

# Characteristics of common infections in Nicaragua



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# **Characteristics of common infections in Nicaragua**

## **Kenmerken van veel voorkomende infecties in Nicaragua**

(met samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op  
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door

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geboren op 21 mei 1958 te Ocotal, Nueva Segovia, Nicaragua

Promotor: Prof. Dr. I.M. Hoepelman

Co-promotor: Dr. E. Hak

Dedicated to my patients



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# Chapter 1

## Introduction



## **Introduction**

### ***Nicaragua's history***

Nicaragua is located in Central America, bordering both the Caribbean Sea and the North Pacific Ocean between Costa Rica and Honduras. The Pacific coast of Nicaragua was settled as a Spanish colony from Panama in the early 16th century. Independence from Spain was declared in 1821 and the country became an independent republic in 1838. Britain occupied the Caribbean Coast in the first half of the 19th century, but gradually ceded control of the region in subsequent decades. Violent opposition to governmental manipulation and corruption spread to all classes by 1978 and resulted in a short-lived civil war that brought the Sandinista guerrillas to power in 1979. Free elections in 1990, 1996, and again in 2001 have been done. The country has slowly rebuilt its economy during the 1990s, but was hard hit by Hurricane Mitch in 1998.

### ***Economy***

Nicaragua, one of the hemisphere's poorest countries, faces low per capita income, widespread underemployment and a heavy external debt burden. Distribution of income is one of the most unequal on the globe. While the country has progressed toward macro-economic stability in the past few years, GDP annual growth rate has been far too low to meet the country's needs, forcing the country to rely on international economic assistance to meet fiscal and debt financing obligations. Nicaragua qualified in early 2004 for some \$4 billion in foreign debt reduction under the Heavily Indebted Poor Countries (HIPC) initiative because of its earlier successful performance under its International Monetary Fund policy program and other efforts. In October 2005 Nicaragua ratified the US-Central America Free Trade Agreement (CAFTA), which will provide an opportunity for Nicaragua to attract investment, create jobs, and deepen economic development. High oil prices helped drive inflation to 10% in 2005, leading to a fall in real GDP growth to 3.5% from over 5% in 2004. Emigration and internal migration have a strong impact on the country's economy. According to the National Quality of Life Survey conducted in 1998 by the National Statistics and Census Bureau as of 1998, 47.9% of the population was living in poverty and 17.3% was living in conditions of extreme poverty. The Gross National Product (GNP) per capita is 455.80 US dollar a year, one of the lowest among Latin American countries<sup>1-4</sup>.

### ***León-Utrecht collaboration***

The capital of Nicaragua until 1857, León, 90km north of Managua, is a provincial city with the presence of the Nicaraguan National Autonomous University of León, (UNAN), the country's premier academic institution. The Nicaraguan National Autonomous University and the National Law School were (and perhaps still are)

hotbeds of revolutionary ferment and the presence of these institutions have contributed enormously to León's Liberal bent.



*Cathedral of León, Nicaragua*

The first contacts between Utrecht and León date from the summer of 1983, when a group of academics from Utrecht visited Nicaragua. After a period of orientation and project identification the cooperation started around 1987 with small and concrete projects, such as the construction of latrines, of a tree nursery and (in 1990) a production unit for building materials. The cooperation in concrete projects created common experience and established mutual trust, enabling the set up of bigger and more institutional projects. Because of the success of the projects, the Dutch Minister of Developing Cooperation decided to include a 'Plan Maestro for spatial and economic development of León' in the bilateral program between the Netherlands and Nicaragua. In the beginning of 1996 León and Utrecht completed this assignment. The outcome of the plan was: an 'overall-vision' on the future of León. The key concept was: sustainable development of both urban and rural areas. Moreover, the plan formulated several strategic projects for the near future. Between 1996 and 2003, Utrecht and León, following this Master plan or Plan Maestro, set out to tackle a number of issues:

- Deciding on a 'León-Utrecht agreement for sustainability' by both city councils, related to an action program focused on chromium recycling at tanneries, the introduction of solar energy, promotion of cycling and on nature and environment education;
- The start of a concrete long-range city expansion program for South-East León. Utrecht and León hope to continue this program till 2008, after which León, thanks to a closing exploitation set-up, can continue this independently;

- The development of a 'Strategic Plan for Municipal Development' based on the Plan Maestro.

Thanks to all of this some important conditions are fulfilled through which León can make itself more qualified for the flow of money from organizations such as the World Bank, the Inter-American Developing Bank and from the most important donor countries. After all, the international donor community has acquitted Nicaragua's burden of debt for 80% in the beginning of 2004. The combating of systematic poverty can be tackled better now. An important challenge is: the organization of a successful lobby from the community of León (together with other communities in the region) towards the national government of Nicaragua (regardless of political differences).

### ***Utrecht and León collaboration in health sciences***

The University Utrecht has 26,787 students, of which 6,098 new first-year students. It has 176 academic programs: 49 Bachelor programs, 109 Master programs, and 18 teacher-training programs. Including the faculty of Medicine there are currently 8,224 members of staff. The University Utrecht harbors 12 Nobel price laureates. One of the missions of the University is to address social issues and work towards solving them. Therefore, it was decided in the mid-nineties to join the collaboration which exists between the city of Utrecht and León.

One of the identified topics of mutual interest was general medicine and especially infectious diseases. In 1996 the department of Infectious Diseases of the University Medical Center Utrecht was officially asked to participate in establishing an infectious disease management structure in León. Actual partnership started with the training of a specialist in the Infectious Diseases field in the UMC, Utrecht (A. J. Matute, MD). Further, a program was established to strengthen the diagnosis and therapy for Infectious Diseases at the laboratory of HEODRA (Hospital Escuela Oscar Danilo Rosales Arguello). This was officially approved by both universities and subsidized by the University of Utrecht from 2002-2005 and by an additional grant from the city of Utrecht in 2004.

### ***Health care structure***

Health care services in Nicaragua are provided through the Ministry of Health (MINSa), private contractors (*empresas*) to the social security system (INSS), and non-governmental organizations. MINSa is the primary provider, officially covering about 70% of the population. It provides services directly through its public hospitals, and through health centers that are under the supervision of provincial administrative units called SILAIS. INSS, which covers formal sector workers, finances care for about 10% of the population, although some of this is provided through MINSa hospitals (on a fee-for-service basis). NGOs provide services mainly in under-served

rural areas. Nicaragua's health sector strategy is supported by the World Bank and the Inter-American Development Bank (IDB).

Over the last 15 years Nicaragua's health system has been transitioning from the socialist model implemented under the Sandinista regime of the 1980s and early 1990s. During this time, successive governments have adopted generally more market-focused economic policies across most sectors. In the health sector, these policy changes have taken the form of increased private sector activity, and the decentralization of publicly provided services. The health system exists of 32 hospitals, 176 health centers and 849 health posts. Most of the hospitals are concentrated in the cities. In Nicaragua per 10,000 inhabitants 1.7 medical specialists, 2.2 general physicians, 3 professional nurses, 7.9 auxiliary nurses and 0.5 dentists are in function. The first level of attention is destined to offer attention, promotion, prevention and basic recovery. These functions are realized in 97% of the health establishments. Of these establishments, 82% are posts health, 15% are health centers. The second level of attention of the MINSA represents 3% of the health establishments. The MINSA is the main supplier of services hospitable in the country. In the hospitals medical attention offers as much general as specialized, ambulatory and with internment, in basic areas. The second level of attention comprises national centers of cardiology, radiotherapy, ophthalmology, dermatology, psychiatry and the National Center of Diagnosis and Reference<sup>5</sup>.

### ***Framework of the thesis***

In 2001, a small group of medical professionals was organized. The goal of this group was to collect baseline data for common infections and management of health problems in Nicaragua. The project initially was conducted as a pilot project during the period June 2002 to 2005. The project began with the strengthening of diagnostic capabilities for infectious diseases at the laboratory area of the school Hospital Oscar Danilo Rosales Arguello (HEODRA), UNAN, León. The scientific data collected were needed to develop guidelines for diagnosis and treatment of main infectious diseases adapted for the Nicaraguan reality. One of the first activities of the pilot project was to define which types of infectious diseases should be studied. During the collaboration of the Infectious Diseases Department of the UMC and the students from the University of Utrecht several strategies were followed:

- Upgrading of the laboratory and exchange of laboratory personnel. At the end of 2001 the former head of the Utrecht primary health care laboratory J. de Bruin, MD, went to Nicaragua to help to upgrade the laboratory together with a technician, Mrs. A. McArthur, from the University Laboratory for Microbiology of the Utrecht University;
- The goals of the student exchange program (2002) started by Prof. I.M. Hoepelman, MD, PhD, were:

- Benefit the students and expose them to Medicine and Culture in a different environment;
- Benefit the knowledge and possibilities in León which could help the primary goal of the collaboration.

An exchange program was established in 2002 in which by now more than 20 students participated. The students performed research, within concrete projects, on local infectious disease problems;

- Establishing a student exchange program.

In 2005 the hospital of HEODRA in León was officially identified as one of the candidate hospitals in the world for training of students in Internal Medicine by the educational institute of the University Medical Center in Utrecht. In the forthcoming years other specialties will probably follow. At the end of 2005 a formal contract between the University Medical Center Utrecht and HEODRA was signed;

- Improve the scientific expertise in HEODRA.

### ***Burden of infectious diseases in Nicaragua***

About 15 million (>25%) of 57 million annual deaths worldwide are estimated to be related directly to infectious diseases<sup>6</sup>. The burden of morbidity and mortality associated with infectious diseases falls most heavily on people in developing countries, and particularly on infants and children. Infectious diseases are in the fifth place among the leading causes of death in Nicaragua. For the total population the average life expectancy at birth is 70 years, for males 68 years and females 72 years (compared to 77 and 81 years, respectively, in the Netherlands). The infant mortality rate is 29 per 1,000 live births in Nicaragua whereas in the Netherlands the corresponding figure is 5 deaths per 1,000 live births<sup>4, 7</sup>.

In developed nations, infectious disease mortality disproportionately affects indigenous and disadvantaged minorities<sup>8</sup>. Four of the six countries in Latin America with the highest estimated HIV prevalence as of end 2001 are in Central America—Belize, Honduras, Panama, and Guatemala. Overall, in Central America, HIV is still a concentrated epidemic, but with important exceptions: in Belize, the epidemic is generalized, in Honduras, generalized in some areas, and in Nicaragua, the epidemic can still be categorized as low level, or nascent<sup>9</sup>.

Tuberculosis remains a global epidemic, with one-third of the population infected and 9 million active cases. Mono- and multidrug resistance in six World Health Organization (WHO) regions have been assessed in 40% of the global cases diagnosed by positive results of sputum testing. The 2004 report of the WHO Global Project on Anti-Tuberculosis Drug Resistance Surveillance confirms earlier findings

that drug-resistant tuberculosis is ubiquitous and that multidrug-resistant tuberculosis has increased alarmingly<sup>10</sup>. In Nicaragua, the incidence of most types of tuberculosis has decreased to 50% over the last 10 years. Nevertheless, its relation with the HIV/AIDS epidemic must be considered.

The increasing spread of infectious diseases such as HIV/AIDS, malaria, dengue and tuberculosis is having a profound economic and social impact worldwide. These epidemics are hitting with particular strength Nicaragua, a Central American country with low income per capita, but the rest of Central American countries are not immune from the diseases devastating consequences. As globalization and increased international traffic of persons facilitate economic interdependency, the risks of cross-border spread of emerging infectious diseases are on the rise. The HIV/AIDS epidemic in Central America is serious and is worsening. On the basis of information from 2001, four of the six countries in Latin America with the highest estimated HIV prevalence are in Central America—Belize, Honduras, Panama, and Guatemala<sup>9</sup>. Although the estimated prevalence in Nicaragua of adult HIV was 0.20% in 2001<sup>11</sup>, the epidemic is in a nascent stage, and the prerequisites for a more serious epidemic, such as a high level of migration and mobility and a culture that stigmatizes the use of condoms, are in place.

Nicaragua has seen some changes in the last two decades which might indicate that there will be an increase in the prevalence of HIV in the future; increased prevalence of syphilis, increased mobility and increased commercial contacts. In Nicaragua there is no mandatory HIV testing for pregnant women nor is there counseling to recommend an HIV test. Testing for syphilis though is mandatory in the first trimester of pregnancy. Monitoring the prevalence and incidence of HIV is essential to controlling the AIDS epidemic, yet in some countries, such as Nicaragua, there is a lack of reliable data on the prevalence of HIV.

The most common or main emerging infectious diseases of public health importance in Nicaragua beside HIV-AIDS are currently acute respiratory infections with a morbidity rate of 2270 per 10.000 inhabitants, and 18% comprises pneumonia with a prevalence of 444 per 10.000<sup>7</sup>. Management of community acquired pneumonia (CAP) in Central America and especially Nicaragua is complicated by the lack of knowledge about the antibiotic resistance of respiratory pathogens. In 20% to 50% of the cases the causative agent could not be identified and a mixed etiology is present in 2% to 11% of the cases<sup>12-14</sup>. Identifying the etiological pathogens is one of the key challenges in adequate treatment of CAP.

Among other important infectious diseases urinary tract infections are common. Symptomatic urinary tract infections (UTI) among men and women are common in Nicaragua. *Escherichia coli* has been documented to be the most important pathogen

associated with symptomatic urinary tract infections in many countries<sup>15-17</sup>. For optimal clinical management of UTI, the risk profile of a patient is essential. Increasing age, female gender, pregnancy and presence of diabetes are well known risk factors for urinary tract infections. The antibiotic of choice is currently highly dependent on the local situation with regard to antibiotic resistance of the pathogenic bacteria

It can be expected that in countries as Nicaragua with relatively non-regulated prescriptions of antibiotics, resistance is currently a major threat to clinical treatment. Among other health problems in Nicaragua is the overuse of antibiotic by prescribers. Surgical site infections and associated mortality is between 2 and 5%, and 0.64% respectively when appropriate antibiotic prophylaxis is used<sup>18, 19</sup>. Inadequate prophylaxis led to an incidence of 15% of surgical site infections while adequate prophylaxis reduced it to 5%<sup>20</sup>. Protocols for antibiotic prophylaxis are designed worldwide to optimize local administration of antibiotics. Monitoring and intervention can be effective in increasing the adherence to a protocol as was shown in studies in which the appropriateness of antibiotic prophylaxis was increased from around 50% to 95-100% by the stricter implementation of an existing protocol<sup>21, 22</sup>. A restrictive policy minimizes antibiotic resistance and by preventing treatment of surgical site infections, prophylaxis is cost-effective<sup>23, 24</sup>.

### ***Scope of the thesis***

Following the agreement between León and Utrecht University and the objectives set in the projects, the main aims of the current thesis were to obtain insights into basic aspects of some common infectious diseases in Nicaragua. As previously stated, the present thesis describes the diseases that have either a huge impact or may become epidemic in the near future in the Nicaraguan population. The results of these studies might further support the Ministry of Health in the management and prevention of diseases in Nicaragua.

Chapter 2 describes the etiology and resistance in symptomatic urinary tract infection (UTI) in León, Nicaragua. This is the first large prevalence study in Nicaragua of patients with symptomatic UTI seen in the Accident and Emergency Department or after admission. The aim of this study was to determine the pathogenesis and bacterial resistance against commonly used antibiotics. The prevalence study included consecutive patients with UTI presenting to the university hospital HEODRA from June to November 2002.

Chapter 3 describes the etiology and resistance pattern of community-acquired pneumonia (CAP) in León, Nicaragua. The aim of this study was to identify the micro-organisms and the resistance pattern in patients diagnosed with CAP in Nicaragua.

We designed a prevalence study including consecutive patients with CAP presenting to the university hospital HEODRA of León, Nicaragua during the period from July 2002 to January 2005.

In chapter 4 we describe the application of guidelines on pre-operative antibiotic prophylaxis in León, Nicaragua. The aim of the study was to determine the adherence to guidelines for pre-surgical antibiotic use in Nicaragua. We designed a prevalence study in a four-week period in 2005 in the University Hospital of León, Nicaragua. All consecutive persons of any age undergoing surgery in the departments of general surgery, orthopaedics, gynaecology and obstetrics, and paediatrics were eligible for inclusion into this study.

In chapter 5 we describe the prevalence of HIV and syphilis in pregnant women in León, Nicaragua. The aim of this study was to determine the prevalence of HIV and syphilis, and to identify risk factors, among pregnant women visiting antenatal clinics in León, Nicaragua. We conducted a prevalence study involving pregnant women in the period from February to April 2004 in León, Nicaragua. Blood samples from pregnant women were collected after written consent had been obtained. The samples were tested for antibodies against HIV and *Treponema pallidum*.

Chapter 6 describes the epidemiology of clinically apparent HIV/AIDS in Nicaragua. The aim of the study was to describe the epidemiology of HIV/AIDS infection in Nicaragua and to discuss the reasons why the numbers of new cases are increasing compared with other Central American countries. Patient data from 1987 to 2004 were collected from the Nicaraguan STI/HIV/AIDS national program, which collects relevant information from registers held in all integrated local health system (SILAIS) across the country.

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# Chapter 2

## Resistance of uropathogens in symptomatic urinary tract infections in León, Nicaragua

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## Abstract

Management of urinary tract infections (UTI) in Central America and especially Nicaragua is complicated by the lack of knowledge about the antibiotic resistance of uropathogens. We conducted a prevalence study to gain more insight into the aetiology, bacterial resistance and risk factors for symptomatic UTI in the region of León, Nicaragua. In 2002, all consecutive patients with UTI symptoms and pyuria  $\geq 10$  WBC/hpf were admitted to the study. Positive cultures from midstream urine specimens were defined as  $\geq 10^5$  cfu/ml of a single uropathogen. Susceptibility tests were performed with disc diffusion tests using the Kirby–Bauer method and broth microdilution using National Committee for Clinical Laboratory Standards criteria both in León and a reference laboratory in Utrecht. A positive culture was present in 62 of 208 study subjects (30%). *Escherichia coli* (56%), *Klebsiella* spp. (18%) and *Enterobacter* spp. (11%) were the most frequent pathogens isolated. Presence of cystocele, incontinence and increasing age were risk factors for bacterial UTI. *E. coli* was least resistant to ceftriaxone, amikacin and nitrofurantoin (>90% susceptible). We observed high resistance rates in *E. coli* to amoxicillin (82%, MIC<sub>90</sub> 128 mg/l), trimethoprim-sulphamethoxazole (TMP-SMX) (64%, MIC<sub>90</sub> 32 mg/l), cephalothin (58%, MIC<sub>90</sub> 32 mg/l), ciprofloxacin (30%; MIC<sub>90</sub> 32 mg/l), amoxicillin/clavulanate (21%, MIC<sub>90</sub> 8 mg/l) and gentamicin (12%, MIC<sub>90</sub> 2 mg/l). Our results suggests that community acquired uropathogens in Nicaragua are highly resistant to many antimicrobial agents. The use of amoxicillin, trimethoprim-sulphamethoxazole and cephalothin against uropathogens needs to be reconsidered. High quinolone resistance rates among *E. coli* in Nicaragua gives cause for great concern.

## Introduction

Symptomatic urinary tract infections (UTI) among men and women are common in Nicaragua. Most such infections occur via the ascending route by bacterial colonization of the peri-urethral tissue followed by infection of the bladder. In some cases the kidneys may become affected leading to pyelonephritis and in rare instances to bacteraemia. *Escherichia coli* has been documented to be the most important pathogen associated with symptomatic urinary tract infections in many countries<sup>1-3</sup>. Other relatively less frequently isolated bacteria include *Klebsiella*, *Enterobacter* and *Serratia* species, *Streptococcus faecalis* and *Pseudomonas aeruginosa*. However, the relative contribution of each of these bacteria differs between countries and is relatively unknown in Central American countries such as Nicaragua.

For optimal clinical management of UTI, the risk profile of a patient is essential. Increasing age, female gender, pregnancy and presence of diabetes are well known risk factors for urinary tract infections<sup>4-6</sup>.

In general,  $\beta$ -lactam antibiotics, trimethoprim-sulphamethoxazole (TMP-SMX) and fluoroquinolones are used most often in uncomplicated UTI. In the case of a high-risk patient profile due to complicated factors, quinolones might be added to the armamentarium of treatment. However, the antibiotic of choice is currently highly dependent on the local situation with regard to the antibiotic resistance of the pathogenic bacteria<sup>7,8</sup>.

It can be expected that in countries such as Nicaragua with relatively non-regulated prescriptions of antibiotics, resistance is currently a major threat to clinical treatment. We therefore conducted a prevalence study to gain more insights into the pathogenesis, bacterial resistance against commonly used antibiotics and risk factors for symptomatic urinary tract infections in Nicaragua.

## **Patient and Methods**

### ***Setting and study population***

Our study was designed as a prevalence study. Enrolment of study subjects took place during the period between June and November 2002 in the university hospital of León, Nicaragua. All consecutive patients that entered our hospital either directly or via primary care or emergency departments with a suspected symptomatic urinary tract infection were admitted to the study cohort if they met the following criteria: presence of signs and symptoms suggestive of symptomatic UTI including fever, chills, flank pain, costovertebral angle tenderness, dysuria, frequency and urgency and pyuria defined of  $\geq 10$  WBC/hpf.

