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ACCESS TO HEALTH CARE FOR CHILDREN IN AMAZONIAN PERU

FOCUS ON ANTIBIOTIC USE AND RESISTANCE

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To my sister, my father and my mother
For insisting that nothing is impossible

ABSTRACT

Background: Infectious diseases remain a big problem in low and middle income countries (LMIC). Problems of access to adequate health care (including antibiotics) prevail despite the availability of many elaborate interventions. Antibiotic resistance further endangers access to effective infectious illness management. The Peruvian state insurance SIS, had formally granted full access to health care and antibiotics for children living within the study areas.

Main objective: To assess health-seeking behaviour, antibiotic use and socioeconomic status for children aged 6 – 72 months in two communities of the Amazonian area of Peru. In addition, to study associations between antibiotic use and socioeconomic factors related to antibiotic resistance among the same study population.

Methods: Two cross-sectional surveys of caregivers were carried out in the two urban Amazonian communities, Moyobamba and Yurimaguas, in 2002. A similar cross-sectional survey was carried out later in 2005, in Moyobamba only. Caregivers were interviewed on health care seeking strategies and medication for their children in relation to reported symptoms and socioeconomic status using a structured questionnaire. Self-reported symptoms were classified into illnesses based on the IMCI algorithm (Integrated Management of Childhood Illnesses). Wealth index was generated by Principal Component Analysis using household assets and characteristics and was used as a proxy for economic status. Faecal samples were collected from the children and the antibiotic susceptibility of *E. coli* was analysed by a rapid resistance screening method.

Results: Many caregivers consulted health professionals for their children's illnesses, (Yurimaguas 42% and Moyobamba 30%) in year 2002 but the poorest caregivers consulted health professionals less frequently (33%) than the least poor (71%) for severe illnesses such as pneumonia (I). In Moyobamba the number of caregivers that consulted health professionals (medical doctors, nurses or health technicians) decreased from 91% in 2002 to 74% in 2005 (p<0.001) (III). The majority of the antibiotics used were prescribed by health professionals (71%), but the amount of antibiotics recommended by pharmacy staff increased in 2005 (18%) as compared to 2002 (6%) in Moyobamba (III). Health professionals prescribed equally often, whether or not antibiotics were recommended for the illnesses. Pharmacists were more discriminatory (II). Caregivers self-caring for their children were restrictive with antibiotics for all illnesses. The amount of children receiving antibiotics free of charge through the SIS had decreased in 2005 as compared to 2002 (III). There were a high number of children carrying antibiotic resistant clones of *E. coli* in both communities, more commonly among the least poor children (IV).

Discussion: The high affordability mediated by the SIS likely contributed to the high utilisation of the public health services. However, inequitable utilisation and under-use of health services for severe illnesses indicate that there are still barriers to access. Antibiotics were prescribed for illnesses where it is not indicated, wasting resources and potentially contributing to emerging antibiotic resistance. The high carriage of antibiotic resistance in the commensal bacterial flora, more commonly among the least poor than the poorest children, underlines the importance of including all groups in society in attempts to improve adequate use of antibiotics.

Keywords: equitable access to health care, antibiotic use, health insurance, policy implementation, inequity, antibiotic resistance

LIST OF PUBLICATIONS

I.   Kristiansson C, Gotuzzo E, Rodriguez H, Bartoloni A, Strohmeyer M, Tomson G and Hartvig P. Access to health care in relation to socioeconomic status in the Amazonian area of Peru. *International Journal for Equity in Health 2009, 8:11*

II.   Kristiansson C, Reilly M, Gotuzzo E, Rodriguez H, Bartoloni A, Thorson A, Falkenberg T, Bartalesi F, Tomson G and Larsson M. Antibiotic use and health-seeking behaviour in an underprivileged area of Peru. *Tropical Medicine and International Health 2008, 13:3, 434-441.*

III. Kristiansson C, Petzold M, Gotuzzo E, Pacheco L, Strohmeyer M, Hartvig P, Bartoloni A and Tomson G. Insurance does not ensure access: Problems in Amazonian Peru. *Manuscript.*

IV.   Kristiansson C, Grape M, Gotuzzo E, Samalvides F, Chauca J, Larsson M, Bartoloni A, Pallecchi L, Kronvall G and Petzold M. Socioeconomic factors and antibiotic use in relation to antimicrobial resistance in the Amazonian area of Peru. *Scandinavian Journal of Infectious Diseases, 2009; 41: 303-312.*

These papers will be referred to in the text by their roman numerals, I-IV.

CONTENTS

LIST OF ABBREVIATIONS

ARI	Acute Respiratory Infection
CAP	Community-acquired pneumonia
CI	Confidence Interval
DIGEMID	Dirección General de Medicamentos Insumos y Drogas
ESSALUD	Seguro Social del Peru
IEC	Information Education Communication
IMCI	Integrated Management of Childhood Illness
INEI	Instituto Nacional de Estadística e Informática
INS	Instituto Nacional de Salud
LMIC	Low and Middle Income Countries
LRI	Lower Respiratory Infection
MDG	Millennium Development Goals
MOH	Ministry of Health
OR	Odds Ratio
PAHO	Pan American Health Organization
PCA	Principal Component Analysis
RR	Relative Risk
SES	Socio Economic Status
SIS	Seguro Integral de Salud
SISVRA	Sistema de vigilancia de la resistencia a los antimicrobianos
URI	Upper Respiratory Infection
UNICEF	United Nations Children's Fund
WHA	World Health Assembly
WHO	World Health Organization

OPERATIONAL DEFINITIONS:

Health provider has been defined as a medical doctor, nurse or and midwife, health technician, pharmacy staff member and traditional healer. These were indicated in the questionnaire as "persons who work with health issues".

Health professionals as used in this thesis include all types of staff caring for patients at *public and private health facilities*: medical doctors, nurses, midwifes and health technicians.

Pharmacy staff as a type of health providers is defined in reference to the interviews, in which the interviewers took special care to understand the caregivers' purpose for visiting a pharmacy. If the caregiver visited the pharmacy with the intent to consult the pharmacy staff in order to ask for advice on how to treat their children, the visit was regarded as a consultation with a health provider.

Self-care was defined in line with Levin (Levin and Idler 1983) as all those activities undertaken in the household to treat illness without professional assistance. It was regarded as self-care if the caregivers had visited the pharmacy with the intent to buy drugs on own initiative and not with the purpose of consulting with pharmacy staff on how to treat a sick child.

The term **antibiotic use,** as it has been used in the Results and Discussion sections of this thesis include all antibiotics that were consumed by the children in the studies, regardless of whether they were provided by health providers or used as part of self-care. Antibiotic use included any use of antibiotics, regardless of type and duration.

Adequate/Rational use of antibiotics: The concept of rational use of antibiotics includes many components, such as adequate type and dose of antibiotic for the right duration of time. In this thesis I have not assessed whether the correct type of antibiotics had been used or if the duration of use had been correct. Adequate use of antibiotics has been defined as those instances where any type of antibiotics has been used for illnesses when the IMCI guidelines (WHO/UNICEF 2003) have recommended antibiotic use.

Antibiotic resistance as assessed in this thesis concerns microbial resistance, not clinical resistance. Antibiotic resistance is defined as recorded results from disc-diffusion tests, where the growth inhibition zone was smaller than the established breakpoint or where single colonies were growing inside the inhibition zone. Two resistance measures were considered in this thesis: "total resistance" and "dominant resistance". The "total resistance" corresponds to children carrying bacteria with any kind of resistance to the antibiotic in question, including low frequent clones. The variable "dominant resistance" did not include low frequent clones. It is an approximation to children carrying bacteria where the dominant florae is resistant to the antibiotic in question.

Wealth as allocated by an asset analysis based on Principal Component Analysis (PCA) has been used as a proxy for **economic status** in this thesis.

Access: This thesis has assessed utilization of health services and antibiotics from a community perspective, using self-stated data from caregivers of children, as a proxy for access to health care and antibiotics.

1 PREAMBLE

The research I conducted in Peru formed part of a larger EU funded project (ANTRES) aiming to contain antibiotic use and resistance by implementation of communication interventions addressing the community members and health care providers. The ANTRES project was conducted in collaboration with Italian and Peruvian research partners (web page: http://www.unifi.it/infdis/antres/default.htm). My responsibility in the project was to plan and carry out all the research related to health-seeking behaviour and antibiotic use. Families were interviewed to learn how they had acted when the children were sick. I had assumed that the pattern of antibiotic use would be similar to what I had experienced in other parts of the world with mostly self-medication and use of private pharmacy staff who had advised caregivers to use antibiotics for every conceivable health problem. To my surprise I found that the majority of the antibiotics came from the public sector, contrary to my own past experiences as well as to what my Peruvian friends and colleagues had seen in Lima. I saw little self-medication with antibiotics and most children had been prescribed their antibiotics by medical doctors. I checked my datasets, discussed with the interviewers and my Peruvian colleagues to find out if I had missed, misinterpreted or misunderstood something. I introduced narratives where the interviewers wrote a qualitative account of the health-seeking behaviour to see if the questionnaires were filled-in incorrectly. And when I didn't find any errors I went on to visiting and re-visiting my neighbours and friends, and the friends of my friends. I talked to young and old people in the villages where I was living, Yurimaguas and Moyobamba.

I started to see the complex web of antibiotic use and health seeking behaviour that existed right in front of me. Even if I had considered in theory before, I now experienced first-hand mothers telling me that the patterns of use are closely linked to the ability to access health care and antibiotics. The context of health finance in Peru, with risk pooling (such as the new SIS insurance), gave at least theoretical financial access to health care and antibiotics for all children in the two communities where I lived and conducted my studies. The caregivers explained to me that "it is cheaper to go to the doctor now when we have the SIS, so why would I go somewhere else?". Even if the health care and antibiotics were affordable in practice, however, I also met groups of children who had not received any antibiotic at all for illnesses where it would likely have been needed. The gap between theory and practice was obviously still not filled. Health-seeking behaviour is complex. As patients, we gather experience from every encounter with the health services and form and re-form our opinions, just as easily: some parts based on prejudice, some parts on coincidence and some parts validated as truths.

The unexpected results of the many months and years of living and working with health providers, families and children in the Amazonian communities stimulated my interest in other aspects of antibiotic resistance. Instead of health communication and intervention aiming to decrease self-medication with antibiotics my research came to

focus on factors influencing adequate infectious disease treatment for children, such as access to antibiotics and health care, especially for poor children, as well as antibiotic use and resistance. I started to think about how all these factors are linked together and how antibiotic resistance further complicates an already complex web: resistance is just another piece in the puzzle of access to health. If the cheap generics cannot be used any longer due to antibiotic resistance this will have a major impact on the access to effective health care. If the drugs themselves are not effective, then it does not matter whether drug procurement works perfectly and that all children have access to health services.

In this thesis I have investigated some of the factors linked to infectious disease management, such as health-seeking behaviour, equitable health care utilisation and antibiotic use, all in a context where children, in theory, can access health care and antibiotics without cost. I have also assessed the distribution of antibiotic resistance between different socioeconomic strata within the community as well as resistance in relation to use.

2 BACKGROUND

2.1 CHILD HEALTH

Children in low and middle income countries (LMIC) are vulnerable to a wide variety of diseases that account for a high mortality and chronic morbidity among this age group. Infectious diseases remain a major killer of children despite established interventions for prevention and care. Such deaths have been regarded as preventable (Black, Morris et al. 2003). According to an assessment mandated by WHO, 54% of deaths in 2000-2003 among children under five years of age were due to the diseases diarrhoea (18%), pneumonia (19%), neonatal pneumonia or sepsis (10%) and malaria (8%) (Bryce, Boschi-Pinto et al. 2005). Mortality resulting from infectious diseases is similar across all WHO regions of interest, with the exception of the African region, where malaria accounts for a high percentage of child death. Poverty is an underlying factor. For example, malnutrition, as a consequence of poverty, is associated with increased risk of morbidity and mortality of a number of infectious diseases, and an underlying cause of 53% of all deaths in children younger than age 5 years (Bryce, Boschi-Pinto et al. 2005). Over-crowding, poor access to clean water and improper waste disposal also contribute substantially.

Diarrhoea is a major cause of death for children in LMIC. Approximately 2 million children below 5 years of age die annually from diarrhoea (Bryce, Boschi-Pinto et al. 2005). The most common diarrhoea-causing pathogens include viruses, such as adenovirus, rotavirus and Norwalkvirus, and bacteria, such as *Escherichia coli* (*E. coli*), campylobacter, salmonella and shigella. There are also parasitic causes of diarrhoea, such as *Entamoeba histolytica* and *Giardia lamblia* (Merson, Black et al. 2005). Cholera is a type of diarrhoea caused by the bacteria *Vibrio cholerae*. Determining the aetiology of diarrhoea is often difficult, and in LMIC this often becomes even more complicated by the lack of laboratory facilities. A serious and life-threatening complication of diarrhoea is dehydration. Continued loss of fluid leads to collapse of essential body functions and, if untreated, eventual death (Merson, Black et al. 2005). Cholera infections are characterized by a rapid fluid loss and can therefore be fatal in a short period of time. Dysentery, commonly caused by shigella bacteria, is characterized by passing of stool with blood.

Acute respiratory infections (ARI) include both upper respiratory infections (URI), such as coughs and colds, and serious lower respiratory infections (LRI), such as pneumonia (WHO 2001). A majority of respiratory infections are URI, and most are simple coughs or colds that remain self-limited. Viruses, such as rhinovirus or coronavirus that result in URI, are recognized as the predominant aetiological agents in ARI (McIntosh, Halonen et al. 1993). The LRI pneumonia is much more severe than most URI, and can have both viral and bacterial causes. Viral pneumonia is more common than bacterial pneumonia, but most often has a lower risk of death (Berman

1991). Data on the causative agent of community-acquired pneumonia (CAP) in LMIC are often scarce, mainly due to a lack of adequate diagnostic tools (Nascimento-Carvalho, Ribeiro et al. 2008). Studies conducted in LIMC have, however, identified *S. pneumoniae* and *H. influenzae* as main bacterial causes of bacterial pneumonia, and rhinovirus and the respiratory syncytical virus (RSV) as causing viral pneumonia in the regions examined (Nantanda, Hildenwall et al. 2008; Nascimento-Carvalho, Ribeiro et al. 2008; Cevey-Macherel, Galetto-Lacour et al. 2009).

A study reviewing the incidence of pneumonia in LMIC has established a median incidence of 0.28 episodes per child per year on a global level (Rudan, Tomaskovic et al. 2004). The estimated proportion of deaths attributed to pneumonia varies between studies, but the disease remains the most important cause of death in all regions (Rudan, Boschi-Pinto et al. 2008).

Risk factors for pneumonia include those related to the child, such as malnutrition (Victora, Barros et al. 1990) and low birth weight, and environmental factors, including over-crowding and lack of vaccination (Fonseca, Kirkwood et al. 1996; Rudan, Boschi-Pinto et al. 2008). Studies have also shown a higher prevalence of pneumonia among poor children. Indoor pollution has shown to be a risk factor, since children living in households using biomass fuel have two to three times higher risk for developing LRI than those who have cleaner fuel (Fullerton, Bruce et al. 2008).

2.2 HEALTH CARE AND TREATMENT

Case management is based on the diagnosis of disease. The treating health professional needs to define which organism causes the disease to be able to administer correct treatment. Defining aetiology is often difficult, a phenomenon that is also true for high income countries having ready access to laboratories. Treatment is often empiric, and the patients are monitored for progress. In LMIC, the situation is even more complicated since access to laboratory facilities is often limited and the health professional is forced to base a diagnosis on clinical signs.

The WHO guidelines on diarrhoea management have focused on key interventions which are vital regardless of the aetiology of the diarrhoea (WHO 2003). Unless the diarrhoea is considered severe, dehydration from acute diarrhoea can be effectively treated with oral rehydration therapy irrespective of which microbe has caused it. Oral Rehydration Salts (ORS) contain salt and glucose and is dissolved in water to form solution. A new ORS solution has been developed that is even more effective and reduces the need for supplemented IV fluid therapy. Zinc supplements have also been shown to reduce the severity and duration of diarrhoea, and further reduces the risk over the following 3 months (Bhutta, Black et al. 1999). Bloody diarrhoea (dysentery) and persistent diarrhoea with malnutrition are also important causes of death. According to the WHO recommendations, essential treatment of a child with diarrhoea is to provide ORS solution, zinc supplement and to continue feeding the child.

Antibiotics should be used only for the children having bloody diarrhoea, in severe cholera cases and for diarrhoea due to serious non-intestinal infections (WHO 2003).

Information regarding the aetiology of ARI is important to guide its treatment, as the success of correct treatment is linked to a correct diagnosis: antibiotics should be used only when bacteria causes the infection, and the correct type of antibiotic should then be selected (Peterson, Hamilton et al. 2001). As the difficulties of isolating the etiological agents become extreme in LMIC due to the lack of adequately equipped laboratories (Petti, Polage et al. 2006), health providers will have to base the diagnosis of bacterial or viral origin on clinical signs, treat empirically and monitor the progress of the patient. The WHO recommendations on clinical evaluation of ARI include identification of children who should be assessed for possible pneumonia based on "entry criteria", such as rapid breathing, chest indrawings and cough. Respiratory frequency and chest in-drawing are the two signs most predictive of pneumonia. Because bacterial pneumonia can lead to rapid death it is important that antibiotic therapy be administered on time. ARI is the leading rationale for administration of antibiotics to children under 5 years of age. In most cases, use of antibiotics is unnecessary and inappropriate (Petti, Polage et al. 2006). The WHO has therefore proposed very selective guidelines for the use of antibiotics in the treatment of ARIs, and antibiotics should be used for children with signs of pneumonia, but not for children with URIs. Most children with cough do not need antibiotics, but the caregivers need to be trained to look for the signs of pneumonia.

Pneumonia remains one of the challenges to child health and survival, despite that many risk factors have been identified, and that validated prevention and treatment measures are available (UNICEF/WHO 2006). According to the world health report 2007 (WHO 2007), pneumonia kills more children than all other illnesses together in low income countries. Still, it has been virtually ignored (Bryce, Arifeen et al. 2003; UNICEF/WHO 2006). A focused and integrated approach to implement and scale up available interventions are urgently needed (UNICEF/WHO 2006). Poor coverage rates have been shown for proper case management of pneumonia and diarrhoea (Bryce, Daelmans et al. 2008). These reports identify that children from the poorest families are less likely to receive the prevention interventions.

One response to high child mortality has been the introduction of the integrated management of childhood illnesses (IMCI), introduced by UNICEF/WHO (Victora, Huicho et al. 2006). The IMCI algorithm guides health workers in correct diagnosis and treatment, including recommendations on antibiotic treatment, using key symptoms and danger signs. The IMCI algorithm follows the logic of inclusion and exclusion criteria in a flow-chart mode. Key symptoms include symptoms such as rapid breathing, cough and fever, which can be assessed by the health worker and help determine whether the child should receive treatment directly or be referred to the next health care level.

Community health management and community IMCI have also been developed to improve the timely case management of childhood illnesses, and to provide a cost-

effective way to increase the coverage of health care and prevention (Marsh, Gilroy et al. 2008).

2.3 HEALTH-SEEKING BEHAVIOUR

A factor confounding vulnerability in children's health is their obvious reliance on caregivers to appropriately seek care on their behalf. The first step of health-seeking behaviour is, therefore, the correct recognition and interpretation of symptoms. Perceptions of severity as well as cultural beliefs about health and ill-health also contribute to the response of caregivers to their children's symptoms: the local understanding of illness becomes important for the interpretation of the symptoms. There are examples in the literature showing that natural and supernatural causes could be interrelated to illness narratives, with merged concepts from biomedicine and traditional medicine that lead to an alternating use of traditional and biomedical health care resources (Hausmann-Muela, Ribera et al. 2002; Nsungwa-Sabiiti, Kallander et al. 2004). Not only the severity of symptoms, but also their duration and type direct the choice of action taken (Develay, Sauerborn et al. 1996; Heuveline and Goldman 2000). One report conducted across five low income countries identified that a perception of increased severity of diarrhoea made caregivers more prone to seek help at health facilities as well as to administer treatment themselves (Yoder and Hornik 1996).

In general, health-seeking practices are influenced by basic underlying factors, such as household resources, experience, knowledge and cultural beliefs of the individuals, community factors, and the characteristics of the health system. In addition, the underlying factors are shaped by context-specific political, economic and social factors (Hausmann-Muela, Ribeira et al. 2003).

Most health care actions and treatment take place at home, in what is called the 'popular sector' (Ahmed, Tomson et al. 2005). The importance of home treatment has been shown in numerous studies: for example, most caregivers in Guatemala had administered some kind of treatment in the home, most commonly drugs (Heuveline and Goldman 2000). In self-care, both over-use and under-use of drugs is a potential problem.

The choice to seek care outside the home results in consultations with both formal and informal sectors, with informal sources including biomedical and traditional providers. Several studies report how caregivers have chosen to buy drugs directly from market places or drugs stores and how private pharmacies represent major health providers (Larsson, Kronvall et al. 2000; Viberg, Tomson et al. 2007).

Health beliefs do not necessarily explain directly the choice of health provider. Further, non-biomedical health beliefs about the causes of illnesses do not necessarily result in health-seeking behaviour directed toward traditional healers. Heuveline and Goldman show how visits to biomedical health providers are far more common than explicit biomedical health beliefs about the causes of illnesses (Heuveline and Goldman 2000).

It is important to keep in mind that illness symptoms are often diffuse. Patients facing uncertainty about the course of an illness or about treatment options often follow a trial and error search in order to solve the health problem (Ryan 1998). Further, extensive knowledge about an illness does not automatically lead to correct recognition of symptoms during an actual illness episode, and correct knowledge does not automatically lead to adequate health-seeking behaviour (Hausmann-Muela, Ribeira et al. 2003). Further factors influencing health-seeking behaviour include treatment expectations, access to health services, decision-making structures within the household, etc.

2.4   ACCESS TO HEALTH CARE

Preventive measures as well as treatments for many infectious diseases are well known and documented; however, access to necessary interventions remains a problem. Access to health services is defined as the timely use of services according to need, but has many dimensions (Gilson, Palmer et al. 2005), and many aspects should be fulfilled so that the target populations can benefit from the interventions. The Countdown Survey reported poor coverage rates for child survival interventions across 60 countries (Bryce, Terreri et al. 2006). Children from the poorest families were less likely to receive prevention interventions. According to Pan American Health Organization (PAHO), 20-25% of the Latin American and Caribbean population has no regular or timely access to health services (PAHO 2007).

The Andersen Behavioural Model of Health Services Use is the most often cited model in research concerning access to health services (Andersen 1995; Ricketts and Goldsmith 2005). In this model, patient and caregiver decisions about where and how to seek health care are influenced by three components: "predisposing" components (i.e. characteristics of the individuals seeking health care), such as age, gender, religion, ethnicity, education, occupation, social capital, knowledge; "enabling" components (e.g. system or structural characteristics) include availability of services and health financing along with prior experience; and "need" components, such as perceived severity of the disease, effect of the disease etc. This model emphasises the role of feed-back loops within a health system. The outcomes of previous health care utilisation and personal health practices are fed back to a process that takes into account predisposing, enabling and need components. In this way, the concept of learning from experience becomes included in the model via a more iterative and dynamic process.

Penchansky (Penchansky and Thomas 1981; Ricketts and Goldsmith 2005) proposed a different approach to understanding access, focusing on the "fit" between patient needs and the ability of the health system to meet these needs. This model introduced five dimensions to measure the fit of a health care system: 1) Availability, which refers to the volume of health services, the match between the supply of health providers and services and the demand; 2) Accessibility, referring to the physical distance or travel time from the users to the service delivery points; 3) Accommodation, as the match between the organization of the health care and the expectations of the users, for

example, with regard to opening hours; 4) Affordability, which is defined as the degree of fit between the cost of health care and the individuals' ability to pay; 5) Acceptability refers to the social and cultural distance between health care systems and their users.
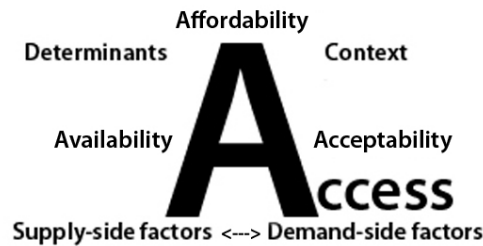

Figure 1. Penchanskys Access model, as illustrated by Gilson et al. (Gilson and Schneider 2007)

Criticism against previous research on health care access includes the fact that access has been primarily understood as a function of policy decisions guiding health facility infrastructure and financing. Gilson underlines that the dimension of acceptability – also called 'cultural access' – has often been ignored in discussions about access and that most policy conclusions have focused on the need to extend health care facilities to under-served areas or on addressing financial barriers to services (Gilson and McIntyre 2007). Her illustration of the Penchansky model presents the access dimensions in relation to supply and demand (Gilson and Schneider 2007). Similarly, Obrist et al underlines that the many dimensions of access indicate that other types of interventions than the traditional ones that focus on supply are needed to ensure access to health care (Obrist, Iteba et al. 2007).

An additional problem considered by Ricketts and Goldsmith (Ricketts and Goldsmith 2005) is that the dimensions of time and experience have not been sufficiently analysed in access research. Health-seeking is a dynamic process where experiences of provided health care affect the next health-seeking decisions. Even though the Andersen model takes into account an iterative process, this has yet to be reflected in practical applications of the model.

Access research has described various factors pre-determining the utilisation of health care. Most reports acknowledge that affordability plays a substantial role. Combined with the results of the Countdown Survey showing that children from the poorest families are less likely to receive prevention interventions (Bryce, Terreri et al. 2006), inequity in health as well as in access to health care becomes obvious as an important problem.

2.4.1 Inequity in health and in access to health care

Despite efforts to improve the situation of the poor children in the world the situation remains difficult. Poor children's survival prospects are worse than those children who are less poor and there are signs that the gaps are widening (Victora, Vaughan et al. 2000; Wagstaff 2000). Inequity is defined as an inequality that is considered to be unfair and avoidable. Socioeconomic status (SES) has been shown to be closely linked to health status (Okeke, Lamikanra et al. 1999). Poverty increases exposure to disease and reduces disease resistance and in that way contributes to wide inequities in child survival (Boerma, Bryce et al. 2008). Poor children are more exposed to risks for disease through inadequate water and sanitation, inappropriate nutrition, indoor pollution, crowding, poor housing condition, and high exposure to disease vectors (Wagstaff, Bustreo et al. 2004).

Even though studies have documented greater health needs of the poor, the access to health care is less among this group (Gwatkin, Bhuiya et al. 2004). Socioeconomic inequities exist at every step, from exposure to disease, through care-seeking to the probability to receive prompt and effective treatment (Victora, Wagstaff et al. 2003). The "inverse care law" (Hart 1971) e.g. "the availability of good medical care tends to vary inversely with the need for it in the population served", was stated in the 1970s but remains true today in many parts of the world. Examples show that even government subsidised health care aiming to reach the poor provided greater benefits to the wealthy (Victora, Wagstaff et al. 2003). Obvious inequities in access to health services within countries have been shown for several countries (Makinen, Waters et al. 2000). In Peru 14% of the poorest and 97% of the richest had access to health care services (PAHO 2007). Inequity in access has been shown for several interventions that have been implemented to improve the access to health care, including access to adequate drug use (Wagstaff, Bustreo et al. 2004).

2.5 ANTIBIOTIC USE AND RESISTANCE

Antibiotics revolutionized the treatment of infectious diseases when first brought into use. Antibiotics are classified as life saving drugs, which represent vital elements on essential drug lists and should be provided for all in need. Access remains a problem, due to factors on both the patient and system level. In addition, antibiotic resistance threatens to erode this valuable resource. Antibiotics should be used with care as antibiotic resistance is correlated with antibiotic use (Levy and Marshall 2004).

