify: .....................................................  Cannot remember

7c. If antibiotics were used, how many days did you/have you been using them: ....................

8a. Where did/do you buy them?
   a) National pharmacy  Private pharmacy  Drug agency  Commune health station  Other, please specify: ...........................

8b. Who did/do you consult to buy them?
   a) Decided your-self  According to doctor’s prescription  Ask seller in the pharmacy  Ask
      neighbourhood  Other (please specify): ..........................

9a Have you ever used antibiotics before?
   a) No  Yes  Do not know

9b If yes, when did you treat your child with antibiotics the first time: .........................

9c If yes, when did you treat your child with antibiotics the last time: .........................

10 When you treat your child with antibiotics, to which of the following information do you often pay attention?
   a) Daily dosage  Dosage of treatment  Duration of treatment  The expire date of the drug
      Contraindications  How to take the drug

11. When your child improves, do you continue with the treatment?
    No  Yes  Don't know

    If yes, for how long: .................................
APPENDIX 2: QUESTIONNAIRE TO ASSESS ANTIBIOTIC PRESCRIBING THROUGH C-REACTIVE PROTEIN

Nr:  
Doctors identity:______________________  
Day of interview:______________________  
Child identity:_______________________  

1. Sex (Male       Female   )  
2. Is anyone living in your house smoking?  Yes       No  
3. How long time has your child been sick?  
   0 – 6 hours  
   6 – 12 hours  
   12 – 72 hours  
   > 72 hours  

4. What treatment have you given your child?  
   Antibiotics:   ______________________________________  
   Corticosteroids                              Any other treatment  
5. Does your child have any other disease?  No       Yes  Which:_____________  

CRP Results  

CRP Value (Mg/l)  
<10  
10-25  
25-50  
50-100  
100-200  
>200  

Exact CRP value:________________________
APPENDIX 3: QUESTIONNAIRE TO INTERVIEW PHARMACY STAFF

Interviewer’s name:
Date ......................... Time.........................
Pharmacy name ..........................Pharmacy code ..............
(Spoken questions in bold, Instructions to interviewers in italics, Analysis in ordinary font)

1. What are your business hours?
   (Circle which one it is and write in hours)

   Weekdays Y/ N ........to...... ........to........
   Total per day
   Total per 5 days

   Weekends Y/N ........to....... ........to.....
   1a (Analysis total number of hours pharmacy open each week ............)

2. On average how many customers come into your shop on a typical day?
Write number of customers on a typical day..........

3. Of all the customers who come into your store on a typical day, what percentage has a doctor’s prescription?
Write percentage of customers with prescription .............

4. In a month, how often would you see a person asking for treatment for a child with a cough?
   Often Occasionally Rarely

   If a client comes to you and asks for medicine for his/her 3-year-old son who is coughing, what would you do?
Write down the main points including: questions, names of drugs and number of units and advice. If the pharmacy staff asks about symptoms, the child has no fever, is eating normally, has clear mucus, no wheezing and is taking no other drugs.

   If the interviewer does not ask the client any questions or give advice, then ask the interviewee—only once.

4a. Would you usually ask questions of the client? If so, what? (record the main points)

4b. Would you usually give advice to the patient? If so, what? (record the main points)

5. If a young man comes to you and asks for medicine because he complains of pain when he urinates and finds discharge from the penis, what would you do?
Write down the main points including: questions, names of drugs, number of units and advice

   If the interviewer does not ask the client any questions or give advice then ask the interviewee—only once.

5a. Would you usually ask the client any questions? If so, what? (Record the main points)

5b. Would you usually give advice to the patient? If so, what? (Record the main points)

5c. In the last month, how often have you come across such a case? (Circle which one it is)
   (zero, once, twice, more than twice)

6. If a client comes to you and asks for prednisolone because he/she expresses back pain, what would you do?
   If they will not sell the drugs, ask them:
   “Why will you not sell them?”
   If they will sell the drugs, ask them:
   “Why will you sell them?”

7. If a client comes to you and asks for a few capsules of Cephalexin, what would you do?
   If the pharmacy staff asks about this case, the answer is: “She/he has had a cold for 2 days”
   If they will not sell the drugs, ask them:
   “Why would you not sell the drugs?”
   If they will sell the drugs, ask them:
   “Why will you sell them?”