We classified the patients as complicated and uncomplicated UTI according to a modification of the IDSA guidelines<sup>9</sup> adding women under 12 years and above 65 years of age to the complicated infection category.

### ***Measurements***

All study subjects underwent a clinical examination including an interview with a defined protocol, to collect information on potential risk factors such as demographics (e.g. age, gender, area of residence) and medical history data (e.g. presence of co-morbidity and previous urinary tract infections). Also, physical examinations were carried out to detect potential severe complications from UTI such as pyelonephritis defined as fever and chills, flank pain, costovertebral angle tenderness together with one or more general symptoms such as nausea and vomiting.

All study subjects were asked to supply a midstream specimen of urine for culture within 4 h since last voiding. Urine specimens were cultured at the local hospital laboratory. Urine samples were inoculated on blood and MacConkey agars and incubated at 36 °C for 18–24 h. Susceptibility tests were performed with disc diffusion

tests using the Kirby–Bauer method and the National Committee for Clinical Laboratory Standards (NCCLS) criteria<sup>10</sup>, for amoxicillin, amoxicillin/clavulanate, TMP-SMX, nitrofurantoin, meropenem, gentamicin, cephalothin, ceftriaxone, ceftazidime, ciprofloxacin and norfloxacin. Significant bacterial infection was defined as the growth of  $\geq 10^5$  cfu/ml of a single species cultured from urine. All samples that were tested positive were also sent to the reference laboratory of UMC Utrecht, the Netherlands. MICs were determined for amoxicillin, amoxicillin/clavulanate, cephalothin, ciprofloxacin, ceftriaxone, gentamicin, and TMP-SMX by the use of Etest strips (AB biodisk<sup>®</sup>, Solna, Sweden).

### **Statistical analysis**

All data were analyzed with SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA). Cohen's  $\kappa$  was calculated as measure of agreement between the test results of both laboratories. A value of 1 indicates perfect agreement. A value of 0 indicates that agreement is no better than chance. Odds ratios (OR) derived by multivariable logistic regression analysis and their corresponding 95% confidence intervals (95% CI) were estimated as approximations of relative risks.

## **Results**

We obtained valid information on 208 study subjects. The mean age of the study population was 28.4 years (S.D.  $\pm 20.5$  years) and 78% were female. Of the 208 urine samples that were cultured, 62 (30%) were positive; 47/163 (29%) were from females and 15/45 (33%) from males. The most frequently isolated pathogen in the laboratory in León was *E. coli* (56%) followed by *Klebsiella* spp. (18%), *Enterobacter* spp. (11%). *Proteus* spp. were infrequent (3%) as were *P. aeruginosa* (5%) and *Staphylococcus epidermidis* (3%). When comparing the results of the urine cultures from the two laboratories, the overall  $\kappa$  statistic predicted agreement was excellent (0.65) (data on file). Of the 62 positive cultures 47 (76%) were from females and 15 (24%) were from males. Forty-one (66%) were taken in the Accident and Emergency Department, 17 (27%) within 48 h after hospitalization and 4 (7%) were taken >48 h after hospitalization. Thirty-one (66%) of cultures from women and four (27%) cultures from men grew *E. coli*. Of the complicated UTIs (68% of all UTIs), 58% were associated with *E. coli*, 28% with *Klebsiella* spp. and 14% with *Enterobacter* spp. Of the remaining cases of uncomplicated UTI, 71% were associated with *E. coli*, 18% with *Klebsiella* spp. and 12% with *Enterobacter* spp.

The reference laboratory found that *E. coli* isolates ( $n=35$ ), gave high resistance rates in the disk diffusion tests for amoxicillin (74%), TMP-SMX (63%), ciprofloxacin (29%), amoxicillin/clavulanate (34%) and gentamicin (11%) (Table 1). The most effective drugs against *E. coli* were meropenem, ceftriaxone, amikacin and nitrofurantoin (100% susceptible) and to a lesser extent gentamicin (89% susceptible).

**Table 1.** Resistance rates (in %) for seven antimicrobial agents tested against *E. coli*, *Klebsiella spp* and *Enterobacter spp*.

Antimicrobial tested	<i>E. Coli</i> (n=33)	<i>Klebsiella spp.</i> (n=13)	<i>Enterobacter</i> <i>spp.</i> (n=7)
Amoxicillin	82	100	71
Amoxicillin/clavulanate	21	15	43
Cephalotin	58	15	86
Ciprofloxacin	30	0	0
Ceftriaxon	0	0	29
Gentamicin	12	0	29
TMP-SMX	64	23	29

MIC's were determined only in Utrecht laboratory with the use of E- test strips (AB biodisk®, Solna, Sweden). Resistance was determined with break points according to National Committee for Clinical Laboratory Standards criteria <sup>22</sup>.

All *Klebsiella spp.* were resistant to amoxicillin and 18% were resistant to TMP-SMX. Also, all *Enterobacter spp.* were resistant to amoxicillin. Resistance rates were also high for amoxicillin/clavulanate and cefuroxime (86%).

MIC90 of the tested antibiotics for *E. coli* were amoxicillin (128 mg/l), co-amoxiclav (8 mg/l), cephalothin (32 mg/l), ciprofloxacin (32 mg/l), ceftriaxone (0.25 mg/l), gentamicin (2 mg/l) and TMP-SMZ (32 mg/l), respectively. Resistance rates for *E. coli* (MIC90), from both uncomplicated and complicated UTIs were 92 and 71% for amoxicillin, 83 and 43% for cephalothin, 67 and 57% for TMP-SMX, 42 and 24% for ciprofloxacin, 25 and 14% for amoxicillin/clavulanate and 17 and 10% for gentamicin, respectively.

### **Risk factors for positive culture**

Using multivariate logistic regression, we established cystocele (OR 3.87; 95% CI, 0.98–5.23;  $P=0.053$ ), frequency (OR 2.84; 95% CI 1.30–6.190;  $P=0.008$ ), age 21–44 years (OR 2.69; 95% CI 1.02–7.11;  $P=0.045$ ) and age  $\geq 45$  years (OR 7.52; 95% CI 2.46–22.98;  $P<0.001$ ) as independent risk factors for a positive culture.

## **Discussion**

This is the first large prevalence study in Nicaragua of patients with symptomatic UTI seen in the Accident and Emergency Department or after admission that shows that *E. coli* was the most commonly isolated species (56%). Unexpectedly high resistance rates to frequently prescribed antibiotics were present against most uropathogens. Furthermore, the accuracy of laboratory tests in León was similar to the reference laboratory in Utrecht.

Worldwide, *E. coli* is the most important pathogen for uncomplicated and complicated UTI<sup>1,3,11-15</sup>. Most isolates of *E. coli* were multi-drug resistant. Although the spectrum of bacteria isolated from the urine of patients' world wide has remained largely unchanged over the past few decades, there have been dramatic changes in resistance patterns and sensitivity profiles in some countries<sup>15-17</sup>.

Resistance of *E. coli* and other pathogens to TMP-SMX is a significant problem at our urban hospital in Nicaragua and has also been reported from a number of institutions in Latin America<sup>13,18-20</sup>. Of even greater concern is that increasing resistance is eroding the usefulness of second line agents such as ciprofloxacin, as reliable alternatives for the management of UTI. Current IDSA guidelines do not address the treatment dilemma facing Nicaraguan physicians<sup>21</sup>. Data of Talan and Raz show that if the prevalence of resistance against TMP-SMX exceeds 20%, a fallback alternative would be ciprofloxacin monotherapy for women with uncomplicated pyelonephritis<sup>7,8</sup>. This strategy assumes a high level of susceptibility and efficacy of fluoroquinolone agents in treating bacterial UTI. Our study shows that this would not be a valid option in our hospital. In Costa Rica, Williams et al.<sup>13</sup> found that most of the *E. coli* isolates were also multi-drug resistant. The current situation as seen in Nicaragua, Costa Rica as well as in several other Latin American countries and Asia should be alarming as it may extend to other countries in Europe and to the USA through high intercontinental contact rates.

The increasing resistance trends are likely to have important clinical implications for the empirical use of antibiotics. In high resistance areas such as León, TMP-SMX should not be the empirical drug of choice for either complicated or uncomplicated UTI, because treatment with such treatment of uncomplicated UTI caused by micro-organisms resistant to TMP-SMX results in microbiological and clinical failure<sup>7,8</sup>. Moreover, one should realise that in Central America therapy for uncomplicated UTI is usually given empirically and nitrofurantoin is the only available oral agent<sup>22</sup>. For complicated UTI, based on our results, we will have to rely on parenteral regimens such as a  $\beta$ -lactam, like ceftriaxone.

In conclusion, community acquired uropathogens isolated in the León region are highly resistant to many antimicrobial agents. The use of amoxicillin, TMP-SMX and cephalothin against uropathogens need to be reconsidered. High quinolone resistance rates among *E. coli* in Nicaragua gives cause for great concern.

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# Chapter 3

## Aetiology and resistance pattern of community-acquired pneumonia in León, Nicaragua

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## Abstract

We conducted a prevalence study to gain more insight into the aetiology, bacterial resistance and risk factors for CAP in the region of León, Nicaragua. During the period from July 2002 to January 2005, 130 consecutive patients with signs and symptoms suggesting CAP were included into the study. We collected sputum samples, paired sera and urinary samples for the detection of respiratory pathogens. The most frequently identified pathogens in our study were *Streptococcus pneumoniae* (17%), followed by *Staphylococcus aureus* (5%), *Chlamydia pneumoniae* (5%) and *Mycoplasma pneumoniae* (4%). *Pseudomonas aeruginosa* was cultured from 5% of patients. In 55% no pathogens were identified. All tested *Streptococcus pneumoniae* were sensitive to erythromycin and penicillin. In contrast, resistance of *Staphylococcus aureus* against penicillin and erythromycin was high in our study.

## Introduction

Worldwide, community acquired pneumonia (CAP) continues to be an important cause of morbidity, and mortality rates are increasing (up to 6% in Canada and 20% in the United States and Spain).<sup>1-3</sup> CAP is caused by a wide variety of micro-organisms among which *Streptococcus pneumoniae* is the predominant pathogen, notably in studies that incorporated a urinary antigen test for *Streptococcus pneumoniae*.<sup>4</sup> Other common agents include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*, *Haemophilus influenza*, *Klebsiella pneumoniae*, viruses and other pathogens. The attributable fractions of each of these pathogens largely vary depending on the diagnostic possibilities available and accuracy of testing. In 20% to 50% of the cases the causative agent could not be identified and a mixed aetiology is present in 2% to 11% of the cases<sup>5-8</sup>. Identifying the etiological pathogens is one of the key challenges in adequate treatment of CAP.

Apart from knowledge about the aetiology, the sensitivity of micro-organisms to the antibiotics used is essential to effective treatment of CAP. For example, the global spread of drug-resistant *Streptococcus pneumoniae* has been increasing over the last decades. The incidence of penicillin-resistant *Streptococcus pneumoniae* is relatively high in the United States and particularly in South East Asia<sup>9,10</sup>. Macrolide-resistance is currently a major threat in Europe<sup>11</sup>. However, resistance data from other countries such as Nicaragua are scarce or even lacking. It was hypothesized that bacterial resistance may be an underestimated threat to clinical treatment in Nicaragua, because specific guidelines for prescription of antibiotics are lacking. Moreover, previously we detected high rates of resistance in uropathogens<sup>12</sup>.

The aim of this prevalence study was to identify the micro-organisms and the resistance pattern in patients diagnosed with CAP in Nicaragua.

## **Patients and methods**

### ***Setting and study population***

We conducted a prevalence study at the University Hospital of León, Nicaragua. During the period from July 2002 to January 2005, all consecutive patients over 12 years of age who visited the emergency department and internal ward with signs and symptoms suggestive of CAP were eligible to be included into the study. Patients were excluded from the study if they met any of the following criteria: primary lung cancer or another malignancy, metastasis to the lungs, cystic fibrosis, HIV or AIDS, known or suspected *Pneumocystis carinii* infection, or known or suspected active tuberculosis or previous recent use of antibiotics. The study was approved by the local ethical committee in the University Hospital, León.

### ***Data collection***

After informed consent was given, a structured interview was conducted to collect information on demographics, co-morbidities, potential risk factors and clinical signs and symptoms. Subsequently, diagnostic clinical examinations were performed to verify whether the patient met the criteria of CAP defined according to the ATS criteria (2001). According to these criteria, CAP is present if a new infiltrate on chest X-ray or progression of an existing infiltrate is present in combination with at least two of the following five criteria: 1) cough, 2) production of purulent sputum ( $\geq 25$  PMN and  $< 10$  squamous epithelial cell/HPF) or a change in character of sputum, 3) auscultatory findings on pulmonary examination such as rales, rhonchi or bronchial sounds suggestive of pneumonia, or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds or echophony), 4) dyspnoea or tachypnea, 5) fever,  $> 38^{\circ}\text{C}$  taken axillary; or leucopenia with total WBC  $< 4500/\text{mm}^3$  or leukocytosis with total WBC of  $\geq 12 \times 10^9/\text{L}$ . Physical examinations also included tests to verify the presence of any of the exclusion criteria.

### ***Microbiological analyses***

All included patients were asked to supply a sputum sample together with a midstream specimen of urine before antibiotics were given. Venous blood was obtained and serum was stored at  $-20^{\circ}\text{C}$ . Blood cultures were not performed because appropriate material was not available. Urine samples were collected directly after admission to hospital. All samples were analyzed in the laboratory in the University Hospital of León. The sputum was examined microscopically and was rated into Q0 to Q3 according to Murray and Washington<sup>13</sup>. Only sputum samples with a Gram stain with a property exceeding Q2 ( $< 10$  squamous epithelial cells and

≥25 polymorphnuclear neutrophils per lower power field) were further processed. Sputum samples were inoculated on blood and agars from MacConkey and Merck. The plates were incubated at 36°C for 18-24 h. Micro-organisms cultured were recorded and stored. In addition, Binax NOW®-tests were used to detect antigens of *Legionella pneumophila* and *Streptococcus pneumoniae* in urine samples.

Microbial susceptibility for *Streptococcus pneumoniae* was performed in León while other identified micro-organisms were sent to the Eijkman Winkler laboratory of the University Medical Center Utrecht, a reference laboratory in the Netherlands. Any pathogen isolated from the respiratory specimen was tested for antimicrobial susceptibility using the Kirby Bauer Method by the National Committee for Clinical Laboratory Standards<sup>14</sup> (NCCLS). The following antibiotics were selected for screening on antimicrobial resistance because they are used as first-line therapy in Nicaragua: erythromycin, oxacillin, and penicillin, and MIC's were determined by the use of E-test strips (AB biodisk®, Solna, Sweden).

Acute and convalescent sera were obtained at hospital admission and 2-3 weeks later. For logistical reasons, sera could not be collected after a period of three weeks. The samples were properly stored and evaluated in the Eijkman Winkler laboratory in the Netherlands for *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*. For *Mycoplasma pneumoniae*, a fourfold or greater increase in titre in paired sera or a single titre of greater than or equal 1:40 was considered indicative of infection (Immune fluorescence agglutination, Serodia-Mycoll®, Fujirebio, inc.)<sup>15</sup>. For *Legionella pneumophila*, a fourfold increase in the antibody titre to 1:128 or greater or single titres of 1:256 or more were considered suggestive of *Legionella pneumophila*<sup>16</sup>. For *Chlamydia pneumoniae*, detection of IgM above established values, seroconversion of IgG between acute and convalescence samples, high amounts of IgG in single titres or a combination of these tests were considered serological evidence of presence or absence of infection according to the manufacturers instructions (ELISA, Savyon Diagnostics Ltd).

The diagnosis of pneumococcal pneumonia was confirmed when the criteria of CAP were fulfilled, in combination with one or more of the following criteria: 1) the Gram stain of sputum showed Gram-positive, lancet-shaped diplococci, 2) isolation of *Streptococcus pneumoniae* in a sputum culture, or 3) a positive pneumococcal urinary antigen test.

### **Statistical analysis**

All data were analyzed with SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics as frequencies and means or medians were calculated. Predictors for pneumococcal pneumonia were determined by use of multivariable logistic regression analysis. Odds ratio's (OR) and 95% confidence

intervals (95% CI) were given as approximations of the relative risks. P-values given were two-sided.

## Results

In all, 134 patients with CAP that met inclusion criteria were eligible for the present study. We excluded four patients from the analysis; in three patients baseline data were missing and one patient appeared to have an immune-deficiency detected after admission. The majority of the remaining 130 study patients were female (56%) and mean age was 52 years (standard deviation [SD] 24 years, range from 12 to 97 years). The majority of patients lived in the city León (62%) and the remainder lived in the country. Most patients were housewife (34%), some were farmer (12%) or student (12%) and 9% was unemployed. The most common co-morbidity was chronic obstructive pulmonary disease (COPD) (29%) followed by renal disease (19%), heart failure (7%), liver disease (2%) and malignancy (2%). Ten study patients (8%) died in our hospital. The characteristics of these patients are outlined in Table 1.

*Table 1 Characteristics of patients who died with CAP in our hospital (N=10).*

Female	6 (60%) <sup>1</sup>
Age	59 ± 23
Leukocytosis	11.6 ± 3.4
Fine score	146 ± 57
Comorbidities	
- renal disease	5 (50%)
- COPD	6 (60%)
Gram stain	
- Gram negative bacillus	3/6 (50%) <sup>2</sup>
Infiltrate	
- Alveolar	7 (70%)

<sup>1</sup> Numbers between bars represent percentages

<sup>2</sup> *E. cloacae*, *P. aeruginosa*, *E. agglomerans*

Almost all patients had acute cough (97%) and dyspnoea (86%) (Table 2). Crepitations of the lungs were noticed in 96% of patients. Chest or pleural pain was less frequently reported (34%). Radiographic examination showed an alveolar infiltrate in 62% of cases. An interstitial infiltrate was seen in 20%, and a reticulo-interstitial infiltrate in 18% of cases. The average severity of pneumonia was moderate, with a mean Fine score of 75 points (SD 44). The mean Fine score in patients that died was considerably higher 146 ± 57 (Table 1). The average amount of leukocytes counted was 13.8 10<sup>9</sup>/L (SD 6.7) and mean creatinin level was 1.85 mg/dL (= 166 µmol/ L) (SD 2.5, Normal value: 0.5-1.1 mg/ dL).

Table 2. Diagnostic predictors of patients with pneumococcal pneumonia (n=22) compared with patients with pneumonia caused by other micro-organism than *S.pneumoniae* (controls, n=51)\*

Predictor	Patients with pneumococcal pneumonia (n=22) N (%)	Controls (n=51)* N (%)	Multivariable odds ratio (95% CI)	P-value
COPD	2 (9)	17 (33)	0.2 (0.03-0.8)	0.024
Chills	21 (96)	33 (66)	13.0 (1.6-108.0)	0.017
Fever	21 (96)	41 (82)	-	-
Retractions	19 (86)	47 (92)	-	-
Cough	22 (100)	50 (98)	-	-
Dyspnoe	19 (86)	44 (86)	-	-
Pleural pain	6 (29)	21 (43)	-	-
Crepitations	21 (96)	49 (96)	-	-
Dullness	21 (96)	40 (78)	-	-
Al. infiltrate	18 (82)	28 (55)	-	-
Creat (mean, SD) (µmol/ l)	189 (198)	180 (270)	-	-

\* In sixty-one patients no causative micro-organism was found

### **Micro-organisms and antimicrobial susceptibility**

The most frequently identified pathogen in our study was *S. pneumoniae* (17%). Other pathogens were *S. aureus* (5%), *C. pneumoniae* (5%), *M. pneumoniae* (4%) and *P. aeruginosa* (5%). Only one out of 6 patients with *Pseudomonas aeruginosa* had COPD, despite the fact that structural lung disease is a known risk factor for a *P.aeruginosa* infection<sup>17</sup>. Five out of 6 patients with *P. aeruginosa* were found to have a mixed infection. *Acinetobacter baumannii* was detected in 4% and *Legionella pneumophila* was identified in 3% of the cases. There was a mixed infection in 11% of the cases and the aetiology of the remainder of study patients (55%) remained unknown.

In all, 60 (46%) of 130 patients had paired serum, 89 (69%) supplied urine for Legionella-antigen and 67 (52%) for *Streptococcus pneumoniae* testing; there were 2 positive for Legionella and 5 positive pneumococcal antigen tests. Forty-nine (38%) had sputum cultures. In most people who died, a pathogen was identified (60%). In the majority of cases, a Gram-negative bacterium, like *E. cloacae*, *P. aeruginosa* or *E. agglomerans* was cultured (Table 1). Using multivariate logistic regression, chills (OR13.0; 95% CI: 1.6-108.0, P=0.017), and the absence of Chronic Obstructive Pulmonary Disease (COPD) (OR 0.2; 95% CI 0.03-0.8, P=0.024) were significantly and independently associated with the presence of pneumococcal pneumonia.