2.5.1 Antibiotic use

Antibiotics are only useful for treating bacterial infections. Inadequate use of antibiotics includes overuse, use when not clinically motivated (i.e. for viral infection), and misuse, i.e. inappropriate type, dose, duration and/or frequency of administration. Inadequate use also includes under-use of antibiotics when it is clinically indicated, for example as a result of limited access to antibiotics (Barlow and Diop 1995).

Antibiotic use is influenced by factors on the side of the health provider (supply side) and the patient (demand side). In many countries, patients bypass the formal health care system and use antibiotics without consulting health care providers. Often, people rely on self-medication, and purchase antibiotics directly from pharmacy staff, street vendors or markets (Bojalil and Calva 1994; Delgado, Sorensen et al. 1994; Larsson, Kronvall et al. 2000). Even when health care and drugs from the public sector is available, lack of trust in health professionals can prevent patients from seeking help (Gilson, Palmer et al. 2005). Perceptions of low quality of the antibiotics prescribed can make patients invest in drugs bought over-the-counter at pharmacies or at markets. Antibiotics have been shown to be linked with local, traditional medicines and in that way culturally re-interpreted (Haak and Hardon 1988).

In an ideal context, formal health care professionals would adequately manage infectious diseases as well as the treatment used to combat them. However, prescriptions by health professionals are not by default always rational. A consultation is a complex social interaction between the health provider and the patient, and a number of factors can influence both medical doctors and patients in their decisions to use antibiotics. These include economic factors, as well as lack of time, perceived knowledge and beliefs about antibiotics, and cultural preferences that can influence both medical doctors and patients in their decision to use antibiotics (Sterky, Tomson et al. 1991; Butler, Rollnick et al. 1998; Rowe, de Savigny et al. 2005). Antibiotics provide revenue and signify quality of care from the patients' perspective (Brugha and Zwi 1998; Butler, Rollnick et al. 1998). Examples show how more expensive drugs have been prescribed to increase the profits for the doctors. In China, where the health system has strong financial incentives for drug prescribing, high rates of unnecessary antibiotics prescriptions are estimated (Heddini, Cars et al. 2009). Reasons for health professionals to prescribe antibiotics can also be linked to infrastructural limitations. Often health professionals lack access to laboratory diagnostic facilities or lack trust in the laboratory services (Petti, Polage et al. 2006). Updated knowledge about correct antibiotic treatment may also be lacking, or health professionals may be compelled to prescribe according to availability of drugs in the health facility or according to the limitations of the insurance or basic benefit packages (Radyowijati and Haak 2003). In addition, there can be valid medical and practical concerns behind inadequate antibiotic use. For a medical doctor treating a child who has travelled far to the health facility, and who is unlikely to come for a follow-up visit, treating a potential secondary infection may seem a more rational decision than worrying about eroding the potency of antibiotics in the long run (Stein, Todd et al. 1984).

2.5.2 Antibiotic resistance and access to antibiotics

It is not likely that the Millennium Development Goals (MDG) for 2015 will be met without substantial acceleration in primary health care (Walley, Lawn et al. 2008). Improvements of child health services are needed. The Lancet Alma-Ata working group proposes, among other things, to strengthen health service infrastructure,

including human resources and essential drugs. Availability of essential drugs such as antibiotics is not enough to manage childhood illnesses or to adequately treat bacterial infections. Antibiotic resistance is a world-wide problem, and several studies have reported remarkably high prevalence of antibiotic-resistant clinical isolates in LMIC (Okeke, Laxminarayan et al. 2005). This becomes especially important when high resistance coincides with high burden of infectious illness. Thus, resistance undermines the access to effective antibiotic treatment, because in many settings the inexpensive, first-line antibiotics are no longer effective (Bhutta 2008). This means that the cost increases, both for the patient and the health system. For the individual patient, the cost of second-line treatments can be impossible to meet, thereby limiting access to effective treatment for vulnerable groups (Whitehead, Dahlgren et al. 2001). The emerging antibiotic resistance threatens to "turn back time" to a situation where treatable infections once again become incurable (Cars, Hogberg et al. 2008).

2.5.3 Antibiotic resistance

Human and non-human antibiotic use has been identified as a major contributor to the development and spread of antibiotic resistance (Sullivan, Edlund et al. 2001; Levy and Marshall 2004; Cabello 2006; Malhotra-Kumar, Lammens et al. 2007; Fabrega, Sanchez-Cespedes et al. 2008). Antimicrobial susceptibility or resistance refers to bacteria's capacity to survive exposure to a defined concentration of an antibiotic. However, there are different operational definitions based on whether the purpose is for clinical diagnostics or epidemiological surveillance. The term 'clinical resistance' refers to the bacteria causing infections that have a low probability to clinically respond to treatment, even if maximum doses of the antibiotic is administered (EFSA 2008). The term 'microbiological resistance' refers to bacteria that can tolerate higher concentrations of an antibiotic than the wild-type of the same bacteria. The microbiological resistant isolates differ from the wild-type because they have acquired resistance either by mutation or gene transfer. Bacterial resistance can be either intrinsic, where the bacteria are naturally resistant to an antibiotic, or acquired, where resistant bacteria strains emerge in bacteria that are naturally sensitive (EFSA 2008). Acquired resistance is caused by genetic changes of the bacteria and can be shared between bacteria through horizontal transfer. Co-resistance refers to the event when two or more different resistance genes are physically linked in a larger genetic element such as integrons, transposons or plasmids. As a consequence of co-resistance, selection for one resistance gene included in the larger gene element will also select for the other genes in the same element (EFSA 2008).

Number of multi-resistance strains of intestinal pathogens to inexpensive antibiotics, such as cotrimoxazole, ampicillin and tetracycline, has increased in low-income countries and cause infections not possible to treat with antibiotics that are affordable to the majority of the population (Okeke, Laxminarayan et al. 2005). A Kenyan study reported on *Shigella spp*. with cotrimoxazole resistance of 95%, tetracycline resistance 98% and ampicillin resistance of 83% (Brooks, Shapiro et al. 2003). Resistance against penicillin and erythromycin among bacteria causing acute respiratory infections is a

major problem in Asia, Latin America and Africa (Okeke, Laxminarayan et al. 2005). High *Streptococcus pneumoniae* resistance against penicillin (77%) and erythromycin (31%) was shown in Mexico (Mendes, Marin et al. 2003). Also in Hong Kong, Japan, and South Korea high S *pneumoniae* penicillin resistance (57%, 45% and 72%, respectively) and erythromycin resistance (71%, 78% and 88%, respectively) were shown (Inoue, Lee et al. 2004).

PAHOs annual report from the network of antibiotic resistance surveillance in the Americas region from 2004 show community acquired *Shigella spp* with high resistance against ampicillin and cotrimoxazole (i.e. Bolivia 77% ampicillin and 67% cotrimoxazole; Chile 67% ampicillin and 71% cotrimoxazole) (PAHO 2005). Even though the information reported for each country is a summary of data from different laboratories and geographical areas and the epidemiological usability is limited, such information is important as an indication of antibiotic resistance trends.

The spread of resistant bacteria is an important factor for emerging resistance. Resistant bacteria can be transferred between people, either at community level or at health facilities and through the food and water (Engberg, Neimann et al. 2004; Oteo, Navarro et al. 2006). Food or water contaminated with antibiotic resistant bacteria can contribute to the spread of antibiotic resistant bacteria through the food-chain (Engberg, Neimann et al. 2004). Humans carry bacteria on skin and intestines that normally are not harmful. This normal bacterial florae, the commensal bacteria, act as a barrier against colonisation of potentially harmful bacteria (Sullivan, Edlund et al. 2001). However, some commensal florae bacteria can also cause diseases if the host is immune-compromised or if the bacteria enter the body at sites that are normally sterile (Sharp 1999). *E. coli* acts as a commensal flora, but can also cause urinary tract infections and diarrhoea, among other infections. There are increasing evidence that commensal intestinal bacteria of humans and animals may play an important role in the increase of resistance (Osterblad, Norrdahl et al. 2001; Sullivan, Edlund et al. 2001). Commensal florae could then serve as a reservoir for resistance genes, which could be transferred to more pathogenic hosts (Rao 1998; Levy and Marshall 2004).

All antibiotic use, including appropriate use, selects for resistance as it gives the bacteria that are resistant a comparative advantage. To minimize the selective pressure, unnecessary use should be minimized and basic hygiene measures should be applied, as identified by the WHO recommendations for containment of antibiotic resistance (WHO 2001).

2.6 HEALTH SYSTEMS

The goals of health systems are, according to WHO, to improve the health of the population, to respond to expectations among the population and to protect against any financial consequences of paying for ill-health (WHO 2000). The WHO definition of a health system includes "all actors, organizations, institutions and resources whose

primary purpose is to promote, restore or maintain health" (WHO 2000). Important functions of health systems include service and information provision, maintaining the health workforce, regulating medical technologies and products, health financing and stewardship. The strengthening of health systems in LMIC has been identified as a key requirement for achieving the MDG by 2015 (Travis, Bennett et al. 2004). Progress in health is dependent upon the development of health systems so that they are equipped to respond to these challenges (WHO 2003)

Nearly all Latin American countries have a constitution recognizing health as a human right; however, most countries have not managed to assure this right by making necessary adjustments in their health systems (PAHO 2007). Health systems throughout the Latin American countries have been based on western social security models, but were initially only directed toward special population groups (depending on income, occupation, formal employment, ethnic origin etc). As a consequence, these systems have often been segmented and have consisted of un-integrated subsystems.

One of the main objectives of a health system is to protect the individuals against the financial consequences of ill-health. In LMIC, the chance for the government to finance public health care is lower, and universal access to high-quality services is limited. According to recent World Bank figures, the public share of the total health expenditure is 29% in low-income countries, 49% in middle-income, and 65% in high-income countries (Gottret and Schieber 2006). Often LMIC have problems collecting national general revenue, especially in countries with a large informal sector.

Most LMIC have multiple public and private risk pooling arrangements, which aim to protect households from the impoverishing effects of ill health, and to avoid out-of-pocket payments that endanger the access to health care. Some risk pooling arrangements are state-funded systems through national health services, social health insurances, private insurances and community-based health insurances. However, the amount of out-of-pocket health expenditures is still larger in poorer countries (60% low-income countries; 40% middle-income; 20% high-income).

Discussions about health system design, social welfare, access and provision of health care have been revisited over the past decade in Latin America, triggered by, among other things, the issue of reform, the commitment to fulfil MDG, and a growing concern about inequity, exclusion and poverty (PAHO 2007). Performance of the health system and its ability to implement policy are key issues. Real change comes through implementation.

2.7   POLICY IMPLEMENTATION

Interventions to improve child survival are readily available, however their expected impact on health indicators are often lacking. The step from policy to practice is often long. Examples of barriers to the successful implementation of policies have been identified at the health systems level, as well as on the level of individual health providers. In analysis of policy implementation the perspectives of "top-down" and "bottom-up" are central (Buse, Mays et al. 2005). The "top-down" perspective assumes that policy formulation and implementation are separated and that implementation consists in the lower system levels putting into action the plans formulated by the higher levels. The "bottom-up" perspective, on the other hand, considers the policy implementers as important, as they re-shape the policy through their actions. Walt and Gilson have argued that too much focus has been given to content of health policies (Walt and Gilson 1994). In order to understand why desired policy outcomes are lacking, attention needs to be given also to the contextual factors and processes for policy implementation. In addition, key actors involved are essential, as they could support or resist policy implementation (Walt and Gilson 1994).

Policies meant to ensure equitable access to health care have faced similar implementation problems in many parts of the world. Following health reforms in the 1980s and 1990s, a number of Latin American countries moved away from trying to provide universal coverage (free health care financed by public funds) and instead opted for cost recovery initiatives utilizing, for example, user fees and insurances (Homedes and Ugalde 2005; Ruiz, Amaya et al. 2006; Vos, Ceukelaire et al. 2006). User fees have been shown to represent an important barrier to accessing health services, especially for poor people (Fiedler and Suazo 2002). Waiver system strategies and the like have been difficult to implement in many contexts, due to poor preparedness of the health system, with weak administration, as well as to poor acceptability on behalf of the patients. Fee exemptions have proven stigmatizing and costly since administration measures are needed to identify the poor (Kivumbi and Kintu 2002; Jacobs, Price et al. 2007).

The IMCI was developed to improve the management of childhood illnesses by health workers at the primary health care level. Implementation of the IMCI strategy was successful in some countries, i.e. Tanzania, where the child mortality was reduced by 13% (Armstrong Schellenberg, Bryce et al. 2004). However, implementation in Peru has proven difficult. Evaluation has shown that success of implementation is context dependent and linked to the commitment and preparedness on the health system level, both on the side of the health workers and the authorities (Huicho, Davila et al. 2005).

In 1998, the World Health Assembly expressed concern about antibiotic resistance and adopted a resolution urging Member States to take a number of measures to contain antimicrobial resistance (WHA resolution 51.17). By 2001, the WHO issued the Global Strategy for Containment of Antibiotic Resistance which included a wide range of recommendations (WHO 2001). However, implementation of this strategy has been

slow and success varied across and within regions. The WHA re-emphasized the need for comprehensive and integrated approaches to contain antibiotic resistance in a resolution adopted 2005 (WHA resolution 58.27). The resolution included core components such as stewardship, appropriate use of antibiotics, education, as well as increasing awareness, monitoring, prevention and control, reducing the use of antibiotics in food-animal production and mobilizing resources. Implementation of this resolution has also been slow. The link from the resolution and strategy formulated at global level to the level of the national policy makers has been proposed as weak, and leadership, coordination, and financial and human resources are lacking (Cars, Hogberg et al. 2008).

For successful implementation of health policies to occur, aspects such as acceptability at the level of both health workers and community members need to be taken into account. Also the administrative aspects of the health care system need to be strengthened. Implementation strategies with a participatory approach are likely to have increased possibilities for success.

2.8   FACTORS INVESTIGATED

Several interrelated topics associated with access to adequate health care and antibiotics for children have been investigated in this thesis. Caregivers' actions as a response to their children's illness have been assessed through cross-sectional household surveys including a large number of variables. Health-seeking behaviour has been investigated in the sub-studies I, II and III, including stated health care utilisation. In sub-study I the health-seeking behavior was further assessed in relation to SES. Access to and use of antibiotics have been described in the sub-studies I, II and III, with sub-study II investigating the rationality of the antibiotic use in more detail. Antibiotic resistance associated to antibiotic use and SES was assessed in sub-study IV.

Figure 2. Factors investigated in this thesis with respective sub-studies I-IV

2.9 RATIONALE

Infectious diseases remain a large problem in LMIC (Black, Morris et al. 2003; PAHO 2007). Interventions are available both for treatment and prevention, but children in these regions often lack access to them (Black, Morris et al. 2003; Huicho, Davila et al. 2005; Bryce, Daelmans et al. 2008), which is true especially for poor children (Victora, Wagstaff et al. 2003; Wagstaff, Bustreo et al. 2004). Antibiotics are a key element in infectious treatment, but they are often misused. This misuse causes problems with both case management and emerging antibiotic resistance. Antibiotic resistance threatens to further endanger access to adequate treatment for infectious illnesses (Levy 1998).

The consequences of antibiotic resistance become more severe for populations not able to afford expensive second-line treatment. Few studies describe antibiotic resistance from a community perspective or describe carriage of resistance in relation to SES.

Constraints to the access of health services, and the poor coverage of the interventions falls on the side of both supply and demand (Hanson, Ranson et al. 2003). It is therefore important to assess health service utilisation from beyond a health facility perspective. Health-seeking behaviour, the actions taken, must also be investigated from a community perspective, from the point of the caregivers. The behaviour of people not using the health services is also important to investigate. Health-seeking behaviour has been investigated in many LMIC, but there is a lack of community-based information on health-seeking for children in relation to antibiotic use and SES, especially from Latin America.

Coverage of some child survival interventions, such as antibiotic provision, may be improving in Peru through the public health insurance; however there has not been any community-based assessment of actual utilisation in relation to SES. Large intra-country differences exist, with the wealthiest having more access than the poorest (Boerma, Bryce et al. 2008).

Antibiotics are provided directly from pharmacy staff and bought at market places and food shops in many LMIC, in addition to being prescribed by the health sector (Radyowijati and Haak 2003). Antibiotic use and the rationality of antibiotic use have often been described from the prescriber or provider perspective, in studies investigating patterns of antibiotic provision. The problem, especially in Latin America, is that knowledge regarding the total amount of antibiotic used, including antibiotics used through self-medication, often is missing from investigations.

3 OBJECTIVES

3.1 GENERAL OBJECTIVE

To assess health-seeking behaviour, antibiotic use and socioeconomic status for children aged 6 – 72 months in two communities in the Amazonian area of Peru. In addition, to study associations between antibiotic use, socioeconomic factors and antibiotic resistance in the same study population.

3.2 SPECIFIC OBJECTIVES

1. To assess the relationship between socioeconomic factors and health seeking behaviour, including antibiotic use (Paper I);
2. To asses the rationality of antibiotic use (Paper II);
3. To study the changes in health seeking behaviour and antibiotic use over time during the period following policy changes promoting access to health care (Paper III).
4. To investigate the association between antibiotic resistance in *E.coli* commensal florae and socioeconomic status, household characteristics and antibiotic use (Paper IV);

Paper	Data collection Methods	Study population and sample size	Year
			2002
Access to health care in relation to socioeconomic status in the Amazonian area of Peru.	Cross-sectional household surveys 2002 in Yurimaguas and Moyobamba. Interviews with caregivers using structured questionnaires.	Caregivers of 798 children in Yurimaguas and 800 children in Moyobamba aged 6 to 72 months.	
Antibiotic use and health-seeking behaviour in an underprivileged area of Peru.	Cross-sectional household survey 2002 in Yurimaguas.	Caregivers of 798 children in Yurimaguas.	2002
Insurance does not ensure access – problems in Amazonian Peru.	Cross-sectional household survey 2002 in Moyobamba. Cross-sectional household survey 2005 in Moyobamba.	Caregivers of 800 children in Moyobamba Caregivers of 800 children in Moyobamba	2002 and 2005
Socioeconomic factors and antibiotic use in relation to antimicrobial resistance in the Amazonian area of Peru.	Cross-sectional household surveys 2002 in Yurimaguas and Moyobamba. Faecal samples collected from the children during the survey and the antibiotic susceptibility of *E.coli* isolates analysed by a rapid resistance screening method.	Caregivers of 798 children in Yurimaguas and 800 children in Moyobamba	2002

Table 1. Overview of papers and data collection

4 MATERIAL AND METHODS

4.1 CONTEXT

Peru is topographically diverse and is comprised of costal areas, the Amazonian jungle and the Andean highlands, creating dramatic contextual differences among the population. In 2001, when this study was first designed, more than half of the Peruvian population (54%), roughly 12.8 million people, lived below the poverty line with an estimated 24% in extreme poverty (INEI 2006). Over time, the economic conditions in the country have improved and Peru is now considered one of the fastest growing economies in the region, with the main growth sector found in industry – mining, petroleum, fishing, textiles and steel. Despite economic advances, however, the wealth remains unevenly distributed within the population as a whole. Poverty continues to be focused mainly in the rural areas, where more than two-thirds of the rural population is still considered poor and one-third remains in extreme poverty. The jungle and highlands areas remain among the poorest in the country. The health care sector in Peru reflects this uneven distribution of wealth. Infant mortality, a well known indicator for the general health status of a specific population, is shown for Huaucavelica (the poorest region in the country) as 71 infant deaths/1000 live births, while only 31/1000 for the entire country. The Peruvian population faces a number of substantial health problems. Chronic diseases were among the main causes of death in 2004, after a reduction in mortality from communicable diseases between 1990 and 2000 (PAHO 2007). However, acute respiratory infections were the leading

BOX 1. DEMOGRAPHIC INDICATORS

Population	27 millions		
- under 5	2.5 millions		

Literacy rate			
- women	83%		
- men	94%		

	National average	**Poor homes**	**Non-poor**
Public drinking water	64%	48%	77%
Public sewerage services	51%		

Department	**Poverty 2001**	**Poverty 2004**
Loreto	70%	70%
San Martin	67%	61%
Country average	46%	52%

Source: INEI 2002, INEI 2005, PAHO 2007

BOX 2. HEALTH INDICATORS

Infant mortality rate	23 per 1000
Child mortality rate	31 per 1000
Life expectancy	70 years
ARI prevalence children under 5	17%
Diarrhoea prevalence under 5	15%
Cronic malnutrition	
-children under 5 rural areas	39%
-children under 5 urban areas	10%

Source: PAHO 2007

cause of death in 2004. For children under 5 years of age over one third of death occurred during the neonatal period. Other common causes of death are ARI (17%) and diarrhoea (15%) (PAHO 2007). Chronic malnutrition is high among children under 5 years old and there has been no significant change between 1996 (26%) and 2004 (24%).

Health care provision

Health care in Peru is currently provided by public facilities run by the Ministry of Health (MoH; 59% of all services), the social security health facilities (ES SALUD; 26%), private health facilities (10%) and the military and police force health facilities (5%). Facilities run by the MoH provide health care for the whole population, by charging a user fee or by providing free of charge to those covered by the public health insurance Seguro Integral de Salud (SIS). The ES SALUD social security covers only the working population and their families, and includes health care services and medication. The cost for coverage is 9% of the monthly income. ES SALUD runs its own hospitals that are equipped with pharmacies and laboratories; 17.6% of the population was covered by ES SALUD in 2004 (PAHO 2007).

BOX 3. HEALTH CARE PROVISION

Source of care

- MoH	59%
- social security	26%
- military & police	5%
- private	10%

SIS coverage

	2002	2003	2004	2005
Population in Poverty	37%	39%	30%	29%
Non-poor population	21%	22%	16%	15%

Source: PAHO 2007, INEI 2006 and INEI 2008.

In addition to the public SIS and the social security-based ES SALUD insurance schemes, there are also private insurance companies covering a small part of the population. However, the majority of the population has no insurance coverage at all, and has to pay out-of-pocket for all health care, diagnostics and medicines.

The SIS health insurance was created in 2002 by merging the previously existing "Maternal/Infant" insurance with the "School" insurance. In theory, the SIS was intended to provide free health care, essential generic drugs and diagnostic services via the public health care sector to the poor, to pregnant women and to senior citizens, according to insurance schemes that were specified by target group for a minimal inscription fee. In areas with a poverty level higher than 60%, such as the Amazonian jungle area, all children up to 18 years of age qualified for the SIS insurance during the study period, irrespective of their parents' economic status. However, insurance coverage was not automatic and the children had to be registered each calendar year at the hospital SIS office. According to the National Household Surveys 2002 to 2005, 58% to 44% of the population was affiliated with this insurance (INEI 2005; INEI 2008).

The MoH increased its participation in health care, mainly in primary health care facilities, as a result of health reforms during the 1990s aimed at improving health care access. Since 2001, the Peruvian government has initiated a modernization of the health sector, aiming to create universal access to health services and social security through components such as universal insurance, financing for the poorest and modernization of the MoH. Some of the strategies, such as the SIS, have since increased the access to health care. However, the National Household Survey ENAHO 2004 (INEI 2005) identifies about 35% of population as seeking health care in health facilities for health problems. There is a concentration of private providers, ES SALUD facilities and specialized care facilities (private, ES SALUD and public special care) in urban areas, especially in Lima, the Peruvian capital. This high concentration of private providers in urban settings is thereby likely to make access for the poor living in rural communities more limited. A staff shortage remains throughout the country and the availability of health professionals varies between the different regions, with fewer health professionals available in the rural or poor areas.

Antibiotic use in Peru
The MoH department DIGEMID (Direccion General de Medicamentos Insumos y Drogas) manages and is responsible for all normative work, registration and quality control related to antibiotics. Antibiotics for human use are prescription-only drugs and only medical doctors can prescribe, but legislation is not routinely enforced. A petition by DIGEMID/MoH restricted the use of certain antibiotics, such as vancomycin: in order to use these antibiotics, medical doctors must apply to the MoH nosocomial infection committee.

One of the sub departments of DIGEMID is responsible for rational use of medicaments, including antibiotics (URM-ATM). Among the problems identified by this group are: weak therapeutic committees at the hospitals; lack of coordination between the various entities involved in management and control of antibiotic use; lack of standardized guidelines for case management; lack of microbiological information to support the use of antibiotics and lack of training of health staff.

A governmental program aimed at improving financial and geographical access to pharmaceuticals (SISMED) included strategies for better management of medicines. Since implementation, SISMED has improved the shortage of antibiotics in the public health system. However, to some extent problems remain, among other things due to delays in the procurement processes.

The exact number of pharmacies in the country is not known as a large number of the private pharmacies remain unregistered even though formally they should be registered with DIGEMID. The approximate number of pharmacies in Lima is 7000.

The MoH has general clinical guidelines guiding health professionals' prescriptions. In addition, the SIS has pre-printed prescription formats where the medical doctors should motivate prescriptions by stating symptoms and diagnoses, and then tick the

corresponding antibiotic from a pre-defined list. The medical doctors are free to add any brand name of his/her choice to the list but must justify the choice with clinical arguments. The public pharmacy staff then has to cross-check the rationality of the prescription before dispensing the antibiotics. No funds are reimbursed for erroneous prescriptions.

With the support of PAHO, USAID and APUA among others, antibiotic prescription in the department of Callao was analysed in 2005 (OPS 2009). According to the assessment of 36 of the 48 health facilities in Callao, medical doctors prescribed antibiotics to 71% of patients with Upper Respiratory Infections and 89% of patients with diarrhoea.

Antibiotic resistance in Peru
In Peru, the responsibility for monitoring of antibiotic resistance is held by the Instituto Nacional de Salud (INS), which also is responsible for the national public health reference laboratories and the national quality control centre. The national surveillance of antimicrobial resistance, Sistema de vigilancia de la resistencia a los antimicrobianos (SISVRA), started 1997 and includes data from the more than 40 laboratories included in the national network of laboratories, of which 21 are hospital microbiological laboratories. The remaining laboratories are reference laboratories for the health departments throughout the country. The data collected by this agency identifies resistance in respiratory tract pathogens, such as *Streptoccocus pneumoniae* and *Haemophilus influenzae*; resistance in enteric pathogens, such as *Shigella* spp, *Vibrio cholerae*; resistance in *E. coli* from urinary tract infections; and resistance in various pathogens isolated from hospital acquired infections, such as *Klebsiella spp* and *Staphyloccocus aureus*.

The INS surveillance results from 2004 (PAHO 2005) show that resistance against ampicillin among community acquired *Shigella flexneri* is 68% and against cotrimoxazole is 73%. *Shigella sonnei* resistance against the same antibiotics is 92% and 88%, respectively. However, geographic coverage and the number of pathogens from community acquired infections are still insufficient to draw conclusions on any resistance trends, and the material is not yet representative for conclusion on the national level.

Among the hospital acquired *E. coli* resistance was high against ampicillin (87%), cotrimoxazole (78%) and ciprofloxacin (70%). Also hospital acquired *Staphylococcus aureus* was highly resistant against a number of antibiotics (oxacillin 80%; erythromycin 81%; ciprofloxacin 75%; gentamycin 78% and clindamycin 76%. The laboratories in the surveillance network are regularly evaluated through the External Evaluation Program. Evaluations carried out show that even though the quality is constantly improving, structural problems, shortage of supplies and equipment, and a need for capacity building remain.

4.2 STUDY AREAS AND POPULATION

Figure 3. Map showing the study communities: Yurimaguas, Loreto department and Moyobamba, San Martin Department. EPS-maps.

