

## Introduction

Bacterial resistance to antimicrobial agents represents a global public health problem. It is particularly serious in low-resource countries where bacterial infections remain among the major causes of death, especially in childhood (WHO, 2001). The high prevalence of antimicrobial resistance observed in low-income countries is likely due to a combination of several factors, among which irrational antibiotic usage and conditions of poor sanitation are thought to play a major role, even if the relative importance of additional factors remains unclear. ANTRES is a research project entitled “Towards controlling antimicrobial use and resistance in low-income countries – an intervention study in Latin America”, that aimed at further investigating this phenomenon on a large scale.

The project started on February 2002 and lasted up to July 2006, involving twelve Institutions from Italy, Sweden, Bolivia and Peru.

## Methodology

The **First Year** represented the **pre-intervention phase** of the project including a baseline study carried out in two urban communities in Bolivia (Camiri and Villa Montes) and Peru (Yurimaguas and Moyobamba). Moreover, a very remote community in the Peruvian Amazonas, Angaiza, where the use of antimicrobials was minimal, was investigated. Study design and instruments were finalised during a pilot study, preceded by the first international workshop. Antimicrobial use was assessed in 3174 households, enrolling carers and children, by a household survey approach (HAUS) based on questionnaires and focus group discussions. Antimicrobial resistance was studied, in the same households, through collection of a faecal swab from the youngest child of the family, aged 6-72 months. The samples were investigated for prevalence of antimicrobial resistance in commensal bacteria (*Escherichia coli*) by means of a rapid screening method, refined during the pilot study and confirmed to be particularly suitable to monitor resistance-control programs cost-effectively in low resource countries. Mechanisms of resistance spreading were investigated by molecular analysis. Moreover, the role of other factors influencing antimicrobial use and antimicrobial resistance were analysed, including national drug policy, non-human use of antimicrobials and contamination of water sources.

The **Second** and **Third Year** represented the **intervention phase** of the project. In particular, based on the preliminary results of the baseline study, an Information-Education-Communication (IEC) package was developed, considering *Academic detailing*, to present and discuss the identified problems among providers (medical doctors, pharmacists) with the aim of improving antimicrobial dispensing; *Peer network*, to develop strategies for improving the rational use of antimicrobials in the community and *Community intervention*, to bring up changes in attitudes and habits on antimicrobial use and self-medication. The activities were planned in occasion of the second international workshop. The campaign was limited to one of the two cities both in Bolivia and Peru. During the **Fourth Year** the IEC campaign continued; new inputs resulted from a fruitful exchange of experiences among Bolivian and Peruvian partners after the third international workshop. During the **post-intervention phase**, monitoring surveys were repeated as described previously including 3193 households from the same study areas, to evaluate the efficacy of the IEC package in an intervention group compared to a control group. The last **six months** were dedicated to the analysis, exploitation and dissemination of project results summarised as follows:

Investigation on antimicrobial use indicated that the parents' health seeking strategies include treatments with traditional medicines as well as an extensive utilisation of the public health care system. Often traditional medicine was used as first-choice treatment, regardless of the educational level of the parents. The majority of antimicrobials used to treat the children was obtained from the health care system, and was not given as self-medication. Drugs were provided to a high extent for pneumonia-like symptoms, but less frequently for cough/cold. Medical doctors showed little discrimination in antimicrobial prescription for illnesses recommended or not for antimicrobial treatment according to principles of the integrated management of childhood illnesses (IMCI)

algorithm. High antimicrobial resistance rates in commensal *E. coli* were observed for ampicillin (95%), trimethoprim-sulphamethoxazole (94%), tetracycline (93%), streptomycin (82%) and chloramphenicol (70%). Lower resistance rates were observed for nalidixic acid (35%), kanamycin (28%), gentamicin (21%), and ciprofloxacin (18%), while resistance to ceftriaxone and amikacin was very uncommon (<0.5%). The majority of resistant *E. coli* isolates harbored multidrug resistance (MDR) strains (90%). Mechanisms of resistance spreading were complex and involved both clonal expansion of antimicrobial-resistant strains and horizontal transfer/recombination of mobile genetic elements harboring resistance genes. High resistance rates unexpectedly detected in the isolated community in Peru, where antimicrobial use was very limited, suggested that, in some cases, the spread and maintenance of resistant strains could be not directly related to antimicrobial consumption. Other factors, influencing the kinetics in the communities, could be described. A multifaceted intervention campaign was realized addressing journalists, teachers, students, mothers and families using marionettes, theatre pieces, puppets, “rotafolio”, radio spots and mass media. Posters and panels were distributed in the cities; messages focused on self-medication and compliance to treatment. Household survey to evaluate the impact of the intervention campaign on antimicrobial use were performed and data are underway to be analysed. Changes in antimicrobial resistance rates did not represent a valuable indicator of its efficacy, due to the very limited time period passed between the intervention and the microbiological study. Results, besides confirming the high resistance rates, showed an alarming significant increase in the resistance rates to quinolones (57% vs. 35% for nalidixic acid and 33% vs. 18% for ciprofloxacin) and ceftriaxone (1.7% vs. 0.1 %). The trend was similar overall in each of the 4 studied areas. Dissemination of outcomes occurred through publications in peer reviewed scientific journals (4 articles), presentations on national and international conferences (10 presentations) and mass media. Further preparation of manuscripts is underway. Translation in Spanish of a significant paper was performed to increase locally the diffusion of results. An international meeting followed by various seminars at each partner country has been organised. Moreover, two Medical students, two MDs post-graduating in infectious diseases and two PhD students promoted through the project.

### Conclusions

The project identified innovative tools to control antimicrobial use and resistance in low-income countries (rapid screening method, HAUS method, conceptual framework and intervention package). Results were accepted for publication and judged to represent a valid contribution to better understand the phenomenon of antimicrobial use and resistance. Good teamwork and relationship were the fundament on which the activities were carried out. Each partner contributed with enthusiasm to the program. The theme is still a topic of current interest.