INFECTIONOUS DISEASE INITIATIVE

STRATEGIES AND INTERVENTIONS TO UNDERSTAND, CONTAIN, AND RESPOND TO THE DEVELOPMENT AND SPREAD OF ANTIMICROBIAL RESISTANCE

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<td>American International Health Alliance</td>
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<tr>
<td>APUA</td>
<td>Alliance for the Prudent Use of Antibiotics</td>
</tr>
<tr>
<td>CDC/NCID</td>
<td>Centers for Disease Control and Prevention/National Center for Infectious Diseases</td>
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<tr>
<td>BU/ARCH</td>
<td>Boston University/Applied Research on Child Health</td>
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<tr>
<td>ICDDR,B</td>
<td>International Centre for Diarrheal Disease Research, Bangladesh: Centre for Health and Population Research</td>
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<tr>
<td>INCLEN</td>
<td>International Clinical Epidemiology Network</td>
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<tr>
<td>INRUD</td>
<td>International Network for the Rational Use of Drugs</td>
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<tr>
<td>JHU/FHACS</td>
<td>Johns Hopkins University/Family Health and Child Survival</td>
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<tr>
<td>MSH</td>
<td>Management Sciences for Health</td>
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<tr>
<td>PAHO</td>
<td>The Pan American Health Organization</td>
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<tr>
<td>QAP II</td>
<td>Quality Assurance Project II (USAID)</td>
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<tr>
<td>RPM</td>
<td>The Rational Pharmaceutical Management Project (USAID)</td>
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<tr>
<td>USP</td>
<td>The United States Pharmacopoeial Convention</td>
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<td>WHO/CAH</td>
<td>World Health Organization/Child and Adolescent Health</td>
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<td>WHO/CDS</td>
<td>World Health Organization/Communicable Diseases and Surveillance</td>
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<tr>
<td>WHO/HTP/EDM</td>
<td>World Health Organization/Health Technology and Pharmaceuticals/Essential Drugs and Medicines</td>
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INTRODUCTION

In 1998, USAID launched a new Infectious Disease Initiative to reduce the threat of infectious diseases of major public health importance\(^1\). This 10-year strategy focuses on: antimicrobial resistance (AMR); tuberculosis; malaria; and surveillance and response. Priorities for each of the four areas were developed through a consultative process which involved numerous partners, including the World Health Organization, the Centers for Disease Control and Prevention, the National Institutes of Health, universities, and other organizations.

This document summarizes the AMR-related activities that have been supported by the Office of Health and Nutrition in USAID’s Global Bureau since FY1998 with Infectious Disease funding\(^2\). (The distribution of activities is shown in Figure 1 and Table 1.) AMR activities are listed according to the Agency’s priority areas: (1) Establishing a Global Strategy and Action Plan; (2) Improving the Understanding of AMR; (3) Developing Methods to Detect AMR; (4) Responding to Data on AMR and Drug Use; and (5) Preventing and Slowing the Spread of AMR. Activities were selected by the USAID AMR Working Group based on their ability to:

- Contribute to the development of a comprehensive, evidence-based AMR strategy and action plan;
- Address both key USAID program areas (e.g. Child Survival, Maternal Health, Reproductive Health) threatened by AMR and priority diseases set forth in the USAID Infectious Disease Strategy;
- Address priority areas identified at technical consultations (e.g. WHO’s meeting on Research Strategies for Determining Antibiotic Efficacy in Childhood Pneumonia) and global consensus meetings (e.g. International Conference on Improving the Use of Medicines);
- Fill identified gaps in setting standards, implementing known interventions, and developing new ones.

Initially, Infectious Disease activities funded by the Office of Health and Nutrition in USAID's Global Bureau focused on research, establishing guidelines and standards, and developing/field-testing tools, interventions, and case-management approaches in order to address AMR and antimicrobial drug use. One key activity has been WHO’s development of an AMR Global Strategy and Action Plan to identify research issues and outline effective implementation activities to assist USAID and other partners in identifying priorities, coordinating activities, leveraging resources, and increasing awareness of the importance of limiting the emergence and spread of AMR. In year one (FY1998) of the USAID Infectious Disease Initiative, AMR research was mostly focused on resistance to drugs used to treat acute respiratory infections (ARI) to support the process of revising treatment guidelines and drug policies as appropriate\(^3\). Additional activities addressing AMR as it relates to diarrheal disease, meningitis, nosocomial (hospital-acquired) infections, and sexually-transmitted infections (STIs) have been developed in year 2 and beyond as information from the technical reviews became available (see AMR Component 1: Establishing a Global Strategy and Action Plan). AME surveillance, drug-resistant malaria, and drug-resistant TB are described in documents developed by the USAID Working Groups for surveillance, malaria, and TB, respectively, as such activities are within the purview of those groups.

At the beginning of the Infectious Disease Initiative, country-specific implementation of AMR activities was primarily funded by USAID missions. More recently, however, the Global Bureau’s Office of Health and Nutrition has begun to increase investments in the design and implementation of interventions to address the problem of antimicrobial resistance at the country level.

\(^1\) For more information, see: [http://www.info.usaid.gov/pop_health/webid.htm](http://www.info.usaid.gov/pop_health/webid.htm)

\(^2\) Other AMR activities supported by USAID regional bureaus and country missions are not included in this document.

\(^3\) In developing countries, ARIs are the major killer of children and successful case management with effective, affordable antibiotics is essential for decreasing mortality from ARIs.
Figure 1. Distribution of AMR Activities Supported by the USAID Global Bureau by Region, Activity Type, and Disease.

Regional Distribution
(\(n = 144\))

Activity Distribution
(\(n = 62\))

Disease Distribution
(\(n = 66\))
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AMR Component 1: Establishing a Global Strategy and Action Plan

1.1: Establishing a Global Strategy and Action Plan

Implementing Organization: WHO/CAH, WHO/CDS, WHO/HTP/EDM

Status: On-going (Funded: FY1998; Expected Completion: FY2001)

Objective(s):
1. Define the magnitude of the problem of antimicrobial resistance in different pathogens and patient populations, and quantify the morbidity, mortality and cost attributable to antimicrobial resistance;
2. Define and attempt to quantify the relative importance of the different causal factors favoring the emergence and spread of antimicrobial resistance;
3. Develop a global strategy founded on evidence-based interventions.

Description:
1. Define and maintain updated an action plan with milestones and time lines, indicating roles for partners;
2. Establish a baseline through data gathering (from existing study sites, published literature and commissioned reviews (see "Expert Technical Reviews" listed below) to document levels of resistance (and trends where available) in specified patient groups for priority diseases (pathogens) and data on morbidity, mortality and cost impacts of resistance;
3. Develop a framework of causal factors that favor the emergence and spread of resistance and identify elements that can be targeted for interventions;
4. Seek consensus on framework and relative importance of causal factors;
5. Document interventions that have been shown to effectively target specific elements; define the gaps in knowledge of effective interventions; prepare an inventory of research planned/underway to fill gaps; seek consensus on interventions and the knowledge gaps;
6. Encourage the testing of additional interventions;
7. Assess the cost-effectiveness/cost-benefit of interventions;
8. Develop a programme of evidence-based interventions to be implemented at country level; revise and refine as new data become available;
9. Assist Member States in the introduction and implementation of the containment strategy.

Expected Outcomes, Results and Progress Indicators
1. An action plan updated regularly and shared between partners;
2. Baseline data on magnitude and impacts of antimicrobial resistance in major public health disease priorities;
3. Framework of causal factors with individual elements targeted for interventions; interventions proven and those to be researched;
4. Partners working together to develop and test additional interventions;
5. A global strategy based on the consensus of experts, and implementable at national level

Progress indicators: This is a multi-year project. With the first year funding the following will be used as indicators of progress: Action plan prepared; Data gathering initiated to establish baseline on magnitude and impacts of AMR; Framework of causal factors and interventions drafted; Consensus meeting planned.