The study was carried out in the Amazonian jungle area of Peru, in two departments, Loreto and San Martin. The study sites, Yurimaguas in Loreto and Moyobamba in San Martin, were chosen as they represent one of the poorest, most vulnerable areas with the least access to health services. Each study community has a population of approximately 32,000 inhabitants, most of who are living from subsidence farming. In Yurimaguas, approximately 70% of the population lives below the poverty line, and 41% in extreme poverty (INEI 2005). In Moyobamba the amount of the population living below the poverty line is 61% and in extreme poverty 25% (INEI 2005). Yurimaguas is situated by the river Huallaga, and is a port for the river boats mainly carrying goods and passengers along the Amazonas River. Moyobamba is situated 200 kilometres west of Yurimaguas.

Health services in the study communities
Yurimaguas has one MoH public hospital and one MoH Maternal Health Centre, managed by the community as a Local Committee for Health Administration (CLAS), each with a laboratory and a public pharmacy. There is also an EL SALUD hospital, and two MoH health posts. During the first survey in 2002, the Moyobamba hospital was run by the ES SALUD, and the health centre Llullacucha functioned as the MoH

key health institution. By 2005, the Moyobamba hospital was managed by the MoH. There were four MoH health posts in Moyobamba. In 2002, the health posts were staffed by nurses, midwives and health technicians in both Yurimaguas and Moyobamba. In 2005, medical doctors were attending patients at the health posts on a regular basis in both communities. There were 9 private pharmacies in Yurimaguas and 13 in Moyobamba. The pharmacies had a pharmacist on staff, but in practice, most contacts with the clients were managed by staff members without a formal education, yet trained by the pharmacist. Antibiotic prescription is in theory restricted to medical doctors and midwives, but at the health posts, nurses and health technicians prescribed antibiotics if necessary in both communities.

	Moyobamba	*Yurimaguas*
MoH Public Health Facilities		
Hospital	1 Public hospital since 2005	1 Public hospital
Health centre	1 Health centre	1 CLAS* Maternal Health Centre
Health post	4 Health posts	2 Health posts
Social Security (ES SALUD) Health Facilities		
Hospital	1 ES SALUD hospital during 2002 – 2004	1 ES SALUD hospital
Pharmacies		
Public pharmacy	Pharmacy in the hospital and the health centre, medicine cabinets in the health posts	Pharmacy in the hospital and the CLAS health centre, medicine cabinets in the health posts
Private pharmacy	13	9

Table 2. Health facilities in Yurimaguas and Moyobamba

4.3   DESIGN, SAMPLING AND DATA COLLECTION

4.3.1   Survey design and sampling

Survey Design
Cross-sectional household surveys were conducted in Yurimaguas, Loreto, and in Moyobamba, San Martin, by using household interviews and collecting faecal samples for microbiological analysis. In this thesis, data from three similar surveys is used, two surveys conducted in November 2002 (one in Yurimaguas and one in Moyobamba) and one conducted in November 2005, in Moyobamba. During the surveys, caregivers of children aged 6 to 72 months were interviewed using a structured questionnaire with a small subset of open ended questions. In addition, faecal samples were collected from the children included in the studies, and the antibiotic susceptibility of *E.coli* isolates was analysed by a rapid resistance screening method in the hospital laboratories at each study site.
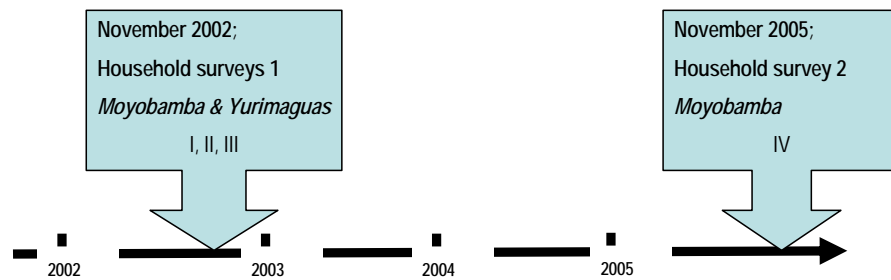
Figure 4. Time line for household survey and sub-study implementation

Sampling

In each survey, a total of 800 children aged 6 to 72 months were included using a modified cluster sampling approach, where 80 clusters were sampled. The sample size was calculated based on expected levels of antibiotic use among children in the communities. Each cluster consisted of 10 children (one per household) selected from the same block or substitute block. Each city was divided into a number of zones of varying sizes containing households distributed in blocks. A list of all blocks was created and a stratified sampling of blocks (within zones) was conducted with a probability proportional to size of the zone to give a total sample of 80 blocks. A detailed map was prepared showing all blocks with numbers. In each selected block the interviewers randomly chose a corner of the block and, following a random direction from the corner, visited households consecutively until they had recruited ten eligible children. The interviewers proceeded to the next house if there was no child aged 6 to 72 months. If no eligible child was found in the block, the interviewers proceeded to an adjacent block, mapped as a substitute. Any child that had three or more loose stools in the previous 24 hours (WHO definition of diarrhoea) was excluded from the study to ensure minimal distortion of the normal intestinal bacterial florae being assessed by the microbiological screening.

4.3.2 Data collection

Interviewers and interviewees

Ten members of staff from the public health sector (health technicians, nurses or midwives) were selected per community for one week of training as interviewers, and then tested through mock interviews. Five were chosen as interviewers and the others allocated as their partners with responsibility for collecting faecal samples from the study children. The faecal samples were brought by the interviewers to the hospital laboratory in each study community at the end of each working day and processed there daily.

Caregivers of the children (mother, father, grandparent or other adult caregiver) were interviewed during the household visit. Study investigators checked the questionnaires with the interviewers daily for missing responses and logical inconsistencies between

responses to different questions. In case of queries, the interviewers returned to the caregivers for clarifications.

Questionnaire
Caregivers of children aged 6 – 72 months where interviewed using a structured questionnaire with a small number of open ended questions, divided into four parts. The first part collected background information concerning the family members and the child included in the study such as age, gender and family composition. The second part collected information on symptoms for the most recent illness episode during the previous two week period and any action taken by the caregivers in relation to the symptoms. All actions taken and their chronological order were recorded, including self-care with or without drugs, traditional medicine and consultations with health providers. Information regarding medication given in the previous two weeks was collected and the theme of antibiotics was given extra attention, including information regarding who prescribed the drug, cost and place of purchase and duration of use. The third part of the questionnaire collected information regarding antibiotic use in the rest of the family, as well as information about household characteristics and assets. The fourth part collected information on use of antibiotics in household animals but the result is not included in this thesis.

The questionnaire was pre-tested and validated during a pilot study where 50 households were included. The pilot study also served to fine-tune the training of the interviewers. Based on the results of the pilot study, the questions as well as the response alternatives were adjusted. The pilot study was performed with a participatory approach, using the experience and expertise of the interviewers.

4.3.3 Microbiological analysis

The susceptibility of normal faecal flora, in particular *E. coli* was analysed by means of a simple rapid resistance screening method. This method screens directly for resistance in a one-step procedure, in contrast to conventional resistance screening methods that isolate single colonies of the bacteria of interest and subsequently test for antibiotic resistance. The rapid resistance screening method was originally devised to describe the prevalence of carriers of any resistant *E. coli,* regardless of frequency of the resistance in each carrier (Datta 1969; Lester, del Pilar Pla et al. 1990). A drawback of using this method is the scarcity of studies using the same method, making comparisons difficult. In the methodological validation it was found possible also to assess the dominant *E. coli* flora in the carriers, which would be correlated more closely to the regular measures of antibiotic resistance. This made it possible to approximately compare with studies where a randomly selected *E. coli* from each sample is tested (Bartoloni, Cutts et al. 1998; Kronvall, Larsson et al. 2005; Bartoloni, Benedetti et al. 2006).

The collection of faecal samples and the microbiological analysis of the antibiotic susceptibility of *E. coli* were carried out in the framework of the ANTRES project. The investigations were carried out by other research colleagues and the methods and

results have been published previously (Bartoloni, Pallecchi et al. 2006). The outcomes from the published study have been used in the analysis' that have been presented in this thesis.

In brief, the screening was carried out as follows: A rectal swab was obtained from each child included in the study at the time of the household interview. The rectal swabs, stored in transport medium, were transferred in a cold box to the hospital laboratory within 3 hours of collection. The susceptibility screening was carried out in the two hospital labs of Yurimaguas and Moyobamba. Both laboratories participated in national quality control programs, and the same three Italian investigators participated in the work to ensure continuity of methods for both laboratories.

Each faecal swab collected during the household interviews was used to inoculate a plate of selective medium, MacConkey agar, which gives typical colony morphology for *E.coli*. Antibiotic-containing discs were then applied onto the medium surface. The antibiotics tested for each sample were: co-trimoxazole, ampicillin, tetracycline, streptomycin, chloramphenicol, nalidixic acid, kanamycin, ciprofloxacin, gentamicin, nitrofurantoin, amikacin and ceftriaxone. Results from MacConkey agar plates were recorded after 18 hours of incubation at 37°C. The zone diameters around the discs were measured and the following results were recorded as antibiotic resistance: 1) no inhibition zone can be observed; 2) presence of a growth inhibition zone smaller than the defined breakpoint in the dense growth; and 3) single or semi-confluent colonies or dense growth inside inhibition-zones of the majority of the growth, the presumed dominant flora.

Ordinary breakpoints for resistance could not be used for the rapid screening since the method is not standardized and uses other media and inoculates. The breakpoints used in the study were defined after observing the population distribution of inhibitory zone diameters around the antibiotic-containing discs in all the samples collected during a pilot study. The method for establishing new breakpoints was also validated during a pilot study for method development (Kronvall, Larsson et al. 2005; Bartoloni, Benedetti et al. 2006).

4.3.4 Classification of main variables

Classification of socioeconomic status
Income, occupation and education have traditionally been used to estimate social position, either together in composite measures or used interchangeably (Adler and Ostrove 1999). In many LMIC, the access to information traditionally used is to establish whether SES, such as income, is limited. Instead, wealth has been used as a proxy to estimate financial status. In this study, we also used the estimated wealth, measured through an assessment of the household assets in the households of the interviewees. During the interviews, information was collected regarding the following household assets and characteristics: number of rooms, family size, access to electricity, type of floor, type of toilet, type of water source and ownership of fan, TV,

motor-bike and refrigerator. A wealth index was then constructed using the first principal component from a principal component analysis (PCA) to generate scoring "weights" for each of the assets and household characteristics. A wealth value was then assigned to each household. The consistency of the PCA assigned wealth values with ownership of assets was checked by cross-tabulations.

For the purpose of analyzing associations between wealth and other variables, the households were assigned into groups as related to wealth. The population was divided in quartiles based on the value of the wealth variable in order to capture relative variances, as no absolute cut-off point could be assumed.

Illness classification

The children's symptoms (as reported by the caregivers) were classified according to the principles of the IMCI algorithm for health workers classification (WHO/UNICEF 2003) and treatment of infectious diseases in children in low malaria-prevalence areas. Note that these are self-reported symptoms; for example the symptom 'rapid breathing' was not identified by a health worker counting the breaths per minute, but instead is simply what was reported by the caregiver. The adapted algorithm is based on the absence or presence of the following key symptoms: fast breathing, cough, diarrhoea, and/or blood in stool. The children were classified with one of the following illnesses: diarrhoea, dysentery, cough/cold, pneumonia, cough/cold + diarrhoea, pneumonia and/or dysentery (see Table 3). Due to the low prevalence of malaria in the urban communities of Yurimaguas and Moyobamba, fever was not included among the key symptoms and malaria was not classified separately. Based on the principles of IMCI, symptoms were then classified into two categories: illnesses where treatment with antibiotics would be recommended (pneumonia, dysentery, pneumonia and / or dysentery) and illnesses where antibiotic use would not be recommended (cough / cold, diarrhoea, cough / cold + diarrhoea).

Symptom classification	Key symptoms qualifying child for symptom classification
Cough/cold	Fever, cough and other symptoms of cold. Absence of: diarrhoea, blood in stool, 'fast breathing'.
Diarrhoea	Diarrhoea. Absence of: blood in stool, cough and other symptoms of cold, 'fast breathing'
Dysentery	Blood in stool, diarrhoea. Absence of: cough and other symptoms of cold, 'fast breathing'.
Pneumonia	'Fast breathing', cough. Absence of: diarrhoea, blood in stool.
Cough/cold + diarrhoea	Symptoms of cough/cold and symptoms of diarrhoea
Pneumonia and/or dysentery	One of following three combinations: symptoms of pneumonia and diarrhoea, **or** symptoms of pneumonia and dysentery, **or** cough/cold and dysentery

Table 3. Illness classifications based on principles from IMCI guidelines.

Measurement of health-seeking behaviour

The interviewers explicitly asked for what the caregivers did when the child fell ill, instead of asking whether they had consulted a health provider. In the questionnaire, the actions taken were classified as "nothing", "self-care" or "consulting someone who works with health". The "someone who works with health" was then classified further in subsequent questions as private or public medical doctors, health technician, nurse/midwife, public or private pharmacy staff and traditional healers. In the study, self-care was defined as all actions taken in the household without asking for advice or consulting a person that works with health. Consequently, asking for advice/consultation with persons working with health, including pharmacy staff and traditional healers, was considered as "consultations". The training of the interviewers included special emphasis on the distinction between self-care and consultations. It was underlined that there is a difference between visiting the pharmacy staff with the intention to buy medications and visiting the pharmacy with the intention to consult the staff for advice on how to treat a sick child.

Measurement of antibiotic utilisation

In the interviews, the caregivers were asked about all the medicines used for the most recent illness episode in the previous two weeks, including traditional medicines. If no medication had been used to treat symptoms or if the child had not been ill, the interviewers asked for any other antibiotic use in the previous two weeks for the child. The caregivers were asked for the name of the medicines used. The interviewers also asked for the package and checked if the medicines were expired. If the caregivers could not remember the name but could describe the package or the tablet, they were shown samples of antibiotics that the interviewers carried and asked if the medication taken was among the samples. The interviewers carried lists with antibiotic brand names translated to the generic names that were stated in the questionnaire. The caregivers were asked for details regarding the antibiotic use: who prescribed the antibiotic, duration of intake, place of purchase and cost incurred. All of these features are examined in the analysis except the duration of the intake.

Measurement of resistance

The measure of resistance shows the child's carriage of any resistance present in the normal faecal *E. coli*-like flora of the child, regardless of frequency. The procedures and definitions for recording of the results were established in the protocols for the microbiological analysis of the antibiotic susceptibility of *E. coli* carried out in the framework of the ANTRES project. The zone diameters around the discs were measured and the following results were recorded as antibiotic resistance: 1) no inhibition zone can be observed; 2) presence of a growth inhibition zone smaller than the defined breakpoint in the dense growth; and 3) single or semi-confluent colonies or dense growth inside inhibition-zones of the majority of the growth, the presumed dominant flora. The breakpoints used in the study were defined after observing the population distribution of inhibitory zone diameters around the antibiotic-containing discs in all the samples collected during a pilot study. In this thesis, the recorded results

are classified into two variables; "total resistance" and "dominant resistance". The variable "total resistance" includes all results mentioned above (1 – 3) and corresponds to children carrying bacteria with any kind of resistance to the antibiotic in question, including low frequent clones. The variable "dominant resistance" includes the results for 1 and 2 above and is an approximation to children carrying bacteria where the dominant flora is resistant to the antibiotic in question.

4.3.5 Research management

This thesis includes the household surveys conducted in Peru: the surveys 2002 in Yurimaguas and Moyobamba and the survey conducted 2005 in Moyobamba. I was responsible for the survey implementation in the two study sites. During the survey, substantial efforts were made to quality assure the data collected. The questionnaires were validated in cooperation with the interviewers through group discussions and a pilot study. A manual that would guide the interviewers was also elaborated. A system was then developed to train, monitor and evaluate the interviewers in order to obtain data with as high quality as possible. The training was carried out over one week and included lectures, group discussions, role play and mock interviews. The evaluation of the interviewers was carried out in several stages, with the help from supervisors, research assistants and researchers.

For the survey implementation phase, a quality control system was elaborated. In the morning the team met and received instructions for the days work and maps with the blocks that represented the sample for the day. At the end of each work day the interviewers returned to the hospitals and followed an established flow-chart for delivering the faecal samples at the laboratory, get each laboratory sample coded together with the corresponding questionnaire from the household interview and then get the questionnaire reviewed by the supervisors. Daily individual reviews of all the questionnaires were made when the interviewers had completed the interviews for the day. Each interview was discussed; the interviewer briefly reviewed the data collected during each interview with the supervisor. During the data collection phase peer group meetings were conducted every day with the interviewers to discuss any potential problems or queries from the interviewers' sides.

Re-interviews of 5 % of the interviews were carried out by the supervisors. A subset of the data was pre-analysed during the first weeks in order to assess if there were any systematic patterns in the data gathered by each interviewer, i.e. if some interviewers only had certain answers (such as, for example, self-care with antibiotics) among the responses in the interviews. The data were entered in the data base by trained clerks. This work was done during the survey implementation and functioned as an extra quality check as the clerks also could detect inconsistencies that could be corrected by the interviewers.

4.3.6 Statistical analysis

The relationships between variables were explored using univariate analysis. ***Chi-square tests*** were used to compare proportions of categorical variables between groups, except for small groups which were compared using Fisher's exact test. For example, a Chi-square test was used to compare the proportion of antibiotics obtained from different sources by the patients in different wealth strata (I). Relative Risks (RR) were used to compare the rate of antibiotic use for different health-seeking strategies (self-care, consultation with medical doctor or nurse or pharmacy staff), using medical doctors as reference group (II).

Logistic regression was used for the more in-depth analysis. The relationship between level of wealth and different outcomes such as *health-seeking* and *antibiotic use* was explored by ***univariable logistic regression*** (I). Similarly the association between antibiotic resistance and variables, such as wealth and educational level was investigated by univariable logistic regressions (IV). Associations were reported as odds ratio (OR) and corresponding confidence intervals (CI).

Multivariable logistic regression was used to adjust for potential confounding factors: the association between antibiotic resistance and wealth was adjusted for antibiotic use.

5 MAIN RESULTS

5.1 BACKGROUND DATA AND MORBIDITY

For each of the three surveys the sample size was 800 children. For one survey, the Yurimaguas survey, the actual number of children included in the survey was 798 instead of 800. Sub-samples of children have been considered across all studies, depending on the research questions motivating the study design. A number of children were excluded in the analysis examining SES due to missing data on some variables used to establish the wealth index. Figure 5 below shows the number of children included in the analysis for sub-studies I, II and III. For sub-study IV 699 children were considered for the antibiotic resistance correlations with SES for Yurimaguas and 728 children were considered for the same analysis for Moyobamba.

Figure 5. Number of children included in the analysis for sub-studies I-III
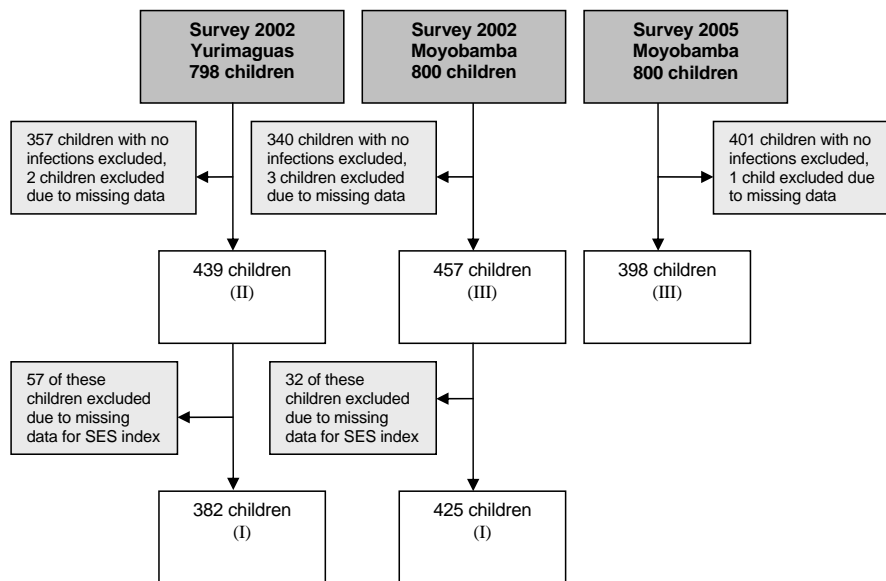
5.2 USE OF HEALTH CARE AND ANTIBIOTICS

5.2.1 Health-seeking behaviour

Household surveys conducted in 2002 and 2005 investigated health-seeking behaviour for self-reported symptoms. Many caregivers consulted health providers for their children's illnesses in Yurimaguas (48%) and Moyobamba (35%) in 2002 (I). Most consulted health professionals (Yurimaguas 42%; Moyobamba 30%) and among those

medical doctors were most commonly consulted. Few caregivers consulted pharmacy staff and even fewer consulted traditional healers.

Even though health provider consultations were common, some caregivers did not consult even for severe illnesses (I). The poorest caregivers in Yurimaguas and Moyobamba consulted health professionals less frequently (33%) for severe illnesses such as pneumonia than the least poor did (71%) (Table 4). The poorest consulted significantly (p<0.05) less frequently (21%) for non-severe illnesses like cough/cold than least poor (51%).

	Children seeking care from health professionals						
Illness	Q1 % seeking care (total no children with illness)	Q2 % seeking care (total no children with illness)	OR	Q3 % seeking care (total no children with illness)	OR	Q4 % seeking care (total no children with illness)	OR
Cough/cold	21% (99)	28% (116)	1.62	28% (128)	1.88*	51% (104)	4.30*
Pneumonia	33% (12)	82% (11)	5.25	50% (16)	1.94	71% (14)	2.92
Cough/cold + diarrhoea	35% (62)	46% (46)	1.70	41% (37)	1.62	50% (30)	3.74*
Pneumonia and/or dysentery	50% (18)	54% (13)	1.17	67% (9)	2	70% (10)	2.33
Diarrhoea	17% (18)	27% (22)	1.05	40% (10)	1.87	20% (15)	0.93
Total	31% (209)	47% (208)		45% (200)		52% (173)	

Table 4. Health-seeking strategy in relation to self-reported symptoms (classified in illnesses based on principals from IMCI) and wealth quarters as defined by principal component analysis (PCA). Quartile 1 (Q1) represents the poorest quartile of the study sample (relatively poorest), quartile 2 (Q2) the second poorest, quartile 3 (Q3) the second least poor quartile and quarter 4 (Q4) the least poor quartile. Amount of children seeking care from health professionals, not including pharmacy staff, showed in percentage, total number of children showed in parenthesis. OR= Odds ratio showing each wealth quarter as compared to quarter 1.
* = p<0.05

Changes in health-seeking behaviour were assessed through comparisons between the surveys conducted in 2002 and 2005 in Moyobamba (III). The percentage of caregivers having consulted health providers increased between 2002 (35%) and 2005 (44%), but the percentage of those that consulted health professionals (medical doctors, nurses or health technicians) decreased from 91% in 2002 to 74% in 2005 (p<0.001) (Table 5). Instead, the percentage of caregivers that consulted pharmacy staff increased significantly to 24% in 2005 compared to 7% in 2002 (p<0.001).

Caregivers sought help less promptly in 2005, as compared to 2002, when the majority (76%) of the caregivers who consulted health professionals did so directly, without applying self-care (Table 5) (III). In 2005 exclusive consulting decreased significantly (p<0.001) only 40% consulted providers without also applying self-care. This pattern of health-seeking behaviour was similar regardless of the socioeconomic status of household.

Health-seeking strategy in relation to health care provider						
	Moyobamba 2002			Moyobamba 2005		
Health care provider	*Exclusively consultation (percent of row)*	*Consultation and self-care (percent of row)*	*Total consultation (percent of column)*	*Exclusively consultation (percent of row)*	*Consultation and self-care (percent of row)*	*Total consultation (percent of column)*
Health sector	111 (79%)	29 (21%)	**140 (91%)**	48 (37%)	81 (63%)	**129 (74%)**
Pharmacy Staff	4 (36%)	6 (64%)	**10 (7%)**	19 (43%)	22 (57%)	**41 (24%)**
Other	2 (67%)	1 (33%)	**3 (2%)**	2 (67%)	1 (33%)	**3 (2%)**
Total	117 (76%)	36 (24%)	**153**	69 (40%)	104 (60%)	**173**

Table 5. Health-seeking strategy in relation to health care provider for caregivers who either exclusively consulted providers or consulted providers in combination with self-care for 2002 and 2005, expressed as numbers and percentage of total numbers of caregivers who consulted health providers (either exclusively or in combination with self-care).

5.2.2 Use of antibiotics

Antibiotic provision
The surveys conducted in 2002 showed that a similar level of antibiotic use during the previous two weeks was reported for children in Yurimaguas (42%) and Moyobamba (36%) (I). The same surveys showed that the most commonly prescribed antibiotic by health providers was ampicillin/amoxicillin (49%), followed by cotrimoxazole (trimethoprim-sulfamethoxazole) (21%). The caregivers that self-medicated their children most commonly used tetracyclin (31%), followed by ampicillin/amoxicillin (24%).

The majority of the antibiotics used by the children in 2002 were prescribed by health professionals. In Yurimaguas, 73% of antibiotics used for infectious illnesses were prescribed by health professionals, mostly medical doctors (56%) (Table 6) (II). Only 19% of the antibiotics used were administered as self-care and only 8% of the antibiotics were provided as a result of consultations with pharmacy staff. In Moyobamba, the majority of antibiotics were prescribed by medical doctors, but the

amount of antibiotics recommended by pharmacy staff had increased in 2005 (18%) as compared to 2002 (6%). Self-care with antibiotics, on the other hand, decreased (III).

Source of antibiotics	Yurimaguas 2002	Moyobamba 2002	Moyobamba 2005
Medical doctor	56%	50%	56%
Nurse/health technician	17%	6%	8%
Pharmacy staff	8%	6%	18%
Self-care	19%	32%	14%
Other	-	6%	4%
Total	100%	100%	100%

Table 6. Source of antibiotics for all the antibiotics used for self-stated infectious illnesses, percentage of total amount of self-stated antibiotic used per community and year.

Rationality for antibiotic use
The rationality for antibiotic use was assessed by classifying the self-reported symptoms as 'illnesses where antibiotic use would be recommended' (pneumonia and/or dysentery) and 'illnesses where antibiotics would not be recommended' (cough/cold, diarrhoea and cough/cold + diarrhoea) based on the IMCI treatment algorithm.

A detailed analysis of antibiotic use for 400 children from the 2002 survey in Yurimaguas showed that there was no significant difference between how medical doctors and nurses prescribed antibiotics for illnesses where antibiotic use would be recommended (medical doctors 69%, nurses 73%) and where it would not be recommended (medical doctors 58%, nurses 50%) (Table 7) (II). Pharmacists provided fewer antibiotics for illnesses not needing antibiotics (30%) and more for illnesses needing antibiotics (86%). Caregivers who cared for their children in the home without consulting anyone only used antibiotics for 14% of the children with illnesses not needing antibiotics. However, they also used antibiotics for only 16% of the children with illnesses needing antibiotics.

Antibiotic provision			
Prescriber	Illnesses where antibiotics is Not recommended	Illnesses where antibiotics is recommended	P-value
Medical doctor	58%	69%	0.24
Nurse	50%	73%	0.17
Pharmacy staff	30%	86%	0.016
Self care	14%	16%	0.76

Table 7. Prescription of antibiotics in relation to prescriber, for illnesses where antibiotics are recommended or not recommended according to IMCI, in Yurimaguas 2002.

