Nguyen Quynh Hoa is pharmacist from Vietnam and MPH of Umeå University, Sweden. In the PhD project, she conducted both quantitative and qualitative studies on antibiotic use and resistance among children in Vietnam. The studies involved three major stakeholders i.e. prescribers, dispensers and caregivers. Laboratory work was done for isolation and susceptibility testing of S. pneumoniae.

High antibiotic use and resistance among children under five
Acute respiratory infections: knowledge and behaviour of caregivers and health-care providers in Vietnam

Nguyen Quynh Hoa
HIGH ANTIBIOTIC USE AND RESISTANCE AMONG CHILDREN UNDER FIVE

Acute respiratory infections: knowledge and behaviour of caregivers and healthcare providers in Vietnam

Nguyễn Quỳnh Hoa

Stockholm 2010
ABSTRACT

**Background:** Increased bacterial resistance is threatening the therapeutic effectiveness of antibiotics. High level of antibiotic use is probably the main factor driving the emergence of resistance. *Streptococcus pneumoniae* is the most significant bacterial cause of community-acquired pneumonia, which is the leading cause of deaths among children under five worldwide.

**Main aim:** To investigate proportion of antibiotic resistance and antibiotic use for acute respiratory infections (ARIs) among children under five, and describe knowledge and behaviour of caregivers and healthcare providers (HCPs) regarding antibiotic use for childhood illness in Vietnam.

**Methods:** This thesis consists of quantitative and qualitative studies. In Papers I and III, 828 caregivers were interviewed using a structured questionnaire and 823 children under five were followed for a 28-day period to collect data on daily illness symptoms and drug use. Clinical examinations were done and nasopharyngeal samples were taken. Etest and disk-diffusion were used to test antibiotic susceptibility of 421 *S. pneumoniae* isolates. Paper II is a qualitative study with six focus group discussions with mothers, fathers and grandmothers. Paper IV used a self-completed structured questionnaire with 392 HCPs regarding management of children under five with ARIs.

**Results:** Of the 421 pneumococcal isolates, 95% were resistant to at least one antibiotic and 60% were multidrug-resistant (I). The resistance to co-trimoxazole, tetracycline, phenoxymethylpenicillin, erythromycin and ciprofloxacin was 78%, 75%, 75%, 70% and 28%, respectively. Low resistance was noted for amoxicillin (4%), benzylpenicillin (4%), and cefotaxime (2%). The intermediate resistance to amoxicillin was 32%. Resistance to commonly used antibiotics was higher among children who had used antibiotics recently (I). Self-treatment was prominent among urban participants, whereas compliance and trust in physicians were more common among rural participants. Caregivers perceived antibiotic use as mandatory for illness with fever (II). During the most recent illness, antibiotics were given to 71%, 86% and 32% of children with mild ARI, severe ARI, and other illness, respectively (III). In the 28-day period, 62% of children used antibiotics. Most of the antibiotic courses were used for mild ARIs (528/843). Most of the incorrect treatment (82%) reported has been recommended by HCPs (III). Only 27% of HCPs demonstrated correct knowledge regarding the consequences of resistance and 19% regarding the antibiotic treatment for ARIs (IV). In the most recent encounter with a sick child, antibiotics were recommended in 90%, 87%, and 78% for treatment of mild ARIs, severe ARIs, and other illness, respectively (IV).

**Conclusions:** Resistance to commonly used antibiotics and multidrug-resistance of *S. pneumoniae* is markedly high. High dose of amoxicillin is the only oral antibiotic that can possibly be used when treatment is required for community-acquired pneumococcal infections. Most of children had used antibiotics unnecessarily during their most recent illness and in the 28-day period during the study. There is a serious lack of knowledge on appropriate antibiotic use among the HCPs as well as the caregivers. Antibiotics are often prescribed or dispensed for common colds.

**Keywords:** acute respiratory infections, antibiotic use, antibiotic resistance, children, caregiver, healthcare provider, Vietnam.
LIST OF PUBLICATIONS

The thesis is based on the following papers, which will be referred to by the Roman numerals I-IV


III. Hoa NQ, Chuc NTK, Phuc HD, Eriksson B, Larsson M, Stålsby Lundborg C. Unnecessary antibiotic use for mild acute respiratory infections in 28-day follow-up of 823 children under five in rural Vietnam. (Submitted)


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<tr>
<td>ARI</td>
<td>Acute Respiratory Infections</td>
</tr>
<tr>
<td>AMOX</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>AMP</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification system</td>
</tr>
<tr>
<td>CAP</td>
<td>Community-acquired pneumonia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIP</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
</tr>
<tr>
<td>COT</td>
<td>Co-trimoxazole (sulfamethoxazole ans trimethoprim)</td>
</tr>
<tr>
<td>CTX</td>
<td>Cefotaxime</td>
</tr>
<tr>
<td>EARSS</td>
<td>European Antimicrobial Resistant Surveillance System</td>
</tr>
<tr>
<td>ERY</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>EUCAST</td>
<td>European Committee on Antimicrobial Susceptibility Testing</td>
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<tr>
<td>FGD</td>
<td>Focus Group Discussion</td>
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<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
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<td>GSO</td>
<td>General Statistics Office of Vietnam</td>
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<tr>
<td>HCP</td>
<td>Healthcare provider</td>
</tr>
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<td>HCS</td>
<td>Health Commune Station</td>
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<td>HSRP</td>
<td>Health System Research Project</td>
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<tr>
<td>ICC</td>
<td>Intra-Cluster Correlation</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illness</td>
</tr>
<tr>
<td>MDR</td>
<td>Multidrug-resistant</td>
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<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
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<td>MOH</td>
<td>Ministry of Health, Vietnam</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PEN G</td>
<td>Benzylpenicillin</td>
</tr>
<tr>
<td>PEN V</td>
<td>Phenoxyymethylpenicillin</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>SRGA</td>
<td>Swedish References Groups for Antibiotics</td>
</tr>
<tr>
<td>TET</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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When I was a young mathematics student, my dream was to study my subject at a university abroad. This dream never came true however, as in 1990 there was no longer any educational collaboration between Vietnam and the former socialist European countries. One day, I made a decision and applied to the Hanoi University of Pharmacy instead of the University of Technology. At that moment I had little idea what pharmacists did or how much I would come to love my profession.

After graduation, I started to work at the Hanoi Health Bureau in the Department of Private Health Management. At that time, the government had just signed the Law on Private Health Practice and the MOH has started to establish a system to promote as well as control private health facilities. Since then, the private health sector has developed rapidly in the whole country, especially in Hanoi. During my eight years working in this field, I realized that, despite positive contributions to the health system, the quality of service in private sector is in need of improvement.

In 1997, I was fortunate to be involved in the multi-intervention study in private pharmacies within EU-GPP project as an inspector and to be in the course on Health System Research (HSR) in Vietnam. While doing fieldwork at FilaBavi, funded by Sida/SAREC Sweden, I became interested in scientific studies and wanted to learn a lot more. In 2003, I went to Umeå University, Sweden to study to become a Master of Public Health. By that time, I had realized that antibiotic resistance was becoming a growing threat to public health worldwide. However, I didn’t have in-depth understanding of the actual situation of antibiotic resistance in Vietnam and the main reasons behind it. Thus I came to Karolinska Institutet for PhD training and joined the research group focusing on “Antibiotics on the health system” at IHCAR, which is lead by my main supervisor.

Now as I am working in the Vietnam Cuba Hospital, a public hospital, as a pharmacist and in the HSR project as a researcher, I could see different aspects of the health system. Availability of antibiotics in both private and public health facilities is convenient to people seeking health care with bacterial infections, but on the other hand it increases the risk of inappropriate use of antibiotics. It is of great importance to understand what the major problems are in relation to irrational use of antibiotics in a limited resource setting.

Armed with experience and knowledge, I have enjoyed diving into the complex phenomenon of pneumococcal antibiotic resistance and antibiotic use in the health system. It was extremely enjoyable as I could apply mathematics to the whole process of research in order to make the findings meaningful and useful. I’m now happy with my choice of pharmacy studies 20 years ago and with the journey that has brought me to Sweden today. I hope that my efforts in the PhD training will contribute to an improvement of the health system both locally and globally, and wish to convey my enthusiasm to everyone reading this thesis. I sincerely hope I will be able to do more in the future.
1 BACKGROUND

1.1 ACUTE RESPIRATORY INFECTIONS

1.1.1 Epidemiology

Acute respiratory infection (ARI) has consistently been estimated as the leading cause of childhood mortality and morbidity (Bryce et al., 2005; Bulla & Hitze, 1978; Mulholland, 2003; Murray & Lopez, 1997; Williams et al., 2002). In 2000-2003, one-fifth of the 10.6 million yearly deaths globally among preschool children, were due to or associated with ARI (Bryce et al., 2005). The three major causes of death from ARIs are pneumonia, bronchiolitis, and acute obstructive laryngitis (Campbell, 1995). Worldwide, more than half of deaths of children under five were attributable to four causes: pneumonia (19%), diarrhoea (18%), malaria (8%), neonatal sepsis or pneumonia (10%) (Bryce et al., 2005). The highest rates of under five mortality remain in sub-Saharan Africa (50%), the second highest in South Asia (32%), and the least high (2%) in Europe (Bryce et al., 2005). About two-thirds of all deaths due to pneumonia are concentrated in 10 African and Asian countries: India, Nigeria, Congo, Ethiopia, Pakistan, Afghanistan, China, Bangladesh, Angola and Niger (You et al., 2009).

There are annually 152 million new clinical pneumonia cases among children under five in low- and middle-income countries and 4 million in high-income countries (Rudan et al., 2008; Rudan et al., 2004). Estimates of pneumonia incidence are highest in South-East Asia (0.36 episodes per child-year), closely followed by Africa (0.33 episodes per child-year), and lowest in the European regions (0.06 episodes per child-year). More than half of new cases of the world’s annual pneumonia occur in five countries: India, China, Pakistan, Bangladesh, and Nigeria. Vietnam belongs to the group of 15 countries with the highest number of new cases of pneumonia (0.35 episodes per child-year) (Rudan et al., 2008).

The variation in pneumonia rates between communities is affected by environmental conditions such as cold air, air pollution; socioeconomic factors and nutritional factors such as poverty, micronutrient deficiencies, lack of exclusive breastfeeding; educational and cultural issues such as housing and mothers’ education (Caulfield et al., 2004; Ezzati et al., 2003; Mulholland, 2003; Rudan et al., 2008; Victora et al., 1987). Deaths due to ARIs were more common in rural than in urban areas (Rudan et al., 2008).

1.1.2 Aetiology

ARI is the collective name for both upper and lower respiratory infection. Upper respiratory infections are very common and typically they are mild and caused by viruses. The causal agents in mild ARI are often rhinovirus, coronavirus, and respiratory syncytial virus (RSV) (Bulla & Hitze, 1978; Monto, 2002). Lower respiratory infections are usually more severe and caused by both viruses and bacteria called co-infection (Cevey-Macherel et al., 2009; Rudan et al., 2008; Shann et al., 1984a; WHO, 1999). The term pneumonia is usually used in the broader sense to refer to severe acute infections of the lung by viral, bacterial or other pathogens. *Haemophilus influenzae* and *Streptococcus pneumoniae* are the main bacterial causes, and RSV is the main viral cause.
of pneumonia (Pitkaranta et al., 2006; WHO, 1999). *H. influenzae* is predominant in children younger than two years and *S. pneumoniae* in children older than 2 years. For children under 2 months, the predominant pathogens of pneumonia are gram-negative bacteria, group B streptococcus, *S. aureus* and viruses (Shann et al., 1984a).

Globally, rhinoviruses are the most frequent (23-35%) viral isolate identified in the overall population suffering from the common cold, followed by coronaviruses (18%), and RSV (11-15%) (Monto, 2002; Regamey et al., 2008). Seasonality is one of the characteristics of respiratory viruses. Worldwide, the seasonality of rhinoviruses and other respiratory agents varies geographically, major peaks occur in the cold season (Gwaltney, 2000; Monto, 1995). The most common infection caused by viruses is in the upper respiratory tract leading to rhinitis, cough, and sometimes fever. Rhinoviruses and coronaviruses may complicate childhood pneumonia (Kahn, 2006; Papadopoulos, 2004).

RSV has been reported as the single most important virus causing a substantial amount of acute lower respiratory infections in children (Broor et al., 2007). The risk of ARI caused by RSV is highest among children under two (Simoes, 1999). In lower-income countries, up to 70% of lower respiratory tract infections are caused by RSV (Weber et al., 1998). The isolation of a virus does not associate to mortality, but it might increase the risk of bacterial invasion leading to a frequent occurrence of virus and bacteria co-infection in children (Cevey-Macherel et al., 2009; Madhi & Klugman, 2004; Nascimento-Carvalho et al., 2008).

Bacterial pathogens become more likely after the age of 6 months. *S. pneumoniae*, also called the pneumococcus, is the main causative agent of community acquired pneumonia (CAP) among children, being identified in 30-50% of the cases (Pitkaranta et al., 2006; Schrag et al., 2000; Shann et al., 1984a; Song et al., 2004a). It is also the most important cause of meningitis (WHO, 1999). *S. pneumoniae* is the major contributor to morbidity and mortality among children under five worldwide. It was estimated that pneumococci caused 826,000 deaths in children aged 1-59 months in 2000 (O'Brien et al., 2009). Africa and Asia together accounted for 95% of all pneumococcal deaths. Globally, the incidence of pneumococcal pneumonia was 13.8 million cases, and the greatest number of cases was from large countries such as India 27%, China 12%, Nigeria 5%, Pakistan 5%, and Bangladesh 4% (O'Brien et al., 2009).

Despite their ability to cause disease, pneumococci are also often found as commensals, colonizing the nasopharynx of healthy preschool children. These children constitute a reservoir of the bacteria in the community, and can transmit both antibiotic-susceptible and antibiotic-resistant strains. Hence, the pneumococcus can be regarded both as a pathogen and as a commensal (Murray et al., 2005). It has been reported that 95% of children had been colonized at least once by the time they were two years old (Gray et al., 1980). The duration of carriage lasts from 2.5 to 4.5 months. The incidence of carriage and associated disease is highest during the colder months (Gray et al., 1980).

When an individual encounters the pneumococcus, the first step is colonization of the nasopharynx, the natural niche for this human-specific bacterium. Asymptomatic carriers
constitute a reservoir of pneumococci in the community, and are therefore important vehicles for transmission of the bacteria. ARIs are transmitted mostly by infected persons’ sneezing, coughing or talking. Pneumococcal disease occurs when organisms spread to the distal loci, such as the lungs (pneumonia), paranasal sinuses (sinusitis), ears (otitis media), and meninges (meningitis) (Koedel et al., 2002). Bacteremia, with subsequent spreading of the disease to other body sites, can occur with all of these infections (Depuydt et al., 2006).

Pneumonia is caused by a combination of exposure to risk factors related to the host, the environment and infection (Rudan et al., 2008). In general, 80% of pneumonia in children occurs in those below 7 years, with a peak in ages 2 to 4 years (Murphy et al., 1981). The risk factors related to the host include: malnutrition, low birth weight, non-exclusive breastfeeding, lack of measles immunization, zinc deficiency, or concomitant diseases (Rudan et al., 2008; van der Poll & Opal, 2009). It has been reported that pneumococcal pneumonia often occurs after a primary infection caused by influenza, parainfluenza or RSV (Brundage & Shanks, 2008; McCullers, 2006; Morens et al., 2008).

The two major causes of bacterial pneumonia, *H. influenzae* and *S. pneumoniae*, in early childhood are vaccine-preventable. In both cases, the vaccines will prevent most pneumonia caused by each pathogen (Isaacman et al., 2010; Kyaw et al., 2006; Ruckinger et al., 2009). Other preventive measures include improving nutrition and breastfeeding among infants, which enhance immune defences and reduce the risk of becoming ill and dying from pneumonia. Vaccines against *H. influenzae* and *S. pneumoniae*, effective case management, breastfeeding promotion and zinc supplementation are cost-effective ways of reducing childhood pneumonia mortality (Graham et al., 2008; Niessen et al., 2009). Other measures include environmental and nutritional intervention, which may reduce pneumonia and provide other benefits (Mulholland, 2003).

1.1.3 Diagnosis and treatment

Since ARI can be caused by a variety of organisms, the ideal approach is to find the causative agent in each case, so that appropriate treatment can be given. However, both viral and bacterial ARI present roughly the same clinical symptoms, making it difficult to clinically differentiate between them. 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 some cases. The location and type of infiltrates seen on chest radiographs can assist in determining whether the infection is viral or bacterial (Bachur et al., 1999). In general, health professionals in primary health facilities often make treatment decisions without laboratory tests because diagnosis results take too long to get or there is a lack of diagnostic equipment. Therefore, a tremendous amount of work is being put into the development of simple and rapid diagnosis techniques as well as effective case management guidelines (Bhatta, 2006, 2007).

Childhood pneumonia caused by sensitive bacteria is easily treatable with simple antibiotics, thus access to basic healthcare services is an important determinant of
pneumonia mortality rates. It has been estimated that many children in low-income countries do not have access to such a basic level of care (Bhutta, 2006; Sazawal & Black, 1992). To help primary health professionals to make management decisions, WHO developed assessment and treatment algorithms, based on clinical signs distinguishing pneumonia from other causes of ARI. The incorporation of the ARI case management programme into the Integrated Management of Childhood Illness (IMCI) strategy has provided a more comprehensive approach to diagnosis, prevention and treatment of ARI (Gove, 1997; WHO, 1984). In IMCI guidelines, the algorithm for ARI management in primary health facilities is provided including management of children for a combination of illness, e.g. identifying those requiring urgent referral, administering appropriate treatment and providing relevant information for caregivers (Gove, 1997; Mulholland et al., 1992; WHO, 1984). According to IMCI, children with four general danger signs including convulsions, inability to drink, persistent vomiting, and lethargy or unconsciousness need urgent referral. Many low- and middle-income countries are implementing IMCI, which has led to a significant reduction of the pneumococcal mortality (Armstrong Schellenberg et al., 2004; Bishai et al., 2008; Gove, 1997; MOH, 2006; Patwari & Raina, 2002; Sazawal & Black, 2003).

Table 1 shows the summary of the classification and management of children presenting with cough or difficult breathing in primary health facilities and at home (MOH, 2006; WHO, 2005a, 2005b). According to the IMCI guidelines, the cornerstone of the ARI case management strategy is based on two clinical signs: lower chest in-drawing and respiratory rate. Chest wall in-drawing, or sternal recession, is the best indicator for children with severe pneumonia (Campbell et al., 1988). These signs have been validated by many subsequent studies and confirmed as having good sensitivity (70-93%) and specificity (67-98%) for the radiological diagnosis of pneumonia (Campbell et al., 1988; Hazir et al., 2004; Mtango & Neuvians, 1986; Mulholland et al., 1992; Shann et al., 1984b). Chest wall in-drawing is present if, in a calm child, a lower part of chest moves in or retracts when inhalation occurs. A child aged 2 months to 2 years with a respiratory rate higher than 50 per minute, or aged over two years, and with a respiratory rate over 40 and cough, is classified as suffering from pneumonia (Gove, 1997; Mulholland et al., 1992; WHO, 1984).

A meta-analysis of the WHO ARI case-management implementation showed that the greatest potential to reduce pneumococcal mortality in health facilities is wider implementation of the current guidelines with a few core activities such as training of healthcare providers, facilitated referral, use of appropriate antibiotics and availability of oxygen (Graham et al., 2008). Whether treatment will be on an outpatient or inpatient basis is determined by the severity of the disease. Children should be transferred to intensive care when the child is shocked, has severe respiratory distress and exhaustion, or recurrent apnoea, or other general danger signs (Coote et al., 2002). After antibiotics, oxygen is the most important treatment to reduce ARI mortality from pneumonia, as hypoxia is a major risk factor for death in children with severe pneumonia (Onyango et al., 1993). Children with pneumonia based on the presence of fast breathing, no visible respiratory distress, and able to tolerate oral medication can be treated at home with oral antibiotics. Those with a common cold or mild ARIs are treated symptomatically (WHO, 2005a).
Mild ARIs are extremely common in children and typically characterized by rhinitis, sore throat, cough, and with or without fever (Gove, 1997; Rosenstein et al., 1998; WHO, 1984). Since mild ARIs are commonly caused by virus, but there are no suitable therapeutic antiviral drugs available and these illnesses are often self-limiting within one or two weeks, the treatment should be only symptomatic, e.g. antipyretics or anti-cough (Hay & Wilson, 2002). A meta-analysis of randomized controlled trials showed that antibiotics if used to treat sore throat or rhinitis have minimal or no benefit on the clinical outcome (Arroll & Kenealy, 2007; Del Mar et al., 2006; Mainous & Hueston, 1996; Rosenstein et al., 1998). Such antibiotic use is not only unnecessary but increases the risk of bacterial resistance and treatment failure for any subsequent invasive infection besides the risk of causing unnecessary adverse reactions.