None of the four *Streptococcus pneumoniae* isolated and tested was resistant to erythromycin and penicillin. In contrast, 67% (4/6) of *Staphylococcus aureus* was resistant to erythromycin and all of those tested for susceptibility to penicillin were resistant (n=5). One isolate (16%) was resistant to oxacillin (MRSA).

Patients received empiric antibiotic treatment. The most frequently prescribed antibiotics were ampicillin and ceftriaxon, followed by azitromycin.

## Discussion

Our study is in agreement with various studies worldwide that show pneumococci to be the most common micro-organisms detected in patients with CAP. Importantly, the four positive tested pneumococcal pneumonias were all sensitive to penicillin and erythromycin. In contrast, most of the pneumonia's associated with *Staphylococcus aureus* showed resistance to penicillin and erythromycin.

In other parts of Latin America, resistance rates of *Streptococcus pneumoniae* for penicillin are substantial. Jardim et al found a moderate to high resistance of 64% in Brazil<sup>18</sup>. From 1993 to 1998, a multi-centre study was performed in several countries in Central and South America to investigate the impact of *Streptococcus pneumoniae* in the development of community-acquired pneumonia in Latin American children. In that study, Hortal et al. found that at the beginning of the study the highest level of penicillin resistance was detected in Mexico<sup>19</sup> (47%), close to the borders of Nicaragua.

*Mycoplasma pneumoniae* was detected in only 4% of our study patients. The difficulty in obtaining a second convalescent serum-sample could have attributed to this relatively low percentage. However, this is especially relevant for Legionella since it may take more than three weeks to develop a rise in antibody titre to this pathogen. We were able to obtain two convalescent samples in 60% of patients. A mixed infection was seen in 11% of patients. Only two patients had a mixed infection with *S. pneumoniae*, combined with *Legionella pneumophila* and *Mycoplasma pneumoniae*. In these cases, erythromycin appeared to be the right choice of treatment. In case of a confirmed or highly suspected pneumococcal pneumonia, for example in the absence of COPD and when chills are present, penicillin is the first choice of treatment.

The resistance rate of *Staphylococcus aureus* for erythromycin and penicillin was substantial. Sixty-seven percent was resistant to erythromycin and all were resistant to penicillin. Bacterial resistance against oxacillin (MRSA) was (17%). Nowadays, multiple resistant *Staphylococcus aureus* (MRSA) is a major threat to clinical management. Though our study was small and the number of *S. aureus* positive isolates was low, our data suggest that resistance rates against macrolides (erythromycin) and penicillin are on the rise in Nicaragua.

In our study we found that 'chills' is a predictor for having pneumococcal pneumonia. This agrees with the findings of Bothe et al. who in univariate analysis proved that 'acute onset of disease' is a risk factor for CAP caused by *Streptococcus pneumoniae*<sup>20</sup>. The fact that the absence of Chronic Obstructive Pulmonary Disease (COPD) was significantly and independently associated with pneumococcal pneumonia in our study is in contrast with the guidelines produced by the Dutch association of lungspecialists and specialists of tuberculosis (NVALT)<sup>21</sup> that indicate that *S. pneumoniae* is associated with patients having COPD. A possible explanation for this discrepancy could be the fact that obtaining sputum from patients with COPD was difficult in our hospital.

In conclusion, penicillin seems to be the first-line treatment of CAP caused by *Streptococcus pneumoniae*. In case of mixed infections, erythromycin is the alternative. Resistance of *S. aureus* against penicillin and erythromycin is high in this study. In 1/6 (17%) of the isolates we found MRSA. The resistance of *S. aureus* could be a major threat to clinical management in Nicaragua. Given these alarming results, a large, multi-centre, prospective cohort study on the resistance rates and outcomes in CAP is urgently warranted in Nicaragua.

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# Chapter 4

## Application of guidelines on pre-operative antibiotic prophylaxis in León, Nicaragua

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## Abstract

**Objective:** To determine the guideline adherence for pre-operative antibiotic use in Nicaragua.

**Methods:** An observational study in the University Hospital of León, Nicaragua. All surgical patients in the departments of general surgery, orthopaedics, gynaecology and obstetrics, and paediatrics during a four week period were included. Patients with infections prior to surgery were excluded.

Main outcome measures were the proportion of patients that received appropriate pre-operative antibiotics based on wound classification, suspected pathogens, administered antibiotics (type and dose), therapy duration and timing according to local protocol.

**Results:** In the study, 297 patients received a total of 395 antibiotics with 2595 doses for a total of 1087 days. Only 68% of patients received antibiotic prophylaxis for indications mentioned in the protocol. Antibiotics were given without indication or as treatment in 23%. In 9% of the cases no pre-operative antibiotic therapy was given (no indication for 6%, but indicated for 3%). Of the 201 patients with an indication for prophylaxis, 25% received more antibiotic therapies than indicated. Antibiotic choice was discordant with the protocol in 69%, dose in 20%, and moment of administration and duration both in 78%. Overall adherence was achieved in 7% of patients. Complete protocol violations were observed in 12%. The 243 patients in the prophylaxis group received 1707 doses of which 83% were administered unnecessarily.

**Conclusion:** Protocol violations are frequent in pre-operative antibiotic prophylaxis in Nicaragua leading to considerable over-prescription. Educational strategies to reinforce protocolised antibiotic use are essential in reducing costs and antibiotic resistance rates.

## Introduction

When appropriate antibiotic prophylaxis is used, the incidence of surgical site infections is between 2 and 5% and the associated mortality is 0.6%<sup>1,2</sup>. Inadequate prophylaxis leads to an increased incidence of surgical site infections up to 15%<sup>3-5</sup>. Studies have shown inappropriate antibiotic prophylaxis, hyperglycaemia, pre-operative condition (ASA score), wound classification and the duration of the operation to be independent risk factors for such infections<sup>3,6</sup>. The aetiology of surgical site infections is dependent on the location of the surgery, the bacterial load in the tissue or blood peri-operatively and the integrity of host defenses<sup>2,4,6</sup>. Adequate prevention of such infections is important because it is associated with increased mortality and hospital costs up to 10-fold<sup>2,4,6-8</sup>. Inappropriate use of antibiotics

(including over-prescription and the unnecessary use of broad-spectrum antibiotics) can also lead to increased bacterial resistance<sup>9,10</sup>. A sound and restrictive policy minimizes antibiotic resistance, prevents surgical site infections and is cost-effective<sup>11-13</sup>.

Protocols for antibiotic prophylaxis are designed worldwide to optimize local administration of antibiotics. Monitoring and intervention can be effective in increasing the adherence to a protocol as was shown in studies in which the appropriateness of antibiotic prophylaxis was increased from around 50% to 95-100% by the stricter implementation of an existing protocol<sup>14,15</sup>.

As baseline data are lacking in Nicaragua, we set out to evaluate the adherence to guidelines for pre-operative antibiotic use in León, Nicaragua.

## **Methods**

### ***Pre-operative antibiotic guidelines***

In Nicaragua, the Ministry of Health published two documents on pre-operative antibiotic treatment in the mid-nineties. In 1997, a nationwide project was initiated to promote rational use of medications on the basis of these documents<sup>16</sup>. In 2000, the University of León and the Ministry of Health collaborated on this topic and published a final protocol for the pre-operative use of antibiotics<sup>17</sup>. To detect deviations from protocols of Western countries, the widely accepted Dutch protocol formulated by the SWAB (Dutch Working Party on Antibiotic Policy) was used as a reference<sup>18</sup>. Even though there are some minor differences between Dutch hospitals, the SWAB guidelines are used in this study as the official Dutch national protocol for comparison purposes. The Nicaraguan and Dutch protocols were compared on a number of points: wound classification, most likely pathogens, suggested antibiotics (primary and secondary), and ideal moment of administration.

### ***Design, Setting and Study population***

We conducted an observational study during a four-week period in 2005 in the University Hospital of León, Nicaragua. All consecutive persons of any age undergoing surgery in the departments of general surgery, orthopaedics, gynaecology and obstetrics, and paediatrics were eligible for inclusion into the study. We excluded patients with current infections or contaminated wounds prior to surgery by review of the patient records. When an infection became apparent during the operation, the initial prophylaxis was switched to treatment. Therefore only the initial dose given prior to surgery was evaluated. Approval for this study was received from the ethical committee in Nicaragua.

### **Measurements**

During the study period, all patient records of the participating departments were checked on a daily basis for new surgical procedures as well as to follow-up the patients already included in the study. For our research purposes, a case record form was developed which included information of patient characteristics, surgical procedures and antibiotic treatments for each subject. Wound classification was obtained from the antibiotics ordering form that was sent for each patient to the hospital pharmacy prior to surgery. When the wound classification was not reported, the wound was classified from the operation report according to the Nicaraguan protocol standards for that type of surgical procedure<sup>16</sup>.

Follow-up data were updated daily with regard to additionally administered doses, changes in type of antibiotic medication and administration intervals as well as for signs of postoperative wound infections. If more than one antibiotic was prescribed, they were evaluated separately. Subsequently, a final assessment of all antibiotics per patient was made. Antibiotic therapy given to patients at discharge was not included. All antibiotics administered within 1.5 hours before surgery were recorded as being concordant with the Nicaraguan protocol<sup>16</sup>.

When the patient record indicated “antibiotics given in the operating theatre”, such antibiotics were regarded as being given at the start of anaesthesia. The authors did not attend the surgical procedures themselves, thus not influencing the timing and administration of antibiotics by their presence. All other moments of administration in relation to the surgery were treated as protocol violations. All antibiotics prescribed were compared with the Nicaraguan protocol.

### **Results**

A comparison of the Nicaraguan and Dutch protocols (table 1) shows only minor differences between them. The moment of administration is stricter in Nicaragua, but the criteria for a second dose during surgery are the same. Moreover, the Nicaraguan protocol does not differentiate between contaminated and dirty wounds. The Nicaraguan and Dutch protocols use the same definition for surgical site infections.

Of the 297 patients, the majority of procedures were done in women (80%) and the mean age was 29 years (standard deviation 18 years). Most patients were from the obstetric wards (45%), followed by general surgery wards (21%), gynaecology (15%), paediatrics (10%) and orthopaedic wards (8%). Co-morbidity was present in 12% of these patients, and 2% had a known allergy for antibiotics. Of all surgical wounds, 77% were clean contaminated, 14% were clean and 9% were contaminated/dirty. The mean duration of the surgical procedure was 56 minutes (standard deviation 39 minutes). Only 1.4% of patients had an infection post-operatively.

Table 1. Protocol comparison.

	Léon, Nicaragua	Utrecht, the Netherlands
<b>Time of administration</b>	90-15 mins before incision	120-30 mins before incision
<b>Additional dose</b>	Every 3-4 hours with: - Operation length > 3 * $t_{1/2}(\text{antibiotic})$ - Blood loss > 2 liters - Extra-corporal circulation	
<b>Wound classification</b>	<p><b>Clean</b> (surgery without trauma or infection, with asepsis, without opening airways, intestinal tract or urogenital system and without implantation of prostheses): no prophylaxis indicated.</p> <p><b>Clean-contaminated:</b> controlled opening of the airways, intestinal tract, biliary tract or urogenital system. Penetrating abdominal trauma without signs of visceral damage or infection during surgery, cardiothoracic surgery, large vessel surgery.</p> <p><b>Contaminated/ Dirty:</b> Therapy required. All surgery that is not clean or clean-contaminated.</p>	<p><b>Clean</b> (elective surgery, closed without drains, no infection found, good asepsis, without opening airways, intestinal tract or urogenital system): no prophylaxis indicated.</p> <p><b>Clean contaminated:</b> controlled opening of the airways, intestinal tract, biliary tract or urogenital system.</p> <p><b>Contaminated:</b> open traumatic wounds, leakage from intestinal tract, open urogenital or biliary tract with infected urine or bile, infection without pus.</p> <p><b>Dirty/ infected:</b> traumatic wounds with necrosis, corpus alienum or (fecal) infection, perforated viscera, acute bacterial infection with pus.</p>
<b>Surgical Site Infection</b>	Manifest themselves after a surgical procedure (within 48 hours) and have a direct relation to this procedure.	

In all, 395 antibiotic therapies were prescribed for these 297 patients (figure 1). The majority, 201 patients (68%), received antibiotics for a proper prophylaxis indication. However, 69 cases (23%) received antibiotics either without indication since the procedure could be considered a clean one (42 patients, 14.1%) or as antibiotic treatment (27 patients, 9.1%) for a contaminated wound. Contaminated wounds are susceptible to infections due to the presence of bacteria in the wound and therefore require more intensive treatment than prophylaxis alone. No antibiotics were received by 27 patients since it was not indicated in a clean procedure (17 patients, 5.7%) or

prophylaxis was indicated but not prescribed (10 patients, 3.4%). All 96 cases that did not receive prophylactic antibiotic treatment were no longer followed up .

In total, 201 patients with an indication for prophylaxis received 282 antibiotic therapies. In 51 patients (25.4%) an additional antibiotic therapy was prescribed, contrary to the protocol. Of these 282 prescriptions, antibiotic choice was discordant with the hospital protocol in 68.8%, dose in 19.9%, moment of administration in 77.7% and duration in 78.4%. Overall, 690 violations of any aspect were recorded in the 282 antibiotic therapies. Overall adherence to the protocol was achieved with only 21 (7.4%) antibiotic therapies, 38 (13.5%) were in accordance with the protocol on all but one item, 41 (14.5%) on two items and 149 (52.8%) were only correctly prescribed on one item (mostly a correct dose).

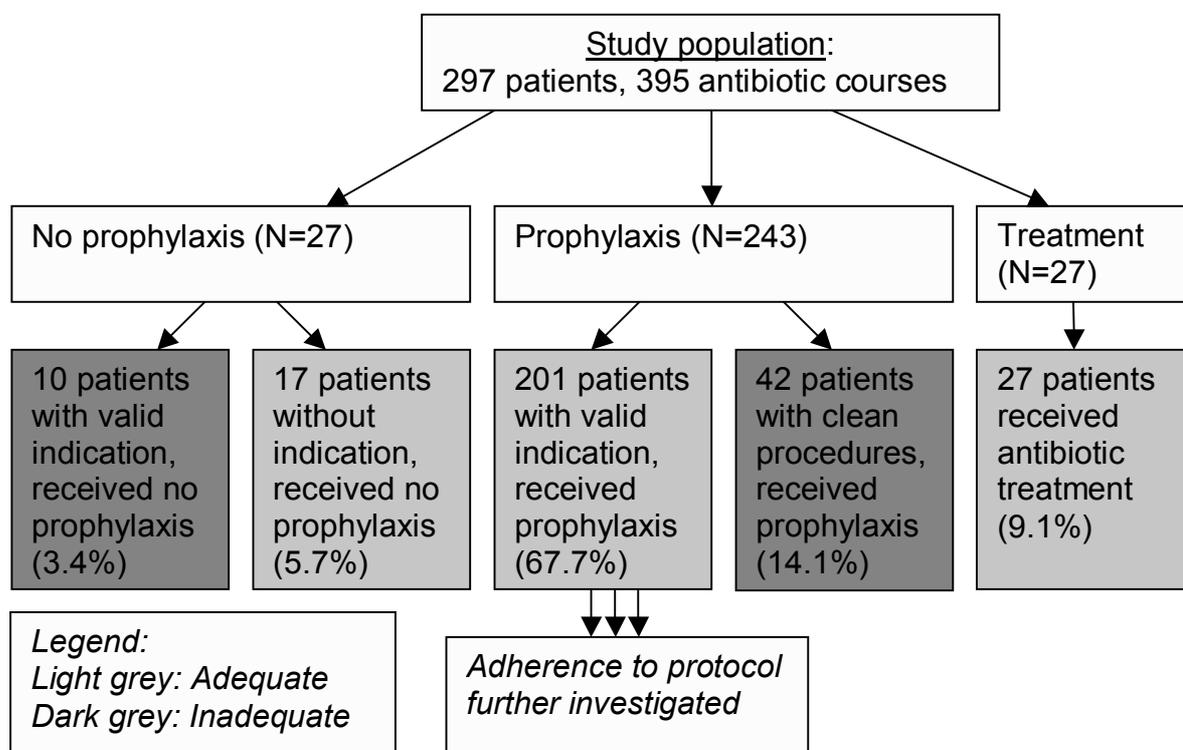


Figure 1. Patient flow chart.

In all, 33 (11.7%) antibiotics were not in accordance with any item mentioned in the protocol. There were no statistically significant differences in protocol adherence between the different surgical wards.

The 201 patients to whom prophylaxis were given, received 211 (of 282) antibiotic therapies peri-operatively; 71 courses (25%) were given additionally at a later time.

Of all 211 initial therapies 78% of antibiotics is administered outside the correct dosing interval. Sixty-three percent were administered after the operation, with a mean delay of 6.9 hours. Fifteen percent of antibiotics were administered 90 minutes or more before entering the operating theatre, on average by 8.8 hours. Only twenty-two percent was administered in the correct dosing interval. Eleven percent of antibiotics were administered between 90 minutes before entry and entering the operating theatre. Another 11% was administered in the operating theatre. For these, it was not possible to establish a more precise moment of administration and it was assumed that they were given prior to incision.

Protocols for prophylaxis propose the preferential use of certain antibiotics over others. An overview of the types of antibiotics used in patients in whom prophylaxis was given for a valid indication is shown in table 2. Ampicillin (58.3%) and cefazolin (13.0%) were most often prescribed. Cefazolin and cefoxitin are the antibiotics that are most often administered correctly according to the protocol. Ampicillin and ceftriaxone are not mentioned in the protocol, but they are often prescribed for prophylactic purposes.

The 243 patients in the prophylaxis group (figure 1) received a total of 322 antibiotic therapies or 1707 doses for a total of 721 days in the four-week study period. According to the protocol, 1409 of these 1707 doses (83%) were administered unnecessarily for 411 days, as regulations indicated that fewer doses would have been sufficient. There were no patient characteristics, wards or types of antibiotic which could significantly predict overprescription.

*Table 2. Administration of antibiotics of the study population (N=201).<sup>1</sup>*

Antibiotic received	% of total	No. of doses	No. of days
Ampicillin	58.3 %	793	272
Cefazolin*	13.0 %	177	93
Gentamicin*	9.8 %	133	90
Penicillin	5.7 %	77	25
Cefoxitin*	4.7 %	64	33
Ciprofloxacin	2.3 %	31	24
Ceftriaxone	1.3 %	17	12
Metronidazole*	1.2 %	16	8
Amoxicillin*	0.6 %	8	6
Others**	3.2 %	44	26
Total	100%	1360	589

<sup>1</sup> Initial first choice therapies only

\* Antibiotics mentioned in the prophylactic protocol.

\*\* dicloxacillin, amikacin, cephalixin, clindamycin, nitrofurantoin, cefadroxil.

## Discussion

When the Dutch and Nicaraguan protocols are compared, there are few differences in timing of antibiotic prophylaxis and wound classification<sup>16-18</sup>. Furthermore, the expected pathogens for each type of surgery and the primary antibiotics recommended are generally the same (Table 3, next page). However, about half of the antibiotics used (table 2) are not mentioned as a suitable prophylactic drug either in the Nicaraguan or Dutch protocols. Of these drugs, ampicillin is used in León by the gynaecologists as standard prophylaxis with caesarean sections. This use is not supported by the local infectious disease specialist and there is no bacterial resistance or sensitivity data that warrant its use. Therefore these cases were considered protocol violations. Many of the studied patients underwent a caesarean section and the use of ampicillin thus influences the results significantly.

The study data indicate that protocol violations are frequent in pre-operative antibiotic prophylaxis in Nicaragua which leads to considerable over-prescription of antibiotics. It has been established in numerous studies that the use of pre-operative prophylaxis reduces the rate of surgical site infections and it is now accepted as standard care (and recommended by the Center for Disease Control)<sup>3-5</sup>.

It was shown that for 68% of patients the proper choice to administer antibiotics is made. In addition in 5% of the cases the proper decision of not administering prophylaxis was made. However, after making the proper indication, antibiotic choice, duration, dose and timing were discordant with hospital guidelines in many patients. Van Kasteren et al. conducted a similar study in 13 Dutch hospitals and found antibiotic choice to be discordant with hospital guidelines in 8%, duration in 18%, dose in 11% and timing in 50%<sup>19</sup>. Considering these much lower discordance rates with the protocol, we may conclude that there is still room for improvement in adherence to the protocol in Nicaragua. A more recent study showed that the implementation of the SWAB guidelines improved long-term adherence<sup>13</sup>. This resulted in a decrease in inappropriate antimicrobial use and lowered costs without impairing patient outcome.

Of particular concern is the timing of the prophylaxis in Nicaragua. The majority of antibiotics are administered outside the correct pre-operative dosing window. Most antibiotics were administered too early or too late leading to ineffective antibiotic blood levels at the time of surgery. A limitation of this study is an inability to comment on the 9% of antibiotics administered in the operating theatre, because it is unclear if the antibiotic was given before or after the incision. In future studies one could consider a method to record the timing more precisely. In some cases antibiotics were given for periods longer than 24 hours.