Partners/Collaborating Institutions: APUA; AIHA; Cambridge University/UK; Canadian International Agency (CIDA); ICDDR,B; CDC; Cochrane Group; Confédération Mondiale de l'Industrie
de la Santé Animale (COMISA); Consumers Union; European Commission; European Medicines Evaluation Agency (EMEA); International Pharmaceutical Federation (FIP); Food and Agriculture Organization (FAO); Global Health Research Forum; Gonococcal Antimicrobial Surveillance Programme (GASP) Collaborating Centres; BU/ARCH; Hoffmann La Roche Pharmaceuticals; INCLEN; International Federation of Pharmaceuticals Manufacturers Associations (IFPMA); INRUD; International Society for Infectious Diseases (ISID); International Society of Chemotherapy (ISC); International Union of Pharmacology; JHU/FHACS; RPM/MSH; Menzies Research Institute/Australia; National Drug Regulatory Authorities; National Governments; School of Public Health/Boston University; South African Institute for Medical Research/Johannesburg; South Africa Universities (various); US Federal Department of Agriculture (USDA); Wellcome Trust Epidemiology Research Centre (University of Oxford)/UK; WHO Collaborating Centre for Surveillance of Antimicrobial Resistance; Brigham and Women’s Hospital/Boston; WHO Divisions (HQ) and Regional and Country Offices; World Bank.

Results to Date: Consensus workshops were held with partner and regional organizations to develop and review the strategy. The final version (WHO Global Strategy for Containment of Antimicrobial Resistance) was published in September 2001 along with the technical reviews listed below.

**Expert Technical Reviews (and Responsible Organization):**

- Antimicrobial Drug Information (USP; see activity 1.3)
- ARI (CDC)
- Behavior, part I (BU/ARCH, RPM/MSH; see activity 1.5)
- Behavior, part II (BU/ARCH, RPM/MSH; see activity 1.7)
- Diarrheal Disease (JHU/FHACS; see activity 1.2)
- Economic Impact of AMR (Global Forum for Health Research, BU/ARCH; see activity 1.4)
- Effects of Provider Reimbursement Mechanisms and Managed Care (RPM/MSH; see activity 1.9)
- Gonorrhea (WHO)
- Magnitudes and Trends of AMR (WHO)
- Malaria (CDC)
- Non-Human Use of Antimicrobial Drugs (WHO; see activity 2.3)
- Nosocomial Infections (JHU/FHACS; see activity 1.8)
- Role of Drug Rotation, Reserve, and Combination (WHO)
- Sentinel AMR Policy Documents (APUA; see activity 1.6)

### 1.2: State of the Art Technical Review of Antimicrobial Resistance of Selected Bacterial Diarrheal Diseases: Shigellosis, Cholera and Campylobacteriosis

**Implementing Organization:** JHU/FHACS

**Status:** Completed (Funded: FY1998; Completed: FY1999)

**Rationale:** In developing countries, antibiotics are clinically useful in a few diarrheal diseases including those due to *Shigella species*, *Vibrio cholerae*, and *Campylobacter jejuni*. Unfortunately, antibiotics are used for diarrhea caused by many other agents for which they are not indicated and an inappropriate antibiotic is frequently used for these specific diseases. The combination of the indiscriminate use and inappropriate use of antibiotics has been followed by the widespread occurrence of antibiotic-resistant strains and these
resistant strains have become dominant in many regions. *Shigella* *spp.*, for example, have become successively resistant to sulfa, tetracycline, ampicillin, trimethoprim, and nalidixic acid. Most of these resistance patterns were due to plasmids (except the quinolones); thus, the *Shigella* could serve as mediators of resistance to other bacteria.

Among the *Shigella* *spp.*, there are four species and multiple serotypes. Of these different varieties of *Shigella*, *Shigella dysenteriae* type 1 (Shiga bacillus) has caused major epidemic disease in Central America, Africa and South Asia, and the widespread use of modern antibiotics, though potentially lifesaving for the individual has rapidly been followed by the spread of clones which are antibiotic resistant. The spread of these antibiotic resistant clones has been devastating with high case fatality rates (>5% with treatment) and high overall mortality. Even when the newest-generation effective antibiotics have been developed, their high costs have prevented their use. If they had been used on a wide-scale, there is concern that resistance would eventually develop to these drugs as well.

Although less dramatic than the epidemic Shiga bacillus, the more endemic *S. flexneri* has actually been a larger public health threat, because of higher overall incidence rates, more widespread disease on a global basis, and interaction on nutrition and growth as well as direct mortality. Antibiotic resistance in this genus has also increased steadily, and rates of antibiotic resistance for ampicillin and trimethoprim are now approaching the same high level as for Shiga.

*V. cholerae* has also become resistant to multiple antibiotics and epidemics due to resistant strains have been widespread in Asia, Africa and South America. As with *Shigella*, the resistance if plasmid mediated, and the emergence of resistant strains seems to follow the inappropriate use of antibiotics. *C. jejuni* is another bacterial cause of diarrhea as well as a cause of Guillain-Barre syndrome. Antibiotics are not generally used to treat this infection in developing countries, still these strains are becoming resistant to common antibiotics, perhaps because of the general antibiotic pressure in the region. Of particular concern are reports of resistance to ciprofloxacin in *C. jejuni*.

**Objective(s):**
1) review the literature on the nature and trends of antibiotic resistance in *Shigella*, *V. cholerae* and *C. jejuni*.
2) define the epidemiological and clinical implications of antibiotic resistance to these organisms.
3) define the policy implications of antibiotic resistance to these organisms and suggest policies for limiting their public health impact.

**Description:** A literature review will be conducted by at least two persons who are expert in the field of. A microbiologist will carry out the review of bacterial mechanisms of resistance and an epidemiologist/clinician will carry out the review of antibiotic resistance in the community and health facilities. Sections of the review will include: a) a summary of basic principles and mechanisms in antibiotic resistance; b) examples of the development of epidemics due to resistant strains as well as examples (if any) of the re-emergence of sensitive strains; c) the clinical implications of case management of patients with resistant organisms including the complications to the patients being treated with inappropriate antibiotics; d) review of programs in which a more rational approach was attempted for using antibiotics in diarrhea; e) review of reasons for the continued use of inappropriate antibiotics; f) cost-effectiveness implications of antibiotic use for diarrhea; g) policy implications for the management of diarrhea.

**Expected Output, Results, and Progress Indicators:** Shigellosis and cholera are major public health problems and occur in both epidemic and endemic patterns. Antibiotics are the major clinical intervention for the individual patient and can be lifesaving, yet appropriate uses of antibiotics are becoming increasingly difficult. The review of antibiotic resistance in shigellosis will assist policy makers
in developing treatment guidelines for management of patients, management of epidemics, and plans for providing essential drugs to countries. Further, it will assist other USAID-sponsored projects which may be monitoring antibiotic resistance and will serve as a useful model organism for intervention studies. By combining microbiological with the clinical and epidemiological aspects, an overall understanding of the nature of the problem will be defined, and will lead to interventions for control and reversal of the antibiotic resistance for this and possibly other infections.

**Countries/Regions:** The work will be done in Baltimore at JHU, with communications with other offices at WHO, PAHO, and international centers.