**Table 1: Classification and management for cough and difficult breathing (MOH, 2006; WHO, 2005a, 2005b)**

<table>
<thead>
<tr>
<th>Signs</th>
<th>Primary healthcare providers</th>
<th>Teach caregivers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Classify as</td>
<td>Identify treatment</td>
</tr>
<tr>
<td>Any general danger signs or chest in-drawing</td>
<td>Severe pneumonia* or very severe disease*</td>
<td>Give first dose of an appropriate antibiotic. Refer urgently to hospital. If referral is difficult: use injections or oral amoxicillin.</td>
</tr>
<tr>
<td>Fast breathing</td>
<td>Pneumonia</td>
<td>Give an oral antibiotic: co-trimoxazole, amoxicillin, or erythromycin. Soothe the throat and relieve the cough. Follow-up in 2 days.</td>
</tr>
<tr>
<td>No sign of pneumonia or very severe disease</td>
<td>No pneumonia: Cough or cold</td>
<td>If coughing &gt;30 days, refer to assessment. Don’t need an antibiotic. Soothe the throat and relieve the cough. Follow up in 5 days.</td>
</tr>
</tbody>
</table>

* The “red box” cases in original handbook (need urgent referral)

### 1.2 ANTIBIOTIC USE AND RESISTANCE

#### 1.2.1 Antibiotics for management of community-acquired pneumonia

Antibiotics have revolutionized the treatment of bacterial infections and, when used correctly, they play a crucial role in reducing child mortality, especially in low- and middle-income countries. Evidence shows that the use of the WHO case-management guidelines significantly reduced pneumonia mortality in children under five by 36%. A substantial part of the reduction in mortality was attributable to antibiotic use (Sazawal & Black, 1992, 2003).
In the management of CAP, obtaining appropriate microbiological information for making a decision about the choice of antibiotics is not feasible in most circumstances. Thus the choice of empirical antibiotics must be based on knowledge of common bacterial pathogens and sensitivity in the region (Bhutta, 2008b). At present, the WHO policy is to treat all children with pneumonia with antibiotics because the reported high prevalence of bacteria isolates, mostly \textit{S. pneumoniae} and \textit{H. influenzae} (WHO, 2005a). The first dose of antibiotics should be given immediately after the first contact to avoid delay in antibiotic administration, to improve outcomes (Houck et al., 2004).

The development of paediatric formulations of antibiotics has enabled better therapy for children. Amoxicillin remains the first choice for oral antibiotic therapy because it is effective against the majority of pathogens which cause CAP, well tolerated, and cheap (Coote et al., 2002; MOH, 2006; WHO, 2005b; Zar et al., 2005). WHO recommends treatment of non-severe pneumonia with co-trimoxazole as a first line empirical antimicrobial treatment in countries with an infant mortality higher than 40 per 1000 live births (WHO, 1991). In general, for childhood non-severe pneumonia, the WHO guideline recommends oral amoxicillin (25 mg/kg/dose) twice daily (WHO, 2005b).

Oral cephalosporins (e.g. cefixime, cefpodoxime) should not be used as the first line treatment for treatment of CAP to prevent bacterial resistance (BTS, 2002). In addition, due to severe hepatotoxicity, fluoroquinolones (e.g. ciprofloxacin, levofloxacin, norfloxacin) are not recommended for children unless there are overriding reasons for their use (Finch et al., 2003). All the children diagnosed as having severe or very severe pneumonia need to be hospitalized for detailed assessment, injectable antibiotics, other supportive therapy, and monitoring (IndiaCLEN, 2010; WHO, 2005b; Zar et al., 2005).

WHO currently recommends injectable chloramphenicol for the treatment of very severe pneumonia (WHO, 2005b). An alternative to chloramphenicol at similar costs could be injectable penicillin plus an aminoglycoside (Duke et al., 2002). Both treatment options will provide a good protection in the blood and the lungs against sensitive strains of \textit{S. pneumoniae} and \textit{H. influenzae}, however chloramphenicol showed better effect toward \textit{S. aureus} which is a common pathogen causing severe pneumonia (WHO, 2005b). The injectable third generation of cephalosporins such as ceftriaxone or cefotaxime is indicated if high-level pneumococcal resistance (MIC>2mg/l), or no improvement after another 48hrs, or disease associated septicaemia and meningitis (IndiaCLEN, 2010; Zar et al., 2005). Where referral is difficult and injection is not available, oral amoxicillin is recommended for severe pneumonia (WHO, 2005b).

1.2.2 Irrational antibiotic use and the emergence of antibiotic resistance \textit{S. pneumoniae}

Antibiotic use is seen as the most important factor in the emergence of bacterial resistance. The use of antibiotics for any infection, in any dose and over any time period forces the bacteria to either adapt or die in a phenomenon known as “selective pressure”. The bacteria that adapt and survive will carry genes for resistance, which can be passed on and multiply very rapidly (Tenover, 2006). For these reasons, improving antibiotic use thereby reducing the selective pressure is a priority in order to curb the further spread of antibiotic resistance.
Irrational antibiotic use has been observed in different geographic regions worldwide and among those involved in the prescribing, sale and use of drugs (Bharathiraja et al., 2005; Chuc et al., 2001; Hoan et al., 2009; Larsson et al., 2000; Muller et al., 2007; Van Duong et al., 1997; Zuckerman et al., 2007). Although physicians realize that antibiotics have no antiviral effect, antibiotics are often unnecessarily prescribed to prevent bacterial complications of viral infections (Gadomski, 1993).

Physicians often face the dilemma “to treat or not to treat” upper ARIs with antibiotics (Henriksen & Hansen, 2004). Irrational treatment with antibiotics might lead to the development of bacterial resistance, but at the same time limited access to antibiotics in cases of bacterial infections is contributing to high mortality. In high-income countries, the treatment of upper tract infection is ideally limited to symptomatic therapy in most patients (Hogberg et al., 2005; Muller et al., 2007; Petersen & Hayward, 2007; Rossignoli et al., 2007). In lower-income countries there are difficulties in ruling out bacterial super-infection on clinical grounds, in accessing appropriate information, and in dealing with high patients’ expectations, therefore a high antibiotic prescription rate for mild ARIs is hard to avoid (Bharathiraja et al., 2005; Cheraghali & Idries, 2009; Dong et al., 2008; Khatib et al., 2008; Larsson et al., 2005).

Drug dispensers often provide advice along with medicines and take part in diagnosis process (Nordberg et al., 2005; Olsson et al., 2002). In Vietnam, as well as other low- and middle-income countries, most patients who seek care at drugstores get antibiotics without prescription (Apisarnthanarak et al., 2008; Chuc et al., 2001; Nizami et al., 1996; Olsson et al., 2002; Syhakhang et al., 2001; Thamlikitkul, 1988; Viberg et al., 2009; Wachter et al., 1999). Antibiotic dispensing without prescription has also been reported in some countries in Europe, such as Spain and Greece (Grigoryan et al., 2007; Llor & Cots, 2009; Plachouras et al., 2010).

Self-medication with antibiotics has been widely reported worldwide. Globally, the access to antibiotics for self-medication is either leftovers from earlier illness episodes (Grigoryan et al., 2006; Kardas et al., 2007; Okumura et al., 2002; Richman et al., 2001) or drugs obtained from pharmacies (Contopoulos-Ioannidis et al., 2001; Kamat & Nichter, 1998; Khe et al., 2002; Larsson et al., 2000; Stratchounski et al., 2003). Evidence from many countries showed that patients often expect antibiotics for common viral infections (Britten & Ukoumunne, 1997; Cockburn & Pit, 1997; Mangione-Smith et al., 1999; Parimi et al., 2004; Weissman & Besser, 2004).

Table 2 shows that the emergence and spread of microbial resistance is a true global threat, affecting many low-, middle- and high-income countries. Antibiotic resistance is driven by numerous interconnected factors, which mainly are linked to antibiotic use (Craig, 2001; Okeke et al., 2005b). The most important risk factor in resistance is prior antibiotic use in the last 3 months of an antibiotic in the same class (Vanderkooi et al., 2005). Higher rates of antibiotic resistance were found in countries with a high consumption of antibiotics (Goossens et al., 2005).
Table 2: Antibiotic resistance rates (%) among *S. pneumoniae* worldwide.

<table>
<thead>
<tr>
<th>Area</th>
<th>Year</th>
<th>No of isolates</th>
<th>PEN*</th>
<th>TET*</th>
<th>CIP*</th>
<th>COT*</th>
<th>ERY*</th>
<th>MDR*</th>
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<td>3,435</td>
<td>22</td>
<td>31</td>
<td>-</td>
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<tr>
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<td>2001-02</td>
<td>6,320</td>
<td>24</td>
<td>36</td>
<td>-</td>
<td>28</td>
<td>37</td>
<td>37</td>
<td></td>
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<tr>
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<td>1996-97</td>
<td>996</td>
<td>23</td>
<td>-</td>
<td>27</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>(Song et al.)</td>
</tr>
<tr>
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<td>6</td>
<td>55</td>
<td>35</td>
<td>27</td>
<td>-</td>
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<td>88</td>
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<tr>
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<td>-</td>
<td>-</td>
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<td>10</td>
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<td>443</td>
<td>48</td>
<td>40</td>
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<td>2007</td>
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<td>28</td>
<td>18</td>
<td>(Mera et al.)</td>
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<td>59</td>
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<td>13</td>
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<td></td>
<td>(Davidson et al.)</td>
</tr>
<tr>
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<td>1999</td>
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<td>12</td>
<td>20</td>
<td>-</td>
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<td>(Hoban et al.)</td>
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<td>8</td>
<td>50</td>
<td>14</td>
<td>1</td>
<td>(Johnson et al.)</td>
</tr>
</tbody>
</table>

(*PEN: benzylpenicillin; TET: tetracycline; CIP: ciprofloxacin; COT: co-trimoxazole; ERY: erythromycin; MDR: multidrug-resistant).

The inter-country variability has been documented in numerous surveillance studies, such as the PROTEKT (1999-2004) (Farrell et al., 2008; Reinert, 2004), the Alexander Project in 1992-2001 (Mera et al., 2005), the SENTRY Antimicrobial Surveillance Program in 1999-2003 (Johnson et al., 2006), and the Asian Network for Surveillance of Resistant Pathogens (ANSORP) in 1996-2001 (Lee et al., 2001; Song et al., 2004b). There was an increase in prevalence of multidrug-resistance (MDR) in the US (Mera et al., 2005) and
other parts of the world, particularly Asia over the last few years (Song et al., 2004b). With the world’s most rapid growth rate of resistance, the threat of antibiotic resistance in China is a major challenge to global health (Heddini et al., 2009; Zhang et al., 2006). There is a trend of decreased prevalence of resistance in the last decade, mainly to beta-lactams, in some parts of the world, such as the US, France, Spain, Belgium, and Israel (Linares et al., 2010; Sahm et al., 2008).

1.2.3 Consequences of antibiotic resistance

The consequences of antibiotic resistance are severe. The growing phenomenon of antibiotic resistance of the bacteria is now threatening to take us back to a pre-antibiotic era. Increased bacterial resistance is threatening the therapeutic effectiveness of antibiotics, increasing the number of treatment failures, and as a result, leading to longer and more severe illness episodes with higher costs and mortality rates (Craig, 2001; Okeke et al., 2005b). Emergence of antibiotic resistance has led to a much higher economic burden on health systems of poor countries because of the higher treatment failure and complications (Bhutta, 2008a).

Evidence shows that pneumococcal resistant to penicillin was associated with a higher mortality rate (Metlay et al., 2000; Tleyjeh et al., 2006; Turett et al., 1999). Poor clinical outcome in empirical treatment of CAP has been associated with macrolide, fluoroquinolone resistance or very high-level penicillin resistance (MIC>4mg/l) (Davidson et al., 2002; Feikin et al., 2000; Lonks et al., 2002). Data from low- and middle-income countries shows that 70% of hospital acquired neonatal infections could not be successfully treated by using WHO’s recommended guideline because of the development of resistance to first line antibiotics (Zaidi et al., 2005). The reported treatment failure rates ranging from 10% to 23% in treatment of non-severe pneumonia cases from several therapeutic trials may relate to differences in antibiotic resistance pattern (Bhutta, 2007).

Treatment factors may contribute to adverse outcomes in patients infected with a resistant pathogen. These factors include decreased effectiveness, increased toxicity, and/or improper dosing of antimicrobial agents available for treatment. In addition, there is an increased need for surgery and other procedures as a result of these infections. Treatment failures due to antibiotic resistant pneumococci have been reported with meningitis (Friedland & Klugman, 1992; Guibert et al., 1995), and otitis media (Jacobs, 1996). There are a number of important issues linked with the impact of antibiotic therapy, such as age of patients, co-morbidities, and severity of infection (Aspa et al., 2008; Feikin et al., 2000; Tleyjeh et al., 2006).

A major challenge for the future is the worrying increased bacterial resistance among *S. pneumoniae*, the key pathogen in CAP. When infections become resistant to first-line antibiotics, treatment has to be switched to second- or third-line antibiotics, which are much more expensive, sometimes more toxic and not available (BTS, 2002; Jacobs & Dagan, 2004). Treatment failures also lead to a longer period of infectivity, which increases the number of infected people moving around the community and exposes the general population to the risk of developing a resistant strain of infection. It is of more
concern as the resistant genes usually persist in a stable form and are not easily reversed (Andersson & Hughes, 2010).

1.2.4 Laboratory tests for antibiotic susceptibility

With the increase of bacterial resistance to traditionally used antibiotics, it becomes more difficult for clinicians to select an appropriate antibiotic for empirical treatment (Okeke et al., 2005b). In combination with the situation that a variety of antibiotics is currently available, selection of appropriate treatment becomes more challenging. The results from in vitro antimicrobial susceptibility tests are useful for clinicians in empirical treatment (Goettch et al., 2000). Antibiotics in the same class may have similar in vitro activities against bacteria. The number of antibiotics to be tested should be limited in order to ensure the relevance and practicality of the test. A representative antibiotic can then be selected that predicts susceptibility to other antibiotics of the same class (CLSI, 2009; EUCAST, 2009b; SRGA, 2008b).

There are a variety of methods by which one can determine the antimicrobial susceptibility of a bacterial pathogen, commonly including disk diffusion, agar dilution or broth dilution, and testing by antimicrobial gradient agar diffusion (e.g. the Etest strip). The selection of a method is based on many factors such as practicality, automation, cost, reproducibility, accuracy, and individual preference.

Disk diffusion is the most common method for antimicrobial susceptibility testing in the clinical laboratory. The main advantages are its low cost, relatively simplicity and that it can be used as a screening test against a large number of isolates (Bauer et al., 1966; Ericsson & Sherris, 1971). Disks containing antibiotics are placed on the surface of an agar plate containing a medium that has been inoculated with a bacterium. The bacterium will grow and fill the disk. The antibiotic diffuses into the medium, and inhibits the growth of the test bacterium. Generally, the size of the inhibitory zone of the bacterium shows how effective the antibiotic is. The larger the inhibitory zone, the lower concentration of antibiotic is required to inhibit the growth of the bacterium. However, this depends also on the concentration of antibiotic in the disk and its diffusibility whereas standardized procedures are important (EUCAST, 2009a; SRGA, 2008a; WHO, 2003).

The Etest is a newer antimicrobial susceptibility testing method that has several advantages including the ability to express minimal inhibitory concentration (MIC) values in mg/l and being as technically simple to perform as disk diffusion. With increasing antimicrobial resistance testing being performed outside of international reference laboratories, the Etest serves as a test method that is both convenient and reliable (Goettch et al., 2000; Jorgensen et al., 1991). It is drug-specific, consists of a thin plastic antibiotic gradient strip that is applied to an inoculated agar plate. MIC is defined as the point of intersection of the ellipse-formed zone of inhibition with the value printed on the Etest strip. The Etest requires less technical expertise and is less time consuming than MIC testing by dilution methods, but it gives comparable results. Etest strips must be consistently stored in a freezer at -20°C. The accuracy and reproducibility of this test are dependent on following a standard set of procedures and conditions in the laboratories (SRGA, 2008a; WHO, 2003).
1.3 VIETNAM

1.3.1 General information

The Socialist Republic of Vietnam is situated in Southeast Asia and borders China in the north, Laos in the northwest and centre, and Cambodia in the southwest. The area is about 330,000 km\(^2\), three-quarters of which are mountainous and hilly. The Red River delta in the North and the Mekong delta in the South are two large lowland areas. The country is largely lush and tropical, though the temperature in the northern mountains can become near freezing in the winter and the central regions often experience drought. There are four seasons in the North (spring, summer, autumn, winter) and two seasons (dry and wet) in the South. The country is frequently affected by typhoons and flooding.

The population in 2008 was approximately 86.2 million comprising almost exclusively indigenous peoples. There are more than 54 ethnic groups of which the Kinh is the majority (86%). Seventy two percent of the population live in rural areas. Vietnamese is the official language. The total fertility rate per woman is 2.11 (GSO, 2009).

When the war against America ended in 1975, the North and the South of Vietnam were reunited under a Socialist government. Between 1975-1980, the growth rate was only 0.4%, and for a period Vietnam even had to import rice. In 1986, Vietnam launched a radial market economic reform called “Doi moi”, which changed the country from a subsidized socialist economy to a market-oriented economy. Since then, Vietnam has been changing rapidly with an economic growth of more than 6% annually. However, Vietnam is still among the poorest countries in the world with a per capita income in 2008 of around 1,062 USD (MOH, 2010). With an extensive and successful primary healthcare network, Vietnam has better health indicators than many other poor countries (Table 3).

**Table 3.** Basic indicators for Vietnam (GSO, 2009; MOH, 2010)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Values</th>
</tr>
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<td>Area (km(^2))</td>
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</tr>
<tr>
<td>Population (million)</td>
<td>86.2</td>
</tr>
<tr>
<td>Female/Male (million)</td>
<td>43.8/42.4</td>
</tr>
<tr>
<td>Adult literacy rate (%)</td>
<td>90.3</td>
</tr>
<tr>
<td>Life expectancy at birth (year)</td>
<td>73</td>
</tr>
<tr>
<td>Infant mortality rate (per 1,000 live births)</td>
<td>15.5</td>
</tr>
<tr>
<td>Under-five mortality rate (per 1,000 live births)</td>
<td>25.5</td>
</tr>
<tr>
<td>Maternal mortality rate (per 100,000 live births)</td>
<td>75</td>
</tr>
<tr>
<td>Low birth weight rate (&lt;2,500 gr, %)</td>
<td>5.3</td>
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<tr>
<td>Under-five malnutrition on weight (%)</td>
<td>20</td>
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<tr>
<td>Number of physicians per 10,000 inhabitants</td>
<td>6.52</td>
</tr>
<tr>
<td>Number of nurses per 10,000 inhabitants</td>
<td>7.78</td>
</tr>
<tr>
<td>Number of pharmacists per 10,000 inhabitants</td>
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</tr>
</tbody>
</table>
The under-five mortality has declined from 42‰ in 1999 to 25.5‰ in 2008 (MOH, 2007b, 2010). Although morbidity and mortality due to infectious diseases has declined in the past decade, pneumonia has remained the highest cause of morbidity and mortality among children (MOH, 2007b, 2010). In 2008, the number of new cases of ARI among children was 623 per 100,000 inhabitants including pneumonia (277), acute pharyngitis or sinusitis (225), and bronchitis or bronchiolitis (121). The number of deaths among 100,000 children attributable to pneumonia was 1.02 (MOH, 2010). The rate due to communicable diseases was much higher in rural areas than in urban and was also predominant among the poor. The under-five mortality among the poorest quintiles is twice as high as that of the richest quintiles (MOH, 2007b).