Table 3. Expected pathogens

Type of surgery (clean-contaminated)	Probable bacteria	Recommended antibiotics	Comments
Head & neck surgery	<b>Utrecht:</b> <i>S. Aureus</i> , Streptococci, Anaerobics, Enterobacteriaceae <b>León:</b> Anaerobics, Gram-negative Enterobacteriaceae, <i>S. Aureus</i> , Streptococci	1: Cefazolin + metronidazole 2: Augmentin 3: Clindamycin 1. Cefazolin 2. Clindamycin + Gentamicin	Only when opening the oropharynx or oesophagus
Stomach*/ duodenal*/ biliary# surgery	<b>Utrecht:</b> Enterobacteriaceae, <i>S. Aureus</i> , Streptococci, Enterococci  <b>León:</b> Gram-negative Enterobacteriaceae, Enterococci, <i>Clostridium Perfringens</i> , <i>S. Aureus</i>	1. Cefazolin  1. Cefazolin 2. Clindamycin + Gentamicin	* Reduced motility, morbid obesity, reduced pH. # > 70y, acute cholecystitis, obstructive icterus, gallstones in gall ducts * Reduced motility, morbid obesity, reduced pH. # > 60y, previous biliary surgery, obstructive icterus, gallstones in gall ducts
Colorectal surgery, appendectomy (non perforated)	<b>Utrecht:</b> Enterobacteriaceae, <i>S. Aureus</i> , Anaerobics, Streptococci, Enterococci <b>León:</b> Gram-negative Enterobacteriaceae, Anaerobics, Enterococci	1. Cefazolin + metronidazole 2. Augmentin 3. Cefoxitin 1. Cefoxitin 2. Clindamycin + Gentamicin	
Penetrating abdominal trauma	<b>Utrecht:</b> <i>S. Aureus</i> , <i>Streptococcus Pyogenes</i> <b>León:</b> Gram-negative Enterobacteriaceae, Anaerobics, Enterococci	1. Cefazolin 2. Flucloxacillin  1. Cefoxitin + Gentamicin 2. Clindamycin + Gentamicin	In absence of visceral lesions
Vaginal surgery, caesarean section\$, abdominal hysterectomies	<b>Utrecht:</b> <i>S. Aureus</i> , (group B) Streptococci, Enterobacteriaceae, Anaerobics <b>León:</b> (group B) Streptococci, Enterobacteriaceae, Anaerobics, Enterococci	1. Cefazolin + metronidazole 2. Augmentin 3. Cefoxitin  1. Cefazolin 2. Clindamycin (+ metronidazole)	\$ Secondary caesarean section

Table 3. Expected pathogens-continued

Cardio-vascular surgery	<b>Utrecht:</b> <i>S. Aureus</i> , <i>S. Epidermidis</i> , Enterobacteriaceae	1. Cefazolin 2. Flucloxacilin 3. Glycopeptid (MRSA)	Clean wound: prophylaxis indicated because infection can have serious consequences
	<b>León:</b> <i>S. Aureus</i> , <i>S. Epidermidis</i> , Gram-negative Enterobacteriaceae	1. Cefazolin 2. Vancomycin	

Research has shown however that effective prophylaxis can be established with short courses of less than 24 hours and that longer administration not only has no benefit but may be detrimental through an increased incidence of resistance<sup>2,20</sup>.

Moreover, during a caesarean section, guidelines advice antibiotic prophylaxis just after cutting the umbilical cord, but in this study, only 14 caesarean sections (11%) were performed correctly as advised. In 21 patients (16%), prophylaxis was given before the caesarean section and in 94 patients (73%) prophylaxis was given on the ward, 0.5 to 24 hours after the caesarean section.

Currently prophylactic antibiotics take up a large part, up to 30% or more, of the prescribed antibiotics in hospitals<sup>14</sup>. Adherence to local guidelines could keep costs to a minimum. Literature suggests different cost-effective strategies to improve protocol adherence. Prado et al. show that when the pharmacy is given a central role in the administration of prophylaxis, the appropriateness of the indication increased from 56% to 100%, while the costs decreased by 40%<sup>15</sup>. Moreover, Zwar et al. found that giving feedback on prescription behaviour increased the appropriateness of the prescriptions<sup>21</sup>. Welschen et al. conclude that by organising a group education and consensus meeting and monitoring prescriber behaviour, prescription errors decreased by 12% compared to controls. Alerany et al. showed that integrating all the above strategies resulted in an increase of the adherence from 51 % to 95 % in surgeries requiring prophylaxis<sup>14</sup>. They used an antibiotic prophylaxis chart in the operating theatres, pharmacy controlled administration and education and prescriber feedback. It can be noted that the main causes of misuse in the article from Alerany et al. were timing and choice which were also problematic in this study.

In León, antibiotics must be ordered at the pharmacy prior to the operations. A specific form must be completed for all procedures, including clean ones. It is the only form on which the wound classification must be indicated and if not filled out completely, the information might be lost. This form was completed for only 25% of the study subjects. It is important for future prescriptions to stress the value of filling out this form. An effort to consistently classify the wounds might result in a better awareness and understanding of the protocol and, subsequently, the adherence to it.

General population statistics show that an allergy against antibiotics presents itself in roughly 5-10% of the population<sup>23</sup>. Thus a 2.4% allergy rate in our study population could be an underestimation.

The incidence of surgical site infections or postoperative infections ranges from 2.5% to 10% depending on the type of surgery<sup>8,24</sup>. It was not part of the objective to study the effectiveness of the protocol in terms of prevention of surgical site infections.

In conclusion, adherence to the pre-operative antibiotic therapy protocol is far from being optimal and in concordance with the Nicaraguan guidelines leading to more than half of the antibiotic doses administered unnecessary according to the protocol rules. This is a huge toll on the budget of the hospital and obviously also plays a serious role in the formation of antibiotic resistance. Successful prescription of antibiotic prophylaxis is dependent on the national policy on the control of antimicrobials, quality of the local protocols, their implementation, hospital staff education, monitoring, and feedback interventions to increase the adherence.

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# Chapter 5

## Prevalence of HIV and syphilis in pregnant women in León, Nicaragua

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## Abstract

**Objectives:** To determine the prevalence of HIV and syphilis and to identify risk factors among pregnant women visiting antenatal clinics in León, Nicaragua.

**Methods:** From February to April 2004, blood samples from pregnant women were collected after written consent had been obtained. The samples were tested for antibodies against HIV and *Treponema pallidum*. A questionnaire was also completed.

**Results:** In total 1059 women were included. Antibodies against HIV were not detected in any of the women whereas antibodies against *T. pallidum* were detected in 16 (1.5%). Risk factors for syphilis included illiteracy and lower education and two or more pregnancies.

**Conclusion:** HIV appeared not to be highly prevalent among pregnant women in León (prevalence 0%, 95%CI= 0.0-0.3). The higher proportion of women infected with syphilis than found in earlier studies suggests that sexually transmitted diseases are circulating in the general population and highlights the increasing importance of HIV prevention.

## Introduction

Since the first AIDS patients were reported in 1981, the disease has become a problem worldwide, and the HIV epidemic is still spreading. In 2003 almost five million people became infected with the virus, the largest increase in infection seen since the start of the epidemic<sup>1</sup>. Global monitoring of the prevalence and incidence of HIV is essential to controlling the AIDS epidemic, yet in some countries, such as Nicaragua, there is a lack of reliable data on the prevalence of HIV. The first HIV infection was diagnosed in Nicaragua in 1987<sup>2</sup>. Official sources reported that 27 people were HIV-positive in 1987 and 376 people in 2004<sup>3</sup>. The WHO currently estimates underreporting to be more than 60%.<sup>4</sup> At the end of 2003, an estimated 6400 people had HIV/AIDS in Nicaragua, a prevalence of 0.2% in adults (15-49 years)<sup>4</sup>. The incidence and prevalence of HIV/AIDS is lower in Nicaragua than in neighboring countries such as Costa Rica and Honduras, where the prevalence of HIV was estimated to be 0.6% and 1.8% at the end of 2003, respectively<sup>1,5</sup>.

Nicaragua has seen some changes in the last two decades which might indicate that there will be an increase in the prevalence of HIV in the future; increased prevalence of syphilis, increased mobility and increased commercial contacts. In Nicaragua there is no mandatory HIV testing for pregnant women nor is there counseling to recommend an HIV test. Testing for syphilis though is mandatory in the first trimester of pregnancy.

The goal of this prevalence study was to determine the prevalence of HIV and syphilis and to identify risk factors among pregnant women visiting antenatal clinics (ANCs) in a medium sized city in the west of Nicaragua. Such information will provide insight into the circulation of sexually transmitted diseases (STDs) in general<sup>4</sup>.

## Methods

### ***Design and Study population***

We conducted a prevalence study involving pregnant women from whom blood samples were collected for 10 weeks in February, March, and April 2004 in León, Nicaragua. Approval for this study was received from the ethical committee in Nicaragua. All pregnant women attending the 'emergencia gynaecologia' of the HEODRA hospital or one of three ANCs in León were invited to participate in the study as were all women who had given birth in the previous 24 hours in the Hospital Escuela Oscar Danilo Rosales Arguello (HEODRA). The latter group visited the hospital for prenatal care in earlier months. Women who had already participated in this study were excluded. Reasons for refusal were recorded.

### ***Clinical methods***

Women gave their written informed consent after they received information about the study. Demographic and sexual/ reproductive data and information about risk factors for STDs and blood borne infections were collected by means of an interview questionnaire. Blood samples were collected and serum samples (in duplicate) were stored at minus 20 degrees at the laboratory of HEODRA hospital before being sent to the Department of Virology of the Eijkman-Winkler Institute of the UMC Utrecht, the Netherlands, for testing for antibodies to HIV and *T. pallidum*.

### ***Laboratory methods***

The sera were tested for HIV antibodies, 2-4 months after the samples were taken, using the Enzygnost Anti-HIV 1/2 Plus test (Dade Behring; Marburg, Germany), which has a sensitivity of >99% and a specificity of 99.3--100%<sup>6</sup>. Positive tests were confirmed by immunoblot (Inno-Lia HIV confirmation, Innogenetics; Gent, Belgium). Testing for antibodies against *T. pallidum* was carried out with an 'automated inhibition ELISA' (Enzygnost, Dade Behring; Marburg, Germany) with a sensitivity of 98.4-100% and a specificity of 99.5% for pregnant women<sup>7</sup>. The presence of syphilis was confirmed with Treponema -pallidum haemagglutination assay (TPHA) (Fujirebio; Tokyo, Japan) and Venereal Diseases Research Laboratory (VDRL) (Abbott Murex, Dartford, UK), but only when ELISA results were borderline or positive. A positive reaction in ELISA, TPHA, and VDRL was considered indicative of recent and/or active *T. pallidum* infection. If the ELISA result was borderline and the TPHA and VDRL remained negative, it was concluded that there was no *T. pallidum*

infection. If the ELISA was positive but the TPHA and VDRL were negative, immunoblotting was performed to confirm or rule out *T. pallidum* infection. A positive ELISA in combination with a positive TPHA or a positive VDRL was considered indicative of (treated) recent *T. pallidum* infection or *T. pallidum* infection in the past.

### **Data analysis**

The data were entered and analyzed using SPSS version 10 for windows (SPSS, Inc, Chicago, IL, USA). Descriptive statistics were used to determine the occurrence of HIV and syphilis. To identify potential risk factors, univariate relative risks and odds ratios with associated 95% confidence intervals and significance levels were evaluated, using the Pearson's  $\chi^2$  test and the Fisher exact test. Because of the low number of outcomes for *T. pallidum* infection (n=16) multivariate analyses were not performed.

### **Follow up**

The participants were invited to return for their test results after three months. At this point they also received counseling on how to prevent HIV and syphilis. The women who were infected with syphilis were contacted; they received free treatment and follow up.

## **Results**

A total of 1059 women (90% of the invited study population) aged 13 to 45 years (mean age 22.9 years) were included in the study. The non-responders (10%) did not seem to be different demographically. Reasons for refusal were: having been injected too often, being in too much pain, finding it emotionally too demanding after a difficult delivery or the loss of a child, or having taken an HIV test before. In some women fear and incomprehension appeared to play an important role in the decision. Of the participating women 702 (66.3%) lived in an urban area and 752 (71.0%) were housewives; 463 (43.8%) were illiterate or had attended primary school only. More than half of the women (628; 59.3%) said they were in an "unión libre"; a steady relationship without being married. The mean number of pregnancies, including the current one, was 2.0. The majority of women (745; 70.7%) reported having had only one sexual partner in the past 5 years. Fourteen women reported that they had had a genital ulcer, 559 that they had or had had vaginal discharge, 14 that they had or had had genital warts, and 8 thought that they had or had had syphilis; 1 woman thought that she was infected with HIV. More than half of the women (634; 59.9%) had been given an injection in the past 12 months, in most cases a tetanus vaccination in the context of the pregnancy. None of the women reported ever having used intravenous drugs. Four women had or had had commercial sex and 75 women had had a blood transfusion in the past.

**HIV prevalence**

None of the women were HIV positive (HIV prevalence 0%, 95%CI= 0.0-0.3).

**Syphilis prevalence**

Sixteen women (1.5%) had evidence of recent or past *T. pallidum* infection. The univariate associations between *T. pallidum* infection and demographic characteristics are given in the table: illiteracy and primary school education only (RR=5.7; 95%CI=1.6-2.0) and two or more pregnancies (RR=5.3; 95%CI=1.9-14.6) were associated with *T. pallidum* infection; there was a trend for commercial sex ( $p=0.059$ ) and there seemed to be a trend for age between 21 and 30 years ( $p=0.076$ ).

Table 1. Univariate relation between potential risk factors and syphilis status of the study population ( $n=1059$ )\*.

	Syphilis status		Relative Risk (95%CI)	p-value
	negative ( $n=1043$ )	positive ( $n=16$ )		
Age 21-30 years	531 (50.9%)	12 (75.0%)	2.893 (0.927-9.027)	0.076
Rural residence	692 (66.3%)	10 (62.5%)	1.183 (0.426-3.281)	0.747
Illiterate + Primary school level	451 (43.2%)	13 (81.3%)	5.681 (1.610-2.000)	0.004
Not moved in last 2 years	802 (77.4%)	14 (87.5%)	2.041 (0.461-9.091)	0.546
“union libre”	616 (59.1%)	12 (75.0%)	2.080 (0.666-6.491)	0.305
>1 partner	302 (29.1%)	7 (43.8%)	1.896 (0.700-5.136)	0.201
>2 pregnancies	251 (24.1%)	10 (62.5%)	5.259 (1.893-14.614)	<0.001
Ulcers	41 (3.9%)	0 (0.0%)		1.000
Discharge	553 (53.0%)	6 (37.5%)	0.532 (0.192-1.473)	0.217
Genital warts	14 (1.3%)	0 (0.0%)		1.000
Prostitution	3 (0.3%)	1 (6.3%)	23.111 (2.272-235.137)	0.059

\* With two risk factors the data of five women at most are missing.

**Discussion**

None of the women tested in León were HIV positive, consistent with an earlier comparable study which did not detect HIV infection among 1185 Nicaraguan women in 1999—2000<sup>8</sup>. However, the prevalence of syphilis (1.5%) in our study was twice as high compared with that study, performed in three medium to large urban districts in the more developed west of Nicaragua<sup>8</sup>. León, the second city of Nicaragua (population in 2004: 180,301) is similar to those urban districts<sup>9</sup>. The prevalence of HIV/AIDS in León is estimated to be slightly lower than that of the capital Managua, Chinandega (a medium sized city near the border with Honduras), and the remote district Región Autónoma Atlántico Norte<sup>2</sup>. Recent unpublished data states that at the time of writing, approximately 6,2 persons per 100.000 are newly infected with HIV each year in Nicaragua. (Matute A, unpublished data) Furthermore, this data also

states that 1672 patients with HIV/AIDS are currently living in Nicaragua. Considering the total population of Nicaragua, this data leads to a prevalence of HIV of 0.03%. The WHO estimated the prevalence of HIV among the Nicaraguan population aged 15 to 49 years to be 0.2% in 2003<sup>4</sup>.

Possible limitations of this study, such as the number of women included, the non-response, and the theoretical possibility of a lower sensitivity and specificity of the laboratory tests due to transport and processing of the samples must be discussed before the data can be interpreted. The precision of this study with regard to HIV prevalence was large with a 95% confidence interval ranging from 0.0 to 0.3%. The estimated HIV prevalence in Nicaragua of 0.2% is contained within this interval which implies that this study performed in 1000 women will yield a result that is sufficiently close to the expected prevalence. Approximately 90% of the invited study population agreed to participate. We do not suspect that the non-responders had a higher risk of being HIV positive. Reasons for refusal were plausible and although we do not have data to prove it, demographically the groups did not seem to differ. There was no apparent participation benefit for the women which might have contributed to non-response as well. Furthermore, the WHO states that refusal may be associated with either higher or lower risk of HIV infection and that it is therefore difficult to draw general conclusions on the strength of the association between refusal and HIV prevalence<sup>10</sup>. The probability that the storage, transport, and processing of the samples led to a lower sensitivity and specificity of the HIV tests is very small because while HIV antibodies were not detected, *T. pallidum* antibodies were. This suggests that the condition of the samples had not deteriorated during transportation. The assays used were reliable and the samples were adequately stored.

Although it was not possible to determine a risk profile for HIV infection, it was possible for syphilis. Unexpectedly, the number of sexual partners a woman had was not a risk factor. This might be explained in two ways. The first explanation might be that women did not answer the question concerning their total number of sexual partners truthfully because of socially desired behavior. Moreover, the “machismo” culture of Nicaragua may make it difficult for women to admit to having several partners<sup>7</sup>. Although we encouraged participants to have a face to face interview they were allowed to be interviewed in the presence of others, if needed. Secondly, the women could have been infected by their steady partner; the number of partners and behavior of the women’s partner could be more important than the number of partners of the woman herself<sup>11</sup>. Earlier research has shown that in 2003 a housewife in Chinandega had a two times higher chance of being infected with HIV than a prostitute<sup>4</sup>. Moreover, half of Nicaraguan women believe that their husbands have extramarital sex<sup>8</sup>.

Physical signs of STDs, such as leucorrhea, genital warts, or ulcers, were also not associated with *T. pallidum* infection. This may have been because we used self-reported data and thus the data may not be entirely reliable.

Although we found no HIV infection in the women, we know the virus is circulating in the population in Nicaragua and León. Of approximately 400,000 people who annually visit the hospital and clinics of León, 45 are being treated for AIDS at the time of writing<sup>12,13</sup>. A possible explanation for why we did not find any infection in this group of women is population selection bias: women who visit ANCs may pay more attention to their health and may have different socio-economic characteristics than women who do not visit ANCs<sup>14</sup>. Moreover, there are indications that HIV-positive women are less fertile than HIV-negative women, and thus may be excluded from such a research population<sup>14</sup>. Lastly, from data already collected, it seems that in Nicaragua, as in most (non-African) countries, HIV infection is concentrated and more prevalent among specific risk populations and in specific risk places. UNAIDS reported a HIV prevalence of 9.3% among homosexual men in the capital Managua in 2001–2002<sup>15</sup>. Most AIDS cases in Nicaragua are also reported in this city<sup>4</sup>.

The prevalence of syphilis appears to have increased since 2000 in Nicaragua, possibly indicating an increase in STDs such as HIV. Several risk factors that increase STD transmission, such as variable sexual contacts, low use of condoms, and increased mobility of the population, are present in Nicaragua. It is difficult to estimate the proportion of people in León who have multiple sexual contacts. It seems that people start having sex at a young age and have multiple sexual relationships, even during marriage. There has been no research on this, apart from the above-mentioned study that half of the Nicaraguan women believe that their husbands have extramarital sex<sup>8</sup>. The use of condoms in both stable and unstable sexual relationships is low: in 1996–2002 only 17% of the Nicaraguan women aged 15 to 24 reported using a condom<sup>8,16</sup>. Furthermore, the mobility of the Nicaraguan population has increased during the past 20 years due to war, socio-economic crises, and natural disasters. The improved economic situation of the last 10 years has increased commercial contacts with neighboring countries, which in turn has increased cross-country transport. These developments may mean that there will be a sharp increase in the prevalence of HIV in the future.

Prevention of the transmission of HIV/AIDS among the Nicaraguan population requires national acknowledgment of the threat that the virus poses, adequate training of medical workers, education of the population regarding the prevention of STDs, the promotion of condom use (even the distribution of free condoms), and free HIV testing. Reliable information about the occurrence of HIV/AIDS in Nicaragua is needed. Follow-up studies of women who visit ANCs in León, Nicaragua, should take special effort to limit the amount of self-reported data. It would also be worthwhile to

study the prevalence of HIV/AIDS among specific populations, such as blood donors or students, or high-risk populations, such as homosexuals, intravenous drug users, or prostitutes.

In conclusion, HIV appeared not to be highly prevalent among pregnant and post-partum women in León. The higher proportion of women infected with syphilis than found in earlier studies suggests that sexually transmitted diseases are circulating in the general population and highlights the increasing importance of HIV prevention.