There is a problem of equity concerning antibiotic use (I). The 2002 surveys showed that the poorest caregivers in Yurimaguas and Moyobamba used significantly less

antibiotics than the least poor for severe illnesses such as pneumonia and/or dysentery (16% and 80%, respectively). The poorest used less antibiotics also for non-severe illnesses as cough/cold (16% and 36%, respectively), where antibiotics should not be used.

The rationality of antibiotic use was compared between the 2002 and 2005 surveys in Moyobamba (III). More children were treated with antibiotics for illnesses where it is not recommended in 2005, as compared to 2002, for cough/cold (32% in 2005; 25% in 2002) and diarrhoea (38% in 2005; 18% in 2002). Both health professionals and pharmacy staff over-prescribed antibiotics more frequently in 2005.

5.2.3 Cost incurred for public health services and for antibiotics

All children in the two study sites qualified for health care and antibiotics from the public health care system free of charge within the SIS system. The analysis of cost incurred for health care showed that caregivers paid out-of-pocket for public sector health care both in Yurimaguas and Moyobamba (Table 8) (I).There was no significant difference between wealth strata in Moyobamba, but in Yurimaguas the poorest paid significantly less often (14%) than the least poor (33%).

The survey 2005 in Moyobamba showed that the amount of caregivers paying for public sector health care remained similar 2005 (22%) as compared to 2002 (19%) (III).

Cost incurred for public sector health care			
	Cost incurred	**No cost incurred**	**Total**
Yurimaguas (2002)	32 (19%)	134 (81%)	166
Moyobamba(2002)	30 (19%)	128 (81%)	158
Moyobamba(2005)	38 (22%)	137 (78%)	175

Table 8. Cost incurred for health care provided by public sector health professionals in Yurimaguas and Moyobamba.

The antibiotics prescribed for children by the public health sector should be provided free of charge within the SIS framework. Results from the 2002 surveys showed that 79% of children in Yurimaguas and 81% of children in Moyobamba actually had received the prescribed antibiotics free of charge (I). There were differences in relation to the socioeconomic status levels. In Yurimaguas the poorest received antibiotic free of charge significantly more frequent (91%) than the least poor (54%). In Moyobamba there was no significant difference between poorest and least poor strata (86% and 72%, respectively) (I). The amount of children having received the antibiotics prescribed by the public professionals free of charge had decreased significantly in Moyobamba in 2005 (55%) as compared to 2002 (82%) (III).

Not all children received their antibiotics through prescriptions from the public health sector. Out of all antibiotics used for children with infectious illnesses, only 48% in

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Moyobamba and 58% in Yurimaguas was provided by the SIS system (I). The remaining was bought from private or public pharmacies or the market place. There were differences in relation to socioeconomic status. In Yurimaguas, the poorest had received overall more free antibiotics from SIS (65%) than the least poor (40%). In Moyobamba, on the other hand, the poorest received antibiotics from SIS overall less frequently (46%) than the least poor (58%).

The place of antibiotic provision changed between 2002 and 2005 in Moyobamba (Table 9) (III). Significantly fewer children (p=0.002) received antibiotics free of charge through the SIS system in 2005 (31%) than in 2002 (48%). The poorest shifted place of purchase to public and private pharmacies and the least poor shifted to private pharmacies.

Place of antibiotic purchase Moyobamba			
Place of purchase		2002	2005
Group1: (cost charged)	Public pharmacy	30(20%)	41(29%)
	Private pharmacy	38(25%)	50(36%)
	Other	11(7%)	5(4%)
Group 2: (free of charge)	Health insurance	74(48%)	43(31%)
Total		153	139

Table 9. Place of antibiotic purchase for 2002 and 2005 in Moyobamba
for all children that were treated with antibiotics, divided into two groups; group 1: public pharmacy, private pharmacy and other, where a cost is charged for antibiotics, and group 2: health insurance, where no cost is charged.

5.3   ANTIBIOTIC RESISTANCE

5.3.1   Antibiotic resistance

The surveys conducted in 2002 showed that there were a high number of children carrying antibiotic resistant clones of *E. coli* in both communities, as has been reported in a previous publication which is not included in this thesis but is part of the larger ANTRES project (see preamble) (Bartoloni, Pallecchi et al. 2006). In the latter publication the measure "total resistance", including less frequent clones, showed highest resistance for co-trimoxazole, ampicillin and tetracycline, and ranged between 89 and 93 percent (Table 10). The measure of antibiotic resistance that was an approximation of the "dominant normal flora" showed lower resistance, but with similar frequency patterns as "total resistance".

	Resistance to E.coli	
Drug	**Yurimaguas**	**Moyobamba**
Ampicillin	92 (76)	93 (83)
SXT*	89 (72)	93 (83)
Tetracycline	89 (71)	93 (81)
Streptomycin	71 (50)	86 (66)
Chloramphenicol	69 (42)	72 (48)
Nalidixic Acid	27 (8)	41 (18)
Kanamycin	22 (8)	23 (9)
Gentamycin	19 (9)	21 (10)
Ciprofloxacin	16 (5)	25 (9)
Amikacin	1 (0.4)	0.4 (0.3)
Ceftriaxone	0.3 (0)	0.1 (0.1)

Table 10. Extract of a table published by Bartoloni et al. (Bartoloni, Pallecchi et al. 2006), showing antibiotic prevalence, expressed as percentage, of healthy children carrying antibiotic drug-resistant *Escherichia coli* (*E. Coli*) as part of their commensal flora. In parentheses: proportion of carriers in whom resistant *E. coli* constituted the predominant florae. The total number of children from whom samples were obtained: Yurimaguas= 797; Moyobamba=793.
*SXT= Trimethoprim-sulfamethoxazole

5.3.2 Antibiotic resistance and influencing factors

Association between resistance and antibiotic use
The children who had either used antibiotics during the previous 6 months (including the previous two weeks) and/or had family members that had used antibiotics during the previous two weeks had significantly higher odds ratios for carriage of resistance when compared to children where no antibiotic use was reported for the child or other family members over the same time period (Yurimaguas: streptomycin, chloramphenicol, nalidixic acid, kanamycin, ciprofloxacin, gentamicin. Moyobamba: streptomycin and gentamycin) (IV). The odds ratio of antibiotic resistance was also significantly higher for children who had used antibiotics the previous two weeks when compared to non-users (Yurimaguas: chloramphenicol, nalidixic acid, kanamycin, ciprofloxacin, gentamicin; Moyobamba: nalidixic acid, gentamicin).

Association between resistance and socioeconomic status
Univariable logistic regressions show significantly higher resistance odds for least poor categories when compared to the poorest categories (Yurimaguas: nalidixic acid, OR=2.13; ciprofloxacin, OR 2.09; chloramphenicol, OR=1.98. Moyobamba: nalidixic acid OR=1.64 and 1.59; ciprofloxacin, OR 1.77 and 1.69) (table 11) (IV). The same higher odds ratios for antibiotic resistance for the wealthiest categories was seen in a subgroup of children where no antibiotic use was reported for the child during the previous 6 months and no use was reported for the other family members during the previous two weeks. No significant difference in carriage of resistance was seen for educational status.

		Type of total antibiotic resistance					
Yurimaguas		**Chloramphenicol**		**Nalidixic acid**		**Ciprofloxacin**	
SES variable		OR	CI	OR	CI	OR	CI
Wealth	Wealth level 2	1.32	0.849 – 2.048	1.20	0.730 - 1.974	1.22	0.677 – 2.207
compared to "Least	Wealth level 3	1.38	0.885 – 2.149	1.26	0.785 -2.108	1.18	0.650 – 2.137
wealthy"	Wealthiest	**1.98**	**1.243 - 3.141**	**2.13**	**1.326 - 3.415**	**2.09**	**1.206 – 3.631**
Antibiotic use							
Atb-use child and family *(compared to no atb-use, by child or other family members)*	Atb used by the child last 2 weeks and/or last 6 months and/or by other family members	**1.39**	**1.006 – 1.913**	**1.72**	**1.194 - 2.480**	**1.86**	**1.180 – 2.928**
Moyobamba							
SES variable							
Wealth	Wealth level 2	1.18	0.746 – 1.878	**1.64**	**1.076 - 2.518**	**1.77**	**1.075 – 2.921**
compared to	Wealth level 3	0.88	0.560 – 1.370	1.40	0.914- 2.155	**1.69**	**1.022 – 2.794**
"Least wealthy"	Wealthiest	1.00	0.635 – 1.586	**1.59**	**1.036 -2.448**	1.48	0.886 – 2.478
Antibiotic use							
Atb-use child and family *(compared to no atb-use, by child or other family members)*	Atb used by the child last 2 weeks and/or last 6 months and/or by other family members	1.30	0.943 - 1.804	1.22	0.903 - 1.656	1.13	0.796 - 1.593

Table 11. Logistic regressions investigating association of "total resistance" with wealth and antibiotic use (Atb-use) in Moyobamba and Yurimaguas for selected antibiotics. Results showed as odds ratio (OR) and corresponding confidence intervals (CI), with statistically significant values marked in bold.

The significant differences between categories for the wealth variable in Yurimaguas remained when controlling for antibiotic use. In Moyobamba, on the other hand, there were no significant differences in resistance when controlling for antibiotic use.

The results of the analysis of the dominant flora also showed increased odds ratios for resistance for the wealthier categories when compared to the least wealthy households. The differences between categories for the wealth variable remained when controlling for antibiotic use.

Association between resistance and material factors related to poverty
The relationship between antibiotic resistance and a number of material factors chosen to reflect the material consequences of SES were also tested (IV). The variables were type of water source (public net, private well, public well, river, other), type of toilet (water closet, latrine, open field, other) and crowding (measured as number of people sleeping in the same room). No statistically significant differences were found in antibiotic resistance between children from households with different material factors.

6 DISCUSSION

This thesis identifies that many caregivers sought health care from public health professionals, and that most of the antibiotics used were also prescribed by the public sector. Some caregivers of children with severe illnesses did not consult health professionals, and poor children utilised health services and antibiotics to a lesser extent even though universal access was granted by the state health insurance, SIS. Children were not always provided with antibiotics in accordance to their needs: some children received too much antibiotic treatment, others not enough. More caregivers consulted pharmacy staff instead of public sector health professionals for their sick children in 2005, as compared to 2002, and fewer caregivers opted for only health provider consultations and instead combined consultations with self care in 2005. There was high carriage of antibiotic resistance among the commensal florae, especially in wealthier children.

6.1 UTILISATION OF PUBLIC HEALTH CARE SERVICES

High utilisation of public services by the study population was observed (I, II and III). In 2002 a high percentage of caregivers sought help from health professionals (Yurimaguas 42%; Moyobamba 30%). This result differs from what has been observed in other LMIC, including within Latin America, where caregivers often seek care from private health professionals and bypass health services by consulting pharmacy staff or traditional healers or they care for their children at home (Bentley, Elder et al. 1995; Develay, Sauerborn et al. 1996; Goldman and Heuveline 2000; Larsson, Kronvall et al. 2000). Most of the antibiotics used during the study period were prescribed by public health professionals, and high public facility utilisation was most likely linked to increased financial access. Affordability of public sector health care was granted by the SIS, which at least in theory provided free health care and essential drugs to all children registered for the insurance. Penchansky has pointed out that affordability is an important factor for health care utilisation (Penchansky and Thomas 1981). Affordability provided by different health financing strategies has been associated with different utilisation patterns. The on-going debate about user-fees has reached some consensus that these are an important barrier to accessing health services, especially for the poor (James, Hanson et al. 2006). In a review conducted by Lagarde and Palmer (Lagarde and Palmer 2008), results suggest that removal of user fees increases health services utilisation, especially during the initial period following fee removal. However, several questions, such as sustainability of the positive effects of fee removal, remain unanswered.

6.2 INEQUITY IN HEALTH CARE UTILISATION

Even if the overall utilisation of public health services in the study population was high, some caregivers did not seek help even for severely sick children (I and II).

Importantly, the results also showed that the poorest children used less health care from public health facilities (I), despite that all the children in the study areas qualified for the SIS insurance. Inequity has been shown before in Latin America (Makinen, Waters et al. 2000; Valdivia 2002) but the theoretical high affordability of health care provided by the SIS makes this study different. Interventions granting universal access tend to reach the poorest more slowly or not at all (Bryce, el Arifeen et al. 2003). The explanations for these shortcomings are complex. Knowledge about new interventions or policies might not reach the poor as easily. In Peru, the SIS had only been recently introduced when the first survey was conducted. Two prior existing insurances, the maternal and infant insurance and the school insurance, were merged 2001 to form one system. The earlier insurances were granted after complex evaluations of the family's economic status, a process that was often perceived as unfair by the community members. It is possible that some caregivers thus hesitated to seek care due to a lack of knowledge about the SIS system.

Factors influencing access have been suggested by several researchers as lack of human recourses, inappropriate health care financing, weak drug supply systems, inappropriate access to and use of health information and sub-standard governance, and political instability (Travis, Bennett et al. 2004; Rowe, de Savigny et al. 2005). However, Gilson has also pointed out that too little emphasis has thus far been placed on the dimensions of demand, as linked to health care access (i.e. the households or individuals), as opposed to supply (Gilson and McIntyre 2005). The original Penchansky model (Penchansky and Thomas 1981) of access also underlines the importance of care being acceptable to patients and the importance of accommodation of health services to the needs of the population in order to provide proper access. During the time of data collection for this thesis, the local health professionals complained that the poorest households were "over-seeking" health care for unnecessary symptoms and thereby wasting resources. This attitude of the professionals could have contributed to preventing truly vulnerable groups of patients from utilizing the health services. Attitudes of health professionals have been shown to be an important factor determining health facility utilisation (Walker and Gilson 2004; Gilson, Palmer et al. 2005; Himmel, Simmenroth-Nayda et al. 2005; Russell 2005); and trust, in the health professionals as well as the system, has been identified as an important component of patient acceptance of health services (Gilson, Palmer et al. 2005).

6.3   CHANGES IN HEALTH-SEEKING BETWEEN 2002 AND 2005

The results of study III indicate that health-seeking behaviour changed between 2002 and 2005. In 2005, more children sought help from pharmacy staff (24% of all children consulting as compared to 7% in 2002). Fewer caregivers exclusively consulted health providers for their sick children, and instead more combined the consultations with self-care. In addition, fewer antibiotics were provided through the SIS, and instead caregivers purchased antibiotics at private and public pharmacies.

In theory, the SIS remained the same in 2005 as in 2002. There were no reformulations of SIS policy affecting formal insurance coverage within the study areas. No other major reforms presumably took place in the study areas. The results identified a gap between policy and practice (III). Some caregivers had paid for public health care, and the number of caregivers paying for antibiotics prescribed from the public health professional had increased in 2005 (45% 2005 as compared to 18% 2002). Interviews with SIS administrators revealed that the implementation of SIS had faced problems not only within the two study sites, but also on a national level (unpublished findings). Problems with provider reimbursements had lead to many public health facilities charging the patients, which was against the regulations of the SIS.

Much of the available literature on policy implementation focuses on the gap between policy objectives and actual implementation (Walt, Shiffman et al. 2008). Walt and Gilson have argued that the traditional focus on policy content neglects other dimensions such as context, process, and actors, which can further explain the difference between effective and ineffective policy implementation (Walt and Gilson 1994). The attitudes of health professionals in the study area might have influenced the observed change in health-seeking behaviour. Kamuzora and Gilson suggest how implementation practice has a major impact on the success of a policy aimed at providing access to health care (Kamuzora and Gilson 2007): implementers of policy act as "street-level bureaucrats" and influence how policies are experienced by the beneficiaries. The actions of administrators and health service managers therefore play a key role in implementation and the success of a policy. This was however not a focus of this thesis.

Weakness within the health system contributes to a risk that interventions aiming to grant universal access lose their momentum before reaching the poorest beneficiaries (Victora, Wagstaff et al. 2003). Policies intending to ensure equitable access to health services have faced implementation problems worldwide. Poor infrastructure and/or poor preparedness of the health system complicate implementation strategies designed to ensure access (Bryce, el Arifeen et al. 2003; Peters, Garg et al. 2008). Within the Latin American context, policy implementation has generally been problematic. Health reforms of the 1980s and 1990s, which also included the creation of mandatory health insurances, proved difficult to implement in many countries due to the failure of health care administrations to provide necessary control measures and to correctly reimburse health facilities (Crocco, Schroeder et al. 2000; Homedes and Ugalde 2005).

6.4   ANTIBIOTIC USE

The majority of antibiotics stated to be used in this study were prescribed by health professionals (I and II). However, use was not always adequate. Health professionals over-prescribed for illnesses where antibiotics were not recommended, according to the IMCI, for conditions such as cough/cold (II). More seriously, children consulting health professionals and children who were managed by self-care did not receive antibiotics for illnesses where they should have been provided.

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Little self-care with antibiotics was found (19% in Yurimaguas in 2002; 32% in Moyobamba in 2002 and 14% in Moyobamba in 2005) (II and III). Similarly, few caregivers who had consulted pharmacy staff received antibiotics, even though the numbers increased in 2005 as compared to 2002. In this thesis, I distinguish between caregivers visiting pharmacies to buy drugs on their own initiative and caregivers who visit pharmacies in order to consult the pharmacy staff on how to treat their sick children. The aim was to investigate in more detail the role of the pharmacy staff in antibiotic use. Pharmacy staff are in many settings regarded as health providers, being consulted for serious health problems. Many studies from LMIC (Tomson and Sterky 1986; Wolff 1993; Bi, Tong et al. 2000; Larsson, Kronvall et al. 2000; Okumura, Wakai et al. 2002), including studies from Peru (Llanos-Zavalaga, Mayca Perez et al. 2002), show how it is common to bypass the formal health services to acquire antibiotics. However, this was not the case in the sub-studies in this thesis (II, III), where few caregivers used antibiotics as part of self-care for their children and few had received antibiotics from consultations with pharmacy staff.

The rate of self-care with antibiotics in Yurimaguas was equally low for illnesses where antibiotics would (16%) or would not (14%) be recommended as treatment according to IMCI (II). The lack of overuse of antibiotics through self-care was, in part, a positive finding. However, the low use also resulted in an under-treatment for those children with serious illnesses where caregivers did not adequately seek proper care. This is yet another example of remaining barriers to access to health care. Antibiotics did not seem to play an important part of self-care for respiratory illnesses (cough/cold, pneumonia), in contrast to reports from other countries (Kunin, Johansen et al. 1990; Hui, Li et al. 1997; Chuc, Larsson et al. 2001). Instead, herbal medicines were widely used within the study communities. Cultural, psychological and social factors, including perception of illness severity, are also factors influencing health-seeking actions (Goldman and Heuveline 2000) as well as the decision to use antibiotics. Among the study population, antibiotic treatment sought in self-care for diarrhoea was likely due to prior experience gained by the caregivers during the cholera epidemics of the 1990s, when cholera was promoted as a serious condition by the Peruvian MoH and tetracycline was widely used as treatment.

Pharmacy staff prescribed antibiotics more adequately than health professionals in the 2002 survey in Yurimaguas (II), even though most of the pharmacy staff lacked formal education for the job they carried out. This is contrary to what has been reported in other studies, where pharmacy staff has been shown to readily prescribe antibiotics, including antibiotics that are not in line with guidelines (Ross-Degnan, Soumerai et al. 1996; Chalker, Chuc et al. 2000; Chuc, Larsson et al. 2001). Viberg et al has described how drug sellers at drugstores in Tanzania with only basic knowledge of pharmaceutical science provided sexually transmitted infections' treatment to clients in a comparatively rational manner (Viberg, Mujinja et al. 2009). The examples of inappropriate provision of antibiotics by pharmacy staff for diarrhoea in study II is consistent with the pattern of higher use of antibiotic for diarrhoea which was seen

among caregivers treating their children with antibiotics as a part of self-care. However, the pharmacy staff provided more antibiotics for illnesses where it was not recommended according to IMCI in 2005 than in 2002. This is likely in response to a higher degree of pharmacy consultations, since fewer caregivers sought care at public health facilities in 2005. Of interest, pharmacies within the study areas also became more aggressive in their marketing towards customers during the years after 2002.

There was no significant difference between how medical doctors prescribed antibiotics for illnesses where antibiotics would be recommended according to IMCI (69%) and illnesses where it would not be recommended (58%) (II). Overuse contribute to unnecessary antibiotic pressure that should be avoided because of known links to antibiotic resistance (Sullivan, Edlund et al. 2001). Importantly, children consulting health professionals did not receive antibiotics for illnesses where they should have been provided. Antibiotic prescription by health professionals is influenced by many factors, including the health care administrative system (Sterky, Tomson et al. 1991; Rowe, de Savigny et al. 2005). Information from key informant's (unpublished results) showed indications that the health facilities in the study areas had restricted the number of health facility visits covered by SIS per month, and thereby limited the health professionals' possibilities to ask the patients to come for follow-up visits. Concerns about the patient and limitations to follow-up on patients with viral infections might have contributed to over-prescription. In addition, the health facilities in the study areas had excluded diagnostic laboratory services from the SIS insurance, and services had to be paid for by the patients. The situation may thus have been further confounded by a lack of diagnostic tools, shown previously to influence prescription patterns (Bosu and Ofori-Adjei 1997). Medical doctors could bypass the existing SIS system that attempted to regulate erroneous prescriptions. The public sector pharmacy staff could be over-ruled in their capacity as quality control of prescriptions and information could be altered after the fact before submitting prescription information to the SIS.

Individual factors likely influenced the prescription patters of the health professionals. Factors such as the lack of adequate information and peer-pressure have been shown to influence prescription of antibiotics (Radyowijati and Haak 2003). In other settings, financial incentives have been shown to have a powerful influence over prescription habits (Heddini, Cars et al. 2009), while patient pressure or perceived patient pressure can also substantially influence the prescription behaviour of health care professionals (Paredes, de la Pena et al. 1996; Brugha and Zwi 1998). To receive a prescription, especially for antibiotics, is considered by the patient as a sign of quality of care (Brugha and Zwi 1998). Patient pressure is likely to have influenced the outcome in the study areas, especially if the health professionals were not content with the SIS or the work load at the health facilities. Giving in to perceived patient pressure would be an easy way to shorten the time with each patient.

6.5 ANTIBIOTIC RESISTANCE ASSOCIATED WITH WEALTH AND ANTIBIOTIC USE

The number of children that were carriers of antibiotic resistant *E.coli* in the commensal florae was high in both Yurimaguas and Moyobamba as reported in other articles from the ANTRES project (see preamble) (Bartoloni, Pallecchi et al. 2006; Bartoloni, Pallecchi et al. 2008). A study using the same resistance screening method as the one used in this thesis, and carried out in Sweden with the aim to validate the screening method, showed lower resistance carriage among healthy adults than what was seen among children in Peru (Kronvall, Larsson et al. 2005). The high carriage of resistance to ampicillin and trimethoprim-sulfamethoxazole in the thesis coincides with the comparatively high use of the same antibiotics in both Moyobamba and Yurimaguas. Commensals are exposed to the selective pressure of antibiotics in a similar way as pathogens. Commensal gut florae have been identified as a reservoir for resistance genes that can be transferred to more pathogenic bacteria. In many studies *E. coli* have been used as an indicator of the dissemination of acquired resistance genes (Lester, del Pilar Pla et al. 1990; Okeke, Fayinka et al. 2000). The results from this ANTRES study refer only to the commensal florae, and therefore cannot be used directly for clinical purposes. Notwithstanding, the findings are indicative of the magnitude and extension of the reservoir of resistance genes in the community (Levy, Marshall et al. 1988).

A significant association was found between use of antibiotics and the carriage of antibiotic resistance for a number of antibiotics (IV). Significantly higher resistance was seen when the children and/or their family members were stated to have had consumed any type of antibiotics for the previous 2 weeks and/or the previous 6 months. These results confirm those from studies showing an association between *E. coli* resistance and antibiotic use both in patients with urinary tract infections and in healthy volunteers (Bruinsma, Stobberingh et al. 2003; Kahlmeter, Menday et al. 2003; Metlay, Strom et al. 2003; Nys, Okeke et al. 2004). However, these previous studies were carried out in hospital settings or compared resistance surveillance data with consumption statistics and linked resistance against one antibiotic to use of the same antibiotic. This community-based study showed an associated antibiotic resistance toward of any type of antibiotic used. The use of ampicillin or co-trimoxazole (trimethoprim-sulfamethoxazole) was most common, and likewise the carriage of ampicillin and trimethoprim-sulfamethoxazole resistance was most frequent. Interestingly, resistance to other antibiotics, such as chloramphenicol and ciprofloxacin, could also be observed among the children who had used antibiotics. One explanation could be co-resistance against several antibiotics. A publication by Bartoloni et al. from the ANTRES study showed that co-resistance against ampicillin/tetracycline/trimethoprim-sulfamethoxazole/chloramphenicol, and also co-resistance including ciprofloxacine resistance, was detected among the *E.coli* isolated from the children included in the study (Bartoloni, Pallecchi et al. 2006).

The carriage of bacteria with the type of resistance defined as "total resistance" was significantly higher in the wealthiest strata for several antibiotics, among them nalidixic acid, ciprofloxacin and chloramphenicol (IV). A similar, non-significant trend could also be seen for other antibiotics. For the dominant flora the same pattern was observed. In other settings, increased resistance among higher socioeconomic strata has been explained by an increased antibiotic use by wealthier families (Garcia-Rey, Fenoll et al. 2004; Nilsson and Laurell 2005). In this study, the explanation is not as straightforward. No interactions between wealth and antibiotic use was seen in relation to antibiotic resistance, and the increased odds ratios for resistance carriage among wealthier children remained when multivariable logistic regression controlled for antibiotic use. Antibiotic resistance in less frequent clones may be associated with other characteristics shared by wealthier families, such as food or water consumption habits. Food can be contaminated with antibiotic resistant bacteria in different ways and stages of the production process. The use of antibiotics in animals is correlated with emerging resistance (Cabello 2006; Fabrega, Sanchez-Cespedes et al. 2008). Contamination with resistant bacteria can then occur during the slaughter and/or the food preparation process (Kruse and Sorum 1994). Further, vegetables or fruit can also be contaminated both pre- and post harvest, for example by irrigation with water contaminated with resistant bacteria as well as unsafe preparation processes leading to contamination. Consequently, habits regarding type of food as well as preparation processes could have an influence on resistance rates in different strata. It is not unlikely that wealthier families buy food from different sources or prepare their food differently from less wealthy families.

6.6 METHODOLOGICAL CONSIDERATIONS

Design
The studies were carried out within the framework of the ANTRES project (Towards Controlling Antibiotic Use and Resistance in Low-Income Countries: An Intervention Study in Latin America) (http://www.unifi.it/infdis/antres/default.htm) aiming to investigate antibiotic use and bacterial resistance in healthy children in Peru and Bolivia. An information-education-communication (IEC) intervention would be developed based on the collected information and involving local health services and evaluated in a controlled study. Yurimaguas was assigned as the intervention site and Moyobamba as the control site. The IEC intervention was in fact implemented in Yurimaguas. This thesis includes the household surveys conducted in Peru, the surveys 2002 in Yurimaguas and Moyobamba and the survey conducted 2005 in Moyobamba. The 2005 survey from Yurimaguas was not included as the IEC intervention implemented in that community likely would have had some influence on the health seeking behaviour and use of antibiotics.

Sample size
The sample size calculations were carried out to serve the design of the ANTRES project which aimed to evaluate the change in antibiotic use as a result of an IEC

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intervention. The sample size was calculated with the intention to detect a difference in antibiotic use to the degree of 10% between the intervention and control group. The desired significance level is 0.05 with a power of 80%. The 800 children in each community represent 20-25% of the children in the chosen age cohort. However, in the types of analysis included in this thesis I have on various occasions had small samples in the subgroups analysed (i.e. health seeking behavior in relation SES or source of antibiotic provision). For some of the smallest samples, I have conducted post-hoc power calculations which indicated sufficient power to detect interesting differences. For example I found no significant change in pecentage of antibiotics prescribed by medical doctors in Moyobamba 2002 versus 2005 (50% and 56% respectively). However, sample sizes had sufficient power (>0.90) to detect a change from 50% to 70%. Likewise, the observed proportions consulting pharmacy staff in 2002, 7% (10 of 153 total consulting caregivers), has a 95% confidence interval of (3% to 12%).