### 1.3.2 Healthcare system

#### The public sector

The Vietnamese healthcare system has four levels (Figure 1):

i. **The central level.** The Ministry of Health (MOH) is responsible for national management for the care and protection of the people’s health. The MOH directly manage public services in 18 general hospitals and 24 specialized hospitals. Since 2000, the MOH has actively participated in developing new laws related to the health sector, such as: Law on Pharmacy, Law on HIV/AIDS control, Law on Control of communicable diseases.

ii. **The provincial level.** There are 63 health bureaus directly coordinated by the MOH as well as the provincial people’s committees. Generally, in each province, there is a general hospital with 200 to 1,000 beds and some specialized institutions. In total, there are 127 provincial general hospitals and 204 specialized hospitals. Provincial health bureaus are responsible for assisting the provincial people’s committees in health management at the provincial level.

iii. **The district level** consists of preventive health centres, a district hospital, several polyclinics and a health department serving a population of approximately 50,000 to 300,000 persons. District health departments are under the management of the district people’s committees for the performance of the state management functions of prevention, care and promotion of people’s health within the districts.

iv. **The community level.** The primary access point for public services is the health commune station (HCS), called “Tram y te”. Over the last 30 years, Vietnam has established an extensive network of HCSs throughout the country. Each HCS is commonly staffed by a physician, three to four other health professionals (assistant physicians, nurses, midwife, or basic pharmacists). This level is responsible for providing primary healthcare and implementing preventive health programmes to a population of 3,000 to 10,000.

HCSs are charged with implementing national health programmes, providing examination and treatment for common diseases, health counselling, referral services for patients with serious illnesses, prenatal and postnatal care, and delivery services. HCSs
also receive short-term inpatients when necessary. The MOH has issued the national benchmark of HCS which provides the standards and tools for assessment, and supports the provincial health services in assessing the quality of HCS services (MOH, 2005). Of the total HCSs, 50% reach benchmark according to the national benchmark (MOH, 2009c).

Village health workers are the extended arms of commune health at the village level. With basic medical education they focus on basic health information, education and communication on hygiene and disease prevention; maternal and child healthcare; and family planning. They also provide first aid and treatment of common diseases.

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<tr>
<td></td>
<td></td>
<td>- National medicine/pharmacy training universities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Central research/professional institutions</td>
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<td></td>
<td></td>
<td>- 42 central hospitals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- General pharmaceutical companies</td>
</tr>
<tr>
<td>Provincial People’s Committee</td>
<td>Provincial Health Bureau</td>
<td>- Provincial health offices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Provincial preventive health centres</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medical training colleges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Provincial drug control centres</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 331 provincial public hospitals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 83 private hospitals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1,879 domestic and foreign pharmaceutical companies</td>
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<tr>
<td>District People’s Committee</td>
<td>District Health Centre</td>
<td>- District health preventive centres</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- District health departments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Maternity homes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1,400 district hospitals/policlinics</td>
</tr>
<tr>
<td>Commune People’s Committee</td>
<td>Health Commune Station</td>
<td>- 10,866 health commune stations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 30,000 private clinics/policlinics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 9,000 private pharmacies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 30,000 drug outlets/drugstores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 118,425 village health workers</td>
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</tbody>
</table>

Figure 1: The healthcare system in Vietnam (MOH, 2010)

The private sector

The development of private health services in Vietnam has been a natural process of adjustment to growing demand. Before 1975, there were many private health services in Ho Chi Minh City. After 1975, private health services were merged into the national
health system. There was an extensive unofficial or illegal private health service and sale of drugs in Ho Chi Minh City. In 1980, Ho Chi Minh City had recognized and regulated private health services (Dung, 1996). Since 1989, after the reform “Doi Moi”, the MOH issued decrees related to private pharmacies and health services and actively supported these facilities (Chuc & Tomson, 1999; Dung, 1996). In 1993, the President signed the Law on private pharmaceutical and clinical practice (SRV, 1993). Thereafter, the private health system has quickly developed in the whole country. At the end of 2008, there were about 83 private hospitals, 30,000 private clinics, 10,000 traditional healers, 1,900 pharmaceutical companies as whole sellers, and 39,000 drug retailers as in Figure 1 (MOH, 2010).

Such a huge amount of private health facilities compared to public facilities shows the increased importance of the private sector in the contemporary Vietnamese health system. The private health sector has absorbed a large proportion of outpatients, relieving the overcrowding in public health facilities and providing more convenient conditions for people in need of healthcare (Ha et al., 2002). Private pharmacies have been actively involved in providing essential drugs throughout the country (MOH, 2007b; Wolffers, 1995).

Despite these positive contributions, private healthcare has been under scrutiny regarding their quality of service. By definition, private providers are profit-oriented. In many cases, they overuse high technologies and expensive medicines. There are large numbers of unlicensed private providers especially in rural areas. The service has been reported as the low-cost alternative with poorer quality, and provided by inexperienced practitioners for the less wealthy parts (Lonnroth et al., 2001). This is often out of the authorities’ control (Lonnroth & Uplekar, 2005; Tuan et al., 2005). Inappropriate treatment among private clinicians has been reported in several studies (Larsson et al., 2005; Tuan et al., 2005). It has been observed that patients’ acceptance of private healthcare was related to service availability, waiting times, providers’ attitude and cost of care rather than medical competence (Tuan et al., 2005).

There was a rapid increase in both the numbers of private pharmaceutical facilities and types of drugs available on the market. Private pharmacies, drugstores and drug outlets are allowed to sell drugs that are approved by the MOH. At present, drug retailers often buy drugs from wholesale centres and then sell them at a profit of about 5-20%. Private pharmacies are licensed for pharmacists with 5 years of working experience, whereas drugstores or drug outlets are for assistant pharmacists or basic pharmacists in rural areas with 2 years of experience (MOH, 2007a). Drug dispensers are often the first port of call for people seeking healthcare in Vietnam (MOH, 2003b). Evidence showed that antibiotics could be easily obtained from drug dispensers without a prescription (Chuc et al., 2001; Van Duong et al., 1997).

1.3.3 The Vietnamese policy for antibiotic management

Since the “Doi moi” policy, the health sector in Vietnam has changed dramatically. In 2007 drug expenditure per capita was 16.5 USD, which represents an eleven-fold increase from 1990 (DAV, 2009; Witter, 1996). Antibiotics represent the highest proportion of total household drug expenditure as well as hospital expenditure (GSO,
Privatization of services, drug availability and pharmaceutical distribution have increased access to antibiotics without securing their appropriateness.

Antibiotics as well as other drugs on the market must be registered (MOH, 2009b). In order to produce or import drugs, a pharmaceutical company must apply for drug registration at the MOH. Imported drugs need to be submitted together with a certificate of Good Manufacturing Practices (GMP), a certificate of analysis, and the certificate of drug registration from the country of origin. The assessment committees, consisting of professionals in regulation, production, drug quality, pharmacology and clinical medicine, are responsible for evaluation and approval of the registered drug documents. At the end of 2008, there were 20,066 registered drugs based on 1,400 substances. Of the ten substances with the highest numbers of registered drugs, eight are antibiotics (DAV, 2009).

The MOH control of drug quality based on standards and guidelines for drug production (Good Manufacturing Practice: GMP), quality test (Good Laboratory Practice: GLP), storage (Good Storage Practice: GSP), distribution (Good Distribution Practice: GDP) and dispensing (Good Pharmacy Practice: GPP). At present, all domestic pharmaceutical factories must apply GMP when producing drugs. There is a drug quality control system with institutions at central and provincial levels. In 2008, the proportion of low-quality drugs among drug samples was 3%, and 27% of those were antibiotics (DAV, 2009). It has been reported that the quality control system does not have the capacity to control all drugs on the market (Falkenberg et al., 2000; MOH, 2007b).

The issue of irrational antibiotic use and antibiotic resistance has been recognized by health policy makers for a long time. There are restrictions on the advertising of antibiotics, which may only be directed at health professionals. According to the Circular of Drug Information and Drug Marketing (No 13/2009), antibiotics are not allowed to be advertised in newspapers, radio or television for lay people. The regulation on prescription-only drugs was first issued in 1995, which allowed drugsellers to dispense eight oral antibiotics without a prescription i.e. amoxicillin, ampicillin, phenoxymethyl penicillin, erythromycin, chloramphenicol, tetracycline, sulphamids, and co-trimoxazole. The regulation was modified in 2003 and has been replaced in 2008 by a regulation stating that all antibiotics need prescriptions (MOH, 2003a, 2008).

To strengthen the supply and rational use of drugs in hospitals, the MOH issued several documents, e.g. the Guidelines for hospital drug and therapeutic committees (1997), the Directive 05/2004 adjusting the supply and use of drugs, and the Circular 10/2007 for a competitive bidding process in procuring drugs, and the major drug list to be used (2008). In recent years, the MOH had issued some official documents for rational drug use, e.g. the Vietnamese National Drug Formulary (2002) and treatment guidelines (2006). The task of the Drug and Therapeutic Committees is to develop a major drug list for the hospitals, check on prescribing and treatment, monitor adverse drug reactions, and develop a good collaboration between pharmacists, physicians and nurses. However, it has been shown that the committees often fail in the promotion of the rational use of drugs, especially antibiotics (MOH, 2007b).
There is a health inspection system with a department of health inspection in the MOH and each provincial health bureau. There are about 500 health inspectors in the whole country with mainly a medical, pharmaceutical or legal background. They inspect professional activities according to the rules or regulations in both public and private health facilities. They have the authority to impose fines when health facilities break the regulations. Health inspectors can also recommend to the authorities the withdrawal of the licenses of private health facilities when they seriously violate regulations. However, there is still a shortage of health inspectors and a lack of intersectional collaboration that leads to a gap in controlling the service and enforcing regulations among health facilities in Vietnam (MOH, 2007b).

1.4 RATIONALE OF THE STUDIES

Antibiotics are important for the world. Since their discovery they have revolutionized treatment of bacterial infections and contributed to a significant decrease of deaths. However the phenomenon of bacterial resistance is now threatening to take us back to a pre-antibiotic era. It has been reported that the growing phenomenon of antibiotic resistance is caused by the use and abuse of antibiotics. This leads to several questions including:

- What is the current situation of antibiotic resistance in Vietnam?
- What factors are associated with increased bacterial resistance?
- What is the actual situation of antibiotic use for children in the community? What are the associated factors relating to the use of antibiotics?
- What do caregivers and HCPs know and practice regarding antibiotic treatment for ARIs among children?

Data regarding the local pattern of antibiotic resistance is valuable information for physicians when making decisions regarding treatment. In general, physicians decide on the treatment without patient-specific susceptibility results. The resistance information among children can thus be used by physicians as a basis for the selection of appropriate antibiotic therapy in a specific area. Further, the resistance data helps in developing an intervention strategy to minimize the emergence of antibiotic resistance both locally and globally.

Some studies in Vietnam have suggested a high level of resistance in *S. pneumoniae* to antibiotics. However, limitations in those studies include that the studies only represent those seeking healthcare, they are retrospective, lack antibiotic use information, lack clinical data, or have a small sample size. We therefore conducted a prospective study in the community with a large sample and, most importantly, we tested bacterial resistance during the same period that data were recorded on antibiotics administered and symptoms presented among children. We evaluated factors associated with the emergence of drug resistance including data on antibiotic use during the previous three weeks, performed in vitro susceptibility testing for nasopharyngeal isolates, and clinically examined the children when collecting the samples.
Irrational drug use has been a major problem contributing to antibiotic resistance in many countries. In Vietnam, the availability of drugs and the dramatic increase in health facilities has successfully controlled communicable diseases, but on the other hand, it leads to irrational use and wasting of scarce resources. Furthermore, irrational antibiotic utilization leads to problems of antibiotic resistance. The consequence of increasing resistance among common pathogens of ARI leads to treatment failure and results in a need for changing antibiotic, which in turn leads to increased resistance to the newer antibiotics.

Caregivers play an important role in the treatment of childhood illness and in rational drug use. They are the ones who decide where to seek care and whether to administer the drugs or not. Appropriate case management can avert most deaths of ARI, but only children’s caregivers can recognize signs of illness and seek care promptly from a trained health worker. So far, little is known about antibiotic treatment for ARIs from the perspective of community members in Vietnam. Therefore, understanding people’s knowledge, perception and health-seeking behaviour pattern for ARIs among children would have major implication for improving antibiotic use.

Healthcare providers in the community are in the front line in the battle against antimicrobial resistance. Through action or inaction, healthcare providers can either worsen the problem or contribute to the solution. It is crucial for them to clearly understand about the pathogens of ARIs, specific symptoms, normal development of illness and potential complications in order to improve their prescribing or dispensing behaviour. However, there is a lack of correct information regarding the knowledge and practice of HCPs about antibiotic resistance and antibiotic use for ARIs. Previously no such study among dispensers and prescribers in both public and private healthcare facilities had been conducted in Vietnam. In order to improve practice of HCPs and consumers, it is necessary to have data on antibiotic knowledge, practice and perceptions of these actors.
2 AIMS

2.1 MAIN AIM

The overall aim was to investigate prevalence of antibiotic resistance and describe knowledge and practice of caregivers, prescribers and dispensers regarding antibiotic use for children under five with acute respiratory infections in Vietnam. The long-term aim is to develop and implement intervention strategies to improve antibiotic prescribing, dispensing and use.

2.2 SPECIFIC AIMS

• To investigate the prevalence of antibiotic resistance in identified *S. pneumoniae* and the relationship with antibiotic use as well as demographic factors of children under five in a rural district in Vietnam (Paper I).

• To describe and understand health-seeking behaviour and drug use for preschool children in rural and urban areas in Vietnam, particularly caregivers’ perceptions about antibiotics (Paper II).

• To assess knowledge and practice among caregivers about antibiotic use for mild acute respiratory infections among children under five in a rural district in Vietnam and to identify demographic factors associated with antibiotic use (Paper III).

• To assess knowledge, practical competence and reported practices regarding antibiotics among healthcare providers in the treatment of acute respiratory infections among children under five in a rural district in Vietnam (Paper IV).
3 METHODS

To fulfil the aims, the present thesis is built around four papers as presented in Figure 2. In this thesis, both quantitative and qualitative approaches were used.

Paper I is a quantitative study to investigate the prevalence of antibiotic resistance in identified *S. pneumoniae* among children and the relationship with recent antibiotic use. Clinical examination and laboratory testing are combined with surveillance of antibiotic use.

Paper II is a qualitative study using focus group discussions (FGDs) to describe and understand health-seeking behaviour and perceptions of caregivers about antibiotics.

Paper III is a prospective quantitative study to assess caregivers’ knowledge and practice regarding antibiotic use for ARIs among children under five in the community.

Paper IV is a quantitative study to assess HCP’ knowledge and reported practice regarding antibiotic resistance and antibiotic use for ARIs among children.

![Figure 2: Overview of the research areas and research framework](image)

The study setting is described in the first part (3.1). A description of sample size and sampling of each study is given in Section 3.2. Data collection is described in Section 3.3. Analysis in line with the papers is presented in section 3.4. Ethical consideration is given in the final part of this chapter (3.5).

Information on design, study groups, data collection methods and data analysis in each paper is presented in Table 4.
Table 4: Design, data sources, participants and analysis in the included papers

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Study groups</th>
<th>Data collection methods</th>
<th>Analysis</th>
</tr>
</thead>
</table>
| I     | Cross-sectional study  
• 28-day prospective follow-up study | 818 children 6-60 months in Bavi district | • Face to face interviews  
• Clinical examinations  
• Nasopharyngeal sampling  
• Susceptibility testing (March-June 2007) | • Description and univariate analysis  
• Multivariate logistic regression |
| II    | Qualitative study | 49 mothers, fathers and grandmothers in 6 groups in Hanoi and Bavi | Focus group discussions (May-June 2003) | Qualitative content analysis |
| III   | Cross-sectional study  
• 28-day prospective follow-up study | • 828 caregivers  
• 823 children 6-60 months in Bavi district | • Face to face interviews  
• Daily self-reported form (March-June 2007) | • Description and univariate analysis  
• Multivariate logistic regression  
• Multilevel logistic regression |
| IV    | Cross-sectional study | 392 prescribers and dispensers in Bavi district | Self-completed questionnaire (July-August 2007) | • Description and univariate analysis  
• Multivariate logistic regression |

3.1 STUDY SETTINGS

The study settings were a rural district, Bavi district (Papers I-IV) and Hanoi city centre (Paper II), in Vietnam.

Hanoi is the capital, the country’s political centre and the second largest city of Vietnam. Hanoi is 3,344 km² and the urban area is approximately 233 km². Greater Hanoi is divided into 10 administrative urban districts, 1 town and 18 rural districts with 145 communes in the urban and 421 communes in the rural area. About 35% of 6.23 million registered inhabitants live in urban areas (GSO, 2009). Hanoi experiences the typical northern Vietnam climate: summers are hot and humid, and winters are relatively cold and dry.
Hanoi is also one of two largest centres in Vietnam in terms of healthcare services as well as pharmaceutical provision. At present, in the public sector there are 16 central hospitals, 24 provincial hospitals, 12 district hospitals, 28 district health preventive centres and 421 HCSs (HHB, 2010). The pharmaceutical network in Hanoi includes about 450 pharmaceutical companies functioning as wholesalers, 1,400 private pharmacies, 414 drugstores and 367 drug outlets. Private health services have dramatically increased to approximately 15 private hospitals, 210 policlinics and 1,700 specific clinics (HHB, 2010).

**Figure 3: Vietnam map, Hanoi city and Bavi district**

*Bavi district* is a rural district of Hanoi (which was formerly Hatay province, including at the time of data collection for this project), 60 km north-west of central Hanoi. The district covers an area of 410 km², divided in lowland, highland and mountainous areas according to geographical characteristics of rivers, hills or mountains. Bavi district includes 32 communes (1 small town), and about 262,000 inhabitants with 91% belonging to the Kinh ethnic group. Minority ethnic groups live in the more mountainous areas. Agriculture is the main occupation. The basic healthcare system includes a district hospital with 150 beds, 3 regional polyclinics, 32 HCSs and approximately 90 licensed private health facilities such as private clinics, pharmacies, drugstores and drug outlets (HHB, 2010).
The Bavi district has been selected as a socio-demographic surveillance site (hereafter called FilaBavi) (Chuc & Diwan, 2003). FilaBavi has been developed to implement a longitudinal epidemiological surveillance that can generate basic health and healthcare data, supply information for health planning, and serve as a background and sampling frame for specific studies. Bavi district was purposively selected because it was heterogeneous in terms of geographical characteristics, typical for northern Vietnam in socio-economic conditions and health status (Chuc & Diwan, 2003).

The sample of FilaBavi was selected as a stratified random cluster sample. A cluster was defined as a village or a part of large village. This cluster sampling procedure was done because a simple random sample was not feasible. It is difficult to have complete list of households in the district while enumerating the clusters was more feasible. The clusters of FilaBavi were selected with probability proportional to size in each stratum (lowland, highland and mountainous areas).

Sixty-nine clusters in the district were selected to constitute the sample for FilaBavi. On average, there are about 160 households and 600-700 inhabitants in each cluster (Chuc & Diwan, 2003). Based on the 3rd re-census survey in 2007, the FilaBavi sample includes approximately 12,000 households, 51,000 individuals; around 4,000 of whom were children under five years of age.

The organisation of the FilaBavi includes a steering committee, project leaders, research students, a field manager, field supervisors, interviewers and administrative staff. To obtain data regularly, 42 female field interviewers have been employed, and these are divided into six groups, each led by a field supervisor. The main tasks of a field supervisor are to manually check all survey forms filled in by the interviewers in the group as well as to re-interview approximately five percent of the respondents in the quarterly follow-up surveys.

In FilaBavi, baseline and re-census surveys have been done every second year. Regular follow-up of vital events is conducted every three months. At baseline and re-census survey, socio-economic information at household level and individual level is collected. E.g. information of households was collected on housing conditions, water resources, latrines, expenditure, income, assets, and agricultural land. Individual information included date of birth, gender, education, occupation, religion, ethnicity and marital status. At follow-up surveys, demographic and household information is updated. Particular events, e.g., marriage, pregnancy, death, birth, or immigration are recorded.