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# Chapter 6

## The epidemiology of clinically apparent HIV infection in Nicaragua

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Submitted

## Abstract

**Objectives:** To describe the epidemic of clinically apparent HIV/AIDS infection in Nicaragua and to discuss the reasons why the changing number of HIV patients presenting in the public health care system is increasing compared with other Central American countries.

**Material and Methods:** From 1987 to 2004 patient data were collected from the Nicaraguan STI/HIV/AIDS national program which collects relevant information from registers held in all integrated local health system (SILAIS) across the country.

**Results:** 1614 HIV-positive patients were officially reported during the period 1987–2004. The estimated number of new cases of clinically apparent HIV/AIDS reported to SILAIS has increased from 3.27 in 2001 to 6.69 in 2004 per 100,000 person-years. Urban areas along the west-central and eastern part of Nicaragua showed the highest year prevalence of AIDS at 54.2 and 32.2 per 100,000 inhabitants, respectively. Most of the infections (91%) were acquired sexually: 65% by heterosexual contacts and 26% by homosexual contacts. Four percent of the HIV/AIDS patients were intravenous drug users. The highest rate of infection was found in men aged between 20 to 39 years, with a peak around 35 to 39 years (annual incidence of 125.6 new cases per 100,000 inhabitants), and in women aged 20 to 34 years old with a peak around 20 to 24 years (annual incidence 46.6 per 100,000 inhabitants). The male to female ratio of infection was 3:1. The distribution of HIV/AIDS was highest among utility workers, laborers, housewives, and sexual workers: 32.8%, 17.4%, 16.4%, and 6%, respectively. The death rate was stable until the beginning of 1999 but increased sharply thereafter up to 2004, the year HAART was introduced in Nicaragua. In 2005, we observed a further increase in the mortality.

**Conclusions:** HIV/AIDS in Nicaragua is in a nascent stage, is concentrated in high risk population such as utility workers, commercial sex workers, men who have sex with men, prisoner, street children, police and military forces. Education of the population is an urgent need to increase HIV/AIDS related knowledge, change attitudes and increase safer sex practice in the community.

## Introduction

The human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic has already devastated many individuals, families, and communities, and is a major public health problem worldwide. Despite increased resources being available to address the global AIDS challenge, the infection continues to spread. The number of people living with HIV has risen in every region, with sub-Saharan Africa, Eastern Europe, and Central Asia being the worst hit<sup>1</sup>. According to estimates for 2004 from the UNAIDS/WHO AIDS, 39.4 million people

are infected with HIV; 1.7 million in Latin America and 400,000 in the Caribbean<sup>2</sup>. The HIV/AIDS epidemic in Central America is serious and is worsening. On the basis of information from 2001, four of the six countries in Latin America with the highest estimated HIV prevalence are in Central America—Belize, Honduras, Panama, and Guatemala<sup>3</sup>. In many of these countries, social and economic factors have shaped the development of the epidemic. For example, Nicaragua is the second poorest country in Latin America and has one of the highest population growth rates in the Americas<sup>4</sup>. Although the estimated prevalence of adult HIV was 0.20% in 2001,<sup>5</sup> the epidemic is in a nascent stage, and the prerequisites for a more serious epidemic, such as a high level of migration and mobility and a culture that stigmatizes the use of condoms, are in place. In recognition of the first reported case of HIV/AIDS in 1987, the Ministry of Health (MINSAL) created the National Program for the Prevention and Control of STI/HIV/AIDS, and the program was implemented, on a short-term basis, in 1988<sup>6</sup>. The fundamental task of the program is to design policies and norms for the health sector, to ensure the fulfillment of the goals of HIV/AIDS epidemic reduction, prevention, control, and monitoring. The 2000–2004 Nicaraguan National Strategic Plan for the Fight against STI/HIV/AIDS encompasses a comprehensive, transversal vision, with strategies that take into account human rights, ethics, gender, decentralization, sustainability, education, and communication, as well as strategies to improve the flow of information between institutional and inter-institutional bodies<sup>7</sup>. Currently, Nicaragua has started to develop the National Plan, however is still too early to evaluate its implementation. Options for disease prevention are limited because of prejudice regarding the use of condoms and the lack of a coherent, official policy. The problem is compounded by unequal socioeconomic development and high population mobility, which promote the spread of HIV in this region. Earlier research has shown that in Central America, HIV is concentrated mainly among socially marginalized sections of populations, many who must migrate to find work<sup>8</sup>.

This article therefore describes the epidemic of clinically apparent HIV/AIDS infection in Nicaragua and discusses the reasons why the numbers of cases are increasing compared with other Central American countries. Signaling an alarming trend, we found the number of new HIV cases in Nicaragua to have increased for the last 6 years in a row after an apparently steady infection during the preceding 5 years.

## **Material and methods**

The epidemic of clinically apparent HIV/AIDS cases was studied from 1987 to 2004. Data on cases were collected from the Nicaraguan STI/HIV/AIDS national program which collects relevant information from registers held in all integrated local health system (SILAIS) across the country. The registers contain information on referred and diagnosed HIV-positives and AIDS cases only. In Nicaragua, the public health

system is the sole institution that can confirm the HIV-positive status of an individual. All samples are sent to the Central Laboratory in Managua, the capital, where samples are tested by Western blotting. Age-specific incidence and prevalence rates were calculated using the number of case patients in the nominator and the Nicaraguan population size in the denominator using SPSS, version 11.

## Results

The estimated incidence of new HIV/AIDS cases reported to SILAIS has increased from 3.27 in 2001 to 6.69 in 2004 per 100,000 person-years (Figure 1), with 1614 patients being officially reported as being HIV-positive in the period 1987–2004.

From the start of the epidemic in 1987 until 1992 there was a steady low incidence of infection, but this started to increase slowly from 1993 to 1998 whereafter the incidence increased sharply, being approximately 22 times that of the period 1987–1992. Urban areas along the west–central and eastern part of Nicaragua showed the highest prevalence rates of detected HIV/AIDS cases with a maximum of 54.2 and 32.2 per 100,000, respectively (Figure 2). The provinces of Chinandega (population 350,000) in the western part of Nicaragua, and Managua (population 1,094,000) appeared to be especially affected.

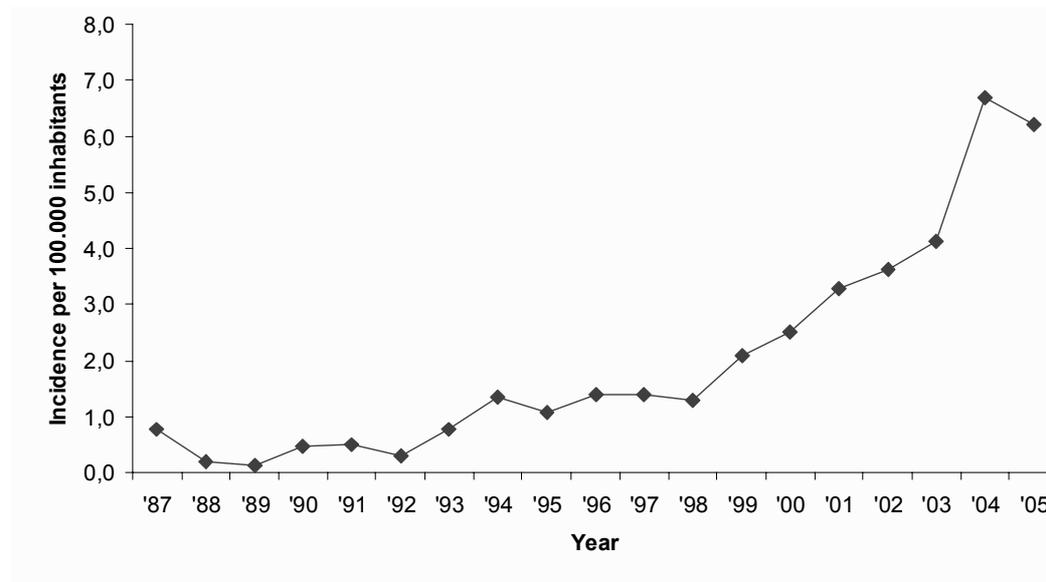


Figure 1. The incidence of HIV/AIDS by year in Nicaragua from 1987 until March 2005

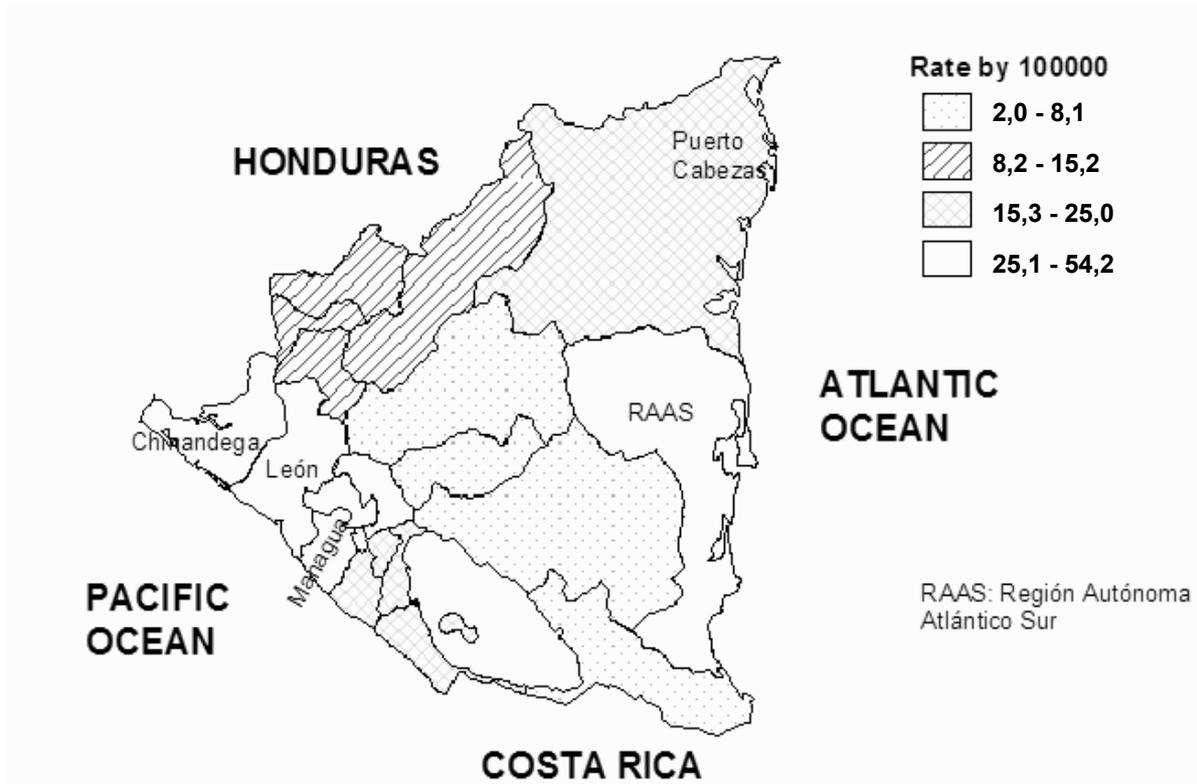


Figure 2. HIV/AIDS by integrated Local Health System Nicaragua, from 1987 until September 2005

Most of the infections (91%) were acquired sexually: 65% by heterosexual contacts and 26% by homosexual contacts. Four percent of the HIV/AIDS patients were intravenous drug users and 3% of infections was acquired by perinatal transmission (Figure 3).

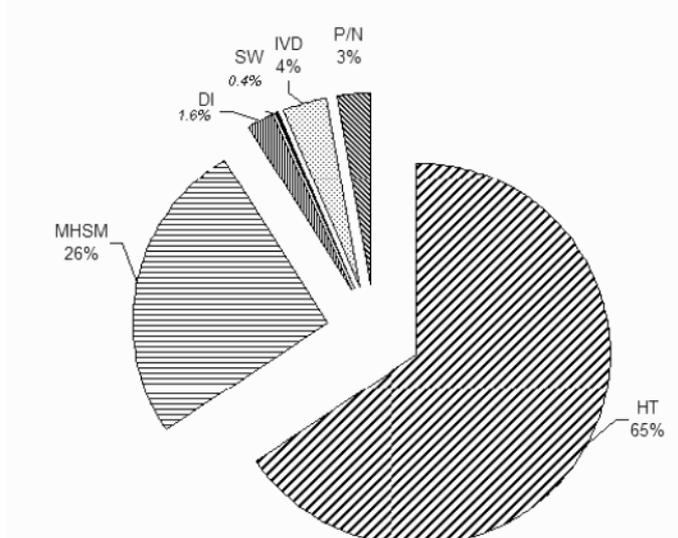


Figure 3. Mechanisms of transmission of HIV/AIDS. From: National Program of STI-HIV/AIDS. HT= Heterosexual, PN= Perinatal, IVD=Intravenous Drugs, SW= Sexual Workers, MHSM= men having sex with men, DI= Incomplete Data

Trend of HIV by year and sex through the epidemic has been increasing, especially since 1999 (Figure 4). Highest increasing trends by age and year were observed among the age groups of 20 – 29 and 30 – 39 years old and among services, laborers and housewives (data on file).

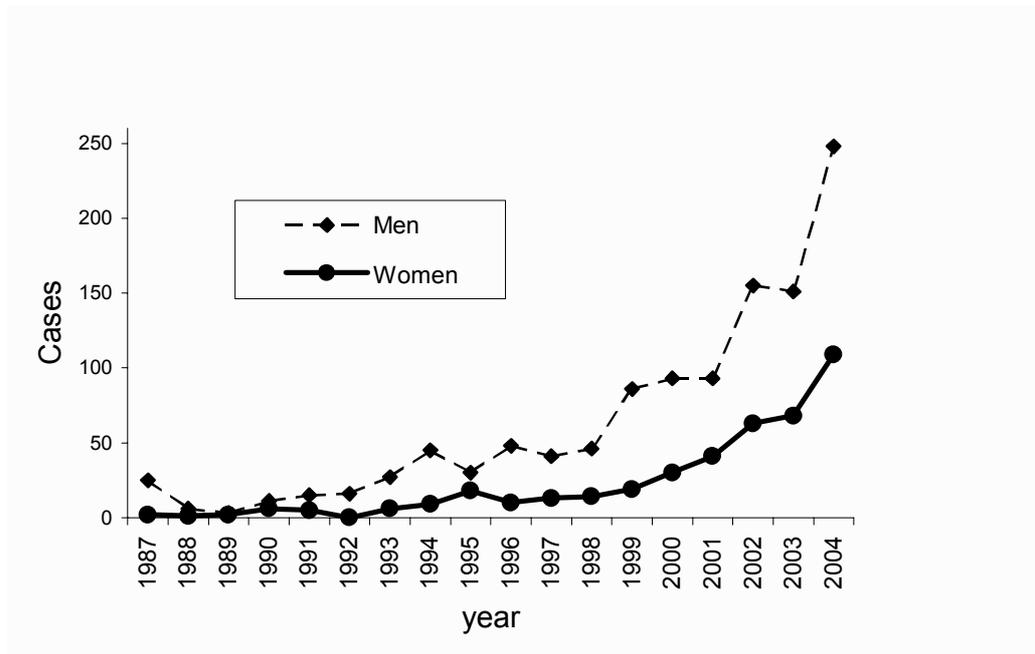


Figure 4. Numbers of cases by year and sex.

Men show a higher rate of HIV infection (figure 5). The highest rate of infection was found in the age groups 20 to 29 years, 30 to 39 years and 40 to 49 years old. The highest rate of infection was found in men aged between 20 to 44 years, with a peak around 35 to 39 years (incidence of 125.6 per 100,000), and in women aged 20 to 34 years old, with a peak around 20 to 24 years (incidence 46.6 per 100,000). The male to female ratio of infection was 3:1.

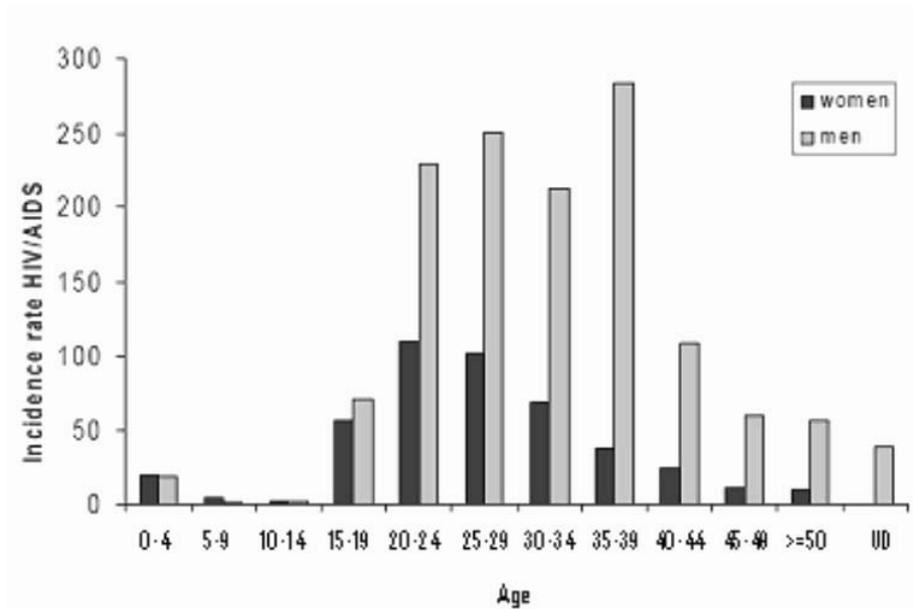


Figure 5. Incidence rates by age (in years) and sex HIV/AIDS Nicaragua. UD= unknown data

The distribution of HIV/AIDS was highest among utility workers (including services such as electricity, communication, water service, municipality workers, fridge and air-condition service), laborers, housewives, and sexual workers, being 32.8%, 17.4%, 16.4%, and 6%, respectively (Figure 6).

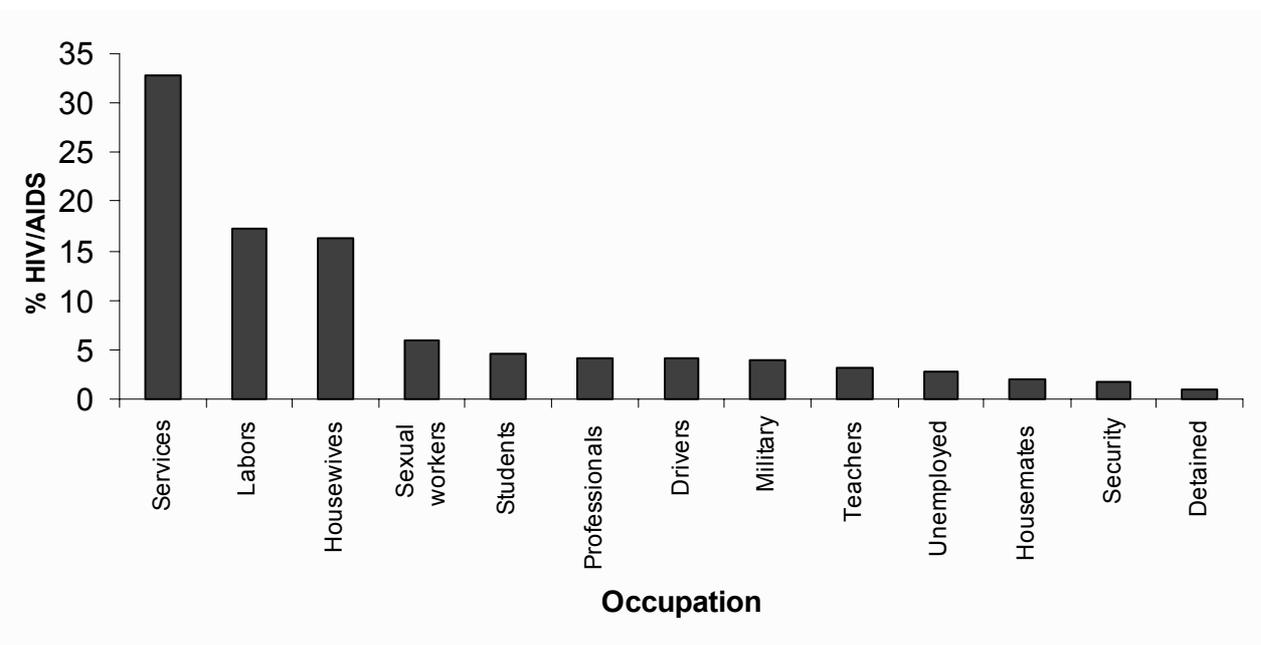


Figure 6. Occupation (%) of HIV/AIDS. Nicaragua 1989 – March 2005.

The death rate was stable until the beginning of 1999 but increased sharply thereafter up to 2004, the year HAART was introduced in Nicaragua. In 2005, we observed a further increase in the mortality (Figure 7).