Sampling bias
In order to avoid sampling bias, the children participating in the surveys were included via a two-step procedure. First a stratified sampling of blocks (within zones) was conducted with a probability proportional to size of the zone to give a total sample of 80 blocks. Then, in each selected block the interviewers randomly chose a corner of the block and, following a random direction from the corner, visited households consecutively until they had recruited ten eligible children. The interviewers proceeded to the next house if there was no child aged 6 to 72 months. If no eligible child was found in the block, the interviewers proceeded to an adjacent block, mapped as a substitute. In some blocks it was difficult to find children in the right ages and in some blocks the caregivers declined to participate. Systematic bias in the sampling could be an issue if the declining caregivers shared certain characteristics, for example, if wealthier caregivers refused to be interviewed. Interviewers kept detailed records of how many households with eligible children declined per block. In general, the acceptance among the caregivers was good, although it cannot be guaranteed that all groups of caregivers were represented. The data analysis showed that the characteristics of the households were homogenous. Households with a wide range of characteristics and assets were represented in the sample.

Exclusion criteria stated that any child having had three or more loose stools in the previous 24 hours (WHO definition of diarrhoea) was excluded from the survey. The reason was to ensure that the children included in the survey had minimal distortion of the normal intestinal bacterial florae, as this was assessed by the microbiological screening that was a part of the survey. This has led to an under-representation of diarrhea cases. However, the purpose of the survey was not to indicate prevalence of any specific symptoms or illnesses, but rather to investigate the health-seeking behaviour associated with the illnesses.

Data collection – Questionnaire interviews

The data collection was carried out during interviews using structured questionnaires. The information collected is self-stated and several factors could have influenced the quality of the data.

- *Information bias*

The illnesses were classified based on the IMCI algorithm for health workers (WHO/UNICEF 2003), using the key symptoms stated in the IMCI guidelines. It might be argued that the illness classification was not valid as a representation of the disease the child had, as caregivers may define symptoms differently than the IMCI guidelines. Illness categories were not intended to be equivalent to a diagnosis given by a health provider, but were an attempt to provide a basis for assessing whether antibiotics were appropriately used or whether health care was sought.

Since information on duration and timing of the symptoms of the children were not collected, the possibility that some of the illnesses were still in progress at the time of the interview could not be excluded, resulting in biased reporting of certain health-seeking strategies. However, a main interest of analysis has been to identify lack of access to health care for severe illnesses. By relying on a few distinctive danger signs (fast breathing and blood in stools) for severe illness, one could argue that if the signs of severe illness were present, treatment should have been administered regardless of duration.

- *Interviewer bias*

The interviewer can, subconsciously or consciously, influence the respondents to answer in certain ways (Yeneneh, Gyorkos et al. 1993). For example, the interviewers could have asked leading questions or could have appeared as if they preferred a certain answer. Efforts were made to minimize this risk by training the interviewers in a rigorous way, with daily supervision and group discussions. The output from the interviews was spot-checked and analysed, and the preliminary data analysis was conducted to assess how the different responses were distributed in relation to interviewers. Despite these measures and even though interviewers were well trained and supervised during data collection, potential influence of an interviewer on the respondent cannot be fully excluded (Yeneneh, Gyorkos et al. 1993; Krause, Schleiermacher et al. 1998).

- *Recall bias*

As the interviews investigated past events, recall bias might have influenced the results. The reliability and validity of the information collected through interviews is influenced by the length of the recall period. The time period is also influenced by the importance of the event. A two-week recall period as used in the thesis is considered adequate for measuring health status or health service utilisation for acute diseases (Tipping and Segall 1996; Fleming and Charlton 1998).

Antibiotic use in this study was self-reported. Probing for specific drugs has been shown to give better sensitivity in answers than asking open-ended questions (Klungel, de Boer et al. 2000). Questions were posed about drug use in a step-wise procedure. First, the interviewers asked a general question about whether any medicines had been given to the child, and then the interviewers probed by

mentioning antibiotics, other drugs and traditional medicine. The interviewers also asked for the container/package. More than half of the households with stated antibiotic use during the previous two weeks still had the package. If the caregivers could not remember the drug name, but could describe the package or the tablet, they were shown samples of antibiotics that the interviewers carried and asked if the medication taken was among the samples.

SES classification
In many LMIC it is problematic to use the traditional measures of economic position. SES was estimated by using an asset analysis to establish the wealth status of the households. During the interviews information regarding household assets and household characteristics was collected and, subsequently, principal component analysis (PCA) established an asset index. The asset index approach has been recommended by several researchers due to the assumption that assets owned by a household reflect the wealth of that household (Wagstaff, van Doorslaer et al. 1999). A study comparing various methods used to weigh assets into a wealth index found that principal component analysis (PCA) showed the best fit to data (Bollen, Glanville et al. 2001). Asset analysis gives a relative measure of wealth. The total amount of households sampled in our surveys was divided into quartiles as the number of children among our various study groups was limited and was thus better represented by the use of a quartile division. Since the analysis compared wealthiest to the least wealthy, this division posed no major limitations.

Resistance measures
The "rapid screening method", used for detecting carriage of resistant *E.coli*, differs from standard screening for antibiotic resistance. A drawback of using this method is the scarcity of studies using the same method, making comparisons difficult. However, the adjusted analysis of the resistance data has resulted in one measure, called "total resistance", including both frequent and rarer clones, and another called "dominant resistance" in the analysed faecal samples (Kronvall, Larsson et al. 2005; Bartoloni, Benedetti et al. 2006). The so-called 'total resistance' is an approximation of the prevalence of carriers of any resistant intestinal *E. coli*, a measure that can also be obtained using a selective culture for each antimicrobial studied. The "dominant resistance" reflects approximately the prevalence of children with resistant *E. coli* as their dominant flora and is closer to the measures used in studies where a randomly selected *E. coli* from each sample is tested.

Resistance analysis
No analysis of a possible association between the use of specific types of antibiotics and resistance was performed. An association between resistance to several different antibiotics was confirmed in a separate ANTRES publication (Bartoloni, Pallecchi et al. 2006). Consequently, use of one antibiotic drug will most probably co-select for resistance to several other unrelated antibiotics. For this reason, I have considered 'use of any type of antibiotics' as the only outcome possible in order to analyse any possible relationship to influencing factors.

7 CONCLUSIONS AND RECOMMENDATIONS

Utilisation of public health care was high but poorer children, via their caregivers, under-utilised health care services. The correct management of self-stated childhood illnesses could not be guaranteed even in this setting where all children qualified for free health coverage and essential drugs. Health service utilisation changed between the 2002 and 2005 surveys, with more caregivers in 2005 choosing to consult pharmacy staff instead of public sector health professionals. Antibiotics were frequently used whether use was recommended according to IMCI guidelines or not.

1. The utilisation of public health care providers was high, but some caregivers did not consult health professionals even for children with severe illnesses.

2. Utilisation of public health services and antibiotics was not equitable. The poorest children consulted public health professionals to a lesser extent.

3. Most of the antibiotics used were prescribed by health professionals and few were used as part of self-care. However, use was not rational, both under-use and over-use in relation to IMCI recommendations was observed. More seriously, children consulting health professionals and children who were managed by self-care did not receive antibiotics for illnesses where they should have been provided.

4. Even though the theoretical availability of free health care and antibiotics remained the same between 2002 and 2005, more caregivers sought care from pharmacy staff in 2005 and fewer children then received antibiotics through SIS.

5. There were a high number of children carrying antibiotic resistant clones of *E. coli* in both communities.

6. Carriage of antibiotic resistant *E.coli* was more common among wealthier children, even when antibiotic use was controlled for.

The Peruvian government has expressed plans to extend the SIS into a universal health plan, providing access to free health services for all members of the population. The results of this thesis indicate that implementation of SIS in the Amazonas had 2005 not succeeded in providing full coverage to its most vulnerable population: the poorest children. Barriers remain on both sides of the supply-demand continuum. To address the demand side, community members should be involved in planning and implementation, in order to consider patient acceptability of services as well as the accommodation of services to patient needs. Caregiver perceptions of need for health care should also be considered when addressing recognition and management of severe illnesses and the home management of non-severe illnesses. Addressing the supply side requires that policy implementation must be conceived in cooperation and consultation with health professionals, including reviews of human resource policies.

Implementation of SIS should be carefully monitored to ensure compliance with rules and regulations so that affordability and availability of health care and related goods are ensured.

The high carriage of antibiotic resistant *E. coli* in the commensal florae is worrisome. Antibiotic resistance therefore needs to be regarded as an integral component of infectious disease management. Information about correct use of antibiotics should address both health providers and community members, and include also community members from the wealthier strata of society since resistance is not only a problem of the poor.

8 ACKNOWLEDGEMENTS

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Research

Access to health care in relation to socioeconomic status in the Amazonian area of Peru

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Abstract

Background: Access to affordable health care is limited in many low and middle income countries and health systems are often inequitable, providing less health services to the poor who need it most. The aim of this study was to investigate health seeking behavior and utilization of drugs in relation to household socioeconomic status for children in two small Amazonian urban communities of Peru; Yurimaguas, Department of Loreto and Moyobamba, Department of San Martin, Peru.

Methods: Cross-sectional study design included household interviews. Caregivers of 780 children aged 6–72 months in Yurimaguas and 793 children of the same age in Moyobamba were included in the study. Caregivers were interviewed on health care seeking strategies (public/private sectors; formal/informal providers), and medication for their children in relation to reported symptoms and socio-economic status. Self-reported symptoms were classified into illnesses based on the IMCI algorithm (Integrated Management of Childhood Ilness). Wealth was used as a proxy indicator for the economic status. Wealth values were generated by Principal Component Analysis using household assets and characteristics.

Results: Significantly more caregivers from the least poor stratum consulted health professionals for cough/cold (p < 0.05: OR = 4.30) than the poorest stratum. The poorest stratum used fewer antibiotics for cough/cold and for cough/cold + diarrhoea (16%, 38%, respectively) than the least poor stratum (31%, 52%, respectively). For pneumonia and/or dysentery, the poorest used significantly fewer antibiotics (16%) than the least poor (80%).

Conclusion: The poorest seek less care from health professionals for non-severe illnesses as well as for severe illnesses; and treatment with antibiotics is lacking for illnesses where it would be indicated. Caregivers frequently paid for health services as well as antibiotics, even though all children in the study qualified for free health care and medicines. The implementation of the Seguro Integral de Salud health insurance must be improved.

Background

Following health reforms in the 1980s and 1990s, many Latin-American countries moved from universal coverage (free health care financed by public funds) towards cost recovery initiatives utilizing, for example, user fees and social insurances [1-3]. However, user fees have been shown to represent an important barrier to accessing health services, especially for poor people[4]. Strategies including fee exemption – aimed at mitigating exclusionary effects – have proven to be stigmatizing and costly since administrational measures are needed to identify the poor [5,6]. It is likely, therefore, that if targeted interventions are to be effective in reaching the poor, special strategies need to be more carefully outlined [7,8].

In Peru, inequity in health service utilization during the late 1990s was shown for adults [9] but no corresponding figures for children have been presented. This lack of attention is surprising since death resulting from infectious disease remains a major health problem for children in low and middle income countries. In Peru, the most common causes of mortality among children under five years of age remain acute respiratory tract infections [10]. Furthermore, several studies have shown a well-established connection between socioeconomic status and health [11,12], where proximate factors, such as health prevention, nutrition and care, have been directly linked to socioeconomic status [13]. These studies make clear that in addition to ill health, the costs for health care and medicines further impoverish vulnerable population groups [14], poor children notwithstanding.

The Seguro Integral de Salud state health insurance (SIS) was implemented in Peru in 2001 and at the time of this study offered free of charge health care and pharmaceuticals, such as antibiotics, to children in the study area, regardless of socioeconomic status. Access to health services and pharmaceuticals following policy implementation has improved, at least theoretically through the SIS, for children from all socioeconomic groups; however, presumptive improvements in the health seeking behavior of poor children have yet to be empirically analyzed or verified. The question of verifiable improvements becomes even more essential when considering poor children who have high geographic access to health facilities. The aim of this study, therefore, was to describe health care access – measured as consultations with health professionals – and antibiotic use in relation to socioeconomic status for children who recently presented symptoms of infectious disease.

Methods

Study area

Population and socioeconomic structure

This survey was conducted in 2002 in two Peruvian communities, Yurimaguas (Department of Loreto) and Moyobamba (Department of San Martin). In 2002, each community had a population of approximately 32000 inhabitants. Both departments represent one of the most underprivileged areas of Peru – the Amazonian region. Approximately 55% of the population lives below the poverty line, and 15% in extreme poverty and the majority of the working population survive on subsistence farming [15]. Yurimaguas is less accessible than Moyobamba which has a better infrastructure and is easily reached from the surrounding communities.

Health services

The study was conducted in urban settings where geographical distances to health facilities are small. Yurimaguas has one Ministry of Health (MoH), a public hospital, a Local Committees for Health Administration (CLAS) Maternal Health Centre [16] and two health posts. In addition there is a Social Security Institute hospital (ES SALUD). In Moyobamba, there are three health posts and one health center. At the time of the study, the hospital in Moyobamba belonged to ES SALUD system, and the MoH facilities either paid the ES SALUD hospital for treatment of public sector patients or referred patients to the nearby city of Tarapoto. At both study locations, the hospital and health center employees mainly included medical doctors, while the health posts were staffed exclusively with nurses, midwives and health technicians.

All licensed, private pharmacies – nine in Yurimaguas and fifteen in Moyobambas – had trained pharmacists on their staff list. However, in most cases, these pharmacies were run by assistants without formal education. Officially, antibiotics could only be sold by pharmacies, but in practice they were also bought without prescription, available at the market place, in food stores or from traditional healers.

The SIS was created by merging the already existing Maternal/Infant and School insurances. In theory, SIS provided health care and essential pharmaceuticals via the public health care sector free of charge to those with low economic status, to pregnant women and to senior citizens, according to insurance schemes specified by target group. In areas with a poverty level higher than 60%, such as the Amazonian area, all children qualified for the insurance, irrespective of their parents' economic status. The insurance covered health care, including essential generic drugs and diagnostic services. Affiliation to the insurance was not, however, automatic and the children had to be registered every calendar year at the hospital's SIS office.

Means of data collection

Design and sampling

The results presented in this paper were generated within the ANTRES project, a collaborative research project funded by the EC INCO-DEV, ICA4-CT-2001-1001, addressing the themes of antimicrobial use and resistance in Peru and Bolivia.

This cross sectional survey used household interviews. Faecal samples were also collected for microbiological studies, which have been reported elsewhere [17]. Children with three or more loose stools in the 24 hours prior to sampling (WHO definition of diarrhoea, 1993) were excluded from the study in order to ensure the implementation of the microbiological study within the same survey. A modified cluster sampling approach was used and included a total of 1600 children, aged 6 to 72 months. Eight hundred children from each village were sampled. Yurimaguas and Moyobamba were divided into zones of varying sizes, containing households distributed in blocks. A stratified sampling of blocks (within zones) was then conducted with a probability proportional to the size of the zone. Eighty clusters were sampled in each community, with each cluster consisting of 10 children (one per household) within a randomly assigned block. Within each block, the interviewers randomly chose a corner of the block and, pursuing a random direction from this corner, consecutively visited households until they had recruited ten eligible children. If they found no child aged 6 to 72 months, the interviewers proceeded to the next house, and likewise, if no eligible child was identified within a block, the interviewers proceeded to a nearby block, which had been mapped as a substitute. In total, 780 children from Yurimaguas and 793 children from Moyobamba were included in the study described in this paper.

Interviews

Household interviews were conducted by ten trained interviewers from the public health sector (health technicians, nurses or midwives) who had extensive experience working with community outreach activities. The children's caregivers (mother, father, grandparent or other adult caregiver) were interviewed using a structured questionnaire (available from the first author) which had been pre-tested and validated during a pilot study. The caregivers were chosen for the interviews on the basis of being present in the household and taking care of the child during the time of the interviewers' visit. The majority of caregivers were mothers (87% in Moyobamba and 85% in Yurimaguas). Interview questions addressed the child's symptoms for the most recent illness during the previous two weeks, as well as all actions taken by the caregivers to cure the symptoms, including medication and healing practices. The interviewers first asked for the symptoms in an open-ended question and then probed by stating all symptoms in the questionnaire one by one while also explaining the symptoms.

A system for checking data quality was developed in order to ensure high quality during study implementation: on a daily basis, study supervisors screened the questionnaires for missing responses and logical inconsistencies and requested re-visits to households where more detailed clarifications where needed. The caregivers were also asked to show interviewers the package or blister pack if antibiotic use was reported. If caregivers were not in possession of the package or did not remember the name of the antibiotic consumed, but could describe the package, bottle or tablet, the interviewers presented them with identifiable antibiotics samples. The interviewers also carried a list of local antibiotic brand names and the corresponding ATC category [18].

The health seeking behavior was classified into "self-care", "exclusive consultation (with persons working with health issues)" and "self care and consultations". Self-care was defined in line with Levin [19] as all those activities undertaken to treat illness without professional assistance. We defined medical doctors, nurses and midwives, health technicians, pharmacy staff and traditional healers as professional assistance or, as stated in the questionnaire, "persons working with health issues".

Illness classification

The symptoms (as reported by caregivers) were classified according to the principles of the IMCI algorithm (Integrated Management of Childhood Illness) for classification and treatment of infectious diseases in children in low malaria-prevalence areas [20]. The algorithm is based on the absence or presence of the following key symptoms: fast breathing, cough, diarrhoea, and/or blood in stool.

The children were classified with one of the following illnesses: diarrhoea (presence of: diarrhoea; absence of: blood in stool, cough and other symptoms of cold, 'fast breathing'), dysentery (presence of: blood in stool, diarrhea; absence of: cough and other symptoms of cold, 'fast breathing'), cough/cold (presence of: fever, cough and other symptoms of cold; absence of: diarrhoea, blood in stool, 'fast breathing'), pneumonia (presence of: 'fast breathing', cough; absence of: diarrhoea, blood in stool), cough/cold + diarrhoea (Symptoms of cough/cold and symptoms of diarrhea), pneumonia and/or dysentery (one of following three combinations: symptoms of pneumonia and diarrhoea, *or* symptoms of pneumonia and dysentery, *or* cough/cold and dysentery).

Analysis of wealth status

In many low-income settings, it is problematic to use traditional measures, such as income or consumption, for the assessment of an individual's financial status, due to practical limitations of collecting accurate data [12]. In this study, wealth was used as a proxy indicator for the economic status, under the assumption that wealth is reflected in the assets owned within a household [21]. Information about household assets and characteristics was collected during the interviews. Principal component analysis (PCA) was used to generate scoring weights for each variable: the number of household members divided by the number of rooms in the house, the access to electricity, type of floor, type of toilet, type of water source, and the ownership of a fan, TV, motor-bike and refrigerator, using the first principal component. The scores were then summed up to assign a wealth index value to each household. The consistency of the PCA-assigned wealth with the ownership of assets was controlled by cross tabulations. No absolute cut-off points for the level of wealth could be assumed based on the wealth index values. Thus, the population was divided into quartiles based on the value of the wealth variable in order to capture relative variances. For the analysis presented in this paper, quartile number one (Q1) was considered as a proxy for the lowest wealth – the poorest, and quartile number four (Q4) as the least poor – the richest.

Data analysis

The data from the questionnaires was introduced into an EPI INFO 2000 [22] database by double-entry and then compared. All discrepancies were verified with the paper originals and corrected. The database was exported to STATA, where it was scrutinised for quality and consistency prior to data analysis. Wealth variables were created separately for the data sets from Yurimaguas and Moyobamba by using the PCA. The respective wealth quarters from each community were then pooled to provide a data set large enough to allow for statistical analysis of variables related to health seeking behavior and use of medicines. The poorest quarter consisted of Q1 from Yurimaguas and Q1 from Moyobamba, and so forth.

The relation between wealth and health seeking behavior and antibiotic use was assessed. Logistic regressions were used to analyze differences between strata. Chi-square tests have been used to assess differences between the poorest half of the population (the two poorest strata pooled together) and the least poor half (the two least poor strata pooled) in relation to cost incurred for health care, cost for antibiotics and place of provision of antibiotics. The difference has been considered significant if the p-value is less than 0.05.

Results

Morbidity

Of a total of 780 children from Yurimaguas included in the study, 382 (48%) children had shown symptoms related to infectious illnesses in the previous two weeks. In Moyobamba, 425 (54%) of a total of 793 children had suffered from symptoms. In total, four children were excluded due to incomplete data regarding health seeking behavior, leaving 803 children for further analysis.

Health seeking behavior

Many caregivers (42%) stated that they had consulted health professionals with regard to their children's health problems (Table 1). The least poor households had consulted health professionals for the non-severe illness cough/cold significantly more frequently than the poorest households (p < 0.05: OR 4.30). Similarly, for the non-severe illness, cough/cold + diarrhoea, least poor households had consulted health professionals to a greater extent (p < 0.05: OR 3.74). The least poor households also consulted more frequently with health professionals for severe illnesses, such as pneumonia and/or dysentery (OR = 2.33) and pneumonia (OR = 2.92), even though the difference was not significant.

In all strata, public sector medical doctors were the most commonly visited health professionals. The least poor households consulted nurses and health technicians to a lower extent (1% and 1%, respectively) than the poorest households (12% and 24%, respectively). Caregivers from all strata paid out-of-pocket for care provided by public sector health facilities (Table 2). In Yurimaguas, significantly more caregivers from the two least poor strata made out of pocket payments, as compared to the two poorest strata (p < 0.05). Also in Moyobamba more least poor caregivers made out of pocket payments, but the difference between strata was not significant.

Use of antibiotics

A similar antibiotic use was reported for the children in Yurimaguas and Moyobamba (42% and 36% respectively). As the patterns of medicine use in relation to socio-economic status and illnesses were similar for the two communities, the pooled data from both is presented in Table 3. For cough/cold, the least poor used significantly more antibiotics than the poorest (OR = 2.29). The same trend could be observed for pneumonia and/or dysentery, with the least poor using significantly more antibiotics (80%) than the poorest (16%).

Location of antibiotic acquisition

The locations for antibiotic provision, including antibiotics for self-medication, were investigated. In Yurimaguas, the two least poor strata had bought their antibiotics (either as a part of self care or with a prescription) at the

Table 1: Children seeking care from health professionals in relation to self reported symptoms and wealth quarters

	Children seeking care from health professionals						
Illness	**Q1** % seeking care (total no children with illness)	**Q2** % seeking care (total no children with illness)	**OR**	**Q3** % seeking care (total no children with illness)	**OR**	**Q4** % seeking care (total no children with illness)	**OR**
Cough/cold	21% (99)	28% (116)	1.62	28% (128)	1.88*	51% (104)	4.30*
Pneumonia	33% (12)	82%(11)	5.25	50% (16)	1.94	71% (14)	2.92
Cough/cold + diarrhoea	35% (62)	46% (46)	1.70	41% (37)	1.62	50% (30)	3.74*
Pneumonia and/ or dysentery	50% (18)	54% (13)	1.17	67% (9)	2	70% (10)	2.33
Diarrhoea	17% (18)	27% (22)	1.05	40% (10)	1.87	20% (15)	0.93
Total	209	208		200		173	

Self reported symptoms classified as illnesses based on principals from IMCI. Wealth quarters were defined by principal component analysis (PCA). Quartile 1 (Q1) represents the poorest quartile of the study sample (the relatively poorest caregivers), quartile 2 (Q2) the second poorest, quartile 3 (Q3) the second least poor quartile and quarter 4 (Q4) the least poor quartile. Amount of children seeking care from health professionals (pharmacy staff not included) is showed as percentage and total number in parenthesis. OR = Odds ratio. The Odds ratio is stated for each wealth quarter as compared to quarter 1. * = p < 0.05

pharmacy (private or public pharmacy) significantly (p < 0.05) more frequently (45%) than the two poorest quartiles (15%) (Table 4). The least poor group received their antibiotics free of charge by the health insurance system (40%) less frequently than the poorest quartile (65%). In Moyobamba, the least poor caregivers more frequently (58%) received antibiotics free of charge from the insurances than the poorest group (46%).

The cost associated with antibiotics prescribed by public sector health professionals was investigated. In Yurimaguas, the two least poor strata had made out-of-pocket payment for the antibiotics to a significantly larger extent (p < 0.05) than the two poorest strata (Table 5). In Moy-

obamba, there was no significant difference between strata.

Discussion

This study shows that the poorest households consulted health professionals for their sick children less frequently. The poorest children were provided with fewer antibiotics for illnesses where the IMCI algorithm recommended antibiotic use. Inequity in access to health care, here measured as consultations with health professionals, prevailed in an urban setting despite of high geographical access to health facilities and the SIS health insurance providing free health care to children. The high theoretical access to health care makes this study unique from other studies

Table 2: Cost incurred for public sector health care

	Cost incurred for public sector health care					
	Yurimaguas			**Moyobamba**		
	Free of charge	Paid out-of-pocket	Total	Free of charge	Paid out-of-pocket	Total
Poorest (Q1)	31 (86%)	5 (14%)	36	13 (87%)	2 (13%)	15
Q2	48 (92%)	4 (8%)	52	24 (92%)	2 (8%)	26
Q3	29 (74%)	10 (26%)	39	25 (81%)	6 (19%)	31
Least poor (Q4)	26 (67%)	13 (33%)	39	34 (81%)	8 (19%)	42
	134	32	166	128	30	158

Number of caregivers paying for the health care provided by the public sector health professionals stated in relation to wealth quartiles (as defined by principal component analysis (PCA)). Quartile 1 (Q1) represents the poorest quartile of the study sample (relatively poorest), quartile 2 (Q2) the second poorest, quartile 3 (Q3) the second least poor quartile and quarter 4 (Q4) the least poor quartile. Number of children whose caregivers paid for the health care provided by the public sector health professional or who were provided care free of charge, stated as numbers, with percentage of total number of children per quartile indicated in parentheses. Chi-square tests have been used to assess differences between two poorest (Q1 and Q2) and two least poor (Q3 and Q4) strata. Significant difference between strata was found for Yurimaguas (p < 0.05) but not for Moyobamba.

Table 3: Antibiotic use in relation to self reported symptoms and wealth quarters

	Use of antibiotics						
Illness	**Q1** % using antibiotics (total no children with illness)	**Q2** % using antibiotics (total no children with illness)	**OR**	**Q3** % using antibiotics (total no children with illness)	**OR**	**Q4** % using antibiotics (total no children with illness)	**OR**
Cough/cold	16% (99)	30% (116)	1.85	39% (128)	2.17*	34% (104)	2.29*
Pneumonia	64% (12)	63%(11)	0.93	56% (16)	0.71	53% (14)	0.63
Cough/cold + diarrhoea	38% (62)	62% (46)	2.64*	47% (37)	1.41	52% (30)	1.73
Pneumonia and/or dysentery	16% (18)	80% (13)	21.33*	70% (9)	12.44*	80% (10)	21.33*
Diarrhoea	35% (18)	43% (22)	1.39	-(10)	-	39% (15)	0.93
Total	209	208		200		173	

Self reported symptoms were classified as illnesses based on principals from IMCI. Wealth quartiles were defined by principal component analysis (PCA). Quartile 1 (Q1) represents the poorest quartile of the study sample (the relatively poorest of the caregivers), quartile 2 (Q2) the second poorest, quartile 3 (Q3) the second least poor quartile and quarter 4 (Q4) the least poor quartile. Amount of children treated with antibiotics, including through self medication, showed in percentage, total number of children shown in parentheses. OR = Odds ratio showing each wealth quarter as compared to quarter 1. * = p < 0.05

focusing on Latin American countries where inequitable results have been shown [9,23].