**Partners:** Not applicable.

**Results to Date:** Review is being prepared for publication.

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1.3: **State of the Art Technical Review of Antimicrobial Drug Information**

**Implementing Partner:** USP

**Status:** Completed (Funded FY1998; Completed FY1998)

**Rationale:** Although individual copies of the USP DI or another source of unbiased drug information may be found in one or two offices in many countries around the world, the vast majority of drug information that is commonly used in developing countries is produced by the pharmaceutical industry. This latter information may be disseminated directly by the manufacturer through product inserts or indirectly through advertising placed by the industry in professional journals and newsletters. Although, by its very nature, a manufacturer’s information is biased toward its own products, the real danger lies in the inconsistent quality of industry information combined with an almost unlimited capacity for dissemination. A state of the art review by country is required to determine the quality of readily available, commonly-used drug information including accuracy, currency, completeness and local relevance.

The pharmaceutical industry accounts for the majority of drug information available in developing countries, however, other sources, especially WHO and other donor organizations are beginning to provide drug information relative to their specific programs, e.g. EPI, UNAIDS, UNFPA, vertical disease programs. In order to fully evaluate the quality of industry and locally-produced information, information disseminated by international organizations must be examined at the same time to identify contradiction and disagreement.

**Objective(s):** To determine what, if any, drug information needs to be created for specific countries or regions to help eliminate practices which lead to antimicrobial resistance and to provide guidance to international bodies attempting to develop drug information for developing countries as part of broader health programs.

**Description:** USP will conduct a review of the most accessible and widely-used AM drug information available in selected developing countries by hiring local consultants to collect the available professional literature, e.g., journals, newsletters, Standard Treatment Guidelines, manuals. At the same time, USP will collect drug information produced by other international organizations for use in support of health sector programs in developing countries. USP staff will review and evaluate the quality of the information, including the content of both the articles and the advertising, against generally accepted prescribing
recommendations, including USP standards in drug information development. Draft versions of the country analyses, with copies of the original information reviewed, will be provided to USP’s International Health Advisory Panel for further input and a request for recommendations. The International Panel will also be called upon to assist with collection of the material. Results of the review will be disseminated through WHO, USAID, FIP, INRUD and other international networks and organizations.

**Expected Outputs, Results and Progress Indicators:** A series of country-specific analyses of the quality of drug information sources and recommendations for modifications or additional information sources required by each country to help reduce antimicrobial resistance.

**Progress indicators:** Number of information materials received from local partners, number of institutional programs reviewed, number of draft analyses documents prepared, number of drafts circulated to Panel, number of Panel comments received by USP, number of completed analyses by end of RPM project, copies of final review disseminated through various channels.

**Countries/Regions:** The state of the art review will cover 6-8 developing countries including Ghana, Mozambique, Nepal, Peru, Russia, and Zambia.

**Partners:** Local governmental and non-governmental organizations, e.g., the Drug Information Network of Nepal, INRUD and PharmedInfo, will be identified to collect the primary information to be reviewed. Institutions to be asked for materials for review: WHO/HTP/EDM; WHO/EPI; UNICEF; USAID supported vertical disease programs; UNFPA; others.

**Results to Date:** Technical review completed for six countries (Ghana, Mozambique, Nepal, Peru, Russia, and Zambia) and results presented at the AMR Partners meeting in Washington in March 2001. An overview of the study has been disseminated to all USAID missions via the monthly mailing. The missions in the six participating countries have received their country report and the overview of the whole study. The drug information centers in Russia, Nepal and Mozambique have also received their respective country reports and the overview.

Recommendations from the review include:
- Efforts should be made to make the concept of access to objective drug information part of national health policy.
- Regulatory support to enhance availability of objective, timely information on drugs and to improve regulation of drug promotion should be a priority.
- Information dissemination strategies should be established to ensure access to appropriate information at all levels (practice and geographic).
- Availability of locally-appropriate information, including information on antimicrobial resistance, should be a priority.
- Development and dissemination of treatment guidelines should be a central part of a drug information strategy.
- Research on how to best effect appropriate prescribing and use should be conducted, if necessary, to appropriately define options.
- Creation of appropriate audience-specific educational materials should be encouraged.
- Model medical curricula and continuing education initiatives, focusing on critical prescribing messages and development of essential skills, should be implemented.
- The central role of the health care provider in patient education should be stressed.
- Effective mechanisms for information and experience sharing (e.g., medication errors) should be explored.
• Initiatives supporting the development of culturally-sensitive drug information for consumers should be implemented.
• Innovative initiatives to enhance consumer understanding of appropriate drug use should be considered (e.g., educating children).

1.4: Costs and Cost-effectiveness Analysis of Antimicrobial Resistance in Developing Countries

Implementing Organizations: BU/ARCH and Global Forum for Health Research

Status: On-going (Funded FY1998; Completed FY2002)

Rationale: The resistance of disease-causing organisms to standard first-line treatments results in a wide range of direct costs (due to prolonged hospital stays, additional treatment with different, often more expensive, antibiotics, etc.) and indirect costs (such as lost labor due to excess illness itself or additional care burdens for other family members). It also extends the period during which individuals are infectious and creates more opportunities for the spread of infection to others.

Although the kinds of costs attributable to AMR are easy to identify, very little is known about their magnitude and impact. A better understanding of these costs and their allocation among households, governments, and society at large is needed to assess the economic burden imposed by resistance and help government policy makers and international donors make more efficient policy, programmatic, and resource allocation decisions. Developing countries are deeply affected by increasing resistance as they have more limited resources to invest in second-line therapy to treat resistant infections or in funds to improve public health and thereby reduce exposures. For these countries, some sense of how the costs of AMR compare to the costs of the diseases with which it is associated, at a national level, is critical for efficient allocation of scarce public health resources.

To begin to fill this gap in our knowledge of the economic impact of AMR, BU/ARCH carried out a detailed assessment of the incremental treatment costs associated with resistance for one disease in one country.

Objective(s): Lay out a methodology for assessing the direct costs of resistance, as a percentage of the total direct costs of childhood pneumonia; apply the methodology to the case of pneumonia caused by S. pneumoniae and H. influenzae among under-five year old children in Pakistan to provide preliminary evidence on how serious the costs of AMR are likely to be; and identify the most important issues for additional research.

Description: The study will start with a systematic review of previous research of the problem of antimicrobial resistance and its costs. Childhood pneumonia in Pakistan was selected for the case study because it is one of the most widely documented examples of AMR. The study will describe the burden of childhood pneumonia in Pakistan, current approaches to treatment of pneumonia, and resistance to the first-line antibiotics used in treatment. A model for identifying and allocating the costs of AMR will be developed and applied to the case study. The results of the case study will be a set of estimates of the incremental costs of treatment of resistant bacterial pneumonia children in Pakistan and a set of recommendations for policy responses and future research.
Countries/Regions: Cambodia, Pakistan, United Kingdom

Partners: Global Forum on Health Research for Development

Results to Date (BU/ARCH): The case study found in Pakistan that the incremental costs of antimicrobial resistance depend almost entirely on the severity of the original case of pneumonia, whether the case becomes more severe after first line treatment fails, and whether the case is treated at a public or private health facility. For a single case of resistant pneumonia, the incremental cost of resistance (as a share of the full cost of treating a resistant case) ranged from a low of 1.5 percent, for a severe case that did not progress and was treated at a public facility, to a high of 95.3 percent, for any non-severe case that did progress to severe or very severe and was treated at a private facility. Aggregated across all cases of resistant bacterial pneumonia among Pakistani children, the impact of AMR was to raise the cost of treating pneumonia by an estimated 7-10 percent. This cost was solely for facility-based treatment; it did not consider any of the indirect costs of AMR, such as the lost labor productivity of parents who take care of sick children, or the costs of the increased transmission of disease that resistance makes possible.

Results to Date (CAH and GFHR): Given the disparate nature of evidence concerning strategies to combat antimicrobial resistance, CAH is collaborating with the Global Forum for Health Research (GFHR) and the University of East Anglia in the UK to:

i. review current knowledge concerning the cost and/or effectiveness of interventions aimed at reducing the emergence and transmission of antimicrobial resistance; and

ii. explore the feasibility of and issues involved in, the development of an economic model to assess the cost-effectiveness of interventions to address antimicrobial resistance.