3.2 SAMPLE SIZE AND SAMPLING

Papers I and III. Drug use survey and susceptibility test of nasopharyngeal samples among children

These two studies were carried out within the FilaBavi sample. The sample size was calculated to obtain 95% confidence intervals not wider than 10% units. The calculation was based on the assumption that antibiotic use in children under five in the community during one month was 70%, as it is the main outcome in the studies (Larsson et al.,
The expected drop out was 30% and the assumed design effect was 2.0 due to clustering (Khe, 2004). We needed a sample of 817 children to follow in the four-week period. Children younger than 6 months were excluded to facilitate nasopharyngeal sampling. All the households in the biggest clusters with equal economic distribution in each of three geographical areas were selected to give about equal numbers in the areas. In each household, one child aged 6-60 months was randomly selected by computer (if more than one such child was present). In total 847 children born from June 2002 to October 2006 were selected from 847 households in 13 clusters (Figure 4).

The final sample of Paper I included 818 children who were examined and from whom nasopharyngeal samples were collected. In Paper III, the final sample included 828 child-caregivers in the knowledge interview and 823 children in the prospective 28-day follow-up study. In the follow-up study, one child was followed up for 7 days, one for 14 days, and 821 children for 28 days, in total 23,009 days.

**Paper II. FGDs among child-caregivers**

Participants were mothers, fathers and grandmothers with preschool children, living in Bavi district and Hanoi inner city. The caregivers were selected by purposive sampling based on their experiences in caring for preschool children and their willingness to participate. In total, three FGDs were conducted in the urban area and three in the rural area with 49 child caregivers. The participants varied in terms of occupation, age and education.

**Paper IV. Self-completed questionnaire among HCPs**

All HCPs prescribing or dispensing western drugs for children under five in Bavi district were eligible to participate in this study. The list of HCPs was compiled from information provided by the Bavi district health office and FilaBavi interviewers. Out of 409 eligible HCPs, 392 (96%) accepted to participate in the study. There were 253 medical personnel (medical physicians, assistant medical physicians, nurses) working in private clinics, HCSs and hospitals and 139 pharmacy personnel (university, intermediate and basic pharmacists) working in drugstores.
BAVI DISTRICT: 32 communes
50,000 HHs; 232,400 persons

FILABA VI
69 clusters, 12,000 HHs
51,000 persons; 4,000 children under 5

Lowland
19 clusters
899 children 6-60 months

Highland
33 clusters
1,998 children 6-60 months

Mountains
17 clusters
1,048 children 6-60 months

5 clusters
285 households

4 clusters
282 households

4 clusters
280 households

Sample of the study
847 HHs - 847 children 6-60 months
(13 clusters)

828 caregivers were interviewed for knowledge (Paper III)

823 children were followed in 28 days (Paper III)

818 children were examined, nasopharyngeal samples collected (Paper I)

Figure 4: Flowchart of sampling procedure and study sample (Papers I and III)
3.3 DATA COLLECTION METHODS

The data collection methods for the whole thesis included face-to-face interviews using structured questionnaires (Papers I, III), clinical examinations (Paper I), laboratory tests (Paper I), FGDs (Paper II), and self-completed questionnaires (Paper IV).

The instruments were developed in consultation with relevant professionals and field-tested outside the study area several times before conducting the studies. Researchers and supervisors were responsible for re-interviewing approximately 5% of the household interviews. About 5% of the entered data was checked against the questionnaires.

**Face-to-face interview and follow-up of children for 28 days (Papers I & III)**

The main child-caregiver in the households was identified and interviewed using a questionnaire regarding antibiotic knowledge for treatment of ARIs, as well as symptoms, drug use and their actions in the most recent illness of the child (Appendix 1).

She/he was requested to fill in a self-report form daily regarding drug use for the child for 28 days (Appendix 2). Each week, the Filabavi interviewers visited the households to interview the main child-caregivers using a structured questionnaire (Appendix 3). The information that was collected for 28 days included: symptoms; type of healthcare sought; drugs administered and the person recommended each drug. All the self-reported forms, prescriptions and medicine containers were used to facilitate data collection. Participants’ characteristics, date of birth, sex, residential areas, main caregivers’ education, occupation, and households’ assets, expenditure, and income were derived from the FilaBavi’s re-census survey in March 2007.

The data collection was performed from March through June 2007. The training of Filabavi interviewers and supervisors was carefully conducted both in theory and field practice. The field supervisors manually checked all the collected questionnaires to ensure the quality of the interviews.

**Clinical examination (Paper I)**

At the third interview after the second week, the interviewers gave written invitation letters to all the households for a clinical examination and information regarding susceptibility tests. The examinations took place in health commune stations on the third Saturday of the 4-week survey period and were performed by paediatricians from district or central hospitals. All the symptoms and diagnosis of the children were recorded in examination forms (Appendix 4).

**Isolation of S. pneumoniae and antibacterial susceptibility testing (Paper I)**

In the clinical examinations, two trained microbiologists collected nasopharyngeal samples. The swabs were immediately placed in a transport tube with a charcoal transport medium. Specimens were transported to Clinical Laboratories of National Institute of Infectious and Tropical Diseases, Hanoi, within 12 hours.
*S. pneumoniae* was isolated and identified in the laboratory by growth characteristics and optochin (Michelow et al., 2002; Murray et al., 2005). Each specimen was plated on 5% sheep blood agar plate. The agar plates were incubated for 24-48h at 37°C in 5% CO₂. On blood agar, colonies suspected for *S. pneumoniae* appear small, shiny, and translucent. They were surrounded by a zone of α-hemolysis. A part of the presumptive colony was picked to do Gram staining. The single presumptive colony, which had a lancet-shaped and Gram-positive bacterium, was plated on the other blood plate with an optochin disc plated prior to inoculation. Identification was confirmed by optochin sensitivity with an inhibition zone diameter of ≥ 14 mm (a 5-mg ethyl hydrocupreine hydrochloride). A single colony of each target bacterium was selected and sub-cultured for purity check and further diagnostic measures of *S. pneumoniae*.

All the isolates were tested for susceptibility using disk diffusion (BIO-RAD Laboratories, Marnes-la-Coquette, France) and Etest (AB bioMérieux plant, Solna, Sweden, formerly AB BIODISK). The following antibiotics were tested: benzylpenicillin and cefotaxime (Etest); erythromycin, co-trimoxazole, tetracycline, and ciprofloxacin (disk diffusion).

Susceptibility testing was done according to the performance standards of the Clinical and Laboratory Standards Institute (CLSI) and manufacturers’ instructions (CLSI, 2007). Viable colonies of *S. pneumoniae* from an overnight blood agar plate were suspended in Mueller-Hinton broth to achieve 0.5 McFarland turbidity. The suspension was used within 15 minutes of preparation. The Etest package was kept at room temperature 30 minutes before being opened. A pair of forceps was used to apply two strips on a 90 mm sheep-blood Mueller-Hinton plate. The applied plates were incubated at 35°C with 5% CO₂ for 20-24 hours before reading the zone diameter or MICs.

*S. pneumoniae* ATCC 49619 were included as control strains for every series of agar plates and antibiotic disks. The results were acceptable if the tests with the control strains exhibited values within published limits (CLSI, 2007). The diameter of the inhibition zone was measured to the nearest millimetre with a pair of callipers. The MIC was read where inhibition growth merged with the strips at the sharp end of the pear-shaped inhibition zone.

**Focus group discussions (Paper II)**

The FGDs were conducted in private and relaxing locations. A moderator together with an assistant and a note-taker conducted each FGD. I was the moderator of 4 FGDs and one of the co-authors (Chuc N.T.K.) was the moderator of the remaining FGDs. Interview themes were used in conducting the FGDs covering general and specific issues (Appendix 5). This was done by asking participants to discuss their own experiences of caring for a sick child and their thoughts on what the general opinion in the community might be. An emergent design was adopted, resulting in slight changes in the themes during the FGDs. Each FGD lasted approximately 1-1.5 hrs and was tape-recorded. The note-taker wrote down the sequence of discussion, and observed participants' reactions and feelings during the FGDs.
**Self-completed questionnaire (Paper IV)**

Data was collected using a structured questionnaire divided into four parts: (i) information on demographic characteristics; (ii) knowledge about and perceptions of antibiotic resistance; (iii) knowledge and practical competence related to the management of children under five with ARIs; (iv) symptoms and named drugs given regarding their latest management encounter with a child under five (Appendix 6). In the third part, knowledge was assessed using the questions directly addressing the need for antibiotics to treat specific ARI symptoms. Practical competence was evaluated using two written clinical scenarios, a "common cold scenario" and a "pneumonia scenario" (Appendix 6). The scenarios were formulated following the IMCI guidelines and discussed with two experienced paediatricians before use. In addition, we conducted several in-depth interviews with HCPs and revised the scenarios to be applicable in primary healthcare facilities.

The questionnaire was administered in a series of meetings at the district health office with about 20-30 HCPs participating each time. In these meetings, questions were first clarified and participants were instructed in how to fill in the questionnaire. The participants completed the questionnaire individually, usually within 30-45 minutes, under supervision of research staff. Those who did not come to the meetings after three invitations were asked to self-complete the questionnaire at their health facility or at home. Six Filabavi supervisors, specifically trained for this study, were responsible for distributing, guiding and supervising the self-completion process of the questionnaire following a standardized data collection procedure.

### 3.4 DATA ANALYSIS

**Quantitative data analysis (Papers I, III, IV)**

Data analysis was done using STATA version 10 (I, III) and SPSS version 13 (IV). Standard statistical methods were used for descriptive analysis. Estimated proportions were done with a 95% confidence interval. Chi-square test was performed to test the significant difference between proportions.

Multiple regression models were used to examine influencing factors to the \textit{S. pneumoniae} carriage prevalence (I), antibiotic resistance (I), main-caregivers’ overall-knowledge of antibiotics (III), antibiotic use among children (III) as well as HCPs’ knowledge and practical competence (IV). The independent variables were sex, age, education, occupation, geographical areas, household’s economic-status (I, III), present ARI symptoms (I), antibiotic use (I), healthcare-seeking places (III), duration of illness (III), and frequency of seeing childhood patients (IV).

In Paper I, interpretative non-meningitis breakpoints based on the CLSI standards were used to interpret the antibiotic susceptibility of \textit{S. pneumoniae} isolates (CLSI, 2009). The inhibitory zone diameters for isolates to be considered resistant were: tetracycline \(\leq 18\)mm, co-trimoxazole \(\leq 15\)mm, erythromycin \(\leq 15\)mm, ciprofloxacin: resistant \(\leq 15\)mm, susceptible \(\geq 30\)mm (SRGA, 2008b). MICs values for cefotaxime in the Etest were: resistant \(\geq 4\)mg/l, susceptible \(\leq 1.0\) mg/l. Modified CLSI breakpoints using EUCAST
breakpoints were used to categorize benzylpenicillin susceptibility as: susceptible MICs ≤0.5 mg/l; intermediate 1.0 mg/l ≤ MICs ≤ 4.0 mg/l; and resistant MICs ≥ 8.0 mg/l (CLSI, 2009; EUCAST, 2009b).

We defined the isolates as susceptible to amoxicillin and ampicillin using the same breakpoints as for benzylpenicillin (CLSI, 2009). Resistance to phenoxymethylpenicillin was derived from benzylpenicillin MICs > 0.06 mg/l (EUCAST, 2009b). We defined MDR as isolates resistant to at least three of the six tested antibiotics.

In Paper III, multilevel logistic regression was used to adjust for intra-cluster correlation (ICC) of antibiotic use for children in the 28-day period in three levels: the mild ARI episode, the child and the cluster.

In Papers III and IV, the illness of children was classified based on the reported symptoms following the IMCI guidelines as: (i) mild ARIs, if the child presented any of following symptoms: cough, stuffy nose, runny nose, sore throat, without fast breathing or chest in-drawing; (ii) severe ARIs, if the child presented at least one of the pneumonia signs: fast breathing, chest in-drawing, or stridor; (iii) others, if the child had any other symptom such as watery faeces, bloody stools, vomit, ear ache, injury, abdominal pain, skin rash, or toothache.

Overall knowledge about antibiotic use for acute respiratory infections among caregivers and healthcare providers was considered as correct if the respondents provided answers to knowledge questions in accordance with the guidelines for all three stated ARI symptoms, i.e “No” for questions 1, 2, 4 and “Yes” for question 3 (Part II, appendix 1, 6).

Drugs used for the participating children or recommended by HCPs in the clinical scenarios were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2008), with the help of VN-pharmacy software (Hanoi University of Pharmacy, 2004). Antibiotics that are classified as antibacterials for systemic use and aggregated at the level of the active ingredient were included (level 5 of the ATC class J01) (WHO, 2008).

Qualitative data analysis (Paper II)

After each FGD, the research team discussed and considered whether all information had been noted. The tapes and notes of the FGDs were transcribed in Vietnamese and then translated into English by two independent translators. The Vietnamese and English versions were used simultaneously side-by-side during the analysis to avoid misunderstanding of the real meaning of the texts.

Data from the transcripts was analyzed using qualitative content analysis (Graneheim & Lundman, 2004) in order to describe and understand what people think, understand and do regarding drug use and seeking healthcare for children. My analysis consisted of a dynamic process between the descriptive and interpretive levels of the content. The descriptive level is referred to as the manifest content and described the visible and
obvious components in the text. The interpretative level is defined as the latent content of the text and deals with interpretation underlying meaning of the text (Graneheim & Lundman, 2004). In practice, the distinction between the descriptive and interpretative level is vague. Graneheim and Lundman (2004) believed that both deal with interpretation, but that the interpretations vary in depth and level of abstraction.

From this point of view, I don’t see the manifest and latent analysis as mutually exclusive. In the analysis process, I was moving back and forth between various levels of abstraction in order to discern underlying meanings and interrelationships of the data. First, I listened to the tapes and read through the text in order to become familiar with it and to gain an overall understanding of the content of the discussions. Meaning units apparently referring to the same content were identified and allotted to the tentative interview themes.

Condensing the meaning unit was done in two steps, descriptions close to the original text and interpretations of the underlying meanings. Reading and comparing the topics and meaning units established sub-themes (Table 5). Several emerging themes among each interview theme were found during analysis by comparing and sorting various sub-themes. In the final step, I compared the findings between the different FGDs, tackled research questions and decided on main themes. I have done this process manually in collaboration with my co-authors.

Table 5: Example of selecting meaning units and establishing sub-themes

<table>
<thead>
<tr>
<th>Meaning units</th>
<th>Condensed meaning units</th>
<th>Sub-themes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Description close to the text</td>
<td>Interpretation of the underlying meaning</td>
</tr>
<tr>
<td>‘It seemed to be amoxicillin. And there was a yellow medicine as well, that was prednisolon.’</td>
<td>Antibiotic and corticoids are often recommended</td>
<td>Children had cough and fever frequently, and antibiotic and corticoids are commonly used for childhood illness.</td>
</tr>
<tr>
<td>‘My child frequently has coughs and fever. I often take him to a private clinic. Once my child had a high temperature for a long period, the physician at private clinic said that he had a sore throat, and gave him Pamin, amoxicillin and Dexa’</td>
<td>Cough and fever are frequent symptoms</td>
<td></td>
</tr>
</tbody>
</table>
3.5 ETHICAL CONSIDERATION

Permission for the FilaBavi surveillance as well as other studies conducted within FilaBavi was obtained from the MOH, local authorities and heads of households. The FilaBavi overall surveillance activities, including data collection on vital statistics have been ethically approved by the Research Ethics Committee at Umea University (No 02-420).

The ethical review board of Hanoi Medical University approved all sub-studies for this thesis (28/HMURB). The aims and procedures of the studies were explained and verbal consent was sought from all the participants. In the community study (Papers I and III), triple consents for caregivers willing to participate in interviews, clinical examination and nasopharyngeal sample collecting were requested. All participants were assured of anonymity, confidentiality and their right to withdraw from the study at any time without any explanation. An invitation letter for a clinical examination of children was sent to households at least three days in advance. In the clinical examination, children having a condition in need of medical treatment were treated and counselled by the paediatricians. In the FGDs, the moderator asked the permission to tape-record and explained the purpose of recording.
4 MAIN RESULTS

4.1 DECREASED *S. PNEUMONIAE* SUSCEPTIBILITY TO COMMONLY USED ANTIBIOTICS (PAPER I)

**What is the prevalence of *S. pneumoniae* carriage among children and which determinants are possibly related to pneumococcal carriage?**

Among the 818 children participating in the clinical examinations, 32% (258/818) were clinically diagnosed with a current ARI. The majority of the diseases were mild ARIs, only one child was diagnosed as having pneumonia. Seven had fever > 38°C. Other diseases such as digestive disorder, toothache, skin rash, and phymosis were recorded for 20% of the children.

*S. pneumoniae* was isolated from 52% of the children (421/818). Children aged 6-23 months were more likely to be carriers than those aged 24-60 months (55% vs. 48%, p<0.05). Carrying the bacterium was more common among those with ARI symptoms (61% vs. 47%). The carriage prevalence was not significantly associated with recent antibiotic use and economic conditions.

**What is the prevalence of antibiotic resistance in isolated strains of *S. pneumoniae* and which are associated factors?**

Ninety-five percent of isolates (401/421) were resistant to at least one of the six investigated antibiotics. Only one isolate was susceptible to all antibiotics. Table 6 shows the in-vitro activity of nine antibiotics against 421 pneumococci isolates.

**Table 6: Susceptibility of 421 *S. pneumoniae* isolates to antibiotic agents**

<table>
<thead>
<tr>
<th>Antibiotic agents</th>
<th>ATC code</th>
<th>Resistant</th>
<th>Intermediate</th>
<th>Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>J01AA07</td>
<td>314 (75)</td>
<td>44 (10)</td>
<td>63 (15)</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>J01CE01</td>
<td>17 (4)</td>
<td>136 (32)</td>
<td>268 (64)</td>
</tr>
<tr>
<td>Phenoxyimethylpenicillin</td>
<td>J01CE02</td>
<td>315 (75)</td>
<td>-</td>
<td>106 (25)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>J01CA01</td>
<td>17 (4)</td>
<td>136 (32)</td>
<td>268 (64)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>J01CA04</td>
<td>17 (4)</td>
<td>136 (32)</td>
<td>268 (64)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>J01DD01</td>
<td>9 (2)</td>
<td>14 (3)</td>
<td>398 (95)</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>J01EE01</td>
<td>329 (78)</td>
<td>47 (11)</td>
<td>45 (11)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>J01FA01</td>
<td>294 (70)</td>
<td>52 (12)</td>
<td>75 (18)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>J01MA02</td>
<td>119 (28)</td>
<td>296 (70)</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>
A high level of resistance was found to co-trimoxazole (78%), tetracycline (75%), phenoxyethylpenicillin (75%) and erythromycin (70%).

Low resistance was found to benzylpenicillin (or amoxicillin, ampicillin) and cefotaxime. Intermediate resistance to amoxicillin was 32%. The distribution of benzylpenicillin (or amoxicillin) and cefotaxime MICs in the Etest is shown in Figure 5. MIC$_{90}$ of benzylpenicillin was 1.5mg/l, while MIC$_{90}$ cefotaxime was 0.75mg/l.

Figure 6 shows that many isolates had no inhibitory zone (6 mm) to co-trimoxazole (200/421) or to erythromycin (250/421).

Most isolates were MDR (60%). The most common pattern of co-resistance was to co-trimoxazole, tetracycline and erythromycin (200/252).

Children living in mountainous area were more likely to carry MDR isolates as well as carry erythromycin, co-trimoxazole resistance than those in other areas. Children who had used antibiotics within the three weeks prior to the study were more likely to be carrying the resistant isolates.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Distribution of MIC for penicillin (a) and cefotaxime (b) against 421 \textit{S. pneumoniae} isolates.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Distribution of estimated inhibitory zone diameter in the disk diffusion.}
\end{figure}
Comments

Almost all of the *S. pneumoniae* isolates from the children were resistant to at least one of the investigated antibiotics. All the oral antibiotics showed a very low level of susceptibility except for high-dose amoxicillin that can possibly be used for treatment of pneumococcal infections. There was a statistical association between antibiotic use and resistance.

The resistance to all commonly used oral antibiotics was markedly higher than previous reports. One of the most serious findings is the high MDR among the isolates (60%). The finding is particularly worrying, as co-resistance to co-trimoxazole-tetracycline-erythromycin is the most common pattern. Co-trimoxazole and erythromycin can be expected to be virtually useless in the area. The practice of combining drugs in empirical treatment in the case of resistance might be not effective in this context.

The phenomenon of high resistance to commonly used antibiotics would imply a challenge for empirical treatment of pneumococcal infections in the area. Cefotaxime has the highest susceptibility but this antibiotic needs to be reserved for severe cases in tertiary hospitals and in selected cases with troublesome resistance patterns. Amoxicillin is the only oral antibiotic that can be recommended as the first choice for the treatment of pneumococcal pneumonia in the study area. To ensure the therapeutic effect for at least 95% of pneumococcal infections, the recommended dose of amoxicillin at 25mg/kg x 3 times daily should be increased.