8. What are the side effects of steroids?
   (Record each one mentioned)

9. What are the dangers of giving a few capsules of Cephalexin?
   (Record each one mentioned)

10. To put this into perspective, please tell me your age and your educational qualification.
(Tick the answer)
10a. Sex: Male Female
10b. Age:
10c. Educational qualification
   Doctor
   Asst. Pharm.
   Asst. Doctor
   Nurse
   Pharmacist
   Other
(Describe..............................)
10d. Did you take part in the last interview? (1: yes; 2: No)

11. Who else works here?
Complete the following column:
   No.          Age             Sex              Qualification (1= Doctor; 2= Asst.Doctor 3= Pharmacist;
   |             |                 |     | 4=Asst.Pharm  5= Nurse; 6= Others)

12. Are there any groups of drugs for which regulations say that they should only be sold with a doctor’s prescription?
   12a. (Circle the answer you choose) Y / N
   If yes:
   12b. Which groups of drugs are those?
   List interviewees’ comments:

13. Does Vietnam have an Essential Drugs List?
   (Circle the answer) Y/N

14. Do you have a copy of the National Essential Drugs List in the pharmacy?
   (Circle the answer) Y/N
14a. If yes, could you show it to me?
   (Circle the answer) Y/N
14b. In your opinion, is this the latest version?
   (Circle the answer) Y/N

15. Are you able to distinguish the trade name from the generic name of a drug?
   (Circle the answer) Y/N
   If yes, how do you distinguish?
   (Write the answer)

16. If a patient gets strange symptoms after taking a drug that you have sold to them, what are you meant to do? (Record)

17. According to your experience, which drugs induce most allergic reactions? (Record)

18. Generally speaking, in your opinion, which drugs are safer, combined drugs or single drugs?
   (Circle the answer) Combined/ Single
18a. Why? (Record)

Thank you very much for your collaboration.
APPENDIX 4: PROTOCOL FOR THE SCM

Example: Upper Respiratory Tract Infection

Scenario:

A simulated client will present herself as a mother/grandmother with a 3-5 year old daughter or son (who is at home) who is coughing since 2 days. The client will ask the person who waits on her for advice about what things to buy. Other than these facts, no information will be presented unless asked for by the shop attendant.

Upper Respiratory Tract Infection is not dangerous, and no specific treatment is necessary. General treatment for children might include treatment of symptoms of headache and nasal obstruction.

Presentation of the problem at the pharmacy:

"I have a (3,4,5) year old (daughter or son) who is coughing since two days. What things should I buy?"

In response to questioning by the pharmacy staff, the client will provide the following information selectively:

- Child’s condition: Describe the child as somewhat tired, a little warm (no high fever) and no headache. The child has no history of nasal allergy. The child has no breathing problem and is eating and drinking normally.

- Throat and Nose: The coughing are not very frequent (1-2 coughings per hour) and your child have no pain in the throat. The child has clear, transparent snot.

- Unusual foods or drugs consumed: The client is not aware of any unusual foods that the child has eaten in the past few days, nor of any other drugs that the child is taking.

Actions:

⇒ The client will take note mentally of any question that the pharmacy staff asks before making a recommendation, any advice about the products recommended, and also any other advice of how to treat the condition.
⇒ You are willing to accept any product or suggestion the pharmacy staff provides.
⇒ Any products recommended should be purchased in the quantities offered
⇒ Always leave the initiative to the pharmacy staff.

All information should be recorded on the information sheets by the assessor at a maximum of 15 minutes after leaving the store.
## Upper Respiratory Tract Infection

<table>
<thead>
<tr>
<th>Pharmacy address, nr</th>
<th>Date</th>
<th>time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Client name, code</td>
<td>1</td>
<td>Encounter code</td>
</tr>
</tbody>
</table>

**Drugs purchased, information given (Shaded areas to be filled in by the supervisor)**

<table>
<thead>
<tr>
<th></th>
<th>NUMBER OF DRUGS BOUGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>TOTAL PRICE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DRUG NUMBER</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Brand name</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Registration number</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>Generic code</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Times/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Number of days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Take before meals</td>
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<tr>
<td>13</td>
<td>Take after meals</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>14</td>
<td>Take as powder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Take with water</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Expire date present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Drug expired</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>20</td>
<td>Banned drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Good labelling</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>22</td>
<td>Combination drugs</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>23</td>
<td>Loose packs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Total amount of drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Upper Respiratory Tract Infection