During the study period, the recently introduced Peruvian state health insurance Seguro Integral de Salud (SIS) aimed to reduce financial barriers to health by providing free health care and pharmaceuticals for the target groups. In the Amazonian area, all children qualified for the SIS due to the high poverty status of the region. However, the formal supply of free health care was not enough to ensure equitable access, and instead, remaining barriers exist which prevented equitable supply. For example, following initiation of the SIS, it is plausible that caregivers lacked adequate information about the benefits and regulations of the new SIS insurance system or that they may have confused it with previous insurance schemes that were granted only after assessment of the families' financial status. Either way, during the implementation of this study, the local health professionals complained that the poorest households were "over-seeking" health care for unnecessary symptoms and thereby wasting resources. Ironically, this attitude would have contributed to preventing truly vulnerable patient groups from seeking health care. Moreover, caregivers' perceptions about qual-

Table 4: Place of acquisition of antibiotics in relation to wealth quarters

	Place of antibiotic acquisition in Yurimaguas						Place of antibiotic acquisition in Moyobamba					
	Public pharmacy	Private pharmacy	Market place	Free of charge through insurance	Other	Total	Public pharmacy	Private pharmacy	Market place	Free of charge through insurance	Other	Total
Poorest (Q1)	2(6%)	3 (9%)	5 (15%)	22 (65%)	-	32	8 (29%)	5 (18%)	1 (4%)	13 (46%)	1 (4%)	28
Q2	5 (10%)	7 (14%)	3 (6%)	33 (66%)	1 (2%)	49	3 (7%)	15 (38%)	4 (10%)	17(43%)	1 (3%)	40
Q3	7 (19%)	11 (31%)	1 (3%)	15(42%)	1 (3%)	35	7 (17%)	12 (29%)	2 (5%)	19 (45%)	2 (4%)	42
Least poor (Q4)	9 (24%)	8 (21%)	1 (3%)	19 (40%)	1 (3%)	38	10 (25%)	5 (13%)	-	23 (58%)	2 (6%)	40
Total	23	29	10	89	3	154	28	37	7	72	6	150

Wealth quarters were defined by principal component analysis (PCA). Quartile 1 (Q1) represents the poorest quartile of the study sample (the relatively poorest caregivers), quartile 2 (Q2) the second poorest, quartile 3 (Q3) the second least poor quartile and quarter 4 (Q4) the least poor quartile. Number of children stated per place of provision, percent of total number of children per quartile and community shown in parentheses. Chi-square tests have been used to assess differences between two poorest (Q1 and Q2) and two least poor (Q3 and Q4) strata. Significant difference between strata for antibiotic acquisition from pharmacies was found for Yurimaguas (p < 0.05) but not for Moyobamba.

Table 5: Type of financing for antibiotics prescribed by public sector health professionals, in relation to wealth quarters

	Financing for antibiotics prescribed by public sector					
	Yurimaguas			**Moyobamba**		
	Free of charge	Paid Out-of-pocket	Total	Free of charge	Paid Out-of-pocket	Total
Poorest (Q1)	21 (91%)	2 (9%)	23	12 (86%)	2 (14%)	14
Q2	33 (92%)	3 (8%)	36	18 (100%)	-	18
Q3	15 (75%)	5 (25%)	20	15 (71%)	6 (29%)	21
Least poor (Q4)	15 (54%)	13 (46%)	28	18 (72%)	7 (28%)	25
	84	23	107	63	15	78

Wealth quarters were defined by principal component analysis (PCA). Quartile 1 (Q1) represents the poorest quartile of the study sample (the relatively poorest caregivers), quartile 2 (Q2) the second poorest, quartile 3 (Q3) the second lest poor quartile and quarter 4 (Q4) the least poor quartile. Number of children receiving antibiotics prescribed by public sector health professionals provided free-of-charge or in return for out-of-pocket payment stated as numbers, with percentage per quartile and community shown in parentheses. Chi-square tests have been used to assess differences between two poorest (Q1 and Q2) and two least poor (Q3 and Q4) strata. Significant difference between strata was found for Yurimaguas (p < 0.05) but not for Moyobamba.

ity of care and pharmaceuticals, as well as attitudes of health professionals, have been shown to be important factors determining health facility utilization [24-27].

The analysis of costs associated with health care services provided by the public health facilities in the two study sites showed that payments were made for consultations with health professionals, more often in Yurimaguas than in Moyobamba. Cost has been shown to be an important factor influencing health seeking behavior [28]. According to information from key informants, as well as the first author's own observations, health facilities in several regions of Peru excluded, based on cost, some aspects of treatment from the SIS benefits, such as diagnostic services, or limited the amount of beneficiaries per day. Reimbursement procedures were also too unclear and facilities feared losing money on the SIS patients. Instead, the patients had to pay services out-of-pocket, which could have caused the poorest group to avoid seeking care rather than facing the risk of unexpected costs. The difference in cost charges between Yurimaguas and Moyobamba could have been the result of the respective communities' interpretation and implementation of the SIS insurance and its benefits at the health facility level. Another important barrier at this level is the time consuming nature of administrational procedures as related to SIS affiliation. It is further possible that people chose to pay for care rather than losing valuable hours waiting in line at the SIS office. The influence of similar health systems constrains on effective service delivery and health seeking behavior has been underlined by other researchers [29].

The poorest children were provided with fewer antibiotics for some of the illnesses where antibiotic use was recommended in the IMCI algorithm. According to our definition, this disadvantage represents a link to the inequity in

heath-seeking behavior. An analysis of the costs paid for the antibiotics and the health care provided by public sector health professionals showed that a number of caregivers had paid for their antibiotics, even though these were supposed to be provided free of charge to all children through the SIS insurance. Our assessment of the location where the antibiotics had been acquired showed that a large part of the antibiotics were bought at public pharmacies. This finding indicates that the SIS implementation was not functioning in an optimal manner, as the health facilities were still charging the patients. On the other hand, purchasing antibiotics rather than receiving them free of charge could also be an indication of problems related to out-of-stock pharmaceuticals in the public sector or that informal payments were charged.

The poorest were mainly self caring for non-severe illnesses such as common cold or non-complicated diarrhea. This is in line with IMCI recommendations [20] and can be considered as rational. In contrast, the least poor frequently sought health care for the same illnesses where consultations were not really necessary. By doing this, they also contributed to a waste of financial resources allocated to health care services. Of note, the least poor children were also frequently given antibiotics for illnesses where it was not indicated according to the IMCI guidelines. This trend coincided to their frequent health care consultations, as the majority of antibiotics were prescribed by the health professionals.

Conclusion

This study shows that even in a setting providing universal access to free health care for children, the poorest seek less care from health professionals for severe illnesses, and that treatment with antibiotics is lacking for illnesses where it should otherwise be indicated. Despite that all

children in the study qualified for free health care and medicines, their caregivers frequently paid for health services as well as antibiotics. Given these findings, the implementation of the Seguro Integral de Salud health insurance must be improved.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CK participated in the design and implementation of the study, acquisition of data, analysis and interpretation of data and helped to draft the manuscript. EG participated in the design and coordination of the study, analysis and interpretation of data and helped to draft the manuscript. HR, AB and MS participated in the design and implementation of the study, acquisition of data and helped to draft the manuscript. GT and PH participated in the analysis and interpretation of data and helped to draft the manuscript. All authors read and approved the final manuscript.

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II

Antibiotic use and health-seeking behaviour in an underprivileged area of Perú

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Summary

OBJECTIVE To describe the health-seeking behaviour and use of antibiotics in the urban community of Yurimaguas in the Amazonian area of Peru.

METHOD Cross-sectional survey of caregivers of 798 children aged 6–72 months by interview using a semi-structured questionnaire. Reported symptoms were classified as illnesses where antibiotics would or would not be recommended based on principles of the integrated management of childhood illnesses algorithm.

RESULTS Forty-one per cent of consultations were with health care professionals; 71% of antibiotics were obtained through the formal public health sector and prescribed mainly by medical doctors. All prescribed antibiotics were on the Peruvian essential drugs list. When prescribing, doctors and nurses hardly discriminated between illnesses where antibiotic treatment was or was not indicated; there was no significant difference in antibiotic prescribing rates between the two (doctors, $P = 0.24$; nurses, $P = 0.32$). Not all caregivers sought help for children with severe symptoms.

CONCLUSION Although most of the antibiotics were prescribed by doctors and nurses, they were commonly prescribed for illnesses where they were not indicated. The use of antibiotics needs to be rationalized, and barriers to health care must be overcome.

keywords care-seeking behaviour, rational prescription practices, antibiotics, barriers to health care, Peru

Introduction

Antibiotics have revolutionized the treatment of bacterial diseases since they were first brought into use; they have reduced child mortality and increased life expectancy globally. Despite this, more than 10 million children continue to die each year from preventable infectious diseases, commonly in combination with undernutrition (Black *et al.* 2003). To improve the management of these diseases, the integrated management of childhood illnesses (IMCI) was introduced (Victora *et al.* 2006), including recommendations on antibiotic treatment. Emerging antibiotic resistance constitutes a serious threat to public health (Levy 1998), and overuse of antibiotics should be avoided. As antibiotic resistance increases, so does the need for more advanced and expensive antibiotics, which

decreases the availability of effective treatment for vulnerable groups (Whitehead *et al.* 2001).

Irrational use of antibiotics, both overuse and underuse, could be influenced by numerous factors related to aspects of supply and demand. Access to affordable health care is limited in many low and middle income countries (LMIC). Hence, people rely to a large extent on self-medication and buy antibiotics directly from pharmacy staff, street vendors or markets (Bojalil & Calva 1994; Delgado *et al.* 1994; Larsson *et al.* 2000). Where health care is available, health professionals may lack up-to-date knowledge, access to diagnostic tools or sufficient time to make correct diagnoses; and they may be influenced by patient expectations (Sterky *et al.* 1991; Rowe *et al.* 2005). Antibiotics also provide revenue and signify quality of care from the patients' perspective (Brugha & Zwi 1998).

In Peru, the most common causes of mortality among children under five years of age are acute respiratory tract infections and diarrhoea. Prescribing inadequate amounts of antibiotics has been reported from Lima hospitals (Llanos-Zavalaga *et al.* 2002) and diagnostics are often not readily available or of low quality. However, data are scant on health-seeking behaviour and antibiotic use among children in rural Peru. The results presented in this paper, which come from the ANTRES project, aim to fill this specific knowledge gap. We describe how health-seeking behaviour relates to various symptoms in children, as well as how antibiotic treatment is related to the children's symptoms and the health-seeking strategy used.

Materials and methods

Study area

This study was conducted in 2002 in the community of Yurimaguas, in Alto Amazonas, Loreto, one of the most underpriviliged parts of Peru. Fifty-five per cent of 31 066 population live below the poverty line, and 15% in extreme poverty. Fifty-seven per cent of the illiterate population (23%) are women (INEI 2005). Most adults are subsistence farmers (INEI 2004).

Yurimaguas has one Ministry of Health (MoH) public hospital and a Local Committee for Health Administration (CLAS) Maternal Health Centre (Iwami & Petchey 2002), each with a laboratory and public pharmacy, staffed by medical doctors, nurses, midwives and health technicians. There is a Social Security Institute hospital (ES SALUD) staffed by medical doctors, nurses, midwives and health technicians, and two MoH health posts mainly staffed by nurses, midwives or health technicians. There are nine private pharmacies, five of which are staffed by trained pharmacists and four by assistants without formal education. Antibiotics can also be bought in the market, in small food shops and from some of the numerous traditional healers.

In 2001, the Seguro Integral de Salud (SIS) was created, providing health care and pharmaceuticals via the public health care sector, free of charge (except for a minimal inscription fee) to those meeting the inclusion criteria. In regions such as Yurimaguas, where more than 60% of the population live in poverty, all children 15 years or younger were covered by the insurance, regardless of the parental economic status.

Means of data collection

This cross-sectional survey used household interviews. We also collected faecal samples for microbiological studies not reported here (Bartoloni *et al.* 2006). A total of 800 children aged 6–72 months were included by means of a modified cluster sampling approach, where 80 clusters were sampled. Each cluster consisted of 10 children (one per household) and was selected from the same block. The city was divided into 11 zones of varying sizes containing households distributed in blocks. A list of all blocks was created and we conducted a stratified sampling of blocks (within zones) with a probability proportional to size of the zone to give a total sample size of 80 blocks. A detailed map was prepared showing all blocks with numbers. In each selected block the interviewers randomly chose a corner of the block and, following a random direction from the corner, visited households consecutively until they had recruited ten eligible children. If there was no child aged 6–72 months in one house the interviewers proceeded to the next house. If no eligible child was found in the block, the interviewers proceeded to a nearby block, mapped as a substitute. If more than one child of appropriate age lived in the house, the youngest was chosen. Any child that had three or more loose stools in the previous 24 h (WHO definition of diarrhoea) was excluded from this study to ensure that there was minimal distortion of the commensal microbiota of the gut being assessed by the microbiological study.

Ten interviewers from the public health sector (health technicians, nurses or midwives) were selected for one week of training, and then tested through mock interviews. Five were chosen as interviewers and the others were allocated as their partners with responsibility for collecting faecal samples from the study children. The caregivers of the children (mother, father, grandparent or other adult caregiver) were interviewed during the household visit. A questionnaire (available from the first author) with structured and semi-structured questions was used. The questionnaire was pre-tested and validated during a pilot study and contained questions regarding the child's symptoms for the most recent illness episode during the previous two weeks and any actions taken by the caregivers, including all medication or healing practice and by whom it was provided. The interviewers first asked for symptoms, and then probed for information by reading the symptoms aloud and explaining them to the caregivers. Study investigators checked the questionnaires with the interviewers daily for missing responses and logical inconsistencies between responses to different questions. In the case of queries, the interviewers returned to the family interviewed. In the case of stated antibiotic use, the interviewers asked for the container and if this was unavailable they asked for the name of the antibiotic. If the interviewee did not remember the name but could describe the container, bottle or tablet, the interviewer showed samples of

antibiotics to help in the identification of the antibiotic used. The interviewers also carried a list of local antibiotic brandnames and the corresponding Anatomic Therapeutic Chemical (ATC) classification (WHO 2006) to classify antibiotics in the questionnaire.

Health providers were defined as medical doctors, nurses, midwives, health technicians, pharmacists and traditional healers. In the presentation of results the nurses, midwives and health technicians were grouped under the heading 'nurses'. Self-care was defined as all situations where caregivers treated the symptoms of their children without consulting any health provider, in contrast to other definitions of self-care where prevention and actions related to consultations with health providers are also included (WHO 1983). Particular care was taken to distinguish between caregivers visiting the pharmacy to ask for advice and those coming to purchase pharmaceuticals. Only those buying pharmaceuticals without asking for the advice of the pharmacy staff were considered to have self-medicated.

All symptoms reported by the caregiver were classified according to the principles of the IMCI algorithm designed to assist health workers in the classification and treatment of infectious diseases in children in low malaria-prevalence areas (Gove 1997), taking into account the limitations of self-reported symptoms. For example, the symptom 'rapid breathing' was not identified by a health worker counting the breaths per minute, but instead is simply what was reported by the caregiver. The adapted algorithm is based on the absence or presence of the following key symptoms: fast breathing, cough, diarrhoea, blood in stool. Children in the study were classified as having one of the following illnesses: diarrhoea, dysentery, cough/cold, pneumonia, cough/cold + diarrhoea, pneumonia and/or dysentery, or other (Box 1). Due to the low prevalence of malaria in the urban community of Yurimaguas, fever was not included among the key symptoms and malaria was not classified separately.

Based on the principles of IMCI, symptoms were classified into two categories: illnesses where treatment with antibiotics would be recommended (pneumonia, dysentery, pneumonia and/or dysentery) and illnesses where antibiotic use would not be recommended (cough/cold, diarrhoea, cough/cold + diarrhoea).

Data analysis

Data from the questionnaires were introduced by double-entry into two identical EPI INFO 2000 databases by two trained data clerks and the databases compared; all disagreements were checked against the paper originals and corrected. The database was exported to STATA (StataCorp.), and checked for quality and consistency prior to data analysis. Chi-square tests were used to test for differences in proportions, and rates of antibiotic prescription were expressed as relative risks using medical doctors as the reference group.

Ethical clearance

This study was approved by the Ethics Committee of the Cayetano Heredia University in Lima, Peru, and the Ethics Committee of the Karolinska Institutet, Stockholm, Sweden (Dnr 02-447). Permission and informed consent was obtained from the Loreto District Health Administration, the Yurimaguas Hospital/Alto Amazonas Health Administration, and from the caregivers interviewed.

Results

A total of 798 children were included in the study and 504 were reported to have had at least one symptom in the previous two weeks, with an average of 3.7 symptoms per child (median 5, range 1–12). Antibiotic use during the preceeding 2 weeks was reported for 182 (36%) of the 502 children with symptoms (excluded were two children with

Box 1 Symptom classifications	
Symptom classification	Key symptoms qualifying child for symptom classification
Cough/cold	Fever, cough and other symptoms of cold. Absence of: diarrhoea, blood in stool, 'fast breathing'
Diarrhoea	Diarrhoea. Absence of: blood in stool, cough and other symptoms of cold, 'fast breathing'
Dysentery	Blood in stool, diarrhoea. Absence of: cough and other symptoms of cold, 'fast breathing'
Pneumonia	'Fast breathing', cough. Absence of diarrhoea, blood in stool.
Cough/cold + diarrhoea	Symptoms of cough/cold and symptoms of diarrhoea
Pneumonia and/or dysentery	One of following three combinations: symptoms of pneumonia and diarrhoea, or symptoms of pneumonia and dysentery, or cough/cold and dysentery
Other	Symptoms that occurred rarely, e.g. fever without other concurrent symptoms, accidents and skin problems

missing data on antibiotic use) and 25 were treated with more than one antibiotic, resulting in a total of 214 antibiotic courses adminstered. Fifty-seven percent of caregivers could show the interviewers packaging of the antibiotics and the rest remembered the name of the antibiotics or pointed out the antibiotics among samples shown to them. Seventy-one per cent of the antibiotics were prescribed by health professionals, mostly medical doctors (54%). Overall 49% of all antibiotics used were provided free of charge through the SIS state health insurance.

The links between illness, health-seeking, and treatment with antibiotics were investigated for the 439 children who had at least one symptom of infectious disease. Many caregivers consulted health care professionals from the public sector (42%) (Table 1), especially medical doctors (31%). Pharmacy staff were seldom consulted (6%). About half the consultations were made without applying any self-care at home (53%). For illnesses defined as needing antibiotics according to IMCI, including pneumonia and pneumonia and/or dysentery, the majority of caregivers consulted health professionals (57%) (Table 1). However, for 38% of pneumonia cases and 34% of pneumonia and/or dysentery cases, no health providers were consulted. For illnesses where IMCI would not recommend antibiotics including diarrhoea and cough/cold, the most frequent strategy used was self-care (60% and 48%, respectively). After eliminating the 32 children for whom no action was taken and a further seven with missing data, there were 400 children available for analysis of antibiotic treatment.

For illnesses needing antibiotics according to IMCI, pneumonia and pneumonia and/or dysentery, medical doctors prescribed antibiotics for 69% of the children. Compared to doctors, nurses prescribed antibiotics to a similar extent (RR: 10.05); parmacy staff prescribed more (RR: 1.24), while caregivers self-medicated their children with antibiotics significantly less frequently (RR: 0.23, CI: 0.10 < RR < 0.53). For illnesses defined as not needing antibiotics according to IMCI, such as cough/cold, diarrhoea and cough/cold + diarrhoea, medical doctors prescribed antibiotics to 58% of children. Nurses prescribed to a similar extent as doctors (RR: 0.96). The risk of receiving antibiotics was substantially lower for self-medicating patients (RR: 0.24) and those consulting pharmacy staff (RR: 0.52) than for those consulting doctors (Table 2). Medical doctors and nurses prescribed antibiotics to a similar extent for illnesses where antibiotics would and would not be recommended with no significant difference in prescription rates for the two classes of illnesses (doctors: $P = 0.24$; nurses: $P = 0.32$, Table 2). Pharmacists provided antibiotics significantly less frequently for illnesses where they would not be recommended (30% compared to 86%, $P = 0.016$). There were very low rates of antibiotic use for self-care, with no significant difference between the two classess of illnesses ($P = 0.78$).

The most common antibiotics prescribed by health professionals were ampicillin or amoxicillin (49%), followed by cotrimoxazole (21%), dicloxacillin (9%) and metronidazol (7%). Among caregivers self-medicating their children, tetracycline was most commonly used (31%) followed by ampicillin or amoxicillin (24%). All antibiotics used were on the Peruvian essential drugs list.

Discussion

Most antibiotics were prescribed by health professionals, mostly doctors and nurses. Their prescribing patterns need to be improved as antibiotics were issued also for illnesses

Table I Health-seeking behaviour of caregivers for children with different symptoms, expressed as number and percentage of children per reported symptom classification. Symptoms are classified based on IMCI algorithm

Reported symptom classification	No action taken*	Health-seeking behaviour (number of children, % of row total)				Total number of children
		Self-care	Consultation			
			Medical doctors	Nurse	Pharmacy staff	
Pneumonia	–	16 (38%)	21 (50%)	3 (7%)	2 (5%)	42 (100%)
Pneumonia and/or dysentery	3 (6%)	15 (28%)	22 (42%)	8 (15%)	5 (9%)	53 (100%)
Diarrhoea	2 (5%)	26 (60%)	9 (21%)	5 (12%)	1 (2%)	43 (100%)
Cough/cold	23 (11%)	97 (48%)	56 (27%)	18 (9%)	10 (5%)	204 (100%)
Cough/cold + diarrhoea	4 (4%)	41 (42%)	28 (29%)	14 (15%)	10 (10%)	96 (100%)
Total number of children (%)	32 (7%)	195 (45%)	136 (31%)	48 (11%)	28 (6%)	439

*This category includes children for which the caregivers chose to take no action to treat the reported symptoms.

Table 2 Number of children treated with antibiotics out of total children, stratified by source of advice and type of symptom classification leading to treatment, and by illnesses where antibiotics are recommended or not. Reported symptoms were classified as illnesses based on the IMCI algorithm. RR = relative risk of receiving antibiotic

| | Reported symptom classification prompting treatment | | | | | | | | | |
| Health provider | Illnesses recommended for antibiotic use* n = 91 | | | | Illnesses not recommended for antibiotic use† n = 309 | | | | | Total |
	Pneumonia	Pneumonia and/or dysentery	Total antibiotic use	RR	Cough/cold	Diarrhoea	Cough/Cold + Diarrhoea	Total antibiotic use	RR	
Medical doctor	13/21	16/21	29/42 (69%)	1.0	32/54	4/9	17/28	53/91 (58%)	1.0	82/133 (62%)
Nurse	2/3	6/8	8/11 (73%)	1.05 (0.70 < RR < 1.59)	10/17	2/5	5/12	17/34 (50%)	0.96 (0.68 < RR < 1.36)	25/45 (56%)
Pharmacy staff	2/2	4/5	6/7 (86%)	1.24 (0.86 < RR < 1.79)	2/9	1/1	3/10	6/20 (30%)	0.52 (0.68 < RR < 1.03)	12/27 (44%)
Self-care	1/16	4/15	5/31 (16%)	0.23 (0.10 < RR < 0.53)	5/97	10/26	8/41	23/164 (14%)	0.24 (0.16 < RR < 0.37)	28/195 (14%)
Total	18/42 (43%)	30/49 (61%)	48/91 (53%)		49/177 (28%)	17/41 (46%)	33/91 (36%)	99/309 (32%)		147/400 (37%)

*The illnesses recommended for treatment with antibiotics based on the IMCI algorithm for illness and treatment classification were *pneumonia, dysentery, pneumonia and/or dysentery.*
†The illnesses not recommended for treatment with antibiotics based on the IMCI algorithm for illness and treatment classification were *cough/cold, diarrhoea, cough/cold + diarrhoea.*

where they are inappropriate according to IMCI, such as cough/cold. Health workers' actions are influenced by many factors, including the health administration system (Sterky *et al.* 1991; Rowe *et al.* 2005). In Yurimaguas, diagnostic tools, such as blood tests, microscopy or cultures of specimen, were not included in the health care provided by the SIS, but had to be paid by the patient. Such lack of diagnostic tools has previously been shown to increase antibiotic prescriptions (Bosu & Ofori-Adjei 1997). For the health care provider another strategy could be to ask the patient to return if symptoms persist or become more severe. The Peruvian state insurance scheme however only allows for a restricted number of free visits and providers may have thus felt compelled to prescribe antibiotics more promptly even for cough/cold and diarrhoea. In addition, perceived as well as actual patient expectations for antibiotic treatment also are a powerful incentive for antibiotic prescription by medical doctors in Peru (Paredes *et al.* 1996). Though the low self-medication with antibiotics in Yurimaguas indicated a low demand, pressure could still have been there, as prescription of drugs was a sign of perceived quality of care in other studies (Brugha & Zwi 1998).

Many caregivers consulted health professionals without first attempting self-care. This differed from other settings (Develay *et al.* 1996; Larsson *et al.* 2000), also in Latin America (Bentley *et al.* 1995; Goldman & Heuveline 2000), where self-care was more common, and may be due to SIS health insurance providing health care and medicines free of charge to all children in the province. Insurances providing health care and medicines free of charge increase attendance at health facilities (Yip *et al.* 1998), whereas introduction of user fees results in decreasing attendance rates (Russell & Gilson 1997; Ridde 2003). However, 38% of children with reported pnemonia-like symptoms, a severe condition, did not seek health care at all. This may be due to socio cultural barriers or lack of responsiveness, both on the system level and on the level of individual health professionals (Travis *et al.* 2004).

The rate of self-medication with antibiotics in Yurimaguas was comparably low for both illnesses where antibiotics would and would not be recommended as treatment. This resulted in an under treatment with antibiotics for children whose caregivers chose not to seek health care for serious illnesses. The low level of self-medication differs from other parts of Peru (Llanos-Zavalaga *et al.* 2002) and from other LMIC in Asia, Africa or Latin America (Tomson & Sterky 1986; Bi *et al.* 2000; Larsson *et al.* 2000; Okumura *et al.* 2002). Antibiotics did not seem to be an important part of the self-medication of respiratory illnesses (cough/cold,

pneumonia), in contrast to other countries (Kunin *et al.* 1990; Hui *et al.* 1997; Chuc *et al.* 2001). Instead herbal medicines were widely used. The more common use of antibiotics for self-medicating diarrhoea was probably due to experience gained by the caregivers during the cholera epidemics in Peru, where tetracycline treatment was widely promoted by the MoH. Cultural, psychological and social factors, including perception of severity of illnesses, additionally influence health-seeking actions (Goldman & Heuveline 2000) and decisions regarding antibiotic use.

Compared to many other LMIC settings including Latin America (Crigger *et al.* 2004; Volpato *et al.* 2005), pharmacy staff in Peru dispensed fewer antibiotics without medical prescriptions (Lönnroth *et al.* 2000; Chuc *et al.* 2002). In contrast to other studies (Kroeger *et al.* 2001; Tumwikirize *et al.* 2004), in the few cases in our study where antibiotics were dispensed by pharmacy staff, they behaved more rationally than other health professionals, and provided fewer antibiotics for illnesses for which they are not recommended according to IMCI. Pharmacy staff, mainly assistants lacking formal training, may have shared the community members' habit of generally low antibiotic, or have been more attentive to MoH information campaigns promoting prompt treatment for rapid breathing. However, the results should be interpreted with caution, due to the low number of consultations with pharmacy staff.