What are the factors leading to the very high level of *S. pneumoniae* antibiotic resistance and MDR in the area? Frequent and irrational use of antibiotics among children probably constitutes a constant selective pressure. The important factors might be the inappropriate practices of prescribers and dispensers, also patients’ misperception and self-medication of antibiotics. The global spread of the pandemic MDR serotypes such as Taiwan 19F and Spanish 23F may partly contribute to the increase of resistance in the area. Further, the genetic determinants for resistant clones usually exist in a stable form, so once resistance is established, it is not easily lost.

### 4.2 CAREGIVERS’ PERCEPTION ABOUT DRUG USE AND HEALTHCARE-SEEKING (PAPER II)

**What do caregivers do when children get sick, especially in case of cough, fever, or diarrhoea?**

Both urban and rural caregivers often self-treated, most frequently with medical herbs. For the rural groups, “take the child to the doctor” was the most common first choice. The rural households tended to seek care at the commune level through private clinics or Health Commune Stations (HCS).
“We buy medicine in the HCS, or go to some doctors who live near us like Mr. H. to buy anti-diarrhoea medicines or antipyretics. I let the children take medicine on the basic of what they have told us” (Grandmothers’ group, rural).

The caregivers believed that their children should have health services at a higher level in more severe cases. The imbalance in the availability of resources and the accessibility to health services between the remote areas and the centre of the country was discussed. In contrast with urban areas, the experience of the rural groups showed limited access to hospital service at the higher levels of the healthcare system, such as district hospitals, provincial hospitals and the National Paediatric Hospital.

Rural and urban groups demonstrated a positive attitude toward private clinics. These facilities were considered to be convenient, effective, and reasonable. In the urban region, private physicians were perceived as being more respectful and committed than physicians in public hospitals. Even so, in cases of severe illness, participants in all the FGDs demonstrated a certain trust in physicians in the public sector.

An example of “best choice” health service was the private clinic operated by a physician working in the public hospital.

“When my child had primary tuberculosis, he was treated for a long time in central hospital “X”, and then went to a specialized central hospital “Y”. After that, I was told to go directly to the home clinic of doctor Z (the director of hospital “Y”). I took my child there; he had him x-rayed and gave him medicines. After 4 months, my son recovered. I think private doctors are more committed” (Mothers’ group, urban).

How do caregivers behave regarding drugs, particularly antibiotics?

The caregivers in the urban area described self-medication as common. The common tendency of urban groups was, when suspecting a recurring disease, to “imitate previous prescriptions”, as well as “consult someone in the community who had experience using medicine”. Even when taking children to the physician, they expressed a mistrust of prescriptions due to the over-prescribing of expensive and unnecessary antibiotics.

“Adults can take antibiotics in the cases the doctors prescribe. But for children, even if the doctors prescribe, we have to consider. When my child is in hospital, I accept him having an injection or antibiotic, otherwise I won’t let him have it because of its side effects. I’m very afraid of antibiotics” (Teacher-mothers’ group, urban).

In the rural area, caregivers took their children to the physicians for examination and got drugs directly from physicians. Rural people tended to have trust with and comply with the provider’s treatment. A rural mother expressed the way she used drugs:
“I don’t know what kind of medicine it is /.../ When I took my child to the private clinic, they gave him a package of several unlabeled drugs /.../ They told me to let him take them twice per day and I had to divide them into two parts. /.../ I always have to work on the farm so I can’t exactly remember the drug names” (Mothers’ group, rural).

Traditional medicines were frequently used, especially in the urban area, because they were regarded as “much safer” than western medicines. However, they often proved to be ineffective and to be used only in the case of “mild” illness. In more severe cases, the caregivers commonly mentioned antibiotics.

“Sometimes we take traditional medicines, but it feels quite ineffective because it doesn’t help to get rid of disease. Only when fever is finished or it is a mild cough, I use Bo Phe syrup [traditional cough syrup]. /.../ I take both traditional and western medicines, antibiotics and Bo Phe syrup” (Teacher-mothers’ group, urban).

Antibiotics were generally perceived as a special drug, such as a “harmful drug”, a “drug for limited usage”, “should not be taken from the beginning”, and “should follow the doctors’ recommendations”. It emerged from the FGDs that, although they wanted to limit antibiotic use, the caregivers experienced antibiotic use as mandatory. Antibiotics were required for treatment of “inflammatory diseases” [=”viem”], such as “pneumonia”, “sore throat”, or “cough”, especially in cases with fever. The participants in the urban area reported self-medicating with antibiotics for a sick child in the family.

“At home I had to store Biseptol [co-trimoxazole] and salbutamol frequently. /.../When she was small she had diarrhoea and had to take Biseptol. Nowadays, when she has coughs only Biseptol makes her get better”. (Teacher-mothers’ group, urban).

The combination of antibiotics and corticoids was experienced as common therapy for children in the rural area.

“/.../Once when my child had a high temperature for a long period, the doctor at private clinic said she had a sore throat and she was given Pamin [paracetamol], amoxicillin and Dexa [dexametazon]/.../Every time we go there, her medicines contain Dexa, ampicilin and amoxicillin”(Mothers’ group, rural).

Participants in both areas perceived that compliance with antibiotic regimes is important. However, a paradox between knowledge and practice leading to over- or under-dosage of antibiotics was reported as a common consequence. Due to the perception of adverse reactions, they would stop using the antibiotic immediately as soon as they felt better.

Socio-economic conditions emerged as factors contributing to the burden of health expenditure, especially in the rural area. The caregivers in the rural area emphasized that health expenditure was a serious obstacle for households. They had “to sell” something or “to borrow money” to cope with the situation. This, in turn, influenced the financial
circumstances of households leading to even poorer conditions. A woman described her worries about the ability to afford the hospital treatment.

“...If our farm breeds badly and the child gets sick 4 times in one month, it will be a problem because everything relates to everything else. We don’t have any other source of income, only some rice, pigs and poultry from our farm”. (Mothers’ group, rural).

Comments

There were different ways of using drugs and healthcare services for childhood illness in the urban and rural areas under study. Common misconceptions about drugs and diseases among child-caregivers may be important factors increasing irrational drug use. Drugsellers and practitioners, both in the public and private sectors, may also have influence. The results provided rich information for the development of quantitative studies on drug use for children in the community.

Caregivers in both areas under study had an incorrect understanding and perception of antibiotics, and/or insufficient information. Misperceptions and misuse of antibiotics would certainly lead to the emergence of antibiotic resistance. Urban caregivers had more experience of self-medication with antibiotics, whereas rural caregivers more often sought care at health facilities for sick children and had trust in physicians.

The results showed the weak regulatory enforcement in the Vietnamese health sector as people freely purchase antibiotics from drugstores without a prescription or purchase directly from physicians in private clinics. Both private and public health facilities are common types of healthcare-seeking, however the quality of service in these facilities needs to be improved.

4.3 HIGH UNNECESSARY ANTIBIOTIC USE FOR MILD ARI AMONG CHILDREN UNDER FIVE (PAPER III)

What do caregivers know about antibiotic use for respiratory symptoms?

Among 828 participating caregivers, mothers were most commonly the main caregivers (83%), followed by grandparents (8%), fathers (6%) and others (3%). Most were farmers and had secondary-school education. There were more boys than girls randomly included (55% vs. 45%) and more children aged 24-60 months than 6-23 months (54% vs. 46%), p<0.05.

In the case management of common colds, 85% of the main caregivers correctly stated that antibiotics are not required in non-febrile cases, but 45% would use antibiotics in febrile cases. In cases with symptoms indicating pneumonia, 47% knew that antibiotics are needed. In fact, 42% of child-caregivers did not believe that antibiotics are required to treat any respiratory symptom, and 37% considered antibiotics are necessary in all cases.
On the whole, only 13% had correct overall knowledge about the use of antibiotics to treat ARIs among children.

Figure 7 shows the percentage of correct answers given by caregivers and their economic conditions, education and geographical region. Caregivers living in the mountainous area had better knowledge than those in the highland or lowland areas (p<0.05).

Higher-educated caregivers had poorer knowledge of antibiotic use in case of cough with fever, but had better knowledge in case of pneumonia (p<0.05).

There was certain homogeneity in antibiotic knowledge among caregivers within clusters (Intra-cluster correlation, ICC=0.16). The highest proportion of correct knowledge was obtained from a cluster in the mountainous area (32%), and the lowest from a cluster in the highlands (4%).

**Where do caregivers seek care when children have illness symptoms?**

Ninety nine percent of the 828 respondents reported about their child’s most recent illness. The symptoms were consistent with mild ARIs (79%), severe ARIs (11%), or other illness (9%). For children with symptoms indicating mild ARIs, the caregivers most often sought care at drugstores (38%), while for those with severe ARI symptoms, healthcare was most often sought at public clinics (52%). Eighteen percent of children with mild ARI underwent two or more forms of treatment (115/654). Higher-educated caregivers were more likely to self-treat and those living in poorer economic conditions were more likely to seek care at public clinics for symptoms indicating mild ARIs.

In the 28-day prospective follow-up, the total number of illness episodes was 1,645. The most common illness was consistent with mild ARI, which was present among 623 children and accounted for 1,048 episodes during 4007 days, 18% of the total number of days. Thirty five percent of children had two or more mild ARI episodes. Forty percent of mild ARI episodes lasted more than 3 days. Seeking care at drugstores (34%) was most common for mild ARI episodes, followed by public clinics (25%), self-treatment (24%) and private clinics (19%).
What is the proportion of antibiotic use for children under five years? What determinants are possibly associated with antibiotic use?

For the most recent illness, the caregivers reported that antibiotics were used for 69% children (565/819). The percentages of antibiotic use for treatment of mild ARIs, severe ARIs and other illness were 71%, 86% and 32%, respectively.

For most recent symptoms indicating mild ARIs, antibiotics were more likely to be recommended by public providers (38%), than drug sellers (33%) or private providers (28%). Those least prone to use antibiotics were caregivers themselves (6%) (Figure 8).

Among the 654 children with most recent mild ARIs, those who were older than 2 years, had duration of illness more than 3 days, lived in the lowland area or lived in poorer economic conditions had been given more antibiotics than the others (p<0.05). Furthermore, seeking care at any healthcare facility increased the risk of using antibiotics inappropriately. There was no statistically significant association between knowledge and reported practice of antibiotic use for the treatment of mild ARIs. There was a low association of antibiotic use reported among children within clusters (ICC=0.06).

In the 28-day prospective period, antibiotics were given to 513 children (62%), for 843 courses for in total 2,986 days. Thirty percent used two or more antibiotic courses. The average duration of the antibiotic courses was 3.54 days (range 1-22 days), median 3.0 days indicating 42% of antibiotics used in short courses (one or two days) and a few over a longer treatment time (15 or more days). Most of antibiotic courses (64%) were used for symptoms indicating mild ARIs (528/843). Half of the mild ARI episodes (528/1,048) and 63% of the children with mild ARIs (392/623) were treated with antibiotics. Most of such unnecessary antibiotic treatment had been recommended by healthcare providers (82%).

Seeking care at any kind of health facilities increased the odds of being given antibiotics for mild ARIs. Children older than 2 years or living in the highland area were more likely to be given antibiotics in cases of mild ARI than others. Furthermore, mild ARI episodes lasting more than 3 days were more likely to be treated with antibiotics than shorter ones. There was a low association of antibiotic use for symptoms indicating mild ARI within
clusters (ICC=0.058). The high level of association among children (ICC=0.68) showed that for one child, mild ARI had been treated with similar regimes.

Figure 9 shows that among antibiotics used, penicillins with extended spectrum such as ampicillin or amoxicillin were most commonly used (49%), followed by cephalosporins (27%), sulphonamides and trimethoprim (11%), macrolides and lincosamides (10%), and other antibacterials including tetracyclins and aminoglycosides (3%). The third-generation cephalosporins (21%) including cefotaxime, ceftriaxone and cefixime were more often used for severe ARIs than mild ARIs.

**Figure 9: Pattern of antibiotic use for 823 children under five in 28-day prospective follow-up period**

**Comments**

Although most of the caregivers stated that antibiotics were not required for mild ARI without fever, 71% of the children had been administered antibiotics during their most recent illness and 62% had used them in the 28-day prospective follow-up period. No evidence about the benefit of antibiotic treatment for the common cold was reported. This situation of very high antibiotic use is putting constant selective pressure on bacteria.

Seeking care at any facility including drugstores, private or public clinics increased the risk of being recommended antibiotics for mild ARI. Irrational prescribing and dispensing of antibiotics may be due to insufficient knowledge among healthcare providers. Other factors might relate to patients’ expectations, a presumed prevention of secondary illness, lack of access to laboratory tests, misdiagnosis of viral infections, or pharmaceutical promotion.

The proportion of self-medication with antibiotics (6%) was lower in this study when compared with results previously reported since we separated the recommendations of drugsellers from the caregivers themselves. There was no statistical association between practice and knowledge regarding antibiotic use among caregivers. This might be due to the fact that the caregivers just followed the recommendation of dispensers or prescribers. To improve antibiotic use in the community, it is necessary to improve caregivers’ knowledge about the causality of common colds and symptomatic self-management of such illness.
4.4 HEALTHCARE PROVIDERS’ KNOWLEDGE, PRACTICAL COMPETENCE AND REPORTED PRACTICE (PAPER IV)

What do healthcare providers (HCP) know about antibiotic resistance and antibiotic use for respiratory infections?

Of all 392 participating HCPs, 97% had heard about antibiotic resistance, whereas 27% displayed correct knowledge about the consequences of resistance, such as treatment failure of patients and possible future effects on other persons seeking treatment for infectious diseases. Almost all respondents (88%) believed that patient-related factors such as self-medication and non-compliance with prescriptions influenced the problems of antibacterial resistance. Many respondents considered inappropriate recommendation of antibiotics from HCPs as a factor contributing to the resistance.

Twenty-one percent of HCPs would recommend antibiotics for cough without fever and 79% if the child has the same symptoms but with fever. Drugsellers were more likely to provide antibiotics in cases of cough without fever, however, and less likely in cases of pneumonia than other providers (p<0.05). In all, 19% of HCPs demonstrated, in accordance with treatment guidelines, correct overall knowledge about the use of antibiotics to treat ARIs among children under five. HCPs located in the highland and mountainous areas had better knowledge than those in the lowland area (Figure 10). The knowledge among HCPs aged 30-49 years was better than those under 30 or over 50 years old (p<0.05).

How do HCPs prescribe or dispense for children with respiratory infections? What determinants are possibly associated with antibiotic prescribing/dispensing?

In the “common cold scenario”, the prevalence of antibiotic recommendation among HCPs who had “correct antibiotic overall knowledge” (67%) was significantly lower than for those who had not (84%). The difference was not statistically significant in the "pneumonia scenario" (Figure 10).

Excluding stated referral cases (198/392), the prevalence of antibiotic recommendation for the “pneumonia scenario” was not significantly different from that for the “common

Figure 10: Percentage of correct overall knowledge and antibiotic treatment in clinical scenarios stratified by region, practice type, and education of HCPs.
cold scenario” (87% vs. 81%). HCPs encountering children on a daily basis were consistently more likely to prescribe or dispense antibiotics to treat ARIs regardless of disease severity.

All the HCPs reported on their most recent encounter with a child under five. The symptoms for those encounters were consistent with mild ARIs (62%), severe ARIs (19%), or other diseases (19%). Among them, 11%, 24% and 34%, respectively, were referred to a higher level in the health system. Drugs were provided in 95% of all cases. Among those, antibiotics were recommended in 92%.

Figure 11 shows that the percentage of antibiotic use to treat mild ARIs (90%) was not significantly different from use to treat severe ARIs (87%), or other diseases (78%). The percentage of antibiotics recommended for mild ARIs was highest among HCS providers (97%) and lowest among private providers (80%).

HCPs recommended in most cases beta-lactam antibiotics in two doses for a five-day course regardless of the severity of the disease. The proportion of cephalosporins was higher in the treatment of severe ARIs compared to mild ARIs (Figure 11). Gentamicin and co-trimoxazole were frequently mentioned as a combination of antibiotics to treat severe ARIs. A few HCPs reported that they recommended phenoxymethylpenicillin for severe ARIs in children met most recently.

Comments

This study indicates a serious lack of knowledge and inappropriate practice regarding antibiotic treatment of ARI among prescribers and dispensers. Most HCPs reported that they had prescribed or dispensed antibiotics for symptoms indicating a common cold. The estimated percentage of antibiotic use for mild ARI cases was not significantly different from the use for severe ARIs. According to their knowledge, this practice was the correct case management. Such misconceptions and malpractice of the healthcare providers may be important factors behind the increasing antibiotic resistance.
Only 21% of HCPs stated that antibiotics are not required for treatment of febrile ARIs. There were even lower results for the correct response for practical competence in the clinical scenario (19%) and reported practice (10%). The noteworthy factor is that the presence of fever increased antibiotic recommendation, even though this does not necessarily indicate a bacterial infection. It is necessary to improve the HCPs’ ability to accurately differentiate between mild ARI and pneumonia and not treat unnecessarily with antibiotics for common colds.

Drugsellers were more likely to recommend inappropriate antibiotic treatment for the common cold than other HCPs. As drugstores are the most common place for people to seek healthcare, there is an urgent need to involve drugsellers in the management of ARI to improve antibiotic use and to contain antibiotic resistance. The fact that the IMCI programme has been implemented since 1999, this programme has, however, not included private providers and drug sellers although they are of major importance for improving antibiotic use. HCPs in Bavi district have not yet been included in the IMCI training.
5 DISCUSSION

The resistance to commonly used oral antibiotics and MDR of *S. pneumoniae* is markedly high (Paper I). Almost all of the pneumococcal isolates are resistant to at least one antibiotic. Many isolates are MDR (60%) with the most common pattern being co-resistance to co-trimoxazole, erythromycin and tetracycline. Although pneumococcal resistance to amoxicillin is low (4%), there is high intermediate resistance (32%) with the consequence that a high dose of amoxicillin is the only investigated oral antibiotic that can possibly be used for treatment of community-acquired pneumococcal infections. There is an association between current antibiotic use and pneumococcal antibiotic resistance (Paper I). Most children with mild ARI had used antibiotics unnecessarily during their most recent illness (71%) as well as in the 28-day prospective follow-up period (Paper III). Poor knowledge and misperceptions about ARIs and antibiotic treatment were found among caregivers (Papers II & III). Seeking care at health facilities increases the risk of being recommended antibiotics for mild ARIs among children under five (III). There is a serious lack of knowledge on appropriate antibiotic use among prescribers and dispensers in the rural area (Paper IV). Most of the unnecessary antibiotics given for children have been recommended by healthcare providers (82%) (Paper III). The percentage of antibiotic recommendations for the common cold scenario (81%) is not significantly different compared to the pneumonia scenario (87%) (Paper IV).

5.1 HIGH ORAL ANTIBIOTIC RESISTANCE AND MULTIDRUG-RESISTANCE: DUE TO CONSTANT SELECTIVE PRESSURE?

5.1.1 High resistance and MDR to oral antibiotics

The resistance percentage of pneumococcal isolates to all commonly used oral antibiotics in this study was markedly higher than previous research in Vietnam (Parry et al., 2000; Parry et al., 2002; Schultsz et al., 2007). Resistance was considerable higher than previously reported in the same area in 1999 (Larsson et al., 2000). The resistance of 421 *S. pneumoniae* isolates in 2007 and of 56 isolates in 1999 to co-trimoxazole was 78% and 32%, to erythromycin 78% and 23%, to ciprofloxacin 28% and 0%, and to more than three antibiotics 60% and 31%, respectively (Paper I). A significantly increase of pneumococcal resistance and MDR to commonly used antibiotics was also noted in Vietnam (Schultsz et al., 2007; Song et al., 2004b).