## Which of the following did the pharmacy staff ask about before making a treatment recommendation?

<table>
<thead>
<tr>
<th></th>
<th>Questions</th>
<th></th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Questions related to coughing</td>
<td>35</td>
<td>Pain when swallowing</td>
</tr>
<tr>
<td>26</td>
<td>Questions related to breathing</td>
<td>33</td>
<td>Convulsions/Chills</td>
</tr>
<tr>
<td>27</td>
<td>Presence of allergy</td>
<td>34</td>
<td>Questions related to weight</td>
</tr>
<tr>
<td>28</td>
<td>Presence of high fever</td>
<td>35</td>
<td>Had the child had these symptoms earlier</td>
</tr>
<tr>
<td>29</td>
<td>weakness/lethargy</td>
<td>36</td>
<td>Cold related to Fan, AC, Rain</td>
</tr>
<tr>
<td>30</td>
<td>Vomiting</td>
<td>37</td>
<td>Has the child visited a doctor or the health clinic</td>
</tr>
<tr>
<td>31</td>
<td>Questions related to feeding/drinking</td>
<td>38</td>
<td>Drugs taken</td>
</tr>
<tr>
<td>32</td>
<td>Presence of sore throat</td>
<td>39</td>
<td>Questions related to allergy from using drugs</td>
</tr>
<tr>
<td>40</td>
<td>Other: write question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>Write answer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Which of the following did the pharmacy staff recommend?

<table>
<thead>
<tr>
<th></th>
<th>Full course of dose was recommended</th>
<th>50</th>
<th>Give extra fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>Visit a doctor if the child vomits</td>
<td>51</td>
<td>Try to clean the child’s nose</td>
</tr>
<tr>
<td>44</td>
<td>Visit a doctor if the child develops breathing problems</td>
<td>52</td>
<td>Don’t use harmful drugs (ex alcohol containing) against cough</td>
</tr>
<tr>
<td>45</td>
<td>Visit a doctor if the child doesn’t eat or drink</td>
<td>53</td>
<td>Don’t bath the child in cold water</td>
</tr>
<tr>
<td>46</td>
<td>Visit a doctor if the child gets persistent fever</td>
<td>54</td>
<td>Continue to keep your child warm</td>
</tr>
<tr>
<td>47</td>
<td>Let the child rest</td>
<td>55</td>
<td>Try to use some traditional drugs for cough</td>
</tr>
<tr>
<td>48</td>
<td>Continue to give fluids and food as usual</td>
<td>56</td>
<td>None</td>
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</tbody>
</table>

56. Other: (write recommendation below):.................................................................
APPENDIX 5: PHARMACY GUIDELINES FOR A MILD ARI, URETHRAL DISCHARGE AND REQUEST FOR CEPHALEXIN AND PREDNISOLONE

Cough in a young child

A mother goes to the pharmacy asking for treatment for her child with a cough.

The drug seller should ask the following questions:

How old is the child?

- > 2 months
  - Has the cough persisted for > 30 days?
    - Yes → Go to health facility (HF) for examination
    - No → Can the child feed? (drink or breast feed)
      - Yes
        - Does the child have abnormal breathing?
          - Yes → Go to HF for examination
          - No
            - Has the child become sicker?
              - Yes → Go to HF for examination
              - No
                - Does the child have a fever?
                  - Yes → Go to HF for examination
                  - No / a little

- < 2 months → Go to health facility (HF) for examination

Treat the child appropriately as follows:

- Soothe the throat and relieve the cough with a safe remedy e.g.:
  - Self-made traditional remedies: Kumquat with honey/sugar, steamed white rose petals with honey/sugar.
  - Commercial remedies: Bo phe chi khai lo (traditional medicine), Acemux, Exomux, Mucomyst, Mucosan, Rhinathiol, Paceladine, Solmux Pediatric.

- Avoid using harmful remedies containing opium or anti-histamines, which could be toxic for children under 5 such as: Allerlene, Alussin, Camixene, Eucalyptine, Hexaneumine, Phenergan, Theralone, Toplexil, Tectpincodein and Benzocain.

Advise the mother to bring the child to a health facility for examination immediately if she notices the following signs at the child when the using above mentioned drugs:

- Abnormal breathing OR Fever OR Not able to drink or breastfeed OR Becoming sicker

If the mother says that she cannot go to a health facility for examination and insists on asking the pharmacy staff for a drug, one of two following drugs can be used:

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Cotrimoxazole (Bisepot, Trimazon) 2 times/day x 5 days</th>
<th>Amoxicillin (Clamoxyl, Hiconcil etc.) 3 times/day x 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight/Age</td>
<td>1 tablet = 480mg</td>
<td>Syrup 240mg/5ml</td>
</tr>
<tr>
<td>4 - 10 kg</td>
<td>1/2</td>
<td>5 ml</td>
</tr>
<tr>
<td>(2 m - 12 m)</td>
<td>10 - 19 kg</td>
<td>1</td>
</tr>
</tbody>
</table>
Asking for two antibiotic capsules

A woman (or man) goes to pharmacy asking for two antibiotic capsules.