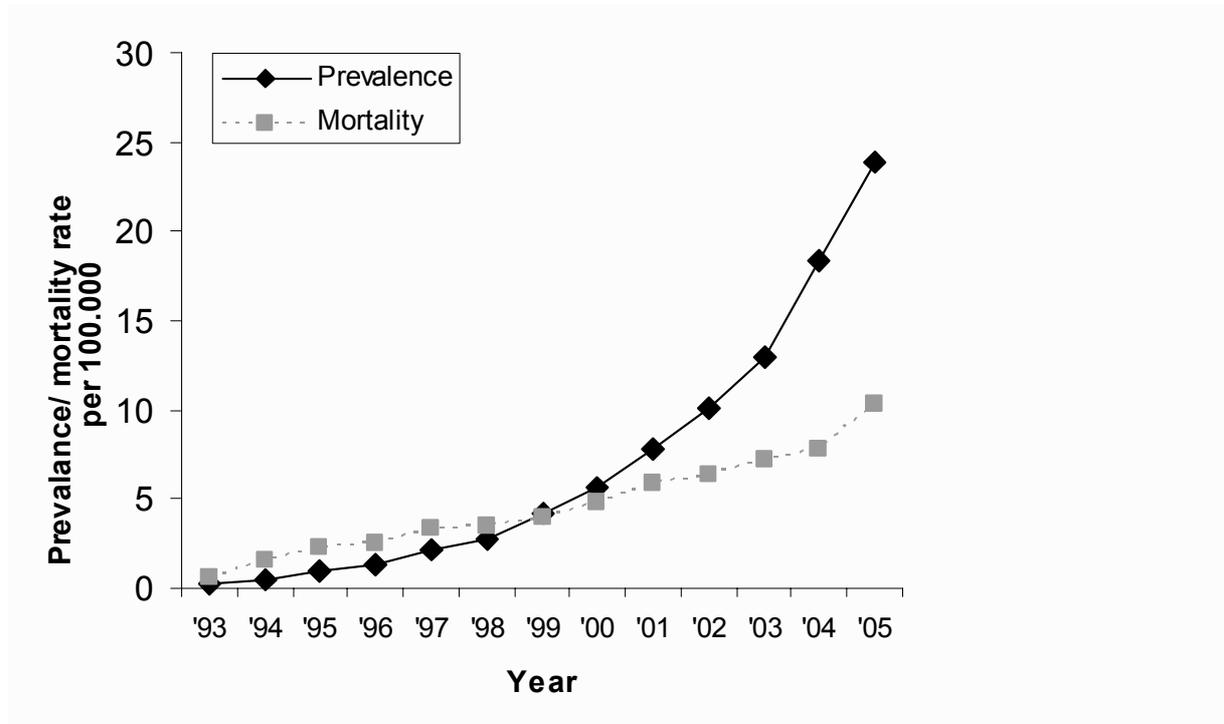


Figure 7. Prevalence and mortality rate by HIV/AIDS. Nicaragua 1993- September 2005.

## Discussion

Nicaragua has a population of more than 5 million (49.8% male and 50.2% female), and 58% of the population lives in urban areas. The first HIV-positive person was identified in Nicaragua in 1987<sup>9</sup>, and since then there has been a rapid spread of the epidemic in some parts of the country. The prevalence rate in adults older than 15 years old was 0.2% in 2004, according to data from the National Program for the Prevention and Control of STI/HIV/AIDS<sup>9</sup>. This is a low prevalence compared to that of other Central American countries. Four of the six Latin-American countries with the high prevalence for HIV infection in adults are found in Central America: Belize (2.0%), Honduras (1.6%), Panama (1.5%) and Guatemala (1.0%). The other Central American countries report a lower prevalence: El Salvador (0.6%), Costa Rica (0.6%) and Nicaragua (0.2%)<sup>10</sup>. Interestingly, one of the highest rates was in the province of Chinandega, which is on the Honduran border. Our data show a progressive increase of the changing numbers of HIV patients presenting to the public Health care system since the start of the epidemic in Nicaragua, with 1999 being the year the epidemic

“took off”. The increasing numbers of those tested positive and subsequently entered into the registers may be accounted for by a cohort effect related to the maturation of the epidemic in Nicaragua. In other words, in the 1980s and early 1990s, most HIV positive people in Nicaragua had probably only recently been infected and therefore only a small percentage were symptomatic enough to present to SILAIS. As the epidemic matured, a growing number of people developed advanced disease and sought attention through SILAIS. The real number of HIV patients collected by the Nicaraguan STI/HIV/AIDS national program is underestimated due to the fact that an active surveillance does not exist. The year-prevalence of HIV in adults in 2010 is estimated at 2.0% per year if this trend of a progressive increase in prevalence is sustained over time<sup>10</sup>. This increase can be explained by several factors. More cases may be being detected as more people join the surveillance program, which provides testing, and more people have access to the health system. The coverage of primary health care has been expanded through innovative approaches and reaches populations with the greatest need. The contraction out of the delivery of health services has promoted a greater equity in access to health services<sup>11</sup>. Moreover; non-governmental organizations are active in prevention, diagnosis, care, and treatment. Some of these organizations are supported by government or international agencies<sup>12</sup>. Nicaragua has been a site of political and economic instability, this situation has a big impact in the health system. The Nicaraguan population is highly mobile, and an estimated 20% of the population migrates to other countries in search of better opportunities<sup>13,14</sup>. Although this immigration is considered temporary and cyclical in nature among female immigrants, those who have returned from Costa Rica believe that they will go back again, and those who are in Costa Rica say they are there only temporarily<sup>15</sup>. This high mobility potentially increases the number of partners an individual has and could explain the introduction of new infections into less mobile populations, such as housewives<sup>16-18</sup>. The lack of condom use is a major problem in all potential preventive strategies. Religious institutions often argue that condoms are unreliable and do not prevent the transmission of HIV but also cling to the popular belief that sexual education increases the desire for sexual experimentation at an earlier age<sup>19</sup>. A study of the effect of provision of health-education material and condom use in Managua, Nicaragua, showed that condoms were used more often for commercial sex than for non-commercial sex (60.5 vs. 20.2%)<sup>20</sup>. This supports the attitude of the Nicaraguan population to condom use, namely that condoms should be used mainly with sex workers to prevent sexually transmitted infections<sup>21-23</sup>. Moreover, the “macho” culture of Nicaragua makes women vulnerable to HIV infection. While women are expected to be faithful to their husbands, in some sections of society it is accepted that the male can have other sexual contacts. Thus, women are at lower risk of HIV infection from their own behavior but at higher risk from their partner’s behavior<sup>24</sup>. The latest data (2003) from the National AIDS Program on AIDS cases occupation showed that housewives are at high risk. It needs to be determined whether these women are infected by their

men or by their partner or some of them by working as sexual workers<sup>25,26</sup>. The same trend has been observed in the Andean area, where HIV is spreading increasingly to the wives and girlfriends of men who buy sex and of men who have sex with other men. Heterosexual transmission was the main route of transmission. We found that most infections were acquired through heterosexual contacts (65%) and bisexual together with homosexual (26%) sex; the latter category is probably underreported. Consistent with this, infection rates among female sex workers in the cities of León and Chinandega have increased dramatically<sup>27</sup>. In 2004, the estimated male: female ratio of HIV infection in Nicaragua was approximately 3:1, therefore the need to educate men is of a great importance. Honduras has the lowest male to female ratio with people living with HIV/AIDS in all of Latin America, approaching 1:1, with heterosexual transmission being the main mode of infection (about 65%), with about 10% being due to homosexual transmission<sup>28</sup>. In Costa Rica sexual transmission is the main route of infection (85% of reported cases), especially among men having sex with men<sup>29</sup>. In Central America, where the epidemic is largely concentrated in major urban areas, the number of HIV infections is increasing. Roughly one third of HIV infections in Panama and Nicaragua are attributable to unprotected sex between men; in Panama, a 2002 study among men who have sex with men found almost 11% were infected with HIV<sup>30</sup>. According to a World Bank report, the HIV/AIDS epidemic in Central America is generally concentrated in high-risk populations such as commercial sex workers, men who have sex with men, prisoners, street children, and police and military forces<sup>31</sup>.

Our results suggest there is an urgent need to educate the population, and especially men and people working in service and utilities, about AIDS/HIV in order to increase HIV/AIDS-related knowledge, change attitudes, and increase safer-sex practices in the community, initiatives which may help to decrease the incidence of HIV<sup>22</sup>. Other relevant activities include expansion of health care delivery, training workshops, voucher distribution activities, quality control initiatives, and support activities. With assistance from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Nicaragua started to scale up the delivery of antiretroviral (ARV) therapy to HIV-positive eligible patients in early 2004<sup>32</sup>. Nicaragua has developed National ARV Treatment Guidelines, which emphasize a structured and standardized approach to all aspects of ARV delivery, including monitoring and evaluation. As a result there has been a significant change in life expectancy, hospital admissions, and treatment costs, with an increased demand for outpatient services and a decrease in hospital care services. It has also led to improvements in the quality of life for HIV-positive individuals who participate in the STI/HIV/AIDS National Health System. Actually, the National Strategic Plan is not fully implemented yet. Despite these advances, projected estimates for 2005 indicate a rapid increase in the prevalence of HIV/AIDS (from 0.2% to 0.34%). Areas of concern are transmission from neighboring, high-prevalence countries, deteriorating social and economic conditions, high-risk

behavior, and the high prevalence of sexually transmitted infections<sup>33</sup>. Due to the fact that Nicaragua has a 0.2% prevalence of HIV/AIDS cases, the country has a real opportunity to prevent larger-scale epidemic. It is very important to learn from the lessons of the epidemic in countries that have either been very successful or examples of poor management of the epidemic. The successful responses in Cambodia, Thailand, and Uganda all point to the importance of leadership, commitment, and continued effort from all sectors of society, including people living with HIV and AIDS to a successful national response.<sup>34</sup> Two common interventions for HIV/AIDS prevention exist: 1) Syndromic Management: Staff at local health centres are trained and provided with drugs to treat STIs according to algorithms which address specific sets of symptoms, rather than relying on clinical diagnosis; and 2) Behavior change interventions: Interventions may promote delayed sexual debut, reduced number of partners, reduced coital frequency, increased condom use, or some combination thereof.<sup>35</sup> Finally, prevention efforts must work to understand and address the socioeconomic and cultural realities in which sexual behaviors are shaped. Furthermore, prevention strategies must explicitly aim to provide local communities, and local leaders, freedom to shape interventions to local circumstances, and to local understandings.<sup>36</sup> The current situation remains a challenge to governmental and non-governmental organizations and requires the development of a health education intervention to change the knowledge, attitudes, and practices in the population at risk, in order to decrease the vulnerability of Nicaraguan people.

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# Chapter 7

## Summary and perspectives

## Summary and Perspectives

The main purpose of the studies outlined in this thesis was to gain empirical epidemiological and therapeutic knowledge of some common infectious diseases in Nicaragua. So far, relatively little was known about the incidence, etiology, management and antibiotic resistance patterns of common infections. Of importance is to note that because of a lack of knowledge, currently many patients are unnecessarily treated with antibiotics for a presumed infection or the choice for the specific drug is untargeted. Such inefficient use of antibiotics may accelerate adverse drug reactions, increase costs, and most importantly contributes to the emerging problem of antibiotic resistance. The studies were therefore set up to provide tools to tackle common health problems effectively in the coming years. To provide the required knowledge, we conducted several prevalence studies in the source area of León, Nicaragua within the framework of the collaboration of the universities of León and Utrecht in close collaboration with epidemiologists, intensivists, medical microbiologist and infectious diseases specialists in the field. We focused on the common infections such as urinary tract infection and community acquired pneumonia (chapter 2, 3). In chapter 4 the adherence to a specifically developed protocol of antimicrobial prophylaxis before surgery was studied in a third prevalence study. In the final chapters (5, 6) we report on the prevalence of HIV and syphilis in pregnant women and the epidemiology of clinically apparent HIV infection in Nicaragua. Based on the results, we further elaborate on the recommended strategy to improve daily medical and preventive practice within the health system and the community.

### **Chapter 2. What is the impact of antibiotic resistance in uropathogens in León Nicaragua?**

The first study (chapter 2) showed that in León, Nicaragua, bacterial urinary tract infections are common and these uropathogens are highly resistant to most common antimicrobials used. Urinary tract infections are one of the most common illnesses for which patients seek medical attention worldwide. We designed a prevalence study from June to November 2002 in the university hospital of León, Nicaragua. We admitted to the study (208) consecutive patients that entered our hospital either directly or via primary care or emergency departments with a suspected symptomatic urinary tract infection.

We found 62 (32%) patients with positive urinary culture, *Escherichia coli* (56%), was the most frequent pathogens isolated, followed by *Klebsiella* spp. (18%), *Enterobacter* spp. (11%). High resistance rates in *E. coli* to multiple antibiotics were observed (i.e. amoxicillin, trimethoprim- sulphamethoxazole, cephalotin, ciprofloxacin and amoxicillin/clavulanate). The picture of emerging resistance against first-line antibiotics in Nicaragua is alarming and if this trend is not reversed, the choice for

adequate treatment will become limited in the near future. In high resistance areas such as León, TMP-SMX should not be the empirical drug of choice for either complicated or uncomplicated UTI because such treatment of disease caused by micro-organisms that are resistant to TMP-SMX results in microbiological and clinical failure. The emerging problem of antibiotic resistance in the treatment of UTI appears to be shared by various institutions in Latin America. Of even greater concern is that increasing resistance is eroding the utility of second-line agents, ciprofloxacin, as reliable alternatives for the management of UTI in this area. In central Nicaragua, the validity of that assumption diminishes as the prevalence of fluoroquinolone resistance among outpatient urine isolates rises. Moreover, ciprofloxacin resistance levels of 30% among hospital ward and outpatients urine isolates is an ominous harbinger of future developments in the outpatient setting, where the range of alternative therapies is limited. Fortunately, our data reported here show that the prevalence of resistance to nitrofurantoin among urinary *E. coli* isolates is (0%), which suggests that nitrofurantoin may be a short-lived therapeutic option in the outpatient setting, although, for maximal efficacy, in cystitis nitrofurantoin could be used only. Rational use of antibiotics could lead to the decrease of bacterial resistance. Patients, providers, and healthcare leaders must make a serious commitment to changing the dynamics of outpatient prescribing.

### **Chapter 3. What is the etiology and resistance pattern of community-acquired pneumonia in León, Nicaragua?**

In chapter 3 we showed that in León, Nicaragua, community-acquired pneumonia is a common disease requiring hospitalization and the pathogenic organism most frequently observed was *Streptococcus pneumoniae*. We conducted a prevalence study at the University Hospital of León, Nicaragua from July 2002 to January 2005 in 130 consecutive patients over 12 years of age. In 45% of the patients a respiratory pathogen could be identified. This prevalence study is the first evidence from Nicaragua and other Central American countries therefore it is impossible to compare our data with other regional data. Several surveillance programs have evaluated the antimicrobial susceptibility of *S. pneumoniae*. However, the number of isolates from the Latin American region is usually low and the studies showed that resistance rates may vary significantly among regions. Importantly, antimicrobial susceptibility of *S. pneumoniae* varies significantly among Latin American countries<sup>1</sup>.

For empirical treatment strategies in patients with CAP several diagnostic tests from medical history and physical examination as well as laboratory and radiographic findings can be used to determine the severity of the disease and consequently the probability of non-fatal and fatal complications. An adequate diagnostic strategy can be useful in setting priority in inpatient or outpatient treatment of patients with CAP.

Based on our results and those of others, we suggest suspecting the early recognition of CAP caused by *S. pneumonia* when a combination of variables as cardiovascular diseases, acute onset, pleuritic pain, gram-positive bacteria in the sputum Gram stain, and leucocyte count is correctly performed predicted the cause of CAP. It is concluded that data on history, together with the result of the Gram stain of sputum and the leucocyte count, can help to distinguish *S. pneumoniae* from other pathogens causing CAP.

#### ***Chapter 4. What is the guideline adherence for pre-surgical antibiotic use in León, Nicaragua?***

In chapter 4 we reported on an observational study conducted in a four-week period in 2005 in the University Hospital of León, Nicaragua. All 297 consecutive persons of any age undergoing surgery in the departments of general surgery, orthopedics, gynecology and obstetrics, and pediatrics were eligible for inclusion into the study. We showed that in León, Nicaragua, complete adherence to the protocol was achieved in only 21 (7%) antibiotic prescriptions (based on indication, choice, dose, time and duration of administration). In addition, according to the protocols, 1707 doses (83%) were administered unnecessarily. This failure to the adherence has direct consequences for the hospital, for the patients and for the predisposition to resistance. A large portion of the budget of the hospital is being used inadequately. According to other studies pre-surgical prophylaxis accounts for approximately 30% of the total hospital budget. Besides the costs associated with over-prescription, the inadequate administration of antibiotic prophylaxis could eventually lead to nosocomial infections. This in turn, leads to an increase of the hospitalization length for the patient and adds even more costs. Furthermore, aside of to the economical aspect, over-prescription and inadequate administration of antibiotics will inadvertently lead to bacterial resistance posing a realistic threat in the future. Bacterial resistance will lead to a limited antibiotic choice in the treatment of future infections, higher costs and an increased mortality. It is therefore important to adhere as much as possible to existing prophylaxis protocols to prevent the above mentioned consequences. Studies have shown that it is possible to increase the adherence to protocols when some strategies are introduced in practice. Moreover these measures have proven to be highly cost-effective. This study was of importance because it evaluated the current situation in León, Nicaragua. The results showed a high discordance with the protocol. It is more than likely that a similar situation exists in other places in Nicaragua. With these results in hand it is now of crucial importance to attempt to improve the adherence to the protocols.

#### ***Chapter 5. What is the prevalence of HIV/syphilis among pregnant women in León, Nicaragua?***

Chapter 5 reports on a prevalence study involving 1,059 pregnant women aged 13 to 45 years from whom blood samples were collected in the year 2004 in León,

Nicaragua. None of the tested women were sero-positive for HIV. However, the prevalence rate of syphilis was 1.5%. The HIV/AIDS epidemic in Nicaragua is in a nascent stage and is currently concentrated in certain high-risk groups. The prerequisites for a more serious epidemic, such as a high level of migration and mobility and a culture that stigmatizes the use of condoms, are present. León is a city that is situated between Chinandega and Managua; the two most prevalent HIV cities from Nicaragua. Furthermore, León is over-crossed by the roadway where international transportation comes from Honduras for commercial activity. Honduras is a country with one of the highest prevalence's of HIV/ AIDS in Central America. León city is therefore vulnerable to the increased risk to acquire the HIV diseases. The higher proportion of women infected with syphilis than found in earlier studies suggests that sexually transmitted diseases are circulating in the general population and highlights the increasing importance of HIV prevention.

***Chapter 6. What is the epidemiology of clinically apparent HIV/AIDS in Nicaragua?***

Chapter 6 shows that HIV/AIDS in Nicaragua is in a nascent stage and is concentrated in high-risk populations. Patient data from 1987 to 2004 were collected from the Nicaraguan STI/HIV/AIDS national program, which collects relevant information from registers held in all integrated local health system (SILAIS) across the country. The first HIV-positive person was identified in Nicaragua in 1987, and since then there has been a rapid spread of the epidemic in some parts of the country. Our data describes that the incidence of HIV in Nicaragua has been increasing dramatically in the last five years starting with an annual incidence rate of 3.27 per 100,000 person incidence in 2001 to 6.69 per 100,000 person-years in 2004. Most of the infected persons were infected by sexual contact. The situation is worrisome because the diseases have begun to spread from the risk group to the community. We detected housewives with HIV that were previously undetected as a risk factor for HIV transmission. This suggests that transmission originates from their spouses. The HIV/AIDS epidemic in Central America is serious and is worsening. In Latin America, the highest rates of HIV prevalence are seen in the Central American countries of Belize (2%), Guatemala (1.4%), Honduras (1.9%) and Panama (1.54%) and on the Caribbean coast in Guyana (3%) and Suriname (1.3%). Transmission within these countries is predominantly through heterosexual intercourse.

Though the epidemic in Nicaragua is in a nascent stage, conditions are in place to jump to a big magnitude and this situation could be out of the hands if prevention measures are not done now to stop or modify the trend. The socioeconomic situation is one of the main causes of the increased risk for transmission of the disease. The Nicaraguan population is highly mobile; annually more that one million of the Nicaraguan population migrate to other countries searching for better opportunities. This high mobility potentially increases the number of partners an individual has and

could explain the introduction of new infections into less mobile populations such as housewives. The high pressing for migration caused by poverty and the lack of economic opportunity make it more likely that both women and men will migrate in search of income and employment which can destabilize and disrupt stable social and familial relationships and expose both men and women to increased risk of infection. Moreover, in most settings, migrant populations are more likely to be socially marginalized with restricted access to economic assets and information and services.

The lack of condom use is a major problem in all potential preventive strategies. The attitude of the Nicaraguan population to condom use, namely that condom should be used mainly with sex workers to prevent sexually transmitted infections is a problem. Furthermore the “macho” culture of Nicaragua makes women vulnerable to HIV infection.