The majority of antibiotics reported were included in the first line treatment guidelines and on the Peruvian essential drugs list (DIGEMID 2005). This contrasts with studies in other LMIC, where adherence to recommendations on essential drugs was poor (Hogerzeil *et al.* 1993).

Methodological considerations

This study collected retrospecive, self-reported information from caregivers on events that had taken place during the previous two weeks. Recall bias may thus have influenced the results. Even though interviewers were well trained and supervised during data collection, influence of an interviewer on the respondent cannot be excluded (Yeneneh *et al.* 1993; Krause *et al.* 1998). Since we did not collect information on duration and timing of the symptoms of the children, we could not exclude the possibility that some of the illnesses were still in progress at the time of the interview, resulting in biased reporting of certain health-seeking strategies. However, by relying on a few distinctive danger signs (fast breathing and blood in stools), one could argue that if signs were present, treatment should have been administered regardless of duration. The lack of

information on symptom timing and duration was also a constraint in illness classification. It can also be argued that the illness classification was not valid as a representation of which disease the child had, as caregivers may define symptoms differently than a health provider. However, these are generic challenges in real world research (Robson 2002). The illness categories used were not intended to be equivalent to a diagnosis given by a health provider, but were an attempt to provide a basis for assessing whether antibiotics were well used. The exclusion of children from the survey if they had symptoms of diarrhoea within the previous 24 hours has likely led to an underrepresentation of diarrhoeal cases in the sample, but this was necessary in order to not distort the microbiological investigations being part of the same study (Bartoloni 2006).

Conclusions

The majority of antibiotics provided were prescribed by providers from the public health care sector. As doctors and nurses commonly prescribed antibiotics for illness where they were not recommended, interventions for improving prescription habits are needed. On a systems level, availability and use of diagnostic tools could be included as part of services provided free of charge by the remuneration system. Remaining system barriers to health care should be adressed in order to avoid underprescription of antibiotics for severe illnesses.

Acknowledgements

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III

Insurance does not ensure access - problems in Amazonian Peru

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Abstract

Objectives

To compare health-seeking behavior for children in the Amazonian urban community Moyobamba, San Martin, Peru, at two time points during the years after the introduction of the Peruvian State Health Insurance Seguro Integral de Salud (SIS).

Methods

In two cross sectional studies caregivers of children aged 6-72 months (800 in year 2002 and 800 in year 2005) were interviewed on health seeking strategies and medication in relation to reported symptoms (classified into illnesses based on IMCI guidelines).

Results

The number of caregivers consulting health professionals decreased significantly in 2005 (74%) ($p<0.001$) compared to 2002 (91%). Significantly more ($p<0.001$) sought help from pharmacy staff (7% in 2002; 23% in 2005). The proportion of caregivers consulting health facilities without self caring decreased significantly (40% in 2005 and 76% in 2002, $p<0.001$). The percentage of children receiving antibiotics free of charge after consulting public health professionals decreased significantly 2005 (55%) ($p<0.001$) compared to 2002 (82%).

Conclusions

Evidence shows that implementation of the policy, meant to ensure access to health care, including for the poor, did not function. The implementation of the insurance policy should be improved to foster equitable access to good quality health care, including rational use of antibiotics.

Background

Access to affordable health care is limited in many low and middle income countries (LMIC) and health systems are often inequitable, providing less health services to the poor who need them most (Gwatkin, Bhuiya et al. 2004). In addition, ill health and the costs for health care and important medicines such as antibiotics further impoverish vulnerable population groups (Whitehead, Dahlgren et al. 2001). In LMICs the most substantial part of health financing often come from out-of-pocket expenditures.

Many low and middle income countries have given up the idea of universal coverage of health care free of charge, instead health financing relies more on cost recovery through user fees and social insurance (Leighton 1995; Collins, Quick et al. 1996). There is evidence that user fees represent an important barrier to accessing health services, especially for poor people (Fiedler and Suazo 2002). However, strategies targeting this population group, such as fee exemption mechanisms, can be stigmatizing and also costly as administrative measures are needed to identify the poor. For targeted interventions to be effective in reaching the poor, special strategies need to be carefully outlined (James 2006). As stated by Whitehead et al (Whitehead, Dahlgren et al. 2007), there is a need to investigate the impact of health policies on families and communities, with research focusing on households rather than the suppliers, in order to avoid policy making based on ideology and assumptions rather than evidence.

To improve access to health care, a state health insurance scheme, Seguro Integral de Salud (SIS) was introduced in Peru in 2001. One of the SIS strategies was to provide free health care and drugs to all children up to 15 years of age in provinces where poverty exceeds 60%, irrespective of their parent's economic status. Our previous findings from

the same area show that a high percent of consultations were with health care professionals and that 71% of antibiotics were obtained through the formal public health sector (Kristiansson, Reilly et al. 2008). This study compares health-seeking behavior in 2002 (right after the introduction of SIS) with that in 2005 (4 years after implementation (of SIS)) for children in households in Moyobamba, a small Amazonian urban community of Peru.

Methods

Study area

Population and socioeconomic structure

Two surveys were conducted in 2002 and 2005 in the Peruvian community of Moyobamba (Department of San Martin). The community has a population of approximately 32000 and represents one of the most underprivileged areas of Peru, the Amazonian Region. In Moyobamba the amount of the population living below the poverty line is 61% and in extreme poverty 25% (INEI 2005). The majority of the working population lives from subsistence farming (INEI 2004).

Health services

The study was conducted in urban settings with small geographical distances to health facilities. At the time of the first survey, the hospital in Moyobamba belonged to the Social Security Institute (ES SALUD), and the Ministry of Health facilities either referred patients to the nearby city Tarapoto or paid the ES SALUD hospital for treatment of public sector patients. At the time of the second survey the hospital was run by the

MoH. Moyobamba had three health posts and one health centre. The hospital and health center staff included medical doctors, whilst the health posts in both communities were staffed exclusively with nurses, midwives and health technicians.

In Moyobamba there were fifteen licensed private pharmacies. All had trained pharmacists on their staff list. However, in most cases they were run by assistants without formal education. The health facilities run by the MoH all had public pharmacies where generic drugs are sold, or provided free of charge if the SIS insurance covers the cost of the type of drug prescribed and the patient is enrolled in the SIS insurance scheme. Officially, antibiotics could only be sold by pharmacies to patients carrying a prescription, but, in practice they were bought without prescription at the pharmacies, the market place, in food stores or from traditional healers.

In 2001, the Maternal/Infant Insurance and the School Insurance were merged, creating the SIS. In theory, SIS provided consultations with health professionals, diagnostic services and essential pharmaceuticals from a pre-defined list free of charge via the public health care sector to those with a low economic status, pregnant women and senior citizens during the study period. In areas like the Amazonian area, with a poverty level higher than 60%, all children up to 15 years of age qualified for the insurance, irrespective of their parents' economic status. Affiliation to the insurance was not automatic and the children had to be registered every calendar year at the health facility's SIS office.

Means of data collection

Design and sampling

This cross-sectional survey used household interviews. Faecal samples were also collected for microbiological studies, which are not reported here (Bartoloni 2006). Children with three or more loose stools in the 24 hours prior to sampling (WHO definition of diarrhoea, 1993) were excluded from the study in order to ensure the implementation of the microbiological study within the same survey. A modified cluster sampling approach was used, where 80 clusters were sampled in each survey, including a total of 800 children aged 6 to 72 months, in 2002 and 800 in 2005. The city was divided into zones of varying sizes containing households distributed in blocks: each cluster consisted of 10 children (one per household) selected from the same or adjacent block. A stratified sampling of blocks (within zones) was conducted with a probability proportional to the size of the zone. In each selected block the interviewers randomly chose a corner of the block and visited households consecutively until they had recruited ten eligible children. If there was no child aged 6 to 72 months in a household, the interviewers proceeded to the next house.

Interviews

Interviews were conducted by ten trained interviewers from the public health sector (health technicians, nurses or midwives). The children's caregivers (mother, father, grandparent or other adult caregiver) were interviewed in the households using a structured questionnaire (available from the first author) which had been pre-tested and validated during a pilot study. The questions addressed the child's symptoms for the most recent illness during the previous two weeks and all actions taken by the caregivers to

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cure the symptoms, including medication and healing practices. A data quality system was developed in order to ensure high quality of the interviewers work during study implementation. On a daily basis, study supervisors screened the questionnaires for missing responses and logical inconsistencies and requested re-visits to households when more detailed clarification was needed. The interviewers also asked to see the package or blister pack if antibiotic use was reported by the caregivers. If interviewees were not in possession of the package anymore and did not remember the name of the antibiotic consumed but could describe the package, bottle or tablet, the interviewers presented them with samples of antibiotics in an attempt to identify the drug used. For similar purposes, the interviewers also carried a list of local antibiotic brand names and the corresponding ATC category (WHO 2006).

The health seeking behavior was classified into "self-care", "exclusive consultation (with persons working with health issues)" and "self care and consultations". Self-care was defined in line with Levin (Levin and Idler 1983) as all those activities undertaken to treat illness without professional assistance. We defined medical doctors, nurses and midwives, health technicians, pharmacy staff and traditional healers as professional assistance or, as stated in the questionnaire, "persons working with health issues".

Illness classification

The children's symptoms (reported by the caregivers) were classified in accordance with the principles of the Integrated Management of Childhood Illness (IMCI) algorithm for health worker classification and treatment of infectious diseases in children in areas with low malaria-prevalence (Gove 1997). The algorithm is based on the absence or presence

of the following key symptoms: fast breathing, cough, diarrhoea, and/or blood in stool. The sick children were classified with one of the following illnesses: diarrhoea, dysentery, cough/cold, pneumonia, cough/cold + diarrhoea, pneumonia and/or dysentery (Box 1).

Symptom classification	Key symptoms qualifying child for symptom classification
Cough/cold	Fever, cough and other symptoms of cold. Absence of: diarrhoea, blood in stool, 'fast breathing'.
Diarrhoea	Diarrhoea. Absence of: blood in stool, cough and other symptoms of cold, 'fast breathing'
Dysentery	Blood in stool, diarrhoea. Absence of: cough and other symptoms of cold, 'fast breathing'.
Pneumonia	'Fast breathing', cough. Absence of: diarrhoea, blood in stool.
Cough/cold + diarrhoea	Symptoms of cough/cold and symptoms of diarrhoea
Pneumonia and/or dysentery	One of following three combinations: symptoms of pneumonia and diarrhoea, **or** symptoms of pneumonia and dysentery, **or** cough/cold and dysentery

Box 1.

Analysis of economic status

In many low-income settings, it is problematic to use traditional measures such as income or consumption to assess an individual's financial status, due to practical limitations in collecting accurate data (Gwatkin 2000). In this study, *wealth* was used as a proxy indicator for economic status, under the assumption that *wealth* is reflected in the assets owned by a household (Wagstaff, van Doorslaer et al. 1999). Information regarding household assets and characteristics was collected during the interviews. A wealth index was constructed using principal component analysis (PCA), based on the following household assets and household characteristics: access to electricity, type of floor, type of toilet, type of water source and ownership of fan, TV, motor-bike, refrigerator and number of household members divided by number of rooms in the house. We used the first principal component to construct the wealth index. The consistency of the PCA assigned *wealth* scores with ownership of assets was controlled by cross tabulations. In order to capture relative variations, the population was divided in quartiles based on value of *wealth index variable*, as no absolute cut-off point could be assumed. For the analysis presented in this paper, quartile number one (Q1) was considered as a proxy for the lowest *wealth* - the poorest, and quartile number four (Q4) as the least poor – with most *wealth*.

Data analysis

The data from the questionnaires was entered into an EPI INFO 2000 database by double-entry and then compared. All discrepancies were checked against paper originals and corrected. The database was exported to STATA, where it was scrutinised for quality and consistency prior to data analysis.

The relations between *wealth,* health-seeking behaviour and antibiotic use at the two time points (2002 and 2005) were assessed.

Results

Morbidity

In 2002, caregivers reported that 460 (58%) of a total of 800 children included in the survey (Table 1) had shown symptoms classified as infectious illnesses in the previous two weeks. Of these, 3 children were excluded from further analysis because of missing data, leaving 457 children with reported infectious illnesses. In 2005, caregivers reported that 399 (50%) of the 800 children included in the survey had suffered from symptoms classified as infectious illnesses. One child was excluded due to missing data, leaving 398 children with reported infectious illnesses.

Health seeking behaviour

Many caregivers stated that they had consulted health professionals for self-reported symptoms classified as infectious illnesses according to the IMCI algorithm, both in 2002 (34%) and 2005 (44%) (Table 2). For non-severe illnesses such as cough/cold and diarrhoea, self-care was more common than consultation with health providers (60% 2002; 49% 2005), while for severe illnesses such as pneumonia or illnesses when a child had a mix of symptoms self-care was less common than consultation. In 2002, for non-severe as well as severe illnesses, the majority of caregivers who consulted health providers (including pharmacy staff) did so without attempting self-care (76%) (Table 3). In contrast, in 2005 the majority of caregivers who consulted health providers had also

self-cared for the children (60%) (Table 3). This pattern of change in health-seeking behaviour was similar regardless of the socio-economic status of households.

Even though the percentage of caregivers for children with reported infectious illnesses who had consulted a health provider had increased between 2002 and 2005, the number of caregivers who had consulted health professionals such as medical doctors, nurses or health technicians decreased from 91% in 2002 to 74% in 2005 ($p<0.001$) (Table 3). In contrast, the proportion of caregivers who chose to consult pharmacy staff increased significantly to 24% in 2005 compared to 7% in 2002 ($p<0.001$).

Caregivers sought help more promptly in 2002, when the majority (76%) of the caregivers who consulted health professionals did so directly, without applying self-care. In 2005 exclusive consulting decreased significantly ($p<0.001$) only 40% consulted providers without also applying self-care. The change was most marked among caregivers who consulted health professionals from the health sector (Table 3). This pattern of change in health-seeking behaviour was similar regardless of the socio-economic status of households.

Use of antibiotics

Compared with 2002, in 2005 more children were given antibiotics for illnesses for which such treatment is not recommended according to the IMCI guidelines. This was the case for cough/cold (32% in 2005; 25% in 2002) and for diarrhoea (38% in 2005; 18% in 2002). This was due to increased prescription of antibiotics by health providers. Self medication with antibiotics decreased in 2005, for all illnesses. For pneumonia the use of

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antibiotics had decreased (25% in 2005; 68% in 2002). In 2005 a higher percentage of the total use of antibiotics was as a result of consultation with pharmacy staff (6% and 18%, in 2002 and 2005 respectively) (Table 4) (p=0.002).

Cost charged for consultations with public sector health providers and drugs

According to the results, caregivers had paid out-of-pocket for antibiotics prescribed by the public sector even though they should have been provided free of charge within the SIS system. The percentage of children who received antibiotics free of charge after consulting a health professional decreased significantly (p<0.001) from 2002 (82%) to 2005 (55%). Similarly, costs were charged for health care services provided by public health providers, both in 2002 (19%) and 2005 (22%).

The place of purchase of antibiotics changed between 2002 and 2005. The proportion of all children with reported infectious illnesses that received antibiotics free of charge through SIS decreased from 48% in 2002 to 31% in 2005 (p=0.002) (Table 5). The change had been most substantial for the poorest and the least poor quartiles of the households. The poorest shifted place of purchase to public and private pharmacies and the least poor shifted to private pharmacies.

Discussion

We found that in spite of the presence of Seguro Integral de Salud (SIS) policy which provided formal financial access to health care for all children, the utilization of public health services in Moyobamba, Peru, had decreased in year 2005 compared to year 2002

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whilst the number of caregivers seeking advice from pharmacy staff increased. The study results show that many children seeking care from the public health services in 2005 had paid for the services, even though they should have qualified for free care. This was not the case in 2002.

Policies to ensure equitable access to health services have faced implementation problems worldwide. The functioning of user fee exemptions has been difficult in several countries (Russell and Gilson 1997; Kivumbi and Kintu 2002). Poor infrastructure, and/or poor preparedness of the health system, has complicated the implementation of strategies to ensure access to health care services (Bryce, Victora et al. 2005; Peters, Garg et al. 2008). In Latin America, the health reforms of the 1980s and 1990s, driven by the World Bank and other international agencies, promoted decentralization and privatization, including the creation of mandatory health insurances (Crocco, Schroeder et al. 2000; Homedes and Ugalde 2005). Also in the Latin American context, policy implementation has been problematic. In several countries the health care administration proved to be too weak to provide the necessary control measures and correct reimbursements to health facilities. A previous publication from our study has shown inequities in access to health care, in spite of the presence of a health policy formally providing free health care for children (Kristiansson, Gotuzzo et al. 2009).

The utilization of health services for children in Moyobamba was high in year 2002, shortly after SIS was introduced, and many caregivers sought help directly, without practicing self-care. In 2005, on the other hand, more caregivers sought help at pharmacies or waited before seeking help from health services. Similar patterns of change were seen for all socio-economic strata, there were no differences in change in

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health-seeking behaviour in relation to wealth. In the years 2003-2005 SIS faced implementation problems similar to those experienced in other Latin American countries (Homedes and Ugalde 2005). Information from key informants (unpublished data) revealed that administrative problems delayed or redirected health facility reimbursements. As a consequence some health facilities started to charge patients or restricted the number of patients per day to receive free health care. In addition, many facilities charged for laboratory services that should have been free. User fees are known to act as an effective barrier to health service access (Palmer, Mueller et al. 2004). The administrative aspects of SIS were other barriers. To benefit from the insurance the patients needed to register formally every year and the opening hours of the registration office were limited. The health workers' observed negative attitude to the policy could have contributed to the subsequent decreases in prompt consultations. Walker et al (Walker and Gilson 2004) showed how policies removing financial barriers to access in South Africa were compromised by worsened health provider attitudes towards patients. Providers worried about the increased workload and had the impression that patients abused the free services made available.

The number of caregivers who consulted pharmacy staff increased during the study period. A similar situation - bypassing health services in favour of private pharmacy consultation has been described in several studies, both in Latin American and other regions (Chuc and Tomson 1999; Larsson, Kronvall et al. 2000; Llanos-Zavalaga, Mayca Perez et al. 2002). The increase in private pharmacy consultation could also be linked to the availability of pharmaceuticals, including brand-name antibiotics, in the pharmacies. In Moybamba the MoH health facilities provided only generic

pharmaceuticals, which are often not appreciated by patients (Himmel, Simmenroth-Nayda et al. 2005). Also stock-outs of pharmaceuticals could have been a problem. DIGEMID (the Peruvian Direction for Management of Consumables and Drugs) confirmed that some provinces suffered delays in the procurement and distribution of drugs during the decentralization of pharmaceutical management (Romero 2002). In addition, Peruvian private pharmacies have started to market themselves more aggressively. The provinces have followed the trend previously seen in Lima, where the large regional well-established pharmacy chains directly, and very actively, promote their services to consumers.

The irrational use of antibiotics increased in 2005 compared to 2002. The use increased for diarrhoea and ARI, illnesses that should not be treated with antibiotics according to the IMCI (Gove 1997). The increase noticed consisted mainly of antibiotics prescribed by health professionals or recommended in consultation with pharmacy staff. Self medication with antibiotics, on the other hand, decreased for all illnesses. Perceived patient pressure is a well-known influencing factor for provider performance (Paredes, de la Pena et al. 1996). The increased prescription of antibiotics could be an attempt to keep patients satisfied as the health professionals were aware that an increasing proportion of caregivers turned to pharmacies for health advice.

The caregivers changed their purchase place of antibiotics. In total, fewer children received antibiotics through SIS in 2005. The new place of purchase differed depending on socio economic status. The least poor shifted to private pharmacies while the poorest caregivers started purchasing antibiotics from both private and public pharmacies. The caregivers who bought their antibiotics from public pharmacies would have received the

same type of drugs as the SIS offered, as the public pharmacies only provide generic antibiotics. As the practical benefits with purchasing antibiotics from the public pharmacy as compared with SIS are few for the patients, it seems unlikely that it is linked to an active choice based on for example perception of higher quality of drugs. Rather, this indicates a poor policy implementation with the health services either failing on providing the services as stated in the SIS policy or failing in informing the patients of their rights to free services for the children. Examples from other policy implementation also show problems if the approach is top-down (Nsabagasani, Jesca Nsungwa et al. 2007).

This study gathered retrospective, self-reported information from caregivers on events that had taken place during the previous two weeks. Thus, like in all studies of this nature recall bias may have influenced the results. However, the interviewers were carefully trained in asking detailed questions to understand the details of health seeking events. Both individual and group supervision meetings were held daily, through-out the survey, to review the daily interviews and reinforce the interview technique.

In conclusion, the implementation of the insurance policy should be improved to foster equitable access to good quality health care, including rational use of antibiotics. Members of the community should be involved in the improvements of SIS implementation. They should have ready access to information about the rules and regulations of the insurance. These improvements to implementation are even more important as the Peruvian Government is currently restructuring the SIS to cover the whole population, not only the groups previously targeted.

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Ethic clearance

This study was approved by the Ethics committee of Universidad Peruana Cayetano Heredia in Lima, Peru, and Karolinska Institutet, Stockholm, Sweden (Dnr 02-447). Permission and informed consent was obtained from the Loreto District Health Administration, Yurimaguas Hospital, and from the caregivers.

Competing interests

The authors declare that they have no competing interests.

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Prevalence of illnesses

Illness	2002	2005
Cough/cold	55% (288)	62% (292)
Pneumonia	4% (19)	3%(12)
Cough/cold + diarrhoea	20% (106)	6% (30)
Pneumonia and/or dysentery	2% (11)	1% (7)
Diarrhoea	6% (33)	12% (57)
Subtotal Infectious illnesses	87% (457)	85% (398)
Other	13% (67)	15% (71)
Total	524	499

Table 1. Illnesses based on self-reported symptoms (classified in illnesses based on principals from IMCI) in Moyobamba 2002 and 2005.

Health-seeking behaviour in relation to illness groups

Illness group	2002					2005				
	No action taken	Self-care	Exclusively consultation	Consultation and self-care	Total	No action taken	Self-care	Exclusively consultation	Consultation and self care	Total
Non-severe	36(11%)	192(60%)	72 (22%)	21 (7%)	321	28 (8%)	172 (49%)	60 (17%)	90 (26%)	350
Severe	1 (3%)	9 (30%)	12 (40%)	8 (27%)	30	-	7 (39%)	5 (28%)	6 (33%)	18
Mix of non-severe symptoms	12 (11%)	49 (46%)	33 (31%)	12 (12%)	106	1 (4%)	15(50%)	4 (13%)	10 (33%)	30
Total	49 (11%)	250(55%)	117 (25%)	41 (9%)	457	29 (7%)	194(49%)	69 (17%)	106 (27%)	398

Table 2. Health-seeking behaviour in relation to illness groups. Illness groups defined as following: *Non-severe* includes cough/cold and diarrhoea; *Severe* includes pneumonia and Pneumonia and/or dysentery; *Mix of non-severe symptoms* includes Cough/cold + diarrhoea.

Health-seeking strategy in relation to health care provider

Health care provider	Moyobamba 2002			Moyobamba 2005		
	Exclusively consultation (percent of row)	*Consultation and self-care* (percent of row)	*Total consultation* (percent of column)	*Exclusively consultation* (percent of row)	*Consultation and self-care* (percent of row)	*Total consultation* (percent of column)
MD public sector	94 (80%)	24(20%)	**118 (77%)**	38 (42%)	52 (58%)	**90 (52%)**
MD private sector	6 (75%)	2 (25%)	**8 (5%)**	5 (36%)	9 (64%)	**14 (8%)**
Health technician	11 (79%)	3 (21%)	**14 (9%)**	5 (21%)	19 (79%)	**24 (14%)**
Nurse	-	-	**-**	-	1 (100%)	**1 (1%)**
Subtotal health sector	111 (79%)	29(21%)	**140 (91%)**	48 (37%)	81 (63%)	**129 (74%)**
Public pharmacy staff	1 (50%)	1 (50%)	**2 (1%)**	4 (40%)	6 (60%)	**10 (6%)**
Private pharmacy staff	3 (38%)	5 (63%)	**8 (5%)**	15 (48%)	16 (52%)	**31 (18%)**
Subtotal pharmacy	4 (36%)	7 (64%)	**10 (7%)**	20 (43%)	23 (57%)	**41 (24%)**
Other	2 (67%)	1 (33%)	**3 (2%)**	2 (67%)	1 (33%)	**3 (2%)**
Total	117 (76%)	36 (24%)	**153**	69 (40%)	104 (60%)	**173**

Table 3. Health-seeking strategy in relation to health care provider for caregivers who either exclusively consulted providers or consulted providers in combination with self-care for years 2002 and 2005, expressed as numbers and percentage of total numbers of caregivers who consulted health providers (either exclusively or in combination with self care). Due to missing data, five children were excluded in 2002 and two children were excluded in 2005.

Source of antibiotics	Moyobamba 2002	Moyobamba 2005
Medical doctors	50%	56%
Nurse/health technician	6%	8%
Pharmacy staff	6%	18%
Self-care	32%	14%
Other	6%	4%
Total	100%	100%

Table 4. Source of antibiotics for all the antibiotics used for self-stated infectious illnesses, percentage of total amount of self-stated antibiotic used per community and year.

Place of antibiotic purchase

Place of purchase		2002	2005
Group1: (cost charged)	Public pharmacy	30(20%)	41(29%)
	Private pharmacy	38(25%)	50(36%)
	Other	11(7%)	5(4%)
Group 2: (free of charge)	Health insurance	74(48%)	43(31%)
	Total	**153**	**139**

Table 5. Place of antibiotic purchase for years 2002 and 2005 for all children that were treated with antibiotics, divided into two groups; group 1; public pharmacy, private pharmacy and other, where a cost is charged for antibiotics and group 2; Health insurance, where no cost is charged.

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ORIGINAL ARTICLE

Socioeconomic factors and antibiotic use in relation to antimicrobial resistance in the Amazonian area of Peru

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Abstract

Our objective was to correlate antibiotic resistance in gut E. coli flora of children, aged 6–72 months, with use of antibiotics, socioeconomic status (SES) and household characteristics in the urban communities of Yurimaguas and Moyobamba in the Amazonian area of Peru. Caregivers of 1598 children were interviewed using a structured questionnaire in a cross-sectional survey. Faecal samples were collected from the children and the antimicrobial susceptibility of E. coli was analysed by a rapid resistance screening method. Significantly higher odds for resistance were seen for children who had used antibiotics, both during the last 2 weeks and the last 6 months. Children from wealthier families had significantly higher odds for resistance to a number of antibiotics than children from the least wealthy families (Yurimaguas: nalidixic acid, OR = 2.13; ciprofloxacin, OR = 2.09; chloramphenicol, OR = 1.98. Moyobamba: nalidixic acid, OR = 1.59; ciprofloxacin, OR = 1.69). Thus, the children of wealthier families had a significantly increased odds ratio for resistance, also when controlling for the family's antibiotic use. Unknown factors related to socioeconomic status seem to contribute to the results seen in the study area.

Introduction

Antibiotics are one of the most important medical discoveries of the last century. However, the emerging resistance among pathogens gradually diminishes their potency. In many countries, the cost of newer antibiotics which replace drugs that have become powerless due to resistance, is a burden both to the individual and to society. Although antibiotic resistance is a worldwide problem, several studies have reported remarkably high prevalence of antimicrobial-resistant clinical isolates in low- and middle-income countries [1]. There is increasing evidence that non-clinical bacterial strains, such as commensal intestinal bacteria of humans and animals, may play an important role for the increase of resistance [2]. It is well documented that commensal intestinal bacteria represent a major reservoir for resistance genes [3], which can be transferred to more pathogenic hosts. Another risk factor is the dissemination of resistant bacteria within the community, between people and into water sources [4]. The human and non-human use of antimicrobials has been identified as a major contributor to the development and spread of antibiotic resistance. However, the association between antibiotic use and antibiotic resistance has seldom been described at a community level.