The drug seller should ask the client the following questions:

- Why do you want two antibiotic capsules?
- Who will be taking the drug?
- What are the symptoms of the patient?

The drug seller should advise the client not to use only two antibiotic capsules because:

Antibiotics only have efficacy when used for treating disease caused by bacteria, which are sensitive to the antibiotic. Furthermore, the concentration of antibiotics used must reach a certain level in the blood, so that the antibiotics only have efficacy on the bacteria. On the other hand, the antibiotic has to be used for a certain number of days (at lest for 5 days) in order to eliminate all the bacteria at its different periods of growth. If antibiotics are used for a shorter time, the bacteria at a non-sensitive period will survive and develop.

It is a fact that some people who had got a common cold only took 2 tablets of antibiotics, and then recovered. They assumed that using the drug cured the cold. They told other people about this experience. Instead of taking the full dose of antibiotics, people discontinue the use of the drug when the symptoms such as fever, cough etc. disappeared. These behaviours of antibiotic use are very harmful, not just for the user but for the community.

Using an insufficient dose of antibiotics allows the bacteria to become acquainted with the antibiotic. A new type of bacteria, which resists the antibiotic, is generated. This bacteria spreads resistance in the community. The antibiotic will lose its efficacy for everyone not just for you.

The drug seller can recommend the client to use the appropriate drugs depending on her or his symptoms.

Steroid use

A man or woman comes to your pharmacy asking for 4 tablets of prednisolone (or other steroids).

You should ask the following questions:

- Why do you want steroids?
- How long have you had backache (for example)? What is it like?

Then you should advise him or her as follows:

> “You should go to see a doctor. Steroids are prescription drugs. We only sell these drugs when you have a prescription from a doctor. On the other hand, steroids are dangerous since they have many side effects such as:

- Steroids lead to ulcers at gastro-intestinal tract.
- Steroids lead to myotrophy.
- Steroids make infections worse since they take away the immune response and increase blood sugar.
- Steroids may cause Cushing’s Syndrome due to a disorder of lipid distribution.
- Steroids lead to osteoporosis.
- Steroids lead to hypertension due to a disorder of electrolytes.
- Steroids take over the body’s natural production of cortisol, therefore, when the drugs are no longer taken there is a danger of sudden death.

You should emphasize that if inflammation is caused by an infection, the steroids will make the infection worse (plus other effects). The disease will not be cured but become more severe. In addition, when taking steroids, the adjustment of the dose must be considered. Therefore, prescription is first required when using steroids.

You can recommend better drugs, which are appropriate for treating his or her condition such as:

- Medicine sticker: Salonpas etc.
- Paracetamol: Efferalgan, Dafalgan etc.
- Non-steroid anti-inflammatory drugs: With two precautions: first, these drugs are contra-indicated for those with history of gastric ulcer; second, they must be taken after meals.
  - Aspirin: 2 5g/day divided into 4 times
  - Voltaren (Diclofenac): 100-150 mg/day divided into 2-3 times
  - Alaxan (Ibuprofen 200mg and Paracetamol 325mg): 1-2 tab. x 3 times/day
  - Felden (Piroxicam): 10-40 mg
  - Profenid (Ketoprofen): 200-300mg/day divided into 2-3 times
  - Surgam (Tiprofenic acid): 400-600mg/day, divided into 3-4 times.
Urethral discharge

A man goes to the pharmacy complaining that he has noticed a discharge from the penis. He felt pain and discomfort in the genitals. He is asking the drug seller for drugs.

The drug seller should ask him the following questions:

- **Do you have a genital ulcer?**
  - Yes → Refer to a physician
  - No

- **Do you have a discharge from the penis?**
  - Yes
    - Do you feel painful and hot when urinating?
      - Yes
        - Have you had sex before these symptoms presented?
      - No

**Advise** the client to go to see a physician, if he insists on asking for a drug the following treatment for gonorrhea and chlamydia would be:

**Treatment**

Ciprofloxacin 500 mg, or pefloxacin 400mgs x 2 tablets, one dose and Doxycyclin 100 mg, twice daily for 7 days or tetracycline 500 mg 4 times a day for 7 days.

**Advise** the client:

1. To always use a condom.
2. That partner(s) should be treated in the same way.
3. To go to see a doctor if the symptoms are still present after taking the drugs.