One third of HIV infections in Panama and Nicaragua are attributable to unprotected sex between men and data from Honduras, report that four out of five infections occur due to unprotected heterosexual interactions. Heterosexual transmission is the main route of transmission in Nicaragua, Honduras, Guatemala, and Belize, men who have sex with men accounts for the greatest number of infections in Costa Rica and Panama. Prevention measures must urgently be developed and adapted for the Nicaraguan population. Interventions with educational programs need to be developed to cause the changing of the knowledge, attitudes and practices in the population at risk in order to decrease the vulnerability of the Nicaraguan people.

## **Perspectives**

The results of the studies described in the present thesis emphasize the health problems associated with common infections and may provide directions into the steps that need to be taken to reduce the burden for the Nicaraguan community.

First, data from the UTI study should be used to further rationalize medical practice through the development of management guidelines. We have in Nicaragua on the basis of our study established guidelines for treatment of UTI in León. Moreover, they are accepted now as the standard in Nicaragua as a whole. At the moment UTI's are treated according to these guidelines. The contribution is to rationalize the use of antimicrobial agents.

Second, regional and local surveillance programmes are necessary to guide empirical therapy of pneumococcal infections in Latin American countries.

Third, strategies to improve the adherence to local protocol for surgery prophylaxis need to be developed. In such strategies, involvement of the pharmacy department is essential in the sustainability of presurgical antibiotic prophylaxis quality over a longer period because the antibiotic drugs must be dispensed by the established investigational drug service. Also a display schematic surgical procedure table in the operating theaters has been a useful reminder of the guidelines for presurgical antibiotic prophylaxis. Further, the pharmacy is essential to give feed back on prescription behavior to increase the appropriateness of the prescriptions, to organize groups of education and to organize consensus meetings to monitoring antibiotics thereby possibly diminishing the development of bacteria resistance in the future. Is it well known from previous studies that with good antibiotic stewardship, meaning the use of appropriate antimicrobial agents on good indication, at the right dosage and for a sufficient duration of time<sup>2-6</sup> will lead to decrease of the resistance development. Antibiotic control programs such as formularies and education, combination antibiotic treatment, restriction programs and the cycling of antimicrobial agents<sup>7-12</sup> are also strategies to accomplish this prescribing behavior, and to sep up interventions when situation needed.

Fourth, in Nicaragua at present there is no mandatory HIV testing for pregnant women nor is there counseling to recommend an HIV test. In places where the HIV is spreading into the general population, ongoing HIV surveillance in women attending antenatal care can give a good indication of trend within a population. Testing for syphilis though is mandatory in the first trimester of pregnancy. We hope the health system of Nicaragua could capacitate human resources to offer counseling for HIV in the ANCs program also this counseling could be offer to the private clinic. Moreover the early diagnosis of HIV in the pregnant women could guarantee early intervention to prevent vertical transmission.

Fifth, several preventive strategies need to be developed to modify the spread of HIV transmission among the population<sup>13,14</sup>:

- Public sector condom promotion and distribution;
- Make HIV testing a routine part of medical care;
- Prevent new infections by working with persons diagnosed with HIV and their partners;
- Creating HIV/AIDS patient meeting clubs;
- Decrease perinatal HIV transmission, offering Counseling to all pregnant women since the early stages of the pregnancy in the antenatal care clinic;
- School-based AIDS education in all level primary, secondary and university;
- Outreach programmes for commercial sex workers and their clients;
- Mass media campaigns.

***Perspectives of the collaboration Utrecht/ León***

We expect that this fruitful collaboration will continue in the future to deepen the professional relations between the two institutions. Areas of further collaboration may include the potential of training medical and non-medical students from Utrecht in health care in less-privileged societies which has enormously contributed to their career development. Moreover, the numbers of patients in HEODRA can help to improve their clinical expertise in Infectious Diseases, Internal Medicine, Obstetrics, Surgery and Pediatrics. Besides the student exchange program, we will work to extend this program to attract professionals in the area of infectious diseases from Utrecht to collaborate with León in the increasing of the capacities of human resources in León. Of major importance will be the consolidation of the actual structure of the infectious diseases with further support to the microbiology laboratory from the school hospital of León and the work relation with the Center of Infectious Diseases (CEI) of UNAN, León. One of the final goals is to develop a national and international status infectious diseases structure in León. To reach this goal, the next step will be to start up further collaboration in the field of epidemiology. For that reason collaboration with the Head of the Department of Epidemiology and the current dean Prof. Dr. Rodolfo Peña, Director of Research Center in Demography and Health (CIDS) from Medicine Faculty, UNAN, León, and the Head of the Julius Center for epidemiology and primary health care, Prof. Dr. D.E. Grobbee are being established.

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# Chapter 8

**Samenvatting en perspectieven in het Nederlands**



## Samenvatting en perspectieven

Het voornaamste doel van het in dit proefschrift uitgevoerde onderzoek was het verzamelen van epidemiologische en therapeutische kennis en deze vergelijken met de al bestaande empirische kennis over de meest voorkomende infectieziekten in Nicaragua. Tot op heden was er weinig bekend over het voorkomen, de etiologie, de resistentiepatronen en management van veelvoorkomende infecties. Het is van groot belang erop te wijzen dat veel patiënten wanneer een infectie wordt vermoed op dit moment door gebrek aan kennis onnodig worden behandeld met antibiotica. Inefficiënt gebruik van antibiotica kan geneesmiddelen reacties veroorzaken, doet de kosten stijgen en, mogelijk het belangrijkste, het draagt bij aan het ontstaan van antibioticaresistentie. Het onderzoek is daarom uitgevoerd om ons middelen te verschaffen om in de komende jaren op effectieve wijze de algemene gezondheidsproblemen te kunnen aanpakken. Om de vereiste kennis te verkrijgen hebben we verschillende prevalentie-onderzoeken uitgevoerd in de omgeving van León, Nicaragua, in het kader van de samenwerking tussen de universiteit van León en van Utrecht; in nauwe samenwerking met epidemiologen, intensivisten, medische microbiologen en infectiologen. We hebben ons geconcentreerd op algemene infectieziekten zoals urineweginfecties en op longontsteking opgelopen in de samenleving (community acquired pneumonia) (hoofdstuk 2, 3). In hoofdstuk 4 onderzochten we in een derde studie hoe het specifiek voor de antimicrobiële profylaxe ontwikkelde protocol dat voorafgaat aan chirurgisch ingrijpen werd nageleefd. In de laatste hoofdstukken (5, 6) geven we informatie over de prevalentie van HIV en syfilis bij zwangere vrouwen en de epidemiologie van patiënten met klinisch zichtbare HIV-infectie in Nicaragua.

Op grond van deze resultaten ontwikkelden we strategieën ter verbetering van de dagelijkse medische praktijk en preventieve maatregelen in het gezondheidssysteem en de gemeenschap.

In **hoofdstuk 2** hebben we aangetoond dat urineweginfecties (UWI's) algemeen voorkomen en dat de uropathogenen in hoge mate resistent zijn voor de antimicrobiële middelen die gewoonlijk worden gebruikt. Urineweginfecties zijn een van de meest voorkomende infecties waarvoor patiënten over de hele wereld medische hulp zoeken. We hebben van juni tot november 2002 een prevalentie-onderzoek opgezet in het universiteitsziekenhuis te León, Nicaragua. We hebben 208 opeenvolgende patiënten die ons ziekenhuis bezochten met het vermoeden van een symptomatische urineweginfectie in het onderzoek opgenomen. We zagen 62 (32%) patiënten met een positieve urinekweek. *Escherichia coli* (56%) was de meest frequent geïsoleerde pathogeen, gevolgd door *Klebsiella* spp. (18%) en *Enterobacter* spp. (11%). Er werd een hoog resistentiepercentage waargenomen bij *E. coli* voor meerdere antibiotica (bijv. amoxicilline, trimethoprim-sulphamethoxazol, cefalotine, ciprofloxacine en amoxicilline/clavulanaat). In Nicaragua is de toename van de

resistentie tegen de eerstelijnsantibiotica alarmerend en als deze tendens niet wordt gestopt zal de keuze voor een adequate behandeling in de nabije toekomst beperkt zijn. In gebieden met een hoge resistentie, zoals León, kan TMP-SMX niet meer het empirische geneesmiddel zijn van eerste keus voor gecompliceerde of niet-gecompliceerde urineweginfecties, omdat deze behandeling bij urineweginfecties met TMP-SMX resistente bacteriën leidt tot microbiologisch en klinisch falen. Het probleem dat voortkomt uit antibioticaresistentie bij de behandeling van UWI's lijkt te worden gedeeld door verschillende onderzoeksinstituten in Latijns-Amerika. Van nog grotere zorg is de toename van resistentie voor tweedelijns antibiotische middelen, zoals ciprofloxacin, een betrouwbaar alternatief voor de behandeling van UWI's in dit gebied. In Nicaragua neemt de waarde van dit alternatief al af aangezien de prevalentie van de resistentie van geïsoleerde micro-organismen in urine voor de fluoroquinolonen bij niet opgenomen patiënten toeneemt. Verder vormt het niveau van resistentie voor ciprofloxacin van 30% bij de geïsoleerde micro-organismen in de urine van in het ziekenhuis opgenomen en niet opgenomen patiënten een toenemend gevaar bij de toekomstige behandeling van patiënten buiten het ziekenhuis waarbij alternatieve behandelingen beperkt zijn. Gelukkig laten de hier gepubliceerde gegevens zien dat het voorkomen van resistentie tegen nitrofurantoïne bij de *E. coli* in de urine 0% is, wat betekent dat nitrofurantoïne voor een korte periode een behandeloptie kan zijn bij niet opgenomen patiënten. Nitrofurantoïne dient echter slechts bij cystitis te worden gebruikt.

Een weloverwogen gebruik van antibiotica zou kunnen leiden tot een afname van bacteriële resistentie. Patiënten, voorschrijvers en bestuurders in de gezondheidssector moeten serieuze afspraken maken om het voorschrijven aan niet opgenomen patiënten te veranderen. Op grond van de resultaten van ons onderzoek in Nicaragua hebben we richtlijnen voor behandeling van UWI's opgesteld. Momenteel worden UWI's behandeld overeenkomstig deze richtlijnen. Ze dragen bij aan een meer doordacht gebruik van antibiotica.

In **hoofdstuk 3** tonen we aan dat in León, Nicaragua, de community acquired pneumonia (CAP, longontsteking opgelopen in de samenleving) een ziekte is die ziekenhuisopname vereist en dat de meest frequent voorkomende ziekteverwekker de *Streptococcus pneumoniae* (pneumococ) is. We hebben van juli 2002 tot januari 2005 een prevalentie-onderzoek uitgevoerd in het universiteitsziekenhuis van León, Nicaragua, bij 130 opeenvolgende patiënten ouder dan 12 jaar. Bij 45% van de patiënten kon een verwekker van de longontsteking worden geïdentificeerd. Dit is het eerste prevalentie-onderzoek met informatie over Nicaragua en Centraal Amerika. Hierdoor is het onmogelijk onze data te vergelijken met andere data uit deze regio. Verschillende surveillance programma's hebben antimicrobiële middelen geëvalueerd waarvoor de *Streptococcus pneumoniae* gevoelig is. Het aantal geïsoleerde pneumococci in de Latijns-Amerikaanse regio is gewoonlijk laag en

studies toonden aan dat de resistentiepercentages significant kunnen verschillen tussen de verschillende Zuid Amerikaanse landen. Uiterst belangrijk is dat de gevoeligheid van de *Streptococcus pneumoniae* significant varieert tussen de Latijns-Amerikaanse landen. In ons onderzoek troffen we 0% resistentie van de *Streptococcus pneumoniae* voor penicilline aan.

Voor het bepalen van een goede empirische behandelingsstrategie bij patiënten met CAP kunnen verschillende diagnostische testen gebruikt worden om de ernst van de ziekte vast te stellen en de kans op voorkomen van niet-fatale en fatale complicaties in te schatten. Deze testen behelzen het uitvragen van de medische voorgeschiedenis, het lichamelijk onderzoek, laboratorium- en röntgen onderzoek. Op basis van onze resultaten en die van andere schrijvers stellen we dat er vermoeden is op CAP veroorzaakt door *Streptococcus pneumoniae* wanneer er een combinatie van variabelen aanwezig is, zoals een bestaande cardiovasculaire aandoening, een plotseling begin, pijn aan het longvlies (pleurale pijn), Gram-positieve bacteriën in het sputum bij de Gramkleuring, en wanneer de leukocytentelling de oorzaak van de CAP correct voorspelt. We kunnen concluderen dat de informatie over de medische voorgeschiedenis samen met de resultaten van de gramkleuring van het sputum en de leukocytentelling kan helpen bij het onderscheiden van de *Streptococcus pneumoniae* van andere ziekteverwekkers die CAP veroorzaken.

In **hoofdstuk 4** doen we verslag van een observationele studie die in 2005 gedurende een periode van vier weken is uitgevoerd in het universiteitsziekenhuis van León, Nicaragua. Voor dit onderzoek werden 297 opeenvolgende patiënten van alle leeftijden geïnccludeerd die een chirurgische ingreep zouden ondergaan op de afdelingen algemene chirurgie, orthopedie, gynaecologie en verloskunde en kindergeneeskunde. We hebben aangetoond dat het naleven van het protocol in León, Nicaragua, slechts in 21 (7%) van de voorgeschreven antibiotica lukte (gebaseerd op de indicatie, keuze, dosis, tijdstip en duur van toediening). Bovendien werden in overeenstemming met de protocollen 1707 dosis (83%) onnodig toegediend. Dit niet volgen van het protocol heeft directe gevolgen voor het ziekenhuis, de patiënten en de ontwikkeling van bacteriële resistentie. Een groot deel van begroting van het ziekenhuis wordt inadequaet gebruikt. Overeenkomstig ander onderzoek beslaat de pre-chirurgische profylaxe ongeveer 30% van de totale begroting van het ziekenhuis. Naast de kosten door het te vaak voorschrijven, kan het inadequate toedienen van profylactische antibiotica leiden tot nosocomiale infecties. Dit leidt dan tot een langere opnameduur en gaat gepaard met nog hogere kosten. Naast het financiële gedeelte leidt het overmatig voorschrijven en inadequaet toedienen van antibiotica onopgemerkt tot resistentie voor antibiotica wat een wezenlijke bedreiging in de toekomst oplevert. Antibioticaresistentie leidt tot een beperking van de keuzes voor de behandeling van infecties, tot een kostenstijging en

tot toename van de sterfte. Daarom is het belangrijk dat we ons zoveel mogelijk houden aan de protocollen voor chirurgische profylaxe om de al genoemde gevolgen te voorkomen. Verschillende onderzoeken hebben aangetoond dat het mogelijk is deze protocollen beter na te leven wanneer er een aantal strategieën in praktijk worden gebracht. Deze maatregelen hebben bovendien bewezen uitermate kosteneffectief te zijn. Dit onderzoek is van groot belang omdat het de huidige situatie in León, Nicaragua, heeft geëvalueerd. Het laat zien dat er een groot gebrek aan overeenstemming bestaat met het in León opgestelde protocol. Waarschijnlijk is er een zelfde situatie in andere ziekenhuizen in Nicaragua. Met de kennis van deze resultaten is het van cruciaal belang dat we proberen het naleven van de protocollen te verbeteren.

In **hoofdstuk 5** vermelden we een studie naar de prevalentie bij 1059 zwangere vrouwen in de leeftijd van 13 tot 45 jaar, bij wie in 2004 in León, Nicaragua, een bloedmonster is afgenomen. Geen van de onderzochte zwangere vrouwen bleek HIV-seropositief te zijn. Syfilis kwam echter bij 1,5% voor. In Nicaragua is de HIV/AIDS-epidemie in opkomst en concentreert zich op dit moment in hoog-risicogroepen. De noodzakelijke voorwaarden voor een ernstiger epidemie zijn aanwezig, zoals de grote migratie en mobiliteit en een cultuur die het condoomgebruik stigmatiseert. León ligt tussen Chinandega en Managua, de twee steden in Nicaragua waar HIV het meest voorkomt. Een andere belangrijke risicofactor is dat León over land verbonden is met Honduras, dat een belangrijke en constante verbindingroute is. In Midden-Amerika is Honduras het land waar HIV het meest voorkomt. Daarom is León kwetsbaar voor toename van HIV. De forse toename van met syfilis geïnfecteerde vrouwen, in vergelijking met eerdere onderzoeken, doet vermoeden dat seksueel overdraagbare infecties algemeen bij de bevolking voorkomen en benadrukt het belang van HIV preventie.

**Hoofdstuk 6** laat zien dat HIV/AIDS in Nicaragua in een beginfase verkeert en zich concentreert in hoog risico bevolkingsgroepen. De patiënten gegevens uit de periode van 1987 tot 2004 zijn afkomstig uit het nationale programma 'ITS/VIH/SIDA' (SOA/HIV/AIDS) van Nicaragua. Dit is relevante informatie die is verzameld en geregistreerd via alle lokale gezondheidssystemen (SILAIS) uit het hele land. In 1987 werd de eerste HIV positieve persoon in Nicaragua geïdentificeerd en sindsdien heeft de epidemie zich snel verspreid over een aantal delen van het land. Onze gegevens laten zien dat het voorkomen van HIV in Nicaragua in de laatste vijf jaar dramatisch is toegenomen, beginnend met een voorkomen per jaar van 3,27 per 100.000 personen in het jaar 2001 tot 8,7 per 100.000 personen in 2005. De meeste personen werden geïnfecteerd via seksueel contact. Dit is een zorgwekkende situatie aangezien de ziekte zich uit is gaan breiden naar groepen die een risico voor de samenleving vormen. We maken melding van huisvrouwen die seropositief zijn voor HIV bij wie eerder geen risicofactor voor de overdracht van HIV was vastgesteld. Dit

doet vermoeden dat de overdracht via hun echtgenoten plaatsvindt. De HIV/AIDS-epidemie in Midden-Amerika is ernstig en zorgwekkend. In Latijns-Amerika komt HIV het meest voor in de Midden-Amerikaanse landen Belize (2%), Guatemala (1,4%), Honduras (1,9%) en Panama (1,54%) en het Caribische kustgebied van Guyana (3%) en Suriname (1,3%). In deze landen vindt overdracht vooral plaats via seksueel contact. Hoewel de epidemie in Nicaragua in een beginstadium verkeert, zijn de voorwaarden aanwezig voor het overslaan op grote groepen en deze toestand kan uit de hand lopen als er nu geen preventieve maatregelen worden genomen om deze tendens te stoppen of te wijzigen. De sociaal-economische situatie is een van de voornaamste oorzaken van het toegenomen risico voor de overdracht van de ziekte. De bevolking van Nicaragua is bijzonder mobiel; jaarlijks migreert meer dan een miljoen Nicaraguanen naar andere landen op zoek naar betere mogelijkheden. Deze grote mobiliteit zorgt voor een toename van het aantal partners van een individu en dit zou de introductie van nieuwe geïnfecteerden in een minder mobiele bevolking, zoals huisvrouwen, kunnen verklaren. De grote druk om te migreren, veroorzaakt door armoede en het gebrek aan economische mogelijkheden, zorgt ervoor dat mannen en vrouwen wegtrekken op zoek naar inkomsten en werk, waardoor hun sociale en familierelatie wordt gedestabiliseerd en gewijzigd en zowel vrouwen als mannen worden blootgesteld aan een toenemend risico op een infectie. We kunnen hieraan toevoegen dat in de meeste scenario's degenen die emigreren vaker behoren tot de sociaal achtergestelden, met een beperkte toegang tot economische voordelen, informatie en diensten. Van alle mogelijke strategieën ter preventie is het ontbreken van condoomgebruik het grootste probleem. De houding van de Nicaraguaanse bevolking ten opzichte van het gebruik van condooms is een probleem. Deze houdt expliciet in dat het condoom vooral gebruikt zou moeten worden door degenen die werkzaam zijn in de seksindustrie, ter voorkoming van seksueel overdraagbare infecties. Verder maakt ook de "macho" cultuur van de Nicaraguaan vrouwen kwetsbaar voor de HIV-infectie. Eenderde van de infecties in Panama en Nicaragua is toe te schrijven aan onbeschermd geslachtsverkeer tussen mannen. Gegevens uit Honduras laten zien dat vier op de vijf besmettingen plaatsvinden via een onbeschermd heteroseksueel contact. In Nicaragua vindt overdracht voornamelijk via heteroseksuele contacten plaats, net zoals in Honduras, Guatemala en Belize. Homoseksueel contact vormt de oorzaak van de meerderheid van geïnfecteerden in Costa Rica en Panama. Preventieve maatregelen moeten met spoed worden ontwikkeld en aangepast worden aan de Nicaraguaanse bevolking. Er moeten educatieve programma's worden opgezet om een verandering in gedrag, houding en gewoonten bij de risicogroepen te stimuleren, om zo de kwetsbaarheid van de bevolking van Nicaragua te verminderen.