The MDR (60%) among the isolates of the community children (Paper I) was however still lower than those reported among hospitalized children (75%) (Bogaert et al., 2002; Song et al., 2004b; Vu et al., 2008). MICs for benzylpenicillin (1.5 mg/l, Paper I) among the isolates of community children was lower than those from isolates of hospitalized children with acute lower respiratory infections in national hospitals (4 mg/l) and provincial hospitals (2 mg/l) (Song et al., 2004b; Vu et al., 2008; Watanabe et al., 2008). This might be due to greater antibiotic selective pressure on bacteria and higher risk of resistant genes being transferred among hospitalized children compared to community children (Amorim et al., 2007).
It was reported previously that a significantly higher resistance in *S. pneumoniae* was carried by urban children compared to rural children in Vietnam (Parry et al., 2000; Quagliarello et al., 2003; Schultsz et al., 2007). In 1999, resistance in isolates from urban and rural children to erythromycin was 90% and 21%, to co-trimoxazole 94% and 59%, to tetracycline 81% and 64%, respectively (Quagliarello et al., 2003). The easy access to HCPs and high proportion of antibiotic use in urban areas could explain the difference between rural and urban resistance figures (Chuc et al., 2001; Quagliarello et al., 2003). Whereas the resistance proportion to antibiotics remained high in the urban area, Ho Chi Minh City, the proportion has increased significantly in the rural area, Khanh Hoa province, from 18% to erythromycin in 1997 to 42% in 2004 (Schultsz et al., 2007). One could expect that antibiotic resistance in *S. pneumoniae* is undergoing a serious emergence in many other areas in Vietnam.

The resistance and MDR was distinctively higher than reported from many European countries (EARSS, 2010; Neeleman et al., 2005; Reynolds, 2009) or US (Doern et al., 2005; Draghi et al., 2006). In most northern, central and western European countries, such as Germany, Sweden or the Netherlands, a low prevalence of resistance was observed as less than 1% penicillin resistance and less than 5% erythromycin resistance (EARSS, 2010). Erythromycin and tetracycline non-susceptibility in *S. pneumoniae* in 2007/2008 was found in 8.6% and 5.1% of isolates from the UK, respectively (Reynolds, 2009). The Netherlands, Sweden, UK and Germany all had low rates of MDR (<15%) (Reinert, 2004). On the other hand, high rates of MDR (>50%) has been observed in France, Hungary and Spain (Reinert, 2004). In the US, an increase of MDR pneumococcal prevalence was also reported from 8% in 1992 to 28% in 2001 (Draghi et al., 2006; Mera et al., 2005; Whitney et al., 2000).

Compared to other resistance figures from 11 Asian countries in 2000-2001, the ciprofloxacin resistance of *S. pneumoniae* in this thesis (28%, Paper I) was distinctively higher, as the highest resistance reported there was in Hong Kong (11.8%) and the lowest in Saudi Arabia (2.6%) (Song et al., 2004b). However, the resistance to erythromycin (70%) was relatively lower than those from clinical specimens collected in several countries such as China (74%), Hong Kong (77%), Korea (81%) or Taiwan (86%). The figures are lower than those recently reported from a children’s hospital in China, in which resistance to erythromycin was 100%, tetracycline 94%, co-trimoxazole 84%, and MDR 75% (Chen et al., 2009a). The percentage of co-trimoxazole resistance in this study (75%) was also lower than those from children in North India (82%) or South India (81%) (Coles et al., 2002; Jain et al., 2005). The findings provide evidence of a serious emergence of antibiotic resistance in Asia.

5.1.2 Constant selective pressure and spread of resistant clones

*Constant selective pressure*

In Bavi district, 80% the children had symptoms indicating common cold in the most recent illness as well as in 28-day period (Paper III). As most of children during their most recent illness (71%) as well as in 28-day period under study (62%) used antibiotics, in cases where, according to the WHO guidelines, they would not be needed, there is constant selective pressure on microbial resistance due to the elimination of susceptible
bacterial populations (Tenover, 2006). When a high proportion of children use antibiotics incorrectly, the resistant bacteria adapt and replicate rather than being killed.

In this thesis, high resistance to antibiotics went hand in hand with a high use of antibiotics during the previous 3 weeks (Paper I). The mountainous area with the highest proportion of co-trimoxazole use among children had the highest level of resistance (Paper I). A significant association between regional co-trimoxazole consumption and regional resistance among *S. pneumoniae* isolates was also reported in Finland (Karpanoja et al., 2008). A strong relationship between antibiotic use and antibiotic resistance of *S. pneumoniae* has been documented (Albrich et al., 2004; Bronzwaer et al., 2002b; Cizman, 2003; Goossens et al., 2005; Hoban et al., 2001; Reinert et al., 2002; Riedel et al., 2007). In Europe, countries with a higher total volume of antibiotic consumption such as France and Spain had higher resistance rates (Cizman, 2003; Goossens et al., 2005). An increase of fluoroquinolone resistance in *S. pneumoniae* in conjunction with increased use of ciprofloxacin and respiratory fluoroquinolone was found in Canada (Adam et al., 2009).

That the highest rates of resistance in the world are found in many parts of Asia may be due to a high access to antibiotics without control (Adam, 2002; Okeke et al., 2005b). Some studies suggested that a reduction of antibiotic use would favour a decrease in antibiotic resistance (Apisarnthanarak et al., 2008; Arason et al., 2006; Bass et al., 1994; Cizman et al., 2005; Guillemot et al., 2005). Reduced trimethoprim sales over a 7-year period in the UK was accompanied by a significant decrease in trimethoprim resistance (Apisarnthanarak et al., 2008). In France, an intervention programme led to fewer antibiotics being prescribed in a community setting and also significantly reduced rates of colonisation with penicillin G-nonsusceptible *S. pneumoniae* in children (Guillemot et al., 2005). However, an increase in antibiotic resistance was reported in Sweden during 1997-2003 despite reduced antibiotic use (Hogberg et al., 2006).

**Spread and persistence of resistant bacteria**

The emergence of antibiotic resistance is further complicated by the fact that bacteria and their resistant genes are travelling faster and further (WHO, 2000). A small number of resistant clones dominate the antimicrobial-resistant pneumococcal population and are widely spread leading to a rapid increase in individual antibiotic and MDR (Arason et al., 2006; Reinert, 2004; Tenover, 2006). A significant relationship of resistance to antibiotic in *S. pneumoniae* and those in *H. influenzae* is an evidence for common selective pressure (Jones et al., 2002). Airlines now carry more than two billion passengers annually, vastly increasing the opportunities for the rapid spread of antibiotic resistant bacteria internationally (Zhang et al., 2006). A microbe originating in South-East Asia can arrive in North America or Europe within 24 hours.

Previous studies found two pandemic clones Taiwan 19F and Spanish 23F to be important among pneumococcal isolates in Vietnam (Bogaert et al., 2002; Parry et al., 2000; Parry et al., 2002; Schultsz et al., 2007; Song et al., 2004b). These serotypes increased the risk of antibiotic resistance in other areas in Vietnam as well as in other countries (Anh et al., 2008; Munoz et al., 1992; Parry et al., 2000; Parry et al., 2002; Poulakou et al., 2007; Schultsz et al., 2007; Soriano et al., 2008; Watanabe et al., 2008).
The rapid spread of a few predominant strains, such as 3, 6A, 6B, 9N, 9V, 14, 19F, 19A, 23F, and 23S, was considered to be a major contributor to the emergence of pneumococcal resistance worldwide (Sogstad et al., 2007; van der Linden et al., 2007; Witte et al., 2008). The global spread of the pandemic MDR serotypes possibly contributes to the increase in high resistance in this region (Chen et al., 2009b; Linares et al., 2010; Parry et al., 2002).

Additionally, the genetic determinants for resistant clones usually exist in a stable form, so once resistance is established, it is not easily lost (Enne et al., 2001; Tenover, 2006). A high resistance to tetracycline was found in the area although this antibiotic is not as commonly used as it was three decades ago. The challenge is now to slow down and to reverse the rate at which resistance develops and spreads.

Vaccination is one way to avoid the spread of MDR clones. Implementation of conjugate vaccine could protect against pneumococcal carriage and reduce the risk of developing antibiotic-resistant invasive pneumococcal infection (Bogaert et al., 2002; Dinleyici & Yargic, 2008). However, these vaccines are still expensive and may not help in invasive diseases caused by serotypes not included in the vaccines, some of them also being MDR (Dinleyici & Yargic, 2008; Kyaw et al., 2006; Normark et al., 2001). Characterization of resistant strains could help to develop strategies to contain resistance.

5.1.3 Implications for antibiotic selection in empirical treatment of community-acquired pneumonia

The emergence of pneumococcal antibiotic resistance and MDR has not only complicated the empirical treatment of CAP, but has also led to an increased numbers of treatment failures. In this project, only 4% of the isolates were resistant to amoxicillin, most of them were susceptible or displayed intermediate resistance (Paper I). High resistance to commonly used oral antibiotics including co-trimoxazole, erythromycin, and phenoxymethylpenicillin shows that, for treatment of CAP, these antibiotics can be expected to be virtually useless. Being low-cost, accessible and having a low resistant proportion, amoxicillin should be recommended as the first line antibiotic for treating bacterial CAP among children. Generally, betalactam antibiotics should remain the initial choice in the management of non-severe CAP (Aspa et al., 2008; Jacobs, 2008; Mills et al., 2005).

In the present study, it was found that as many as 32% of the isolates were intermediate resistant to amoxicillin (1≤MIC≤4mg/l) (Paper I). Evidence showed that most of non-susceptible pneumococcal infections with the MIC≤4mg/l still could be treated successfully with high dose of amoxicillin (Falco et al., 2004; Moroney et al., 2001; Yu et al., 2003). High-level penicillin resistance (MIC≥4mg/l) and cefotaxime resistance (MIC≥2mg/l) has been associated with a poor clinical outcome (Feikin et al., 2000). Therefore, a high dose of amoxicillin is widely recommended for treatment of pneumococcal infections, especially for high level of intermediate resistance pneumococci (CLSI, 2009; EARSS, 2010; EUCAST, 2009b; Harrison et al., 2009; Jacobs, 2008; Sevillano et al., 2008).
According to pharmacokinetic-pharmacodynamic principles, the appropriate dose of amoxicillin is the one that maximizes the time when the plasma concentration persists above the MICs of the etiological agent (t >MIC) (Craig, 1998; Ginsburg et al., 1979), even though, antibiotic concentrations do not have to remain above the MIC for the entire dosing interval. For amoxicillin, significant bacterial reduction is achieved when concentrations are above the MIC for approximately 40% to 50% of the dosing interval (Andes et al., 2004; Craig, 1998). It has been illustrated that with MIC≤2.0mg/l, the dose of 15mg/kg three times daily gave a higher percentage of dose interval above MIC than 25mg/kg twice daily, but with MIC=4mg/l both dosing regimes were suboptimal (Fonseca et al., 2003). The concern is how to define the optimal dose for pneumococcal pneumonia with penicillin/amoxicillin MIC≥4 mg/l (Chiou & Yu, 2006; Nascimento-Carvalho et al., 2009).

From the findings, 90% of isolates were inhibited at amoxicillin 1.5 mg/l and 95% of those were at 4 mg/l. There were 11 children who carried pneumococcal isolates MIC=4 mg/l (Paper I). Following the CLSI and EUCAST guidelines (CLSI, 2009; EUCAST, 2009b) and supported by other studies, children with pneumonia with pneumococcal strains MIC=4 mg/l may require either intravenous benzylpenicillin 400,000 units/kg IV administered four to six times daily or intravenous ampicillin 50-100mg/kg administered four to six times daily (Clifford et al., 2010; Jacobs, 2008; Nascimento-Carvalho et al., 2009). To assure the therapeutic effect for at least 95% of pneumococcal infections, the recommended amoxicillin dose of 25mg/kg three times daily appears to be too low (Grant et al., 2009; MOH, 2006; Sevillano et al., 2008).

Time above MIC can be maximized by a more frequent dose, using a sustained release delivering system, or with the concomitant use of a drug that inhibits the elimination of the antibiotic (Andes et al., 2004). A recent study showed that the more frequent the daily dose, the worse antibiotic treatment compliance (Llor et al., 2009). New formulations, new high dose or extended-release amoxicillin clavulanate, have showed efficacy for pneumococcal infections with MIC ≤4 mg/l of a dose 12-hour doing interval (Benninger, 2003; Berry et al., 2005; Craig, 2004; Kaye et al., 2001; Odenholt et al., 2004; Woodnutt & Berry, 1999). Each dose of these formulations includes amoxicillin-clavulanate potassium powder for oral suspension 45 mg/kg for children or a bi-layer tablet of intermediate-release amoxicillin plus clavulanate and sustained-release amoxicillin 2x1000/62.5 mg for adults. However, these new formulations are broad-spectrum antibiotics, costly and may be not available, thus they are not feasible as the first choice in empirical treatment. How to increase the dose among children with pneumococcal infections needs to be further investigated.

The pneumococcal isolates show the highest susceptibility to cefotaxime among the investigated antibiotics (Paper I). Clinicians might thus find it safe to choose this pneumococcal susceptible antibiotic in empirical practice. However, this drug is a broad-spectrum antibiotic and if used widely and indiscriminately, resistance to this antibiotic in S. pneumoniae might emerge in the near future (Bogaert et al., 2002; Vila-Corcoles et al., 2009). Hence, the still effective antibiotics need to be reserved for the severe cases in tertiary hospitals and in selected cases with troublesome resistance patterns. It should not
be used as the first choice even when the price is low. As one physician commented: “A two–year old boy came to me with a cough. I thought that he had bronchitis, so I injected cefotaxime. It costs only seven thousands dong (~0.4 USD) per dose” (unpublished observation).

5.2 UNNECESSARY ANTIBIOTC USE FOR MILD ARI: ROLES OF HEALTHCARE PROVIDERS, CAREGIVERS, OR HEALTH SYSTEM?

In this project, it was found that seeking care at any health facility increased the risk of being recommended antibiotics unnecessarily (Paper III). The studies explored the association between inappropriate antibiotic use for mild ARI in the community and healthcare-seeking behaviour at drugstores, private or public clinics. Most of antibiotic treatment for mild ARI in the 28-day period had been recommended by healthcare providers (82%), whereas only 18% by caregivers themselves (Paper III).

Prescribing or dispensing antibiotics in lower-income countries is a complex phenomenon influenced by many factors inside the health system or other socioeconomic factors (Nordberg P et al., 2005; Okeke et al., 1999; Reynolds & McKee, 2009; Sterky et al., 1991). In primary health facilities, the major influencing factors are providers, patients, information about drugs and treatment guidelines, referral system and facility, medical education and supervision, as well as economical issues (Figure 12).

5.2.1 Lack of knowledge and inappropriate practice of healthcare providers

In Bavi district, only 21% of HCPs knew that antibiotics are not indicated for treatment of mild ARIs with fever (Paper IV). Correct treatment in the clinical scenario (19%) and reported practice (10%) were even lower (Paper IV). The recommended antibiotic percentage of HCP for common colds (81%) was higher than reported from high-income countries such as US, Sweden, Germany. The antibiotic prescription rate for preschool children from the USA in 2000 was 0.7 prescriptions/person per year, and from Sweden and Germany 0.8 prescriptions/person per year (Hogberg et al., 2005; Muller et al., 2007; Petersen & Hayward, 2007; Rossignoli et al., 2007).
The antibiotic prescribing percentage is comparable with that from other low- and middle-income countries such as India (79%), Sudan (66%), and Palestine (59%) (Bharathiraja et al., 2005; Cheraghali & Idries, 2009; Khatib et al., 2008). The proportion of antibiotic prescription for children in Chennai, India was 79%, in which most common symptoms indicated ARI and acute diarrhoea (Bharathiraja et al., 2005). Prescription with antibiotics was approximately half of all prescriptions from village clinics in a rural area of China (Dong et al., 2008).

A concern is that drugsellers had poorer knowledge regarding antibiotic treatment in both mild and severe illness than other providers (Paper IV). These findings are particularly significant as in Vietnam most patients contact drugsellers to buy drugs without visiting a physician (Chuc et al., 2001; Olsson et al., 2002). The strong belief in having expeditious consultation and the efficacy of treatment given are the main reasons leading people to often seek treatment at a pharmacy (Anyama & Adome, 2003; Igun, 1987). Previous studies in private pharmacies in Hanoi, Vietnam reported that 83% of pharmacies dispensed antibiotics for children with a cough (Chuc et al., 2001). In most European countries antibiotics cannot be obtained without a prescription, although it is common in some countries, e.g. Spain and Greece (Llor & Cots, 2009; Plachouras et al., 2010; Vaananen et al., 2006). Dispensers that had poor knowledge of antibiotic treatment were reported from other countries in Asia, e.g. Laos, Thailand, Nepal and India (Apisaranthanarak et al., 2008; Kamat & Nichter, 1998; Sihavong et al., 2007; Stenson et al., 2001a; Wachter et al., 1999). The persistence of arbitrary antibiotic dispensing in Vietnam obviously promotes irrational antibiotic use and emergent antibiotic resistance.

An unexpected and worrying finding is that the estimated percentage of antibiotic use for mild ARI cases was not significantly different from the use for severe ARIs (Paper IV). This indicates a serious lack of knowledge regarding the pathogens of ARIs and a poor ability to recognize the signs for pneumonia. We found that the presence of fever increased antibiotic recommendation (Paper IV), although this sign does not necessarily indicate a serious illness or a bacterial infection (Schmitt, 1984). In fact, fever is the body’s normal response to infection and most fevers are due to viral infections. A meta-analysis about the natural history of acute cough suggested that overall illness had improved or recovered in most of children two days after consultation, but cough and nasal discharge were present one week after that in half of those, and fever was prolonged in some children (Hay & Wilson, 2002). Antibiotic treatment does not lead to a more rapid decrease in temperature (Kramer & Shapiro, 1997).

One explanation for inappropriate prescribing among physicians might be the perception that antibiotics were effective to prevent secondary bacterial infections or complications in severe symptoms of the common cold (Bauchner et al., 1999; Butler et al., 1998; Kumar et al., 2003). The fear of serious complications might be in relation to a reported association between viral isolation and bacterial pneumonia, especially in low-income settings (Bulla & Hitze, 1978; Madhi & Klugman, 2004). However, it has been demonstrated that serious complications from acute cough requiring hospital admission are uncommon (Hay et al., 2004; Hay & Wilson, 2002; Petersen et al., 2007), and antibiotic treatment neither shortens the episodes nor prevents the development of
pneumonia (Gadomski, 1993). Other factors that might relate to inappropriate prescribing are inadequate time for physicians to explain to parents why antibiotics are not necessary, lack of access to laboratory test, and misdiagnosis of viral infections (Mangione-Smith et al., 1999; Pichichero, 1999).

5.2.2 Poor knowledge or high expectation of antibiotics among caregivers?

In this thesis, both the phenomenon of urban people actively self-treating with antibiotics, and that of rural people passively complying with the physician’s inappropriate recommendation may be described as forms of antibiotic misuse and indicators of poor knowledge (Paper II). The caregivers perceive antibiotics as mandatory for the treatment of pneumonia, sore throat, or cough, especially when accompanied with fever (Papers II, III). The proportion of antibiotic use that has been decided by caregivers themselves for children with mild ARI (18%) was higher than the previous study conducted in Bavi in 1999 (11%) (Larsson et al., 2000). A high rate of self-medication (73%) was reported from another study (Hoan le et al., 2009) which might be caused by a high rate of caregivers consulting drugsellers without a clinical examination (Larsson et al., 2000). Comparably high rates of self-medication were found in eastern and southern European countries, such as Spain (15%), Romania (19%) and Lithuania (21%), in which people used antibiotic leftovers from previous prescriptions (Grigoryan et al., 2006). In 19 European countries, the lowest rates of self-medication were reported in the Netherlands (1%) and Sweden 4% (Grigoryan et al., 2006).

Only 15% of caregivers perceived that antibiotics are necessary for non-febrile common colds, but 45% would need them for febrile colds (Paper III). In fact, patients requested antibiotics when they thought that they would be effective. Such was the experience of one physician in the area: “Parents who had children with cough and fever usually ask for antibiotics. If they don’t get them, they feel worried. If the doctor did not prescribe antibiotics, they went to another doctor who would provide antibiotics for their children” (unpublished observation).

One study on antibiotic use carried out in 2001 in nine countries (United Kingdom, France, Belgium, Italy, Spain, Turkey, Thailand, Morocco and Colombia) indicated that a majority of patients were willing to take antibiotics for conditions likely to have a viral origin and patients can exert pressure on physicians to obtain antibiotic prescriptions in all countries (Weissman & Besser, 2004). Patients’ expectations and physicians’ perception of patients’ expectations were found to be the strongest determinants of antibiotic prescribing (Cockburn & Pit, 1997; Mangione-Smith et al., 1999). However, physicians could overestimate or underestimate patient demands (Britten & Ukoumunne, 1997; Mangione-Smith et al., 2006). Studies reported that even when physicians know that the use of antibiotics is unnecessary, they still often use them to maintain good relationships with patients or to make profits (Butler et al., 1998; Reynolds & McKee, 2009). Some physicians prescribed inappropriately to protect themselves from patient pressure (Henriksen & Hansen, 2004).