Two reports have been produced: Interventions against antimicrobial resistance: A review of the literature and Interventions against antimicrobial resistance: Modelling cost-effectiveness that will be published in September 2001.

The next phase of this project, starting in August 2001, includes the development of a model using available data from an experimental site, and a project to pilot test the model under real conditions that will be conducted in Cambodia. A final report is expected at the end of 2002

1.5: Review of Interventions to Improve Antimicrobial Use by Health Providers

Implementing Organizations: RPM/MSH

Status: Completed (Funded: FY1998; Completed: FY1998)

Rationale: A significant force driving the spread of antimicrobial resistance is the inappropriate use of antimicrobials in primary care and hospital settings. Studies have documented problems such as over-prescribing as well as inappropriate selection and dosing of antibiotics by health care providers, unfettered access to antimicrobials by consumers, and a failure to adhere to clinically desirable treatment regimens. Consequently, many educational, managerial and regulatory interventions focusing on health providers have been widely recommended and implemented. However, not all the proposed interventions have been rigorously tested to determine their impact on the use of antimicrobials.

Objective(s): To review and update knowledge about the effectiveness of interventions designed to improve the use of antimicrobials by health providers.
Description: Using explicitly-predefined criteria for appropriate study design, the review will identify: interventions that have been rigorously tested; the settings where the interventions have taken place; the methods used to improve antimicrobial use, and; whether the intervention succeeded or failed to achieve its objectives. The review will cover interventions that target antimicrobial use by health providers working in primary care facilities, hospitals, and retail drug outlets. Interventions to improve community or patient drug use behavior are beyond the scope of this review.

The review will analyze relevant studies that (a) have been previously collected for the 1997 Chiang Mai Conference on Improving Use of Medicines (ICIUM); (b) were presented at the ICIUM Conference; (c) have been published or reported since then. The INRUD bibliography database will be used to identify relevant studies not previously reviewed or reported since 1996. Through RPM collaborators in the Russian Federation and the Newly Independent States, a search will be made for studies that may have been undertaken and reported in Russian and other Eastern European languages.

Expected Outputs, Results and Progress Indicators:
Output: Review paper on the effectiveness of interventions to improve use of antimicrobials by health providers.
Results: 1. Up-to-date critical review of effectiveness of interventions to improve antimicrobial use by health providers is made available for dissemination;
2. Gaps in current knowledge about effectiveness of interventions to improve antimicrobial use by health providers are identified.
Progress indicators:
1. Literature search completed;
2. Review paper drafted.

Countries/Regions: Review will cover studies in Africa, Asia, Latin America, and Eastern Europe/Eurasia.

Partners: INRUD (Ghana); WHO/HTP/EDM; Harvard Drug Policy Group.

Results to Date: The review has been completed and presented to USAID. The review is being added as an attachment to the WHO global strategy to contain antimicrobial resistance, which will be published in September 2001

1.6: Synthesis of Sentinel Policy Documents Concerning Strategies for Curbing AMR

Implementing Organization: Alliance for the Prudent Use of Antibiotics

Status: On-going (Funded: FY1999; Expected Completion: FY2001)

Rationale: Expert study groups such as the American Society for Microbiology, Infectious Diseases Society of America, Centers for Disease Control and Prevention, and Institute of Medicine have reported on the problem of antimicrobial resistance (AMR). Their sentinel reports identify factors that impact resistance and strategies to control its emergence and spread (see Appendix A). Viewed together, these documents represent a consensus of opinion from a variety of relevant disciplines, suggesting actions needed to curb AMR. Documentation of this consensus, as well as variance of opinions on alternate strategies, would provide a useful framework for a global strategy to combat AMR. To capitalize on the
expert opinion represented, these documents should be reviewed to identify points of agreement and dissent on research needs and prevention and control strategies. By creating a single review document, APUA will provide USAID and WHO with a framework for developing a global strategy to improve the use of antibiotics and contain AMR.

**Objective:** Review the expert policy documents concerning strategies for curbing antimicrobial resistance; synthesize their conclusions and recommendations; and in conjunction with members of APUA’s Scientific Advisory Board, develop a single review document, which would assist WHO and partners in the development of the global strategy.

**Description:** APUA staff will: (1) compile the major expert policy documents produced in both industrialized and developing countries, including selected countries from the APUA Chapter Network; (2) review and develop a brief summary of individual documents; (3) create an outline of major issues and strategies to be addressed (i.e. background on AMR--issues and needs; prevention and control of AMR--research, prevention practices, surveillance; strategies and resources to control AMR--public health strategies, resources for research and data-collection; legal, ethical, and regulatory issues related to controlling AMR; conclusions and recommendations); (4) develop a single review document identifying areas of agreement and disagreement; (5) create tables that systematically summarize the information from the major reports on AMR; (6) develop draft document that suggests priorities based on compilation of recommendations; (7) coordinate draft review by selected members of the APUA Scientific Advisory Board; (8) refine document based on committee’s recommendations; (9) submit draft document to USAID and WHO for comments; (10) revise document; and (11) submit the final document to USAID and WHO for input into the process of global strategy formulation.

**Expected Outputs, Results and Progress Indicators:**

**Output:** a review paper that synthesizes the conclusions and recommendations of the existing policy documents on AMR, reflects the insight of APUA’s Scientific Advisory Board as to the global implications and strategy and suggests priority actions.

**Results:** the report will provide an up-to-date overview of findings and recommendations from sentinel documents produced by multidisciplinary expert groups. The document will be of use to the USAID global bureau working group, USAID missions, WHO global strategy partners and policy makers who fund the ID/AMR project. This document will contribute to the development of a framework for the global AMR strategy, and enable decision-makers at all levels to better determine future research and policy directions, and develop an action plan for controlling AMR.

**Progress indicators:** individual reviews completed, outline of paper completed, draft paper and tables completed, meeting of scientific reviewers completed, final paper published and disseminated.

**Countries/Regions:** Not applicable.

**Partners:** None.

**Results to Date:** The review was completed in 2001 and will be published along with the WHO Global AMR Strategy.

1.7: **Reviews of Antecedents of and Interventions to Decrease Inappropriate Antimicrobial Use by Health Providers and Community Members**

**Implementing Organizations:** BU/ARCH and RPM/MSH
**Status:** Completed (Funded: FY1999; Completed: FY2001)

**Rationale:** The 1997 International Conference on Improving Use of Medicines (ICIUM) marked a major milestone in international efforts to promote quality use of medicines by health providers and consumers, and to develop rational pharmaceutical policies. For the first time, there exists a consensus about appropriate methodologies for implementing and assessing interventions in these areas, coherent summaries of previous experience, as well as an agreed agenda of priority policy implementation and intervention research topics.

Research focused on interventions targeting the practices of physicians, paramedics, and other health providers working in primary care, hospital, or retail pharmacy setting are an important contribution, especially if it could be achieved and maintained on a widespread level in the community. However, there are two important issues which make this, on its own, unlikely to succeed. Firstly, self medication is popular in all countries. In many developing countries over 80% of all drugs are purchased by people for themselves or for a family member without prescription (Malek, A, unpublished). Secondly, whether or not consumers consult health workers in formal health care channels, it is ultimately people’s own decision-making and understanding that determines whether a drug will be used or not and whether it will properly used. These decision are in turn shaped by many factors including the social, cultural and economic context in which they live and the commercial pressures to which they are exposed by marketing. When people take medicines, they do so on the basis of rational decisions which at times may contradict what ought to be done from a biomedical perspective. For example the very poor may take medicine because they have come to believe that this offers a way out of misery, hunger and pain. The contradiction between different rationalities and how to bridge them is the challenge for improving drug use in the community (Hardon, A, 1997).