## **Perspectieven**

De resultaten van dit proefschrift maken duidelijk welke gezondheidsproblemen er samenhangen met veel voorkomende infecties in Nicaragua en kunnen aanknopingspunten leveren voor de te nemen stappen om de gezondheidslast te verminderen. Ten eerste zullen we het antibioticabeleid bij urineweginfecties moeten rationaliseren met behulp van management richtlijnen. Deze richtlijnen zijn in ontwikkeling op basis van het onderzoek en zullen als standaard worden ingevoerd in Nicaragua. Ten tweede zijn surveillance programma's nodig om richting te geven aan het empirisch behandelingsbeleid van pneumokokkeninfecties in Latijn Amerikaanse landen. Ten derde moet de compliance met antibiotische prophylaxe bij chirurgische ingrepen worden opgevolgd. Hierin is de rol van de apotheek cruciaal in de bestendiging omdat de antibiotica daar worden uitgegeven. Ook kan de apotheker feedback geven en voorlichting. Tevens is er een schema gemaakt waarin de procedures nader worden omschreven om bij de afdelingen op te hangen. Al met al kan door een multigefaseerd programma de antibioticaresistentie worden terug gedrongen. Antibiotica controle programma's waarin opgenomen formularia, voorlichting, combinaties van antibiotica en restrictieve programma's zijn ook strategieën om het voorschrijfgedrag te veranderen. Ten vierde is er geen verplichte HIV test voor zwangeren en er is geen counseling aanwezig om uitslagen van de test te begeleiden. Op plaatsen waar er aanwijzingen zijn voor verspreiding, kunnen dit soort verplichte surveillance programma's inzicht geven in de trends. We hopen verder dat de Nicaraguaanse gezondheidszorg financieel kan vrijmaken om counseling bij HIV mogelijk te maken. Bovendien kan een vroege diagnose bij zwangeren op deze wijze transmissie naar de zuigeling voorkomen. Ten vijfde zijn er meerdere strategieën nodig om de verspreiding van HIV te beïnvloeden: (1) uitgifte en promotie van condoomgebruik, (2) HIV testen als routine, (3) nieuwe infecties voorkomen door met HIV geïnfecteerden en hun partners te overleggen, (4) creëren van HIV/AIDS counseling clubs, (5) verminderen van perinatale transmissie door testen en counseling van zwangeren, (6) voorlichtingsprogramma's voor scholen, (7) voorlichtingsprogramma's voor commerciële sex industrie en klanten en (8) massale media campagnes.

***Perspectieven in de samenwerking Utrecht/León***

We hopen dat deze vruchtbare samenwerking in de toekomst zal voortduren zodat de professionele band tussen de twee instituten kan worden versterkt. De twee potentiële gebieden voor toekomstige samenwerking zijn: a) opleiding van medische studenten uit Utrecht op het gebied van gezondheidszorg in minder bevoorrechte samenlevingen, dat tot nu toe een grote bijdrage heeft geleverd aan de ontwikkeling van deze studenten. b) Parallel aan het uitwisselingsprogramma voor studenten hopen we dat dit kan worden uitgebreid naar beroepsbeoefenaars op het gebied van infectieziekten van Utrecht bij het opleiden van personeel in León. Verder is van groot belang de consolidering van de huidige structuur van infectieziekten met toekomstige steun aan het laboratorium voor microbiologie van het universiteitsziekenhuis te León en de koppeling met het Centrum voor Infectieziekten (CEI) van de nationale autonome universiteit (UNAN) van León. Een van de hoofddoelen is het ontwikkelen van een nationaal en internationaal erkende structuur in León op het gebied van infectieziekten. Om hieraan bij te dragen is een samenwerking gestart op epidemiologisch gebied die de sector van de volksgezondheid kan bereiken. Daartoe is er al een bijeenkomst vastgelegd met de huidige decaan Prof. Dr. Rodolfo Peña, Director van het 'Centro de Investigación en Demografía y Salud'(CIDS), het Onderzoekscentrum Centrum voor Demografie en Gezondheid van de faculteit voor medische wetenschappen van de UNAN - León en de directeur van het Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde van het UMC Utrecht, Prof. Dr. D.E. Grobbee.





# Chapter 9

**Resume y perspectivas en Español**



## Resumen y perspectivas

El propósito principal de los estudios realizados en esta tesis fue para adquirir conocimientos científico, epidemiológico, terapéutico y contraponerlo al conocimiento empírico existente de las enfermedades infecciosas más comunes en Nicaragua. Hasta ahora, había relativamente poco conocimiento sobre la incidencia, la etiología de los patrones de resistencia de los antibióticos frente a infecciones bacterianas comunes. De mucha importancia es observar que debido a una carencia de conocimiento, se trata actualmente a muchos pacientes innecesariamente con antibióticos para cuando se presume que hay una infección. El uso ineficaz de antibióticos puede acelerar o provocar reacciones adversas; aumenta los costos, y lo más importantemente posible, es que contribuye a la emergencia de la resistencia antibiótica. Los estudios fueron realizados por lo tanto para proporcionar herramientas para abordar problemas comunes de salud con eficacia en los años venideros. Para proporcionar el conocimiento requerido, nosotros condujimos varios estudios de prevalencia en el área de León, Nicaragua en el marco de la colaboración de las universidades de León y de Utrecht; para esto se constó con la colaboración cercana de epidemiólogos, intensivistas, microbiólogos médicos y especialistas en el campo de las enfermedades infecciosas. Nos centramos en las infecciones comunes tales como infección del tracto urinario y neumonía adquirida en la comunidad (capítulo 2, 3). En el capítulo 4 estudiamos la adherencia del protocolo específicamente desarrollado para la profilaxis antimicrobiana antes de la cirugía en un tercer estudio tipo observacional. En los capítulos finales (5, 6) reportamos la prevalencia del VIH y sífilis en mujeres embarazadas y la epidemiología de la infección del VIH clínicamente aparente en Nicaragua. Basados en estos resultados; adicionalmente nosotros elaboramos las estrategias recomendadas para mejorar la práctica médica diariamente y medidas preventivas dentro del sistema de salud y de la comunidad.

En el primer estudio capítulo 2, hemos demostrado que en León, Nicaragua las infecciones del tracto urinario (ITU), son comunes y que los uropatógenos son altamente resistentes a los antimicrobianos más comúnmente usados. Las infecciones urinarias son una de las enfermedades más comunes por lo cual los pacientes buscan atención médica en todo el mundo. Diseñamos un estudio de prevalencia de junio a noviembre de 2002 en el Hospital Escuela Oscar Danilo Rosales Arguello en León, Nicaragua. Admitimos al estudio (208) pacientes que visitaron la emergencia de nuestro hospital consecutivamente con la sospecha de infección urinaria sintomática. Encontramos 62(32%) pacientes con urocultivo positivo, *Escherichia coli* (56%), fue el patógeno más frecuente aislados, seguido por *Klebsiella* spp. (18%), *Enterobacter* spp. (11%). Se observó altos porcentajes de resistencia para *E. coli* a múltiples antibióticos (ej. amoxicilina, trimethoprim - sulphamethoxazole, cephalotina, ciprofloxacina y amoxicilina/clavulanato). La

emergencia de resistencia contra la primera línea de antibióticos en Nicaragua es alarmante y si esta tendencia no es revertida la opción para el tratamiento adecuado llegará a ser limitada en el futuro cercano. En áreas con alta resistencia como León, TMP-SMX no debe ser la droga de elección empírica para infecciones del tracto urinario complicada o no complicada, porque enfermedades causadas por microorganismos resistentes a TMP-SMX resultan en falla clínica y microbiológica. El problema emergente de la resistencia antibiótica en el tratamiento de las ITU parece ser compartida por varias instituciones en América latina. De gran preocupación es el aumento de la resistencia a los antimicrobianos que esta erosionando la utilidad de los agentes de segunda-línea, ciprofloxacina, como alternativa confiable para la terapia de las ITU en esta área. En Nicaragua, la validez de esta asunción disminuye ya que la prevalencia de la resistencia de microorganismos aislados en orina a las fluoroquinolonas entre pacientes no internados esta en aumento. Por otra parte, niveles de resistencia de ciprofloxacina de el 30% entre los microorganismos aislados de la orina de pacientes internados en las salas del hospital y no internados es un peligro progresivo para las futuras terapias de pacientes en las que terapias alternativas serán limitadas. Afortunadamente, nuestros datos publicados aquí demuestran que la prevalencia de la resistencia a la nitrofurantoina entre las *E. coli* urinarias aisladas son (0%), esto sugiere que la nitrofurantoina puede ser por breve duración una opción terapéutica en los pacientes no internados. Aunque, para su eficacia máxima, solamente en cistitis la nitrofurantoina puede ser utilizada. Se recomienda usar de manera general usar Cefalosporinas de tercera generación o aminoglucósidos en casos de pielonefritis.

El uso racional de antibióticos podría conducir a la disminución de la resistencia bacteriana. Pacientes, abastecedores, médicos y los dirigentes del sector salud deben hacer un compromiso serio para cambiar la dinámica de la prescripción en pacientes no internados. Basados en los resultados de nuestro estudio establecimos en Nicaragua guías de tratamiento para las ITU. En el presente las ITU son tratadas de acuerdo a éstas guías. La contribución es racionalizar el uso de antimicrobianos.

En el capítulo 3, mostramos que en León, Nicaragua la neumonía adquirida en la comunidad es una enfermedad que requiere hospitalización y que el patógeno mas frecuente observado fue el *Streptococo pneumoniae*. Nosotros condujimos un estudio de prevalencia en el hospital escuela de León, Nicaragua de Julio 2002 a Enero 2005 en 130 pacientes consecutivos con edades mayores de 12 años. En el 45% de los pacientes se pudo identificar un patógeno respiratorio. Este es el primer estudio de prevalencia que brinda información basada en evidencia sobre Nicaragua y de otros países Centro Americanos fue imposible comparar nuestros datos con información regional. Varios programas de vigilancia han evaluado los antimicrobianos susceptibles para el *Streptococo pneumoniae*. Sin embargo, el número de aislados en la región Latino Americana es usualmente baja y los estudios

mostraron que los porcentajes de resistencia pueden variar significativamente entre las regiones. Importantemente, la susceptibilidad del *Streptococcus pneumoniae* varía significativamente entre los países Latino Americanos. En nuestro estudio encontramos 0% de resistencia del *Streptococcus pneumoniae* a la Penicilina.

Existen estrategias para el tratamiento empírico en pacientes con neumonía adquirida en la comunidad entre ellas tenemos una buena historia medica y un buen examen físico, también hallazgos de laboratorio y radiográficos pueden ser usados para determinar la severidad de la enfermedad y consecuentemente la probabilidad de complicaciones fatales y no fatales. Basados en nuestros resultados y los de otros autores, nosotros sugerimos sospechar el reconocimiento temprano de la neumonía adquirida en la comunidad causado por *Streptococcus pneumoniae* cuando una combinación de variables están presentes tales como enfermedad cardiovascular, inicio súbito, dolor pleurítico, bacterias Gram positivas en el esputo de la tinsión de Gram, y el conteo de leucocitos correctamente predice la causa de la NAC. Podemos concluir que la información sobre la historia, junto con los resultados de la tinsion Gram de esputo y el conteo de leucocitos, puede ayudar a distinguir el *Streptococcus pneumoniae* de otros patógenos que causan NAC.

En el capítulo 4, reportamos un estudio tipo observacional realizado en un periodo de cuatro semanas en 2005 en el Hospital Escuela de la ciudad de León, Nicaragua. Fueron elegidos para el estudio 297 pacientes consecutivos de todas las edades intervenidos quirúrgicamente en los departamentos de cirugía general, ortopedia, ginecología y obstetricia y pediatría. Demostramos que en León, Nicaragua, la adherencia al protocolo existente se logró sólo en 21 (7%) de los antibióticos prescritos (basado en la indicación, escogencia, dosis, tiempo y duración de la administración). Además, de acuerdo a los protocolos, 1707 dosis (83%) fueron administradas innecesariamente. Esta falla en la adherencia tiene consecuencias directas para el hospital, para los pacientes y para la predisposición de la resistencia bacteriana. Una gran parte del presupuesto del hospital esta siendo usado inadecuadamente. De acuerdo a otros estudios la profilaxis pre-quirúrgica comprende aproximadamente el 30% del presupuesto total del hospital. Además del costo asociado con la sobre prescripción, la administración inadecuada de antibióticos profilácticos eventualmente puede conllevar a infecciones nosocomiales. Este tipo de práctica, puede prolongar la estancia hospitalaria para los pacientes y agregar más costos. Además, de la parte económica, la sobre prescripción y la inadecuada administración de antibióticos llevará inadvertidamente a la resistencia antibiótica provocando una amenaza real en el futuro. La resistencia antibiótica conlleva a limitar las opciones para tratar las infecciones en el futuro, aumentar los costos y también incrementar la mortalidad. Por estas razones es importante adherirse tanto como sea posible a los protocolos de profilaxis quirúrgica para prevenir las consecuencias ya mencionadas. Varios estudios han demostrado que es

posible incrementar la adherencia a los protocolos cuando son puestas en práctica algunas estrategias. A un mas estas medidas han demostrado ser altamente costo efectivas. Este estudio fue de gran importancia porque ha evaluado la situación actual en León, Nicaragua. Los resultados mostraron gran discordancia con el protocolo usado en León. Es probable que una situación similar exista en otros hospitales de Nicaragua. Con estos resultados en mano es de crucial importancia intentar mejorar la adherencia a los protocolos. Es necesario tener estrategias para mejorar la adherencia a protocolos locales de profilaxis quirúrgicas.

En el capítulo 5, reportamos un estudio de prevalencia en el que incluye 1,059 mujeres embarazadas en edades de 13 a 45 años a las cuales se les extrajo una muestra de sangre en el año 2004 en León, Nicaragua. Ninguna de las mujeres embarazadas examinadas resultó sero-positiva al VIH. Sin embargo, la prevalencia de sífilis fue del 1.5%. La epidemia del VIH/SIDA en Nicaragua esta en una etapa naciente y actualmente esta concentrada en grupos de alto riesgo. Los prerrequisitos para una epidemia más seria, tales como el alto nivel de migración y movilidad, una cultura que estigmatiza el uso de condón están presentes. León es una ciudad que esta situada entre Chinandega y Managua; las dos ciudades más prevalentes al VIH en Nicaragua. Otro factor de riesgo importante es que León conecta a través de la vía terrestre con la frontera del Guasaule Honduras la cual es una importante y constante ruta de comunicación. Honduras es un país con una de las prevalencias más altas al VIH en Centro América. Por esta razón la ciudad de León es vulnerable al incremento del riesgo para adquirir la enfermedad del VIH. La mayor proporción de mujeres infectadas con sífilis que fueron encontradas comparada a otros estudios previos sugiere que las infecciones de transmisión sexual están circulando en la población en general y demanda un incremento en la prevención del VIH. Esperamos que el sistema de salud de Nicaragua pueda capacitar recursos humanos para ofrecer conserjería para VIH dentro de los programas de las clínicas prenatales, también estas consejerías deberían ser ofrecidas en las clínicas privadas. Cuando se hace un diagnostico temprano del VIH en mujeres embarazadas podrían garantizar una intervención preventiva para la transmisión vertical.

El capítulo 6, muestra que el VIH/SIDA en Nicaragua esta en una etapa incipiente y esta concentrada en poblaciones de alto riesgo. La información de los pacientes comprende el periodo desde 1987 a 2004; esta información fue obtenida del programa nacional ITS/VIH/SIDA de Nicaragua, información relevante que es colectada y registrada de todos los sistemas locales de salud (SILAIS) de todo el país. La primera persona positiva al VIH en Nicaragua fue identificado en 1987, y desde entonces ha habido una rápida diseminación de la epidemia en algunas partes del país. Nuestros datos describen que la incidencia del VIH en Nicaragua ha ido incrementándose dramáticamente en los últimos cinco años comenzando con

una incidencia anual del 3.27 por 100,000 personas en el año 2001 hasta el 8.7 por 100,000 personas en el año 2005. La mayoría de las personas infectadas fue a través del contacto sexual. Esta situación es preocupante porque la enfermedad ha comenzado a propagarse de los grupos de riesgo a la comunidad. Reportamos a mas de casa seropositivas al VIH que no se detectó factor de riesgo previamente para la transmisión del VIH. Esto sugiere que la transmisión se origina de sus esposos. La epidemia del VIH/SIDA en Centro América es seria y es preocupante. En Latino América, la prevalencia mas alta de VIH es observada en los países Centro Americanos de Belice (2%), Guatemala (1.4%), Honduras (1.9%) y Panamá (1.54%) y en la costa del Caribe en Guyana (3%) y Surinam (1.3%). La Transmisión en estos países es predominantemente a través de las relaciones sexuales.

A pesar que la epidemia en Nicaragua esta en una etapa naciente, las condiciones están dadas para saltar a grandes magnitudes y esta situación puede salirse de las manos si medidas de prevención no son puestas en marcha ahora para detener o para modificar esta tendencia. La situación socioeconómica es una de las principales causas del incrementado riesgo para la transmisión de la enfermedad. La población de Nicaragua es altamente móvil, más de un millón de nicaragüenses migran; cada año las personas migran a otros países en búsqueda de mejores oportunidades. Esta alta movilidad incrementa el número de parejas que un individuo tiene y esto podría explicar la introducción de nuevos infectados dentro de una población menos móvil, tales como las amas de casa. La gran presión existente para migrar causada por la pobreza y la falta de oportunidades económicas hace mas posible que mujeres y hombres van ha migrar en búsqueda de ingresos y empleo, lo cual puede desestabilizar y alterar la relación social y familiar y exponer tanto a mujeres como hombres a un incremento del riesgo a la infección. Podemos agregar, que en la mayoría de los escenarios, las poblaciones emigrantes son más propensas a ser socialmente marginadas, con acceso restringido a ventajas económicas, de información y servicios.

De todas las potenciales estrategias preventivas la falta del uso del condón es un problema mayor. La actitud de la población Nicaragüense al uso del condón, es un problema, explícitamente refiere que el condón debería ser usado principalmente con las trabajadoras del sexo para prevenir infecciones de transmisión sexual. Además podemos agregar la cultura de “macho” del nicaragüense que hace vulnerables a las mujeres a la infección del VIH.

Un tercio de los infectados en Panamá y Nicaragua son atribuidos a un sexo no protegido entre hombres. Datos de Honduras, reportan que cuatro de cinco infectados ocurre a través de una interacción heterosexual no protegida. En Nicaragua la ruta principal de transmisión es la heterosexual, también en Honduras, Guatemala, y Belice. Hombres que tienen sexo con hombres constituyen la gran mayoría de los infectados en Costa Rica y Panamá.

Medidas preventivas deben ser desarrolladas urgentemente y adaptadas a la población Nicaragüense. Intervención con programas de educación para promover el

desarrollo de cambios de conductas, actitudes y prácticas en la población de riesgo, en vías de disminuir la vulnerabilidad de la población Nicaragüense.

### **Perspectivas de la colaboración Utrecht/León**

Nosotros esperamos que ésta fructífera colaboración va ha continuar en el futuro para profundizar la relación profesional entre las dos instituciones. Las dos potenciales áreas de futura colaboración son: a) entrenamiento de estudiantes de Utrecht en atención de salud en sociedades menos privilegiadas, lo cual hasta la actualidad ha tenido una gran contribución al desarrollo de la carrera de estos estudiantes. b) Paralelo al programa de intercambio de estudiantes nosotros esperamos que este programa pueda extenderse a profesionales en el campo de las enfermedades infecciosas de Utrecht para León para colaborar en la capacitación de recursos humanos en León. De importancia mayor será la consolidación de la actual estructura de enfermedades infecciosas con apoyo futuro al laboratorio de microbiología del hospital escuela de León y la vinculación con el Centro de Enfermedades Infecciosas (CEI) de la UNAN – León. Una de las metas finales es desarrollar una estructura que sea reconocida nacional e internacionalmente en León en el área de Enfermedades Infecciosas. Para contribuir con esta estructura se ha iniciado el establecimiento de una colaboración en el campo de la epidemiología que sea capaz de alcanzar al sector de la salud pública, para esto se ha fijado ya una reunión con el decano actual Prof. Dr. Rodolfo Peña Director del Centro de Investigación en Demografía y Salud (CIDS) de la Facultad de Ciencias Medicas, UNAN - León y el Director de Epidemiología y atención primaria del Centro Julios, Prof. Dr. D.E. Grobbee.



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# Curriculum Vitae



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## **Curriculum vitae**

*1980 - 1986*

Medical School at the National Autonomous University of Nicaragua, (UNAN), León.

*1987 - 1988*

Social service at UNAN, León as a chief of semiology section.

*1989 - 1992*

Residency at Department of Internal Medicine, HEODRA, León.

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Edwards Kass Fellowship of the Infectious Disease Society of America (IDSA).

*1993 - present*

Member of IDSA.

*July 1998 - March 2000*

Infectious Diseases training at the University Medical Center Utrecht, the Netherlands.

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Infectious Diseases Doctoral training in Infectious Diseases at the University Medical Center Utrecht, the Netherlands.

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Head of Infectious Diseases at HEODRA, León, Nicaragua.