In this thesis, there is a significant association between unnecessary antibiotic use and healthcare-seeking at health facilities, but not with poor knowledge among caregivers (Paper III). The finding raises a considerable concern about unnecessary healthcare-
seeking for mild illness. Misconceptions about the causes and the appropriate treatment of colds are also predictive of increased use of the health service in the US (Lee et al., 2003). To improve antibiotic use for ARIs, caregivers should have adequate information about the natural history of common childhood infections and the drug-intended effect (Abdullahi et al., 2008). Evidence suggested that if fewer patients consulted physicians for common infections, unnecessary antibiotic prescribing would be reduced (Ashworth et al., 2006). Adopting more patient-centred consulting skills might be a tool to rationalize the prescribing of antibiotics (Cals et al., 2009). In addition, improving the ability of caregivers’ self-management of mild illness at home according to the IMCI guidelines might help to decrease consultation rates for common colds in the longer term (MOH, 2006).

In recent decades, the patient’s role has been strengthened due to widely available information on drugs. Patient participation is particularly important in drug treatment, since patients participate in the actual use of the drugs. The role of mothers in the management of childhood illness has been recognized and stated in the IMCI (MOH, 2006; WHO, 2005b). However, the IMCI strategy focuses mainly on training for public health professionals, not for mothers, drug sellers or for private providers. This thesis highlights the need to educate caregivers by focusing on the causes of mild ARIs, the normal development of such illness, and which diseases actually require antibiotics, and thus parental expectations for antibiotics might be reduced (Holloway et al., 2009). In addition, issues regarding antibiotic resistance and the consequences of misuse are dealt with: why full daily doses must be respected, the danger of uncontrolled leftovers use, and the need for a prescription to obtain antibiotics should be discussed with the caregivers.

5.2.3 Health system management

Although causal inferences cannot be made in the present thesis, there are some underlying issues relating to health system management that may explain the high percentage of unnecessary antibiotic use. Factors that play important roles in health systems include e.g. human resources and continuing medical education, prescribing and dispensing behaviour in the open market, and information on drug and antibiotic susceptibility.

Human resources and continuing medical education

In the study area, most of the HCPs treating children were not paediatricians, i.e. many of them have not been specifically trained regarding ARI in children or antibiotic treatment. Also, most of the drug dispensers are basic pharmacists with only one year’s professional training. Thus they are not properly qualified to treat and recommend for serious illnesses. Furthermore, in many other places in Vietnam and other low-income countries, and particularly in rural areas, patients must rely on under-trained clinicians, such as nurses, midwives, drug sellers, or other healthcare workers due to lack of human resources (Chen et al., 2004; Pereira et al., 2007). Community health workers and others with minimal training treat minor ailments (Pearson, 1995). In many contexts, drug sellers function as physicians, providing advice along with medicine, taking part in the diagnosis process and prescribing medicines also for serious diseases (Olsson et al., 2002; Stenson et al., 2001a; Tomson & Sterky, 1986; Viberg et al., 2009).
In many countries, unskilled personnel are less aware of the deleterious effects of inappropriate antibiotic use. For example, drugsellers in Thailand prescribed rifampicin for urethritis and tetracycline for young children (Thamlikitkul, 1988). Unqualified drugsellers in India offer alternative drugs when the prescribed drugs are out of stock or refill prescriptions without consulting the prescriber (Dua et al., 1994). A high proportion of children in Nigeria were treated by untrained practitioners for misdiagnosed non-infectious diseases (Fagbule & Kalu, 1995). Patients with sexually transmitted infections received insufficient care from drugsellers and other providers in Vietnam and Laos (Lan et al., 2009; Sihavong et al., 2007). A study from Tanzania, a resource-limited context, suggested that drug dispensers could provide effective management if they were given the appropriate tools (Viberg et al., 2009).

Continuing medical education or continuous professional development has been recommended as the single most important tool in reducing antibiotic prescription rates (Bexell et al., 1996; Esmaily et al., 2010; Gonzalez Ochoa et al., 1996; Grimshaw et al., 2001). However, education has not been well implemented in Vietnam, especially not for private HCPs, because the government and HCPs cannot afford the time and money required for continuing medical education. Some high-income countries, such as the UK, France, the Netherlands and the US, have initiated national regulatory and educational programmes aimed at promoting rational prescribing in the outpatient paediatric population, and these have resulted in a relevant decrease in antibiotic use (Finkelstein et al., 2003; Majeed & Wrigley, 2002; McCaig et al., 2002; Sabuncu et al., 2009). In Sweden, a national organization, Strama (the Swedish Strategic Programme against Antibiotic Resistance), has been implemented since 1995 with activities within many fields including primary care, hospital care, nursing homes, and day-care centres (Strama, 2010). Strama has played a major part in reducing antibiotic prescriptions and containing antibiotic resistance in Sweden (Molstad et al., 2008).

The IMCI strategy with training modules for 11 days and follow-up 4-6 weeks later increases the quality of care for the sick child and thus improves antibiotic use for ARI in primary health facilities (Armstrong Schellenberg et al., 2004; Cao et al., 2004; Tulloch, 1999). However, the IMCI and former ARI programme had not included providers such as drugsellers and private practitioners although they are of major importance for improving antibiotic use. In order to have a sustainable impact on child health and antibiotic use, implementing short-term training intervention programmes for healthcare providers, such as IMCI, should be incorporated in the curricula for medical and pharmaceutical schools. Also the education should be followed by a regular supportive supervision (Uzochukwu et al., 2008).

“Profit-led” prescribing and dispensing in the open market

Problems relating to economic incentives influencing inappropriate prescribing are widely recognized. It was reported as “the negative relationship” between physicians and pharmacists, whereby physicians receive incentives from pharmacists for recommending drugs (Paper II). An “under-the-table” fee was paid for physicians to receive better service, irrespective of the disease severity (Paper II). The illegal phenomenon that drugs were given directly by private physicians in Bavi district, some of them unlabelled, could be for patients’ convenience and HCPs’ profits (Papers II, IV). “Profit-led” prescription
was perceived as inevitable by private as well as public physicians themselves in some low-income countries such as Vietnam, Pakistan and China (Lonnroth et al., 1998; Nizami et al., 1996; Reynolds & McKee, 2009).

Antibiotics prescribed by physicians may reflect influence exerted by the pharmaceutical companies. It was reported that the industry spent 33% of its revenue on “selling and administration” in 2002 (Reinhardt, 2004). It is a well-known fact that physicians have regular contact with the pharmaceutical industry and its sales representatives, who spend a large sum of money each year promoting to them by way of gifts, free meals, travel subsidies, sponsored teachings, and symposia (Wazana, 2000). There was a lack of postgraduate medical education provided by the public sector, thus participation in continuing medical education of pharmaceutical companies is common among physicians (Relman, 2001; Vancelik et al., 2007). Physicians are well informed about proprietary brands through the distribution of free samples and brochures or through seminars organized by the manufactures. Sometimes pharmaceutical companies could arrange to split profits with prescribers, illegally and covertly (Reynolds & McKee, 2009).

The influence of advertising on prescribing behaviour has been reported previously. Many physicians believe that their interactions with drug companies have educational value for themselves and also for patients (Blumenthal, 2004; Hafeez & Mirza, 1999; Mason, 2008; Vancelik et al., 2007). Industry-supported conferences, seminars, and symposia provide physicians with the most up-to-date information on new medicines and technologies (Relman, 2001). Patients are the ultimate beneficiaries, and ultimately experience the consequences if physicians are not fully informed about the latest medical advances. E.g. pharmaceutical sales representative have a significant impact on physicians’ prescription with inhaled steroids in Denmark (Søndergaard et al., 2009). A reduction in prescriptions per patient encounter and an increase of generic prescriptions was observed in Australia when access to pharmaceutical sales representatives was reduced (Spurling & Mansfield, 2007). Thus advertising appeared to affect prescribing behaviour and should be further addressed.

One factor that might strongly influence inappropriate prescribing or dispensing is the high antibiotic availability in most of health facilities. Caregivers often go to healthcare facilities near their house and are frequently given antibiotics from dispensers or prescribers for mild illness (Paper II, III). As a result of the economic reform “Doi moi” and the private sector expansion, antibiotics are easy to access throughout Vietnam (Chuc & Tomson, 1999; Falkenberg et al., 2000; Van Duong et al., 1997). Eight of ten drugs with the highest number of registered brands are antibiotics, i.e. amoxicillin (131), cephalaxin (106), cefixime (100), spiramycin (91), clarithromycin (86), azithromycin (69), ciprofloxacin (64) and cefaclor (60) (DAV, 2009). In 2008, drugs accounted for approximately 60% of hospitals’ total expenditure, and as much as 33% of drug expenditure was spent on antibiotics (MOH, 2009a). As in other countries, most registered drugs that are on the essential drugs list, therefore HCPs both in public and private healthcare sectors are free to use any of registered antibiotics (Darmansjah & Wardhini, 1991; Weerasuriya, 1993).
These findings concerning the purchase of antibiotics over-the-counter without a prescription or drugs directly sold by physicians have implications for the weak implementation of the prescription-only regulations in Vietnam (MOH, 2003a, 2008). Regulatory enforcement in the drug market has been perceived as weak and ineffective (Chuc et al., 2001; Falkenberg et al., 2000; Van Duong et al., 1997). One reason for ineffective regulation could be that the former regulation from 1995 allowed eight oral antibiotics to be sold without a prescription. The habit of obtaining antibiotics without a prescription over a long time period is hard to change. The regulatory activities have been an important factor in improving the knowledge and practice of drugsellers in Vietnam and other countries (Chuc et al., 2002; Stenson et al., 2001b).

It has been reported that high drug prices are the result of the free market economy and the lack of a pricing policy (Babar & Izham, 2009). More expensive drugs were suggested due to the costs of presentation, distribution and promotion of trademarks but not always due to the nature of the product (Babar & Izham, 2009; Danzon & Furukawa, 2008; Ide & Mollahaliloglu, 2009). Adopting a restrictive rule governing the registration of antibiotics, stricter regulation of drug marketing, implementation of drug price control and promoting the use of generic drugs could help to improve rational antibiotic prescribing and dispensing in Vietnam.

**Information of drugs and bacterial susceptibility**

To be able to prescribe rationally, HCPs require up-to-date, contextual and readily accessible information on drugs as well as treatment guidelines. In fact, HCPs in Vietnam as well as in many low- and middle-income countries have almost no access to relevant information (Katikireddi, 2004). Commercial information provided by pharmaceutical companies or drug labels and package inserts often fail to give accurate information (Lee et al., 1991). Non-commercial drug information such as research publications in medical journals, pharmacologist and pharmacist have been reported to be more useful than commercial information (Tumwikirize et al., 2007). Thus, promoting activities of the national drug information centre and drug information team in each hospital could satisfy physicians’ information needs, and hopefully result in reduced irrational prescribing.

Community-based antibiotic surveillance data is useful for prescribers in the absence of patient-specific antibiotic susceptibility results (Okeke et al., 2005b; Rahal et al., 1997). Current inferences about antibiotic resistance trends in lower-income countries are based on a small number of reports, generated by a handful of microbiology laboratories in some hospitals or in some areas. This data is not representative of a country, because wide variations in antibiotic resistance patterns may exist within countries. Susceptibility testing cannot be done readily because equipment, personnel and consumables are scarce and expensive. Moreover, surveillance should be conducted regularly and continuously because resistance rates can vary by geographical area of a country and over time (Mastro et al., 1991; Okeke et al., 2005a).

The European Antimicrobial Resistance Surveillance System (EARSS) has been in operation since 1998 (Bronzwaer et al., 2002a; EARSS, 2010). The purpose of EARSS
is to collect comparable and reliable resistance data over time and place for policy decisions (Goettsch et al., 2000). The European Surveillance of Antimicrobial Consumption (ESAC) project has been implemented to gather data on antibiotic use (Goossens et al., 2005). Information from routine susceptibility testing, which provides information on resistance trends, in relation to antibiotic consumption data, is essential for clinical practice and for rational policies against antibiotic resistance.

5.3 METHODOLOGICAL REFLECTIONS

5.3.1 Quantitative studies (Papers I, III, IV)

In this thesis, all study tools were pre-tested and revised several times prior to use. All the procedures, e.g., interviews, specimen collections, clinical examination, and laboratory testing were carefully standardized and supervised to assure the quality of collected data. The interviewers have been trained carefully in collecting data for Filabavi in general and for this project in particular. The field supervisors are responsible for checking all forms and re-interviewing five percent of the interviews before submitting them for data entry. As indicated by Kroeger (1983a) and Fabricant & Harpham (1993) the recruiting and training of local interviewers and field supervisors are important measures to avoid systemic errors. The studies were piloted to check if the planned study procedures were feasible in practice. The quality of data has also been controlled by supervising and re-checking of researchers. In the studies included here, few of the answers from the first interviews and re-interviews were not consistent.

Papers I and III in 828 households with children under five in the community

This was a prospective study over 28 days. A large number of children were followed in the community, not in hospitals, clinics or drugstores. Before this study, few prospective studies about antibiotic use and resistance among children in the community had been reported. Structured interviews with questionnaire were conducted using a face-to-face interview technique. By using this interview technique, the interviewers encouraged the involvement of the respondents, and the questions could be clarified during the interviews (Fabricant & Harpham, 1993; Kroeger, 1983b).

There was a high response rate from caregivers in the selected households for the interviews, clinical examination and nasopharyngeal sampling. This is, firstly, due to a good cooperation with households and the commitment of local authorities to the Filabavi. Secondly, the interviewers were female interviewers from FilaBavi, who have been well trained in doing household surveys and have built up good relationships with households. Thirdly, the purposes of the study were clearly explained and caregivers were eager to participate. Lastly, all the processes for designing, implementing the study, and choosing the most appropriate time for data collection were carried out carefully.

The sample for the study was taken from the FilaBavi catchment area. Data on the demographic and socioeconomic characteristics of households had already been collected through baseline and re-census surveys, and can be linked with the studies. As described, two-stage cluster sampling was applied in Papers I and III. Cluster sampling normally gives estimates with larger standard errors than in simple random sampling. The reason is
that the units in clusters tend to be more similar than units in general. Design effect is defined as the ratio of the actual variance obtained from a cluster sample to the variance obtained from a simple random sample of the same size. We doubled the sample size in order to take into account the design effect by the cluster sampling (Kaiser et al., 2006).

**Paper IV with 392 HCPs**

This is a self-completed questionnaire with all the HCPs working in public and private health facilities in the district. Self-completed questionnaire has been seen as an administrative convenience, with a relatively low cost, and a short time period (Wolf et al., 1994). This technique allows anonymity, which encourages respondents to respond frankly. The use of written scenarios might not reflect the full actual competence of HCP because of a lack of information in the scenarios (Madden et al., 1997). Relatively low attendance in the group meetings was solved by asking HCPs to fill in the form at their own workplaces following the standardized data collection procedure. There was no significant difference in knowledge and practical competence among HCPs between the places where the questionnaire was filled.

**Recall bias**

Recall bias has been shown to be an important factor influencing the quality of data. Recall bias depends not only on the length of the recall period but also on the importance of the events (Fleming & Charlton, 1998; Kroeger, 1983b; Ross & Vaughan, 1986). While some authors suggested a two-week recall period (Fabricant & Harpham, 1993; Fleming & Charlton, 1998; Kroeger, 1983b), a four-week recall period has often been used to collect information of health status, healthcare and drug use of households (Hossain et al., 1982; Ross et al., 1994).

In Papers I and III, the recall bias is assumed to be a small problem since we had good collaboration with households in the daily completion of the form relating to self-reported symptoms and drug use. Weekly interviews based on household self-report forms have been chosen to minimize recall bias (Feikin et al., 2010; Goldman et al., 1998).

The possible recall bias was for reported practice of households (Paper III) and HCPs (Paper IV) regarding antibiotic use for children. Reported practice concerned symptoms and drug use for children during their most recent illness in the households and most recent child encounter in the healthcare facilities. As most of the most recent child illnesses (60%) and the most recent child encounters (71%) were within one week prior to the interviews (only a few were longer than four weeks), we would expect the recall bias to be relatively small.

**5.3.2 Laboratory test (Paper I)**

To assure the quality of laboratory work, all the relating procedures including specimen collection, sample transportation, *S. pneumoniae* isolation and susceptibility testing need to maintain good quality. Firstly, the collection of nasopharyngeal specimens was done using swabs. The microbiologists hired to collect the nasopharyngeal samples had prior
experience and were carefully trained. The swabs were stored in charcoal transport medium and were transported to the Laboratory of the Institute of Infectious and Tropical Diseases within 12 hours after sampling. The isolation procedures were done following standardized methods by trained microbiologists and were supervised frequently by researchers. The pneumococcal carriage prevalence from pre-test, pilot and study was higher than 50%. This is expected and in line with other studies (Abdullahi et al., 2008; Jain et al., 2005; Nilsson & Laurell, 2001; Schultsz et al., 2007). Thus, the collection and isolation procedures seem to be of a good standard.

I supervised all the steps of testing following the standardized methods together with a co-author (Trung N.V.). The inhibitory zone diameter in disk diffusion test and MIC in Etest were double-checked. This was also discussed with the manufacturer’s technical staff. The *S. pneumoniae* control strain ATCC 49619 was used for every series of agar plates and antibiotic disks. Being the laboratory for several international projects, the quality of the laboratory of the Institute of Infectious and Tropical Diseases is controlled by external reference laboratories, which are in collaboration with Oxford University (England) and Family Health International (US). The correct results of the test with quality-assurance panels have been frequently confirmed.

There are several standard guidelines regarding susceptibility tests and interpretative breakpoint. So it is difficult to compare the resistance prevalence with other studies because the susceptibility tests and the interpretative breakpoints followed different standard guidelines. Since 2008, the new pneumonia breakpoints are <2, 4, and >8 mg/l for susceptible, intermediate, and resistance to penicillin, respectively (CLSI, 2008). According to the change in pneumonia breakpoints, resistant prevalence to penicillin has dramatically decreased worldwide. Thus to compare the findings from this project with earlier studies, MIC should be used rather than S-I-R classification.

5.3.3 Qualitative study (Paper II)

As the aim was to explore caregivers’ perceptions about drug use for childhood illness, we selected the informants purposively. This sample selection referred to information-rich cases, i.e. child-caregivers who had good knowledge and experience with respect to the study’s research topic. Also, these caregivers were willing to share this information with the researchers.

*Focus group discussions*

FGD is commonly used in qualitative research. This method can indicate a range of beliefs, ideas, practices and opinions of those participating as well as perceptions in the community that they represent (Dahlgren et al., 2004). The advantage is that we use the group interaction to explore caregivers’ own experiences and their knowledge in respect to drug use and healthcare. By discussing and exchanging different experiences and ideas on a few themes, we quickly obtain a broader scope about the topics in focus, than if individual interviews are used (Barbour & Kitzinger, 1999; Long et al., 1999).
Trustworthiness

The concept of trustworthiness was developed by Lincoln and Guba (1985) to judge whether the findings of qualitative study are reliable. Trustworthiness contains the four interlinked components of credibility, transferability, dependability and confirmability, which correspond to the quantitative concepts of internal validity, external validity, reliability and objectivity, respectively. In this thesis, I have applied the technique of triangulation for enhancing credibility.

Three types of triangulation, data sources, investigators and research methodologies, were used. Data has been collected from different people involved in taking care of children, e.g., mothers, fathers, and grandmothers. The different groups of informants varied in terms of socioeconomic status and geographical area. The triangulation of investigators included different professions (pharmacist, medical sociologist, and public health scientist), ages, and cultural backgrounds (Vietnamese and Swedish). The final results represent a negotiated outcome of these perspectives. I was the moderator of 4 FGDs and responsible for the process of description and interpretation of the meaning units. The emerging themes and main themes were frequently discussed with co-authors.