This proposal calls for a comprehensive review on antecedents of and interventions to improve inappropriate antimicrobial use by health providers and community members. It is expected that this review will answer these questions:

- **what do we know about the factors that underlie inappropriate use of antimicrobials?**
- **what do we know about the structure of interventions that have attempted to improve inappropriate use?**
- **have the interventions been well-designed given the causative factors?**

**Objectives:**
1. To identify factors that underlie inappropriate use of antimicrobials amongst health providers and community members.
2. To investigate and document the structure of interventions that have been attempted to improve inappropriate use of antimicrobials by health providers and community members.
3. To investigate whether the interventions have been designed in consideration of causative factors.
4. To recommend strategies to address key priorities in improving the inappropriate use of antimicrobials by health providers and community members.

**Description:** **Source of Materials:** These reviews would access all the material on both health provider and community-oriented interventions collected for the ICIUM conference. The INRUD bibliography would be a primary source for identifying supplementary materials, although the extensive collection on community use of antimicrobials at WHO/EDM and the University of Amsterdam would also be included. Additional search will also be performed within the Med-line, Pop-line database and also other related centers such as the one at the University of Groningen. For these reviews to be reasonably complete, a more active process of information gathering would be needed, since a large amount of useful material of determinants of use has never been published. For example, there is a substantial amount of unpublished materials on community use
of antimalarials. This material gathering could be carried out through existing research networks as was done in collecting the ICIUM review materials.

**Personnel:** The review would be prepared by Dr. Aryanti Radyowijati and Dr. Hilbrand Haak, supervised by the staff from the ARCH project and RPM staff. The supervision covers comments on versions of the manuscript as it develops, and participation in the revision of the draft documents. A meeting will be held at the beginning of the review process to develop a detailed plan for the reviews, and during the revision process.

**Timing:** This review will require six months periods of person-works, divided into two steps. The first step is to gather the existing materials for the review, which is 2 person-months of work. And the second step for reading and writing the review, which is 4 person-months of work.

**Expected Outputs, Results and Progress Indicators:**

- **Output:** a review of Antecedents of and Interventions to Improve Antimicrobial Use by Health Providers and Community Members.
- **Results:** policy makers in developing countries will have access to a framework and results that will help guide policy decisions in designing strategies to encourage appropriate use of antimicrobial drugs.
- **Progress Indicators:** relevant studies identified; relevant studies reviewed; and report drafted.

**Countries/Regions:** The review will cover studies in Africa, Asia, Latin America and Eastern Europe/Eurasia.

**Partners:** WHO/HTP/EDM

**Results to Date:** The review was completed in April 2001 and presented to the USAID AMR working group. The review was well received with some suggestions for additional material to be incorporated. The authors will complete this assignment in 2001.

### 1.8: Research Priorities for the Prevention and Control of Nosocomial Infections in Developing Countries

**Implementing Organization:** JHU/FHACS

**Status:** Completed (Funded: FY1999; Completed: FY2000)

**Description.** The epidemiology, risk factors and etiology of nosocomial infections in developing countries will be reviewed. Epidemiologic information important for the control of nosocomial infections, but for which information is sparse, will be identified and specific research questions proposed. Strategies for the prevention and control of nosocomial infections in developing countries will be reviewed and the data on their effectiveness critically examined. Prevention and control strategies requiring further research will be identified. The emergence and spread of antibiotic-resistant bacteria within health care settings, and strategies to control antibiotic resistance, will also be considered. The review will focus on the epidemiology and control of nosocomial infections in health centers and district hospitals. The use of antibiotics outside health care facilities or in animal husbandry will not be considered in this review.

**Countries/Regions:** Not applicable.

**Partners:** None.
Results to Date: Review is being prepared for publication.

1.9: Review of the Effects of Provider Reimbursement Mechanisms and Managed Care on the Use of Antimicrobial Drugs in Eastern Europe/Eurasia and Developing Countries

Implementing Organization: RPM/MSH

Status: Completed (Funded: FY1999; Completed: FY2001)

Rationale: National health reforms in Eastern Europe/Eurasia and developing countries are introducing changes in health services organization, delivery, and finance. Social health insurance schemes are being implemented, principles of managed care applied, and incentive-based mechanisms to reimburse providers introduced. These changes are expected to influence provider and consumer behaviors in support of cost-effective health systems. However, some changes may introduce new conflicts and unanticipated consequences. Changes in the ways providers are rewarded for providing services would be expected to alter prescribing practices and influence communication with patients about the appropriate use of drugs. Patients’ decisions to purchase and consume a full course of antimicrobial drugs would be expected to be influenced, in part, by the way providers communicate with patients. The influence of health reforms on the use of antimicrobial drugs is extremely important because of the adverse clinical, economical and ecological consequences of inappropriate use and positive effects associated with appropriate use. It is critical to assess the impact of health reforms on the use of antimicrobial drugs so that countries can integrate lessons learned into not only the design of their national reforms but also in monitoring their impact. Provider or “supply side” responses will be the focus of this review. This study will build on a previous review undertaken by RPM that examined, among other things, the impact of patient charges (demand side interventions) on antimicrobial drug use.

Objective(s): To assess both positive and negative lessons learned on the impact of managed care and provider reimbursement mechanisms on the use of antimicrobial drugs in Eastern Europe/Eurasia and developing countries by systematic analysis of findings from published and unpublished studies.

Description: A comprehensive and systematic review of published and unpublished studies on the impact of managed care and provider reimbursement mechanisms on the use of antimicrobial drugs in developing countries will be undertaken. An analytical framework will be developed to provide a structure for evaluating the impact of the above reforms (interventions) on the behavior of providers and consumers in use of antimicrobial drugs. This review will build on the experience of other efforts to identify studies that assess the impact of interventions on drug use in general and antimicrobial use in particular. Previous approaches started from a general drug use perspective. This review proposes to identify relevant studies searching for studies on the impact of managed care and provider reimbursement mechanisms.

On-line search engines, and databases such as the INRUD Bibliography and the Cochrane Library will be used to identify relevant published studies and overviews. In addition, World Bank task managers and USAID contractors that work on health reform in Eastern Europe/Eurasia and developing countries will be contacted to identify unpublished studies. Studies that will be included in the review will have the following characteristics:

- Studies that focus on the use of antimicrobial drugs;
- Studies that examine the impact of one or more of following interventions: managed care, provider
payment mechanisms;
- Studies that include an assessment of the impact of the intervention on the use of antimicrobial drugs;
- Studies of these interventions in developing countries and Eastern Europe/Eurasia.

Because it is anticipated that few rigorous studies will be identified, this review will also search for systematic overviews and relevant primary reports on the impact of managed care and provider reimbursement mechanisms on drug utilization in general and antimicrobials in particular, in North America and Western Europe. This study will then attempt to identify lessons learned from developed country experiences that should be considered in the potential implementation of such approaches in developing countries and Eastern Europe/Eurasia.

Expected Outputs, Results and Progress Indicators:

**Outputs**: include a bibliography of published studies that meet selection criteria and a report on “The Effects of Provider Reimbursement Mechanisms and Managed Care on the Use of Antimicrobial Drugs in Eastern Europe/Eurasia and Developing Countries”.

**Results**: policy makers in developing countries will have access to a framework and results that will help guide policy decisions in designing health reforms that encourage appropriate use of antimicrobial drugs.

**Progress Indicators**: compilation of studies that meet criteria; analytical framework completed; literature review completed; and assessment of lessons learned completed.

**Countries/Regions**: Studies in Africa, Asia, Latin America and Eastern Europe/Eurasia.

**Partners**: WHO/EDM.

**Results to Date**: The research was conducted and a paper written by RPM staff. Final editing of the paper is currently underway and completion of project projected for October 2001. The findings from the review were presented at the Global Health Council annual meeting June 2000.

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**1.10: Technical Paper on Fixed-Dose-Combination (FDC) Drug Products**

**Implementing Organization**: USP

**Status**: Completed (Funded FY1999; Completed: FY2001)

**Rationale**: Although fixed-dose combination (FDC) drug products are generally discouraged in rational drug use strategies, there may be a place in therapy for such combinations when a patient must take multiple medicines and compliance is essential (e.g., treatment of tuberculosis or malaria). Combination drug therapy trials will soon be starting in several African countries to look at the efficacy of artemisinin derivatives in conjunction with other drugs for the treatment of malaria. Pending acceptable outcomes of these trials, the question of need and appropriateness of FDC therapy will have to be addressed. With many issues impacting the decision to accept FDCs (e.g., need for compliance, manufacturing standards, optimal dosing regimens, potential adverse reactions), USP believes it is necessary to identify and analyze the relevant issues and make this information available to procurement offices, manufacturers, essential drugs programs, health ministries, and other concerned parties before decisions on registration and production are made. Only in this way can a responsible plan of action be developed to ensure that safe, needed, high-quality products with proven therapeutic advantages are produced and distributed.

**Objective(s)**: 1) To identify and analyze the issues surrounding use of FDCs. 2) To establish a generic protocol for issues that need to be addressed in the development of FDC products. 3) To examine the
pros and cons of FDC products proposed for malaria therapy and make recommendations for what needs to be considered in developing optimal combinations and ensuring appropriate use.

**Description:** Fixed-dose combination (FDC) drug products are widely produced and marketed throughout the world. Such products represent a relatively simple way a drug manufacturer can extend its product lines (and profits) at a minimal cost. Although most FDCs would be considered as irrational therapy, there is some support for their use in cases where multiple-drug regimens can be reasonably standardized and compliance to therapy is absolutely essential. There is a considerable body of knowledge relating to FDCs. In addition, because of their widespread registration and availability, there is considerable experience with their use in patient care (either by a care-giver or through self-care).

This activity would focus on collecting available FDC information and experiences (by literature and policy review and through interviews with key individuals who are knowledgeable about FDCs), analyzing the issues presented, identifying the pertinent areas of concern, and subjecting the draft report to the scrutiny of experts and other interested parties. As part of the information/experience collection, selected FDCs on the market will be used as case studies/examples; policies of regulatory agencies and manufacturers will be explored; and research relating to the effect of FDCs on patient compliance/adherence will be reviewed. A group of experts will be asked to serve as a reviewing body, with opportunity for public review and comment. The process will be open and transparent. Most of the discussions will make place via mail, telephone, and e-mail, with one face-to-face meeting of the individuals serving on the reviewing body scheduled towards the end of the deliberation period. The final draft document will be published for the review and comment of all interested parties.

**Expected Outputs, Results, and Progress Indicators:**

**Output:** a state of the art examination of the issues surrounding the need for, risks/benefits of, and production and use of FDC drug products (with specific information relating to potential FDCs for use in malaria initiatives).

**Expected results:** 1) an increase in informed decision-making relating to the need for and production and use of FDCs, in general. 2) Appropriate decisions relating to the development of FDCs for use in the prevention and treatment of malaria. 3) An increased understanding of the potential role FDC drug products may or may not have in rational drug therapy.

**Progress indicators:** literature search with evaluation of papers, key person interviews, draft outline of paper, participation of wide body of experts, draft paper, USP panel consensus, public review, final paper.

**Countries/Regions:** Not applicable.

**Partners:** Not applicable.

**Results to Date:** This paper focussed on FDCs using artemisinin and derivatives for malaria and FDCs for tuberculosis. The paper supports the use of artemisinin FDCs provided they are controlled for quality. Artemisinin derivatives are very active; they work quickly and are eliminated quickly, thus it is less likely that resistance to them will develop.

The paper supports the use of FDCs for tuberculosis provided uniformity of individual dosage amounts included in FDCs by different companies and in different countries is improved and quality is monitored, particularly the bioavailability of rifampin in combinations.

The paper has been disseminated to USAID Washington.
2.1 Determining the Relative Importance of Various Factors in the Development of Antimicrobial Resistance

Implementing Organization: JHU/FHACS

Status: On-going (Funded: FY1998; Expected Completion: FY2002)

Rationale: Resistance to antibiotics of several disease-causing microorganisms has emerged as a worldwide public health problem in recent years. Antibiotic resistance has complicated the treatment of malaria, tuberculosis, cholera and sexually transmitted diseases, and is the major concern regarding the efficacy of the case management strategy for controlling childhood pneumonia and bacterial dysentery.

Frequent use of antibiotics has been shown to be the main factor in the development of antimicrobial resistance. This is true on both the individual and population levels, so that individuals with prior treatment with an antibiotic and populations with high rates of antibiotic use have higher levels of drug-resistant organisms. Overuse by populations has a multiplying effect because even those individuals without prior antibiotic use are at increased risk from the resistant organisms in their environment.

Overexposure to antibiotics can occur through their veterinary use in animal feeds and from their inappropriate use by public health programs and facilities, private physicians, pharmacists, other health workers and individuals. What is unknown is the relative influence and interaction of these exposures in determining a population’s carriage rate of resistant organisms, and therefore the most effective approaches to limiting antimicrobial resistance in populations. There is a need to develop and test a method to assess the relative importance and interactions of these factors.

Objective(s): To develop a model in one country that describes the relative importance and interactions of several sources of antibiotic exposure to the level of antimicrobial resistance in the population; to test and refine the model using data from a second country; and to use the refined model to suggest the most effective approaches to limiting antimicrobial resistance.

Description: We propose to develop a model, using data collected in one developing country, that examines the relative importance of a population’s various exposures to antibiotics, and the interrelationship between the exposures, to the population’s carriage rate of drug-resistant bacteria; and to then test the predictive strength of the model in a second country.

In several communities in each country, data relevant to all possible antibiotic exposures of a large magnitude will be collected through site-appropriate methods, including surveys, observation, and examination of records at farms, public health facilities, private physicians’ offices, pharmacies and households. Antibiotic resistance carriage rates will be determined by sampling and testing nasopharyngeal and enteric organisms from children at a variety of sites in each community. Using data from the first country, regression models will be developed to examine the strength of and interrelationship among various types of antibiotic exposures, including for example, possible additive or multiplicative effects among the exposures, in determining a community’s rate of antibiotic resistance. Data from the second
country will be used to test and refine the model.

**Expected Outputs, Results and Progress Indicators:** The expected output of this activity is a statistical model that will attempt to elucidate the relative importance and the interrelationship of various factors in the development of antimicrobial resistance. Development of the model would benefit USAID, other donors and countries in their quest to limit and reverse the trend of increasing antimicrobial resistance. Application of the model by countries should suggest the most effective approaches to this problem in their particular settings and hence relevant policy directions. Progress related to application of the model by a country would be indicated by: (1) the model succeeding in identifying the most effective approach(es) to the problem of antimicrobial resistance in the country, and (2) assuming the implementation of appropriate policies suggested by the country findings, decreasing levels of antimicrobial resistance.

**Countries/Regions:** Peru.

**Partners:** PRISMA. We intend to investigate the possibility of collaborating with WHO/CDS on this study.

**Results to Date:** (Information not provided)

### 2.2 Mathematical Modeling of Antimicrobial Resistance Emergence and Spread

**Implementing Organization:** WHO/CDS

**Status:** On-going (Funded: FY1998; Information not provided on expected completion date)

**Rationale:** Mathematical modeling techniques have been used effectively to map outbreaks and spread of infections and the potential effects of intervention strategies, such as immunization. Similar techniques can also be applied to model the emergence and spread of antimicrobial resistance. In particular, human-to-human spread and animal-to-human transfer of resistant strains and resistance genes can be studied. The impact of resistance containment interventions, such as introduction of antimicrobial usage policies, infection control guidelines and improved hygienic practices in food animal production can be evaluated.

**Objective(s):** Through sharing the expertise available in mathematical modeling at the Wellcome Trust Epidemiology Research Centre, University of Oxford, UK and the access to extensive data sets through WHO and its Collaborating Centres, the objective is to construct models of antimicrobial resistance emergence and spread and to test the effect on the model of the application of specific interventions.

**Description of Activities:** These activities will be undertaken in partnership with the Wellcome Trust Epidemiology Research Centre, University of Oxford, UK.

1. Definition of data sets available to WHO and those required for particular models of human-to-human spread and animal-to-human transfer of resistant strains and resistance genes.
2. Selection of one or two scenarios for which sufficient data exist for construction of models.
3. Establishment of mathematical models for one or two scenarios (depending on data availability and complexity).
4. Examination of effect of resistance containment interventions on the model.
5. Design and execution of a field study to test the interventions which are predicted from the model to be effective. (Further funding will be required for this activity.)
Expected Outcomes, Results and Progress Indicators: The results of activities 1-4 will be mathematical models showing the theoretical effects of specific interventions to contain antimicrobial resistance. The results of activity 5 will show whether interventions effective in the model translate in practice. The process can be iterative and further refinement of the models should be possible on the basis of the results of field studies.

Progress indicators 1998: Agreement established with Wellcome Trust Epidemiology Centre on scenario to be studied; Data needs defined; Appropriate data sets identified; Modeling commenced.

Countries/Regions: To be determined.

Partners: Wellcome Trust Epidemiology Research Centre; University of Oxford, UK; WHO/CDS; WHO Collaborating Centre for Surveillance of Antimicrobial Resistance; Brigham and Women’s Hospital, Boston, USA; Johns Hopkins University, USA; Menzies Research Institute, Australia.

Results to Date: After some delay, discussions are underway with the authors, groups within WHO, and other interested partners. It is anticipated that the activity will be developed during 2001.

### 2.3 Non-medical Uses of Antimicrobials and the Impact on Human Health

Implementing Organization: WHO/CDS

Status: On-going (Funded: FY1998; Information not provided on expected completion date)

Rationale: In addition to the use of antimicrobial in human medicine, significant amounts are used in other sectors, namely food animal production, agriculture and aquaculture, thus adding to the global selective pressure favoring emergence of resistance. However, there are insufficient data available to be able to make a reasonable assessment of the risk to human health of the non-medical uses of antimicrobial. WHO initiated the gathering of information and the definition of priorities at its meeting in 1997 (The Medical Impact of the Use of Antimicrobial in Food Animals. Report WHO/CDS/ZOO/97.4). This Proposal outlines the continuation of this activity and will be supplemented by a review (see the "Expert Technical Reviews" section of activity 1.1: "Establishing a Global Strategy and Action Plan").

Objective(s): Identification of the existing data and the data needed in order to allow risk analysis for the non-medical uses of antimicrobial on human health.

Description:
1. Meetings of a collaborative working group between WHO and key partners to advocate for operational research and data gathering to fill identified gaps, including strengthening of surveillance of antimicrobial resistance in bacteria from food of animal origin;
2. Definition of collaborative activities with industry working group (established with IFPMA and COMISA);
3. Preparation and dissemination of reports.

Expected Outcomes, Results and Progress Indicators: Detailed report of evidence for potential human health impact of non-medical uses of antimicrobial.

Progress indicators in 1998: Establish Working Group with FAO and other partners; Complete review of impact on human health of non-medical uses of antimicrobial (see Component 1); Define agenda for
Working Group.

Countries/Regions: Not applicable.

Partners: WHO/CDS; WHO Food Safety Unit; FAO; European Commission; US Department of Agriculture; US FDA; European Medicines Evaluation Agency; International Federation of Pharmaceutical Manufacturers Associations (IFPMA); Confederation Mondiale de l'Industrie de la Santé animale (COMISA).

Results to Date: A consultation was convened to draft WHO Global Principles for Containment of Antimicrobial Use in Food Animals (January 2000). Subsequently, an electronic discussion group was organized to obtain comment from all stakeholders on draft global principles (March 2000). Consensus was reached at a WHO Consultation (June 2000) that included participation by the Food and Agriculture Organization and the Office International des Epizooties and 14 other international organizations. The WHO Global Principles are available at: http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm. WHO will commission a review of antimicrobial use in aquaculture in 2001.

2.4 Measuring, Understanding and Changing Irrational Drug Use

Implementing Organization: WHO/HTP/EDM

Status: On-going (Funded: FY1998; Information not provided on expected completion date)

Rationale: Irrational use of antibiotics is considered a major contributing factor in the development of antimicrobial resistance. One third of prescriptions in developing countries are for antibiotics. Any intervention to promote rational use of antibiotics should be preceded by analysis of why certain behaviors occur. The set of WHO/INRUD quantitative indicators for rational drug use issued in 1993 is now widely used and has become the global standard to describe prescribing patterns. A similar set of simple standard methods for non-quantitative research has been developed to study why certain drug use patterns exist. Field studies with non-quantitative standards are needed before they can be issued by WHO.

Objective(s): Validated standard methods for non-quantitative research which document why certain drug use patterns exist. This is a fundamental prerequisite to developing interventions to change irrational prescribing behavior. The final standards would be used by rational drug use researchers, national rational drug use and essential drug use programmes and training officers.

Description of Activities: The draft manual of non-quantitative indicators will be field tested in four countries. These tests would be conducted in close collaboration with INRUD/MSH. The final version of the manual would be disseminated to national essential drug programmes, researchers and trainers in rational drug use and relevant non-governmental organizations.

Expected Outcomes, Results, and Progress Indicators: A practical manual on standard methods for non-quantitative research which will allow the definition and understanding of the reasons for irrational prescribing in developing countries (prior to designing intervention strategies).

Progress indicators, Year 1: Protocol for study agreed; locations agreed for field tests in 4 countries; study undertaken; report on results of studies. Year 2: Additional funding needed; final version of manual drafted, agreed and issued; manual disseminated.
Countries/Regions: Potential field test sites include Benin, Indonesia, Kenya, Philippines, South Africa, Uganda, and Zambia.

Partners: WHO; MSH; International Network for Rational Use of Drugs (INRUD); national governments and/or universities in countries of the field test.

Results to Date: The draft manual was compiled by WHO and field tested by MSH in Kenya, Uganda, Ghana and the Philippines. Substantive changes were recommended to produce a simpler, more-concise manual that spends less time on method description and addresses how to use and analyze the information. WHO is now undertaking this process.

2.5 Indicators for Measuring Antimicrobial Use in Hospitals

Implementing Organization: RPM/MSH

Status: On-going (Funded: FY1998; Expected Completion: FY2001)

Rationale: Core indicators and a simple methodology have been developed to study drug use in outpatient settings. These indicators can easily be adapted to study antimicrobial drug use. However, the ICIUM Conference also identified a need to define indicators and design an appropriate methodology to assess drug use in general, and antimicrobial specifically, in hospitals.

Objective(s): Develop and test a rapid assessment methodology and indicators to assess antimicrobial use in hospitals

Description: Tasks include a focused literature review and survey of key researchers and INRUD members. RPM intends to produce a draft instruction manual that would include the rationale, definition, and calculation for proposed indicators, model data collection forms and proposed methods, and techniques to collect data needed to derive the indicators. Key members of the INRUD Network, WHO HTP/EDM, USP advisory panels (Drug Utilization Review and International Health), and leading drug use intervention researchers will be invited to review the proposed methodology and indicators.