To implement tailor-made interventions aiming at containment of antibiotic resistance, it is important to understand how different groups in society are affected by and contribute to the problem of

emerging resistance. Socioeconomic status (SES) has been shown to be closely linked to health [5]. Poverty puts constraints on material conditions of life, linking overcrowding [6], inappropriate nutrition [7] and inability to maintain optimal hygiene practices to increased risk of infections. In addition, financial restrictions per se influence health-seeking behaviour. Many of these factors are also related to emerging resistance [8], but the relationship between SES and resistance is influenced by factors such as spread of bacteria as well as overuse of antibiotics. The few existing studies, from high income settings exclusively, show somewhat contradictory patterns of association between antibiotic resistance and SES [9–11]. There is a lack of studies that describe the association of resistance and antibiotic use at community level.

There is also a lack of studies from low-income countries investigating the association of SES and antibiotic resistance. We therefore investigated the association of antibiotic resistance to antibiotic use in one of the poorest areas in Peru, the Amazonian region. We have also studied the association of resistance to SES and to factors related to spread of bacteria.

Materials and methods

Population and socioeconomic structure

This cross-sectional study was conducted in 2002 in the communities of Yurimaguas, Loreto district, and Moyobamba, San Martin district, in the Amazonian region of Peru. In 2002, both communities had a population of approximately 32,000 inhabitants each. Approximately 55% of the population lives below the poverty limit, and 15% in extreme poverty [12]. 16% of the population is illiterate, the majority (60%) being women.

Data collection

Design and sampling. In this cross-sectional survey, household interviews were performed and faecal samples collected for microbiological analysis. In each community, nearly 800 children, aged 6–72 months, were included using a modified cluster sampling approach, where 80 clusters were sampled. Both cities were divided into zones of varying sizes containing households distributed in blocks: each cluster consisted of 10 children (one per household) selected from the same or adjacent block. A stratified sampling of blocks (within zones) was conducted with a probability proportional to size of the zone. In each selected block the interviewers randomly chose a corner of the block and visited households consecutively until they had recruited 10 children. The

interviewers proceeded to the next house if there was no child aged 6–72 months. Any child that had 3 or more loose stools in the last 24 h (WHO definition of diarrhoea) was excluded from the study to ensure minimal distortion of the normal intestinal bacterial flora.

Interviews. 10 interviewers from the public health sector (health technicians, nurses or midwives) were trained per community. Five were chosen as interviewers and the others allocated as their partners with responsibility for collecting faecal samples from the study children. The caregivers of the children (mother, father, grandparent or other adult caregiver) were interviewed during the household visit by means of a structured questionnaire assessing the family's socioeconomic setting, the health status of the child together with health care and drug consumption patterns, and drug consumption patterns among the other family members. The questionnaire was pre-tested and validated during a pilot study in the study sites. Antibiotic use was assessed through a step-wise procedure. In households where antibiotics had been used, the interviewers asked to see the antibiotic package, and if this was unavailable they asked for the name of the antibiotic used. If the interviewee did not remember the name but could describe the package, bottle or tablet, the interviewer showed samples of antibiotics to help in the identification of the antibiotics used. The antibiotic packages were available for 55% of the consumption in the last 2 weeks in Moyobamba and 58% in Yurimaguas. Study investigators checked the questionnaires daily with the interviewers for missing responses and logical inconsistencies.

Ethical approval was obtained from the Ethics Committee of the Cayetano Heredia University in Lima, Peru, and the Ethics Committee of the Karolinska Institute, Stockholm, Sweden. Permission and informed consent was obtained from the Loreto District Health Administration, the Yurimaguas Hospital/Alto Amazonas Health Administration, and from the caregivers interviewed.

Microbiological analysis. The antimicrobial susceptibility of E. coli was analysed by means of a simple and robust rapid resistance screening method that has been described in the last publication from the same study [13]. The rapid resistance screening method was originally devised to pick up total frequency of resistance [14,15]. A drawback of using this method is the scarcity of studies using the same method, making comparisons difficult. Using rapid screening, it was possible to assess the dominant E. coli flora in the samples correlating to

the regular measures of antibiotic resistance, making it possible to compare with studies using traditional resistance measures, i.e. disk-diffusion susceptibility test. Ordinary breakpoints for resistance could not be used for the rapid screening since the method is not standardized and uses other media and inoculates; however, new breakpoints were established during a pilot study for method development [16].

The measure of total resistance includes all resistance phenotypes present in the normal faecal E. coli-like flora of the child, regardless of frequency. These are cases where no inhibition zone can be observed, cases where an inhibition zone smaller than the breakpoint can be observed or cases of resistant clones of low frequency that are observed as single or semi-confluent colonies or as dense growth inside inhibition zones of the majority of the growth – the presumed dominant flora. Thus, the method gives useful information on the total available gene pool of resistance in the population being surveyed. The resistance in the dominant flora was defined as cases where no inhibition zone was observed and cases where an inhibition zone smaller than the breakpoint was observed.

Socioeconomic analysis. Income, occupation and education have traditionally been used to estimate social position, either together in composite measures or used interchangeably [17]. Oakes and Rossi suggest a definition stating that SES is a summary of level of access to financial, human and social capital [18].

Wealth status was used as an estimation of economic status. In this study no composite measure of SES was constructed, and instead two of Oakes and Rossi's SES components were addressed separately: wealth as a measure of financial capital and educational status as a measure of human capital. A wealth index was constructed using principal component analysis (PCA), based on the following household assets and household characteristics: family size divided by number of rooms, access to electricity, type of floor, type of toilet and ownership of fan, TV, motor-cycle and refrigerator. We used the first principal component to construct the wealth index. For the purpose of cross-analysis of wealth with antibiotic resistance, the households were divided into quartiles based on the value of the wealth index variable in order to capture relative variances, as no absolute cut-off point could be assumed. The lowest quartile was considered as a proxy for the lowest wealth status, the poorest; the highest quartile as the least poor. The consistency of the PCA-assigned wealth scores with ownership of assets was controlled by cross-tabulations.

For the purpose of data analysis, educational status was defined as the highest education achieved by the mother of the child included in the study.

Statistical analyses. The association between antibiotic resistance and wealth and education was investigated by univariable and multivariable logistic regressions. In addition, a number of variables which potentially could explain eventual differences in resistance related to the SES were investigated. Antibiotic use, which selects for resistant bacteria, and horizontal spread of resistant bacteria are both linked to SES, through access to antibiotics and through material consequences of wealth that favour spread of bacteria. The variables investigated in the analysis included: 1) material consequences of financial status, such as access to water, sanitary facilities and crowding that could be related to disease and spread of bacteria; and 2) behavioural consequences, such as antibiotic use. Variables cross-analysed with antibiotic resistance were the following: wealth, educational level of mother, type of water source, crowding (defined as family size divided by number of rooms), type of toilet, and use of antibiotics during the last 2 weeks. In the analysis, the antibiotics with resistance levels close to 100% were excluded (cotrimoxazole, amipicillin and tetracycline), as the high levels prevented meaningful analysis.

χ^2 test and logistic regression were used to assess the association between various variables and resistance to each type of antibiotic tested in the microbiological studies.

Results

Background data

In Yurimaguas, 14% of mothers had a higher education, and in Moyobamba, 25%. In Yurimaguas, 72% of households included in the study had access to the public water net, compared to 92% in Moyobamba. In Yurimaguas, 20% of households lacked access to any sanitary services, while in Moyobamba, 5% of households lacked the same services. Due to these differences between Yurimaguas and Moyobamba, the analyses were performed separately for the two communities.

Antimicrobial resistance

There was a high rate of antibiotic-resistant clones of E. coli in both communities, as has been reported in a last publication from the same study [13]. The measure of total resistance, including less frequent clones, showed highest resistance to cotrimoxazole, ampicillin and tetracycline, with values ranging

between 89% and 93% of the samples. For strepto-mycin and chloramphenicol, resistance values ranged from 69% to 86%. For nalidixic acid, kanamycin, ciprofloxacin and gentamicin, resistance was 19–41%. Resistance to nitrofurantoin, amikacin and ceftriaxone was lowest (range 0.1%–17%). Differences between Yurimaguas and Moyobamba could be observed, with resistance to streptomycin, nalidixic acid, ciprofloxacin and nitrofurantoin significantly more common in Moyobamba than in Yurimaguas ($p < 0.001$). The measure of antibiotic resistance, which is an approximation of the dominant normal flora, showed lower values of resistance, but still with similar patterns.

Patterns of antibiotic use in Yurimaguas and Moyobamba

Ampicillin/amoxicillin was the most common antibiotic given to children and their family members during the last 2 weeks (Table I). Cotrimoxazole was the second most common antibiotic in children. All other antibiotics were used in low frequencies. Fenoxymethylpenicillin was the second most commonly used antibiotic for other members of the household.

Stratification of the reported number of days of antibiotic use showed a similar pattern for both poorest and wealthiest quartiles.

Association between antibiotic resistance and last antibiotic use or use in the family

The children who had either taken antibiotics in the last 6 months (including the last 2 weeks) and/or had family members who had taken antibiotics during the last 2 weeks had significantly higher odds ratios for resistance compared to children where no antibiotic use was reported for the child during the last 6 months or for other family members in the last 2 weeks (Yurimaguas (Table II): streptomycin, chloramphenicol, nalidixic acid, kanamycin, ciprofloxacin, gentamicin; Moyobamba (Table III): streptomycin and gentamicin). The odds ratio for antibiotic resistance was significantly higher for children who had taken antibiotics in the last 2 weeks compared to those who had not (Yurimaguas: chloramphenicol, nalidixic acid, kanamycin, ciprofloxacin, gentamicin; Moyobamba: nalidixic acid, gentamicin, not shown in table). On the other hand, there were no significant differences in odds ratios for children who had taken antibiotics less recently (during the last 6 months but not the last 2 weeks) compared to children who had not taken any antibiotics.

Association between antibiotic resistance and SES

Univariable logistic regressions showed that for wealth, there were significant differences in resistance to antibiotics with an intermediate resistance level. No significant difference in resistance levels was seen for educational status.

The results showed higher resistance odds for the least poor categories compared to the poorest categories (Yurimaguas: nalidixic acid, OR = 2.13; ciprofloxacin, OR = 2.09; chloramphenicol, OR = 1.98. Moyobamba: nalidixic acid, OR = 1.64 and 1.59; ciprofloxacin, OR 1.77 and 1.69). The same analysis was performed in a subgroup of children

Table I. Antibiotic use in the last 2 weeks in Yurimaguas and Moyobamba, for the child included in the study as well as for the other family members.

Antibiotic used last 2 weeks	For the child included in the study		For the rest of the household	
	Moyobamba	Yurimaguas	Moyobamba	Yurimaguas
Ampicillin/amoxicillin	76 (44%)	89 (40%)	101 (63%)	100 (54%)
Sulfamethoxazole + trimethoprim (cotrimoxazole)	36 (21%)	41 (19%)	8 (5%)	9 (5%)
Metronidazole	13 (8%)	19 (9%)	4 (2%)	12 (6%)
Macrolide	11 (6%)	5 (2%)	2 (1%)	5 (3%)
Other	11 (6%)	19 (9%)	1 (1%)	1 (0.5%)
Dicloxacillin	6 (3%)	15 (7%)	8 (5%)	20 (11%)
Tetracycline/doxycycline	13 (8%)	16 (7%)	9 (6%)	3 (2%)
Chloramphenicol	1 (0.6%)	7 (3%)	2 (1%)	4 (2%)
Gentamicin/amikacin	1 (0.6%)	–	2 (1%)	3 (2%)
Fenoxypenicillin	2 (1%)	1 (0.5%)	16 (10%)	20 (11%)
Ampicillin/sulbactam or amoxicillin/clavulanic acid	3 (2%)	8 (4%)	4 (2%)	–
Drugs for treatment of tuberculosis	–	1 (0.5%)	–	4 (2%)
Ciprofloxacin	–	–	4 (2%)	5 (3%)
Total	173	221	161	186

Table II. Logistic regressions investigating association of total antibiotic resistance with SES (wealth and education) and antibiotic use (Atb use) in Yurimaguas. Results shown as odds ratio (OR) and corresponding confidence intervals (CI), with statistically significant values marked in bold. Total resistance includes resistance where no inhibition zone was seen, the inhibition zone was smaller than the breakpoint as well as single or low-frequency resistant colonies. Levels of total resistance are presented in percentage under each antibiotic name.

Yurimaguas

SES variables		Streptomycin 71%		Chloramphenicol 69%		Nalidixic acid 27%		Kanamycin 22%		Ciprofloxacin 16%		Gentamicin 19%		Nitrofurantoin 5%	
		OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Wealth (compared to 'Least wealthy')	Wealth level 2	0.78	0.495–1.241	1.32	0.849–2.048	1.20	0.730–1.974	1.56	0.923–2.633	1.22	0.677–2.207	1.18	0.696–2.009	0.63	0.200–1.949
	Wealth level 3	0.84	0.530–1.338	1.38	0.885–2.149	1.26	0.785–2.108	1.62	0.961–2.733	1.18	0.650–2.137	0.80	0.455–1.412	1.30	0.499–3.365
	Wealthiest	1.13	0.703–1.828	**1.98**	**1.243–3.141**	**2.13**	**1.326–3.415**	1.56	0.923–2.633	**2.09**	**1.206–3.631**	1.49	0.889–2.489	1.70	0.689–4.224
Education (compared to 'no education/ primary school')	Secondary school/ Higher studies	1.12	0.821–1.535	1.09	0.801–1.488	1.36	0.978–1.892	1.41	0.986–2.003	1.44	0.967–2.153	1.18	0.816–1.712	1.02	0.543–1.910
Wealth (compared to 'Least wealthy', in a subgroup with no atb use last 6 months, (including last 2 weeks), for child or rest of family)	Wealth level 2	0.77	0.402–1.473	1.73	0.902–3.311	0.86	0.399–1.856	0.99	0.431–2.259	0.56	0.180–1.722	0.67	0.280–1.589	0.70	0.114–4.321
	Wealth level 3	1.28	0.639–2.548	1.57	0.812–3.016	1.19	0.562–2.501	1.39	0.624–3.088	1.07	0.408–2.824	0.72	0.301–1.722	0.37	0.038–3.647
	Wealthiest	1.85	0.861–3.978	**4.07**	**1.819–9.104**	**2.10**	**1.006–4.369**	1.83	0.823–4.089	1.87	0.730–4.793	1.55	0.699–3.451	2.82	0.677–11.761
Antibiotic use Atb use child and family (compared to no atb use, by child or other family members)	Atb used by the child last 2 weeks and/or last 6 months and/ or by other family members	**1.67**	**1.207–2.308**	**1.39**	**1.006–1.913**	**1.72**	**1.194–2.480**	1.46	0.992–2.139	**1.86**	**1.180–2.928**	**1.91**	**1.243–2.928**	1.514	0.734–3.124

Table III. Logistic regressions investigating association of total antibiotic resistance with SES (wealth and education) and antibiotic use (Atb-use) in Moyobamba. Results showed as odds ratio (OR) and corresponding confidence intervals (CI), with statistically significant values marked in bold. Total resistance includes resistance where no inhibition zone was seen; the inhibition zone was smaller than the breakpoint as well as single or low-frequency resistant colonies. Levels of total resistance are presented in percentage under each antibiotic name.

Moyobamba

SES variables		Streptomycin 86%		Chloramphenicol 72%		Nalidixic acid 41%		Kanamycin 23%		Ciprofloxacin 25%		Gentamicin 21%		Nitrofurantoin 17%	
		OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Wealth (compared to 'Least wealthy')	Wealth level 2	1.03	0.559–1.882	1.18	0.746–1.878	**1.64**	**1.076–2.518**	1.23	0.745–2.025	**1.77**	**1.075–2.921**	1.57	0.953–2.592	1.06	0.603–1.854
	Wealth level 3	0.88	0.488–1.598	0.88	0.560–1.370	1.40	0.914–2.155	1.01	0.607–1.693	**1.69**	**1.022–2.794**	1.05	0.622–1.785	0.86	0.480–1.539
	Wealthiest	0.94	0.512–1.709	1.00	0.635–1.586	**1.59**	**1.036–2.448**	1.28	0.777–2.117	1.48	0.886–2.478	1.10	0.647–1.861	1.43	0.834–2.4659
Education (compared to 'no education/ primary school')	Secondary school/ Higher studies	0.95	0.611–1.465	0.97	0.694–1.351	1.32	0.972–1.796	1.14	0.790–1.630	**1.43**	**1.002–2.050**	**1.51**	**1.023–2.225**	1.04	0.698–1.546
Wealth (compared to 'Least wealthy', in a subgroup with no atb use last 6 months (including last 2 weeks))	Wealth level 2	0.52	0.226–1.208	0.94	0.453–1.961	1.34	0.656–2.754	1.00	0.396–2.532	1.23	0.537–2.808	1.91	0.810–4.534	1.30	0.552–3.084
	Wealth level 3	0.70	0.284–1.698	0.64	0.307–1.324	1.22	0.581–2.566	0.97	0.373–2.541	1.25	0.535–2.916	0.36	0.096–1.342	0.64	0.228–1.784
	Wealthiest	1.49	0.494–4.498	0.97	0.434–2.109	1.70	0.796–3.641	1.96	0.805–4.777	1.35	0.565–3.247	1.28	0.479–3.409	1.59	0.653–3.896
Antibiotic use	Atb used by the child last 2 weeks and/or last 6 months and/or by child or other family members (compared to no atb use, by child or other family members)	**1.67**	**1.109–2.535**	1.30	0.943–1.804	1.22	0.903–1.656	1.39	0.960–2.006	1.13	0.796–1.593	**1.49**	**1.014–2.191**	0.81	0.551–1.191

Type and level of total antibiotic resistance

where no antibiotic use was reported for the child during the last 6 months and no use was reported for the other family members during the last 2 weeks. In this group the same result was seen, with higher odds ratios for antimicrobial resistance for the wealthiest categories.

Multivariable analysis

Multivariable logistical regressions were performed with the variables that had shown significant differences, wealth and antibiotic use in the family. There were significant differences between wealth status categories in Yurimaguas, also when controlling for the family's antibiotic use (Table IV). The same was true when controlling for antibiotic use by the child in the last 2 weeks (not shown in table). There were no significant differences between the wealth status categories in Moyobamba.

Dominant flora

The results of the analysis of the dominant, normal flora showed a similar pattern to the total resistance category with respect to association with wealth levels and with antibiotic use, i.e. the dominant flora also showed increased odds ratios for resistance for the wealthier categories compared to the least wealthy households. The differences between the wealth categories remained when controlling for the family's antibiotic use.

Association between antimicrobial resistance and material factors related to poverty

The relation between antimicrobial resistance and a number of material factors that were chosen to reflect the material consequences of SES was also tested. The variables chosen were type of water source (public net, private well, public well, river, other), type of toilet (water closet, latrine, open field, other) and crowding (measured as number of people sleeping in the same room). No statistically significant differences were found in antibiotic resistance between children from households, reflecting this wide spread of material factors.

Discussion

Antimicrobial resistance to several commonly used antibiotics was shown to be very high in faecal E. coli flora from healthy children. For some of the commonly used antibiotics, as many as 90% of the samples exhibited total resistance, i.e. exhibited either resistant dominant flora or the presence of resistant clones, as reported earlier in publications

from the same study [13]. In both Yurimaguas and Moyobamba, the estimated resistance in the dominant flora was also very high for most tested antibiotics. Comparatively, in Spain 58.5% ampicillin resistance in E. coli was found in the bacterial flora of healthy children [19], while high E. coli resistance levels also have been reported from Peru, Venezuela and Mexico [20].

We found a significant association between last use of antibiotics and resistance for a number of antibiotics. Significantly higher resistance levels were seen when the children and/or their family members had consumed antibiotics for the last 2 weeks and/or the last 6 months. Our study confirms the results from a number of studies that have shown association between E. coli resistance and last antibiotic use both in patients with urinary tract infections and in healthy volunteers [21]. These last studies have, however, been carried out in hospital settings or by comparing resistance data with consumption data from pharmacy statistics [22,23]. Our community based study, on the other hand, has linked self-reported antibiotic consumption for the children included in the study and their family to resistance in faecal E. coli flora of the children and gives information in relation to the total resistance, including less frequent resistant clones.

We have shown that children from high SES families had a significantly increased odds ratio for total resistance – the test level including all resistant clones appearing on the plate – to a number of antibiotics, such as nalidixic acid, ciprofloxacin and chloramphenicol. A similar, non-significant trend could also be seen for other antibiotics. The dominant flora showed the same patterns. In other settings, increased resistance in higher SES strata has been explained by an increased antibiotic use by wealthier families. Antibiotic use has been proposed as the key driver of resistance [24,25]. In Spain, the correlation found between resistance and educational level was explained by differences in antibiotic use, which appeared to be the basic and only force behind the various resistance patterns [26]. In a Swedish study, the association between high SES and resistance was explained by increased antibiotic consumption by inhabitants living in high SES areas [10].

In our study, the explanation is not as straightforward. Children with a reported use of antibiotics during the last 2 weeks had significantly increased resistance to a number of antibiotics, and increased resistance was seen in the children with family members who had used antibiotics. However, the use of antibiotics in children, including the number of days used, was homogeneous across the economic strata. This was probably due to increased access for

Table IV. Logistic regressions investigating association of antibiotic resistance with wealth and antibiotic (Atb) use in multivariable models for total resistance. Results shown as odds ratio (OR) and corresponding confidence intervals (CI), with statistically significant values marked in bold.

Multivariable models		Streptomycin		Chloramphenicol		Nalidixic acid		Kanamycin		Ciprofloxacin		Gentamicin		Nitrofurantoin	
Total resistance															
Yurimaguas	Wealth	1.07	0.766–1.485	**1.42**	**1.025–1.956**	**1.49**	**1.061–2.088**	1.24	0.865–1.769	1.41	0.952–2.102	1.00	0.705–1.496	1.80	0.896–3.624
	Atb used by the child last 2 weeks and/or last 6 months and/or by other family members	**1.75**	**1.243–2.470**	1.25	0.887–1.756	**1.77**	**1.202–2.596**	1.36	0.913–2.020	**1.68**	**1.120–2.823**	**1.97**	**1.260–3.076**	1.62	0.726–3.632
Moyobamba	Wealth	0.83	0.540–1.272	0.82	0.592–1.134	1.11	0.826–1.503	0.98	0.686–1.396	1.14	0.806–1.601	0.80	0.559–1.155	1.13	0.761–1.678
	Atb used by the child last 2 weeks and/or last 6 months and/or by other family members	**1.88**	**1.197–2.856**	**1.46**	**1.038–2.054**	1.29	0.934–1.789	1.39	0.937–2.069	1.11	0.767–1.617	**1.62**	**1.075–2.451**	0.80	0.528–1.206

children to health services and to antibiotics being granted by the state health insurance (SIS). In addition, there were increased odds ratios for total resistance among the wealthiest children who did not use antibiotics in the last 6 months. No interactions between wealth and antibiotic use could be seen in relation to resistance. When multivariable logistic regressions were performed, the increased odds ratios for resistance among wealthier children remained when antibiotic use was controlled for.

The higher antibiotic resistance levels for wealthier children shown in the total resistance category (the dominant flora plus the additional resistant clones that are present in lower frequencies) are not explained by antibiotic use in the children or other family members. Antibiotic resistance in lower-frequency clones may be associated with other characteristics shared by wealthier families. Studies of dynamics of the normal flora show that diversity and distribution of E. coli genotypes shift over short time periods, without previous antibiotic use [27]. These resistant clones may be low frequency clones passing through the intestines without being permanently established in the normal flora. Their presence in the flora of the children in this study probably reflects the presence of such resistant strains in the environment, and is probably a result of other factors correlated with high wealth levels, for example through contaminated food and food handling. In many countries, animals are fed with antibiotics to promote growth and to increase profit for farmers; the use of antibiotics in animals is thought to be correlated with emerging resistance [28,29]. This has also been seen in Peru, where antibiotics are frequently used at, for example, chicken farms and fish farms. In both Yurimaguas and Moyobamba, chicken farms are present and fish farms are situated in the nearby community of Tarapoto. Possibly, wealthier households would consume commercially produced food to a greater extent, with a higher contamination of antibiotics, than food that is self-produced.

Association patterns for the dominant flora were similar as for the total resistance. There was no interaction between wealth and antibiotic treatment of the child in the last 2 weeks, the last 6 months or antibiotics taken by other family members. Austin et al. have modelled how antibiotic use influenced the transmission dynamics of normal flora [30], and numerous studies have shown similar results in hospital settings [31]. Sjölund et al. described long-term persistence of resistance in enterococci up to 3 years after treatment [32], indicating that resistance promoted by antibiotic use may be reasonably stable over time. Composition of the dominant resistant flora described in this study may be

relatively stable and associated with less recent antibiotic use.

We found a difference in resistance between Yurimaguas and Moyobamba, with resistance in dominant flora being higher in Yurimaguas and total resistance being higher for many antibiotics in Moyobamba. This may be associated with the higher antibiotic use that was observed in Yurimaguas.

Methodological considerations

No analysis of association between use of specific types of antibiotics and resistance was performed. Since the levels of resistance are so high for many of the antibiotics analysed, coselection of resistance determinants must be considered an important factor. For this reason, we have considered 'use of any type of antibiotics' as the only parameter possible in order to analyse the relation to possible influencing factors. As a consequence of coselection, use of one common antibiotic drug will most probably cause an increase in resistance to several other antibiotics as well.

The method of detecting resistance used in these studies has resulted in one variable, called total resistance, including both frequent and rarer clones, and another representing the resistance for the dominant E. coli flora in the analysed faecal samples [16,33]. It has become clear in recent years that the normal commensal flora of bacteria, both in the gut and elsewhere, is a source of resistance genes and represents an important reservoir of resistance mechanisms [34]. The so-called 'total resistance recorded' is a powerful measure of the resistance gene-pool accumulated in gut E. coli flora. It is therefore an important feature of the present investigations to include both the total resistance level and to simultaneously assess the resistance in the dominant flora, the first as a measure of the resistance gene reservoir and the second as a measure that can be compared with levels recorded in other studies.

Antibiotic use in this study was self-reported. However, the step-wise procedure of asking for antibiotic use provides a more rigorous way of assessing consumption than simply asking the interviewees to state antibiotic use. More than half of the households with stated antibiotic use in the last 2 weeks still had the package. The validity of the statements indicated that there was a general knowledge about antibiotics in the community.

We estimated SES by an asset analysis, as it is problematic to use the traditional measures of economic position, income or consumption in many low-income settings, due to practical limitations. The asset index approach has been recom-

mended with the assumption that wealth would be reflected in assets owned by the household [35]. A study comparing various methods of weighting assets into a wealth index found that an asset index derived by using principal component analysis (PCA) showed the best fit to the data [36].

Conclusions

The children of wealthiest parents had an increased odds ratio for antimicrobial resistance, and therefore any interventions aiming at containing the emerging resistance must also address this societal group, including efforts to rationalize use of antibiotics. Antibiotic use did not seem to explain the wealth associated resistance. The low-frequency antibiotic resistant clones constitute a part of the gene-pool of resistance determinants, represented by the normal flora and may contribute to a transfer of resistance genes to pathogens. However, other, unknown factors related to socioeconomic status seem to contribute to the results seen in Peru.

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