The issue of the researcher’s subjectivity is important in qualitative research. Being aware of and describing one’s own position and predisposition in the research process makes the findings more transparent and open to scrutiny. During FGDs, my own pre-knowledge and social position with the study subjects could certainly have influenced the way the discussions and interviewed evolved. I sometimes work in Filabavi to supervise interviewers’ activities and to conduct studies. Thus, whilst acting as a moderator for FGDs, I might have influenced the discussion in both directions. I could facilitate the discussion but might also to some extent impede the flow of interaction within the groups as I am considered as “superior” to interviewers and local people. Being aware of this, I always informed clearly about the objectives and did not show that I have pharmaceutical background. As a young female moderator, I could ask naïve questions in order to explore behaviours and perceptions with regard to taking care of childhood illness. In several FGDs some participants were less communicative than others and I tried to keep the discussion on the right track by posing guiding questions, proper probing and encouraging less active participants to talk (Johansson et al., 2000).

5.3.4 Generalizability and transferability

The generalizability of study results must always be carefully considered. In this case, the generalization of the results, the external validity, must be based on the theoretical propositions suggesting that clusters or districts are quite similar in respect of the phenomenon under study, e.g. antibiotic resistance, antibiotic use among children with mild ARI. Nothing indicates that contextually similar rural areas should be very different regarding antibiotic issues. The clusters selected were the largest clusters for logistic reasons. Analysis shows that there is no tendency of higher pneumococcal carriage, resistance, or antibiotic use in the larger clusters. The results can then be the basis for theoretical judgments about the situation in other similar contexts (Yin, 2003). The results emerging from the qualitative study (Paper II) could not be generalized to other settings in the way statistical generalization is used since the sample is not representative.
from a statistical point of view. The results can be transferred to similar social context using theoretical generalization (Lincoln & Guba, 1985).

The combination of quantitative and qualitative methods to collect data regarding antibiotic use for children in the community is one way of triangulation in this thesis. A combination of methodologies is often the best way to handle the research questions (Dahlgren et al., 2004). The qualitative study discovered, categorized and defined differences and problems in relation to antibiotic use and resistance. The quantitative studies investigated the size of the problems and analysed them statistically (Dahlgren et al., 2004). The results from the qualitative study, e.g., insights into perception and views of caregivers with respect to antibiotic use, led to quantitative studies of antibiotic use among children and antibiotic recommendation among healthcare providers. The qualitative study helps to deepen the understanding of results from the quantitative studies, i.e. to understand the high proportion of seeking care at health facilities and partly understand the high antibiotic recommendation. It would provide deeper understanding of the determinants of inappropriate prescribing or dispensing if a qualitative study using in-depth interviews with HCPs was conducted.

Bavi district was chosen due to good logistics and demographical data through the Epidemiological Field Laboratory (Filabavi). It is also similar to many other Vietnamese rural districts in term of socio-economic condition and health status. The weather in this area in the study period, from March through June, varied from drizzling rain to showers, hot and humid. High prevalence of ARI in this period was reported. Therefore, the results presented in this thesis provide an overview regarding antibiotic resistance and antibiotic use in relation to knowledge and practice of both community and HCPs. The findings could constitute an important basis for selection of appropriate antibiotic therapy, for the development of future interventions and implications for effective programmes to contain antibiotic resistance in Vietnam. Furthermore, it can possibly provide valuable insights to other researchers working in other countries or in demographic surveillance sites.
6 CONCLUSIONS

This thesis highlights a markedly high resistance to commonly used antibiotics and high multidrug-resistance in *S. pneumoniae*. High dose of amoxicillin is the only oral antibiotic that can possibly be used when treatment is required for community-acquired pneumococcal infections. This thesis presents a serious lack of knowledge on appropriate antibiotic use among the healthcare providers (HCP) as well as the caregivers. Antibiotics are often over-prescribed or -dispensed for common colds. Most children with mild ARIs had used, what appear to be, unnecessary antibiotics.

The key conclusions of the thesis are:

1. The resistance to commonly used oral antibiotics and multidrug-resistance of *S. pneumoniae* is distinctly high. There is an association of current antibiotic use among children and pneumococcal antibiotic resistance.

2. Use of erythromycin, co-trimoxazole or ciprofloxacin for the treatment of community-acquired pneumonia might be useless due to high resistance. High dose of amoxicillin is possibly the first choice of treatment for community acquired pneumococcal infections among children. Cefotaxime susceptibility among pneumococci is the highest but should be reserved for selected cases.

3. Self-treatment and non-compliance were common among the caregivers in the urban area compared to the rural area. In more severe illness, the caregivers had a tendency towards greater compliance and in cases of mild illness they showed the suspicion that HCPs would prescribe antibiotics irrationally.

4. Caregivers in the rural area frequently seek care at health facilities and have often been recommended antibiotics for mild ARIs. Caregivers trusted HCPs and perceived antibiotics as mandatory for treatment of illness with fever, although they believed that use of antibiotics should be limited as they are harmful.

5. Most children with mild ARIs had unnecessarily used antibiotics during their most recent illness (71%) as well as in the 28-day follow-up period (62%). Most of the unnecessary antibiotics were recommended by HCPs (82%).

6. Most of HCPs prescribed or dispensed antibiotics for symptoms of common cold, especially in cases with fever. The proportion of antibiotic recommendations for the common cold scenarios (81%) was not significantly different compared to those for the pneumonia scenario (88%). The knowledge of healthcare providers correlated with correct case management.
7 POLICY IMPLICATIONS AND FUTURE RESEARCH

The essential components of the control of antibiotic resistance have been well known for a long time, but success in responding to the problem has been limited (Huovinen & Cars, 1998; Okeke et al., 2005b). One reason could be the relative lack of data on the morbidity and mortality attributable to antibiotic resistance. However, once the impact of resistance becomes measurable, it may be too late to reduce resistance levels and regain previous effectiveness of antibiotics (Cars et al., 2008). On the basis of the findings, I would recommend the implementation of following actions to contain antibiotic resistance and improve antibiotic use:

1. The markedly decreased susceptibility of *S. pneumoniae* to first line oral antibiotics such as co-trimoxazole and erythromycin means that the guidelines for treating pneumococcal pneumonia among children under five need to be revised. A longitudinal surveillance program on antibiotic use and resistance in pneumococci using standardized methods should be developed and established.

2. There is a need to strengthen health systems by means of regular training and monitoring for both prescribers and dispensers in the public and private sectors regarding case management of childhood ARIs. This program should target an improvement in HCPs’ ability to accurately differentiate between mild ARIs and pneumonia cases, to clearly understand the normal development of illness and to appropriately select antibiotics for treatment of community-acquired pneumonia. The issues in relation to rational use of antibiotics and antibiotic resistance need to be included in medical and pharmacy curricula.

3. Health authorities in the whole system should put more effort into controlling and enforcing the regulations of prescribed-drugs, the advertising of drugs, and Good Pharmacy Practice. The registering of antibiotics, especially regarding new brands of existing antibiotics should be balanced to assure “access” but avoid “excess” of antibiotics.

4. There is a crucial need to widely educate caregivers about the normal development of mild ARIs and regarding which diseases actually require antibiotics. Health education campaigns to improve caregivers’ self-management ability for mild illness at home and their recognition of danger signs to promptly seek care for severe illness might reduce the consultation rate for common colds as well as expectations for antibiotics.

5. Developing appropriate interventions for the community and HCPs regarding rational use of antibiotics is necessary. Intervention studies are needed to evaluate which interventions or combinations of interventions are most cost-effective and to what extent it is possible to change knowledge, attitudes and behaviour among such stakeholders. Qualitative studies are needed to develop context-appropriate messages as well as to understand HCPs and consumer behaviour in relation to illness and antibiotic use.
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Stockholm, April 21, 2010

Nguyen Quynh Hoa
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Main questions to assess knowledge of caregivers regarding antibiotic use and reported practice in the most recent illness

I. Perception, knowledge of antibiotic resistance

Have you heard about antibiotic resistance? (Yes/No)

How do you understand the term ‘antibiotic resistance’? (Open)

What are the leading causes of antibiotic resistance? (Multiple choices)
  • Irrational prescribing of antibiotics by physicians
  • Arbitrary antibiotic use by patients (self-medication, non-compliance)
  • Violation of regulations for selling antibiotics by drug dispensers
  • Other factors

What is the consequence of antibiotic resistance? (One choice)
  • No consequence in patients and other persons
  • Treatment failure in patients, not in other persons seeking treatment of infectious diseases
  • Treatment failure in patients and future effects on other persons seeking treatment of infectious diseases because bacterium are not susceptible to antibiotics
  • Do not know

II. Knowledge in use antibiotic for children under 5

In case of having respiratory infectious symptoms, when does the child need antibiotics?
  1. Cough, stuffy nose or runny nose without fever (Yes/No)
  2. Cough, stuffy nose or runny nose with fever (Yes/No)
  3. Including one of the following symptoms: fast breathing, chest in-drawing or stridor (Yes/No)
  4. Other respiratory symptoms (Yes/No). Respondents asked to give details.

III. Reported practice of treatment for the child’s most recent illness

• When was the most recent illness of your child?
• Please list all the symptoms.
• Please describe in detail the actions you took for treatment in this most recent illness.
• Did you use any kind of drugs to treat the child?
• If yes, please write name of drugs you used for treatment. Who was the person who recommended these drugs for the child?
## APPENDIX 2

**Daily self-reported symptoms and drug use for the child aged 6-60 months**

(Week...... from Sunday...../..../2007 to Saturday .../...../2007)

Name of household: ..........................................................Name of the child (6-60 months):.................................................................

<table>
<thead>
<tr>
<th>Content</th>
<th>Sunday Date... /..../2007</th>
<th>Monday Date....../..../2007</th>
<th>Tuesday Date...../..../2007</th>
<th>Wednesday Date....../..../2007</th>
<th>Thursday Date...../..../2007</th>
<th>Friday Date...../..../2007</th>
<th>Saturday Date....../..../2007</th>
</tr>
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<tbody>
<tr>
<td>Symptom</td>
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<td>Place of clinical examination</td>
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<tr>
<td>Place of purchase of drug</td>
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<tr>
<td>Name, dose of drug used during the day</td>
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<tr>
<td>Person giving instructions for use</td>
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<tr>
<td>Cost of examination</td>
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<tr>
<td>Cost of drug</td>
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</tbody>
</table>

*Please keep all the containers, prescription of drugs, which have been used for the child this week. Thank you very much for your collaboration!*
APPENDIX 3

Structured interview with caregiver about daily symptoms and drug use in past week of the child aged 6-60 months

I. General information

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<tr>
<th></th>
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<tbody>
<tr>
<td>1. Name of household:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2. Cluster and household ID:</td>
<td>[ ] [ ] [ ] [ ] [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Name of interviewee:</td>
<td></td>
<td>Interviewee’s ID: [ ] [ ] [ ] [ ] [ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Name of the child 6-60m:</td>
<td></td>
<td>Child's ID: [ ] [ ] [ ] [ ] [ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Name of interviewer:</td>
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</tbody>
</table>

Date of interview: ………/……/2007

Place of interview: 1. At household 2. Other place: ………………………………..

II. General information about drug use for the child in the past week

<table>
<thead>
<tr>
<th>Number of days the child had illness symptoms</th>
<th>Number of days the child had treatment</th>
<th>Number of days the child used drugs</th>
<th>Number of days the HH spend money on examination and drug purchase</th>
<th>HH daily self-reported of symptom, drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] [ ] [ ] [ ] [ ]</td>
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<td>[ ] [ ] [ ] [ ] [ ] [ ] [ ]</td>
<td>[ ] Full fill [ ] Not full fill</td>
</tr>
</tbody>
</table>

Interviewers' evaluation of household's collaboration

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Good</td>
<td>1</td>
</tr>
<tr>
<td>Fairly good</td>
<td>2</td>
</tr>
<tr>
<td>Unwilling</td>
<td>3</td>
</tr>
<tr>
<td>Refusal</td>
<td>4</td>
</tr>
</tbody>
</table>

Notes

Interviewers' signature

Supervisor's signature
Appendix 3 (ctn.)

Drug use for the child aged 6-60 months on................., date ....../....../2007

1. Has the child 6-60 months (who has been selected for the study) had any illness symptom on this day?
   - 1. Yes: Continue
   - 2. No: Go to question 5

2. Which symptoms did she/he has? (multi choice)
   - 1. Cough
   - 2. Fever
   - 3. Stuffy nose
   - 4. Runny nose
   - 5. Sore-throat
   - 6. Fast breathing
   - 7. Difficult breathing
   - 8. Abdominal pain
   - 9. Watery faeces
   - 10. Blood in faeces
   - 11. Vomit
   - 12. Ear ache
   - 13. Injury
   - 14. Skin rash
   - 99. Other sign: .......................

3. Did you do anything to treat the illness?
   - 1. Yes: Continue
   - 2. No: Go to question 5

4. What did you do for treatment? (multi choice)
   - 1. Self-treatment without drug
   - 2. Self-treatment with drug
   - 3. Ask friends’, relatives’ advice
   - 4. Go to private pharmacy
   - 5. Go to private clinic
   - 6. Go to traditional healer
   - 7. Go to HCS
   - 8. Go to hospitals

   (Please fill the order on the box: 1. first action; 2. second action; 3. third action...)

5. Have you given the child any kind of medicine that day?
   - 1. Yes: Continue
   - 2. No: Go to question 8

6. What are the drugs had been used for the child that day:

<table>
<thead>
<tr>
<th>Name of drug, content</th>
<th>Dose per time</th>
<th>Times per day</th>
<th>Who recommended drug?</th>
<th>Where did you get drug?</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>


7. How you could describe the name of these drugs (multi choice)
   - 1. Memory
   - 2. Pictures of drugs
   - 3. Drug container
   - 4. Prescription
   - 5. Other: .........................
   - 9. Do not remember

8. Did you spend any money for healthcare and drugs on that day?
   - 1. Yes: Continue
   - 2. No: Finish, interview for next day

9. How much money did you spend for healthcare and drugs on that day
   Payment for healthcare (VND): .....................
   Payment for drugs (VND): .....................
Clinical examination of children aged 6-60 months
Commune: ...................... Date: ....../....../2007

I. General information

1. Name of householder: ......................... HHs’ ID: ..........................
2. Name of the child 6-60 months: ................. ID: ..........................
3. Age: ............months. ☐ Male ☐ Female

II. Results of clinical examination

1. Weight: .......... kg.
2. Body temperature: .......... °C
3. Habitus: ☐ Normal ☐ Obesity ☐ Under-nutrition
   ☐ Other, detail: ........................................................................................................
4. Heart: ☐ Normal ☐ Abnormal symptom: ..................................
   Diagnosis: ..............................................................................................................
5. Lung: ☐ Normal ☐ Abnormal symptom: ..................................
   Diagnosis: ☐ Pneumonia ☐ Bronchitis ☐ Laryngitis
   ☐ Other, detail: ........................................................................................................
6. Ear: ☐ Normal ☐ Abnormal symptom: ..................................
   Diagnosis: ☐ Otitis media ☐ Ear infection ☐ Other: ..................
7. Throat: ☐ Normal ☐ Abnormal symptom: ..................................
   Diagnosis: ☐ Pharyngitis ☐ Amygdalitis ☐ Other: ..................
8. Nose: ☐ Normal ☐ Abnormal symptom: ..................................
   Diagnosis: ☐ Acute rhinitis ☐ Allergis rhinitis ☐ Other: ..................
9. Stomach: ☐ Normal ☐ Abnormal symptom: ..................................
   Diagnosis: ☐ Mild diarrhea ☐ Medium diarrhea ☐ Severe diarrhea
   ☐ Cholera ☐ Digestive disorder ☐ Other: ..................
10. Dermatology: ☐ Normal ☐ Abnormal symptom: ..................................
    Diagnosis: ☐ Dermatitis ☐ Skin rash ☐ Other: ..................
11. Other organisms:
    ......................................................................................................................................
    ......................................................................................................................................
12. Nasopharyngeal sample: Yes ☐ No ☐
13. Fecal sample: Yes ☐ No ☐

III. Conclusion:

...........................................................................................................................
...........................................................................................................................
APPENDIX 5

Thematised guidelines for focus group discussions
(For child-caregivers: mothers, fathers and grandmothers)

I. Greeting, introduction of participants, moderator, note taker.

II. Briefing the objectives of the discussion, asking for permission to tape record.

III. Content

1. What do you do when your children get sick, especially if they have diarrhoea, a cough or get fever?
2. Where do you take your children for a medical examination, to public or private institutions? Which do you believe is better? Why?
3. What kind of drugs do you usually use when the child gets a cough, diarrhoea or fever?
4. What do you understand about antibiotics?
5. When taking the child to a hospital, what kind of fee do you have to pay? What do you know about health insurance?
6. What influences does the cost of treatment have on the economic performance of the family? Have you ever borrowed money for treatment?
7. What do you think about the healthcare system nowadays? How can we improve the health system in Vietnam?
APPENDIX 6

Self-completed questionnaire for healthcare providers

General information
Age; Sex; Level of education; Professional training; Working place; Average service hours.

I. Perception, knowledge of antibiotic resistance
Have you heard about antibiotic resistance? (Yes/No)

How do you understand the term ‘antibiotic resistance’? (Open)

What are the leading causes of antibiotic resistance? (Multiple choices)
• Irrational prescribing of antibiotics by physicians
• Arbitrary antibiotic use by patients (self-medication, non-compliance)
• Violation of regulations for selling antibiotics by drug dispensers
• Other factors

What is consequence of antibiotic resistance? (One choice)
• No consequence in patients and other persons
• Treatment failure in patients, not in other persons seeking treatment of infectious diseases
• Treatment failure in patients and future effects on other persons seeking treatment of infectious diseases because bacterium are not susceptible to antibiotics
• Do not know

II. Perception, knowledge and practice in use antibiotic for children under 5

Knowledge: In case of having respiratory infectious symptoms, when does the child need antibiotics?
1. Cough, stuffy nose or runny nose without fever (Yes/No)
2. Cough, stuffy nose or runny nose with fever (Yes/No)
3. Including one of the following symptoms: fast breathing, chest in-drawing or stridor (Yes/No)
4. Other respiratory symptoms (Yes/No). Respondents asked to present details.

Scenario of common cold: "A parent or guardian comes to you and describes the symptoms or brings a child under 5 years old who has cough, runny nose and fever, but no sign of fast breathing, chest in-drawing or stridor. He/she asks for examination or to buy drugs. How do you deal with this scenario? What advice do you give to the child’s parent/guardian? Do you recommend or dispense any kind of drugs to treat the child? If yes, please write name and dose of drugs you could use for treatment of this child”.

Scenario of pneumonia: "A child caretaker comes to you and describes the symptoms or brings a child under 5 years old who has cough, runny nose, fever above 38,5°C, and fast breathing. He/she asks for examination or to buy drugs. How do you deal with this scenario? What advice do you give to the child’s parent/guardian? Do you recommend or
dispense any kind of drugs to treat the child? If yes, please write name and dose of drugs you could use for treatment of this child”.

III. Reported practice of treatment for the most recent child under five encounter

- When was your most recent encounter with a child under five for examination or drug prescription?
  - □ 1. This week
  - □ 2. Last week
  - □ 3. 2- 4 weeks ago
  - □ 4. 1-3 months ago
  - □ 5. Before 3 months
  - □ 9. Don't remember

- Please list all the symptoms of the child from this encounter.
  - □ 1. Cough
  - □ 2. Fever
  - □ 3. Stuffy nose
  - □ 4. Runny nose
  - □ 5. Sore-throat
  - □ 6. Fast breathing
  - □ 7. Difficult breathing
  - □ 8. Abdominal pain
  - □ 9. Watery faeces
  - □ 13. Blood in faeces
  - □ 14. Vomit
  - □ 15. Ear ache
  - □ 16. Injury
  - □ 17. Skin rash
  - □ 99. Other sign: .................

- Please describe in detail the actions you took for treatment in this most recent encounter.
  1. Asking questions (Open)
  2. Clinical examination (Multiple choice)
  3. Laboratory testing (Multiple choice)
  4. Diagnosis (Open)
  5. Consultation (multiple choice)
  6. Referral (Yes/No)

- Did you prescribe or dispense any kind of drugs to treat the child?
  - □ 1. Yes
  - □ 2. No

- If yes, please write name of drugs you prescribed or dispensed for treatment of the child?

<table>
<thead>
<tr>
<th>STT</th>
<th>Name of drugs, form, content</th>
<th>Dose per time</th>
<th>Times per day</th>
<th>Days of treatment</th>
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