RPM will conduct a field test of these indicators, data collection forms and data collection methods and techniques. It is expected that members of the INRUD network will collaborate in the field test. Results of the field test will be reviewed at a post-field test workshop and the indicators and instruction manual revised accordingly.

Once the manual is revised, its availability will be announced in electronic and print fora (E-drug, INRUD News, Essential Drug Monitor). It will be determined later if it may be appropriate to publish the manual in collaboration with WHO. Field test results may be published in the INRUD News, Essential Drugs Monitor and a peer-reviewed journal. The methodology will be incorporated in the INRUD-WHO Promoting Rational Drug Use and the MSH Managing Drug Supply courses.

Expected Outputs, Results and Progress Indicators:

Outputs: list of key references on Hospital Drug Use Studies and Indicators; compilation of key readings on Hospital Drug Use Studies and Indicators; set of core indicators for hospital drug use (including antimicrobial agents); manual on how to investigate drug use in hospitals.

Results: set of hospital drug use indicators and methodology for data collection available and field tested
**Progress indicators:** literature review completed; key readings compiled; core hospital drug use indicators drafted; manual on how to collect hospital drug use indicator data drafted; hospital drug use indicator methodology field tested; manual on hospital drug use indicator revised.

**Countries/Regions:** Field tests in Ghana and Nepal.

**Partners:** INRUD country core group members are expected to collaborate in technical review of indicators and methodology; WHO/HTP/EDM is expected to collaborate in technical review of indicators and assessment methodology; USP staff and advisory panelists will be asked to provide technical review of indicators and assessment methodology; others to be identified through the literature review.

**Results to Date:** The final draft was completed under RPM and field tested in Ghana and Nepal. Needed amendments were highlighted. Under RPM Plus these amendments have been made and the document is under final editing as an on-going working draft.

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### 2.6 Evaluation of the Impact of IMCI Case Management Approach on Antimicrobial Use Practices and Drug Resistance

**Implementing Organization:** CDC/NCID

**Status:** Discontinued (Funded: FY1998)

**Rationale:** In many countries widespread overuse of antibiotics occurs due to treatment of upper respiratory infections and uncomplicated diarrhea. WHO case management schema — either vertical ARI and diarrheal disease control programs or IMCI — recommend antibiotic use only for children with diagnosed pneumonia or dysentery. Adherence to these recommendations may lead to a substantial decrease in overall antibiotic prescribing. Moreover, when a standardized case management approach is used, the proportion of children who are treated with antibiotic courses of appropriate dose and duration is likely to increase. These changes in antibiotic use practices may have a major impact on the spread of antibiotic resistance within a community.

**Objective:** Evaluate the impact of case management implementation on antibiotic prescribing practices, antibiotic use by patients, and carriage of antibiotic resistant pathogens.

**Description:** Before implementation of case management, baseline data will be collected including rates of antibiotic prescribing and use among children; respiratory tract carriage rates for resistant *S. pneumoniae* and *H. influenzae*; and, if possible, carriage rates for resistant fecal flora. Local investigators will be trained in study methods including epidemiological survey techniques and laboratory methods for isolation, identification, and susceptibility testing of respiratory tract and enteric pathogens. Susceptibility test results from these baseline investigations will inform the selection of appropriate antibiotic therapy for case management guidelines. During case management training, the risk of antibiotic resistance and the importance of strict adherence to prescribing guidelines will be emphasized. After one year of case management implementation (and potentially at intervals thereafter), rates of antibiotic prescribing, use, and resistance will be assessed among patients managed by IMCI-trained providers and compared with rates among patients of untrained providers.

**Expected Outputs, Results and Progress Indicators:** Success of this activity will be assessed by: 1) establishing baseline data on antibiotic prescribing, use, and resistance; 2) training local investigators in
epidemiological and laboratory methods that will lead to sustainability of capacity; and 3) evaluating the impact of IMCI on antibiotic prescribing, use, and resistance. Results of this study may provide an additional impetus for adoption of IMCI as a strategy to decrease the spread of resistance.

Countries/Regions: Areas that are in the process of implementing IMCI would be appropriate for this activity. This includes sites in Central Asia (Kazakhstan), Bangladesh (in conjunction with ICDDR,B), and several sites in Africa or Latin America. We will work with international partners to identify the best site for this activity.

Partners: WHO; BU/ARCH (depending on study site).

| 2.7 Improving the Treatment of Bacterial Meningitis in Developing Countries |

Implementing Organization: WHO/CAH

Status: On-going (Funded: FY1998; Expected Completion: FY2003)

Rationale: Antimicrobial resistance of *S. pneumoniae* to penicillin is increasingly being reported from developed countries but there is limited data from the developing countries. Third generation cephalosporins have become the first line antimicrobial for the treatment of bacterial meningitis in developed countries. Whereas, in the developing countries penicillin + chloramphenicol are still used for the treatment of bacterial meningitis because the third generation cephalosporins are very expensive. Children suffering from penicillin resistant pneumococcal bacterial meningitis do not respond well even to chloramphenicol. These children should be treated with injectable third generation cephalosporins to reduce morbidity and mortality. But, unfortunately information about the prevalence of penicillin resistant *S. pneumoniae* and *H. influenzae* from developing countries is limited. This information will help the countries to decide which antimicrobial to use for the treatment of bacterial meningitis.

Objective(s): To use antimicrobial resistance data to guide treatment of bacterial meningitis.

Description:
1. Designing and implementing a multi-country study to strengthen facilities for CSF; culture and basic susceptibility testing to examine the prevalence of *S. pneumoniae, H. influenzae*, and *N. meningitidis*;
2. Developing facilities for CSF cultures and basic susceptibility testing where they are not available;
3. Developing drug-switch guidelines based on antimicrobial resistance data.

Outcomes, Results and Progress Indicators:
1. To document antimicrobial resistance rates for common bacteria causing meningitis;
2. To help build capacity in epidemiological research and microbiology;
3. To assist developing countries in decision making to change, when appropriate, the first line antimicrobial use guidelines for the treatment of bacterial meningitis.


Country(s)/Region: The study will be conducted in Malawi, Pakistan, South Africa, and Vietnam.

Partners: The WHO Division of Emerging and other Communicable Diseases (EMC) has developed CSF culture facilities for *N. meningitidis* in the meningitis belt countries. There is a need to include *S.*
pneumoniae and H. influenzae cultures in CSF testing, and if possible to extend it to other developing countries. INCLEN has recently conducted invasive bacterial infections surveillance (IBIS) study in several centres and their experience will be drawn upon for this activity. JHU/FHACS and INCLEN along with WHO/CAH are currently testing the clinical efficacy of a short-course treatment for bacterial meningitis (see activity 5.8).

Results to Date: Data collection was initiated in April 2001 and is expected to last 2 years.

### 2.8 Relationship between in vitro Antimicrobial Resistance of S. pneumoniae and H. influenzae Blood Isolates and in vivo Response to Penicillin in Severe Pneumonia

**Implementing Organization:** WHO/CAH

**Status:** On-going (Funded: FY1998; Expected Completion: FY2001)

**Rationale:** WHO ARI case management guidelines recommend penicillin for children suffering from severe pneumonia. Results from the surveillance network for invasive S. pneumoniae in children less than five years old implemented by the SIREVA (Region System of Vaccine – initiative sponsored by PAHO and by the Canadian International Development Agency) in Argentina, Brazil, Chile, Colombia, Mexico and Uruguay have shown a 10-26% reduced susceptibility to penicillin of the isolated strains. There is, however, some controversy whether the clinical outcome of pneumonia reflects the current levels of in vitro penicillin resistance. Results of studies attempting to establish the correlation between diminished susceptibility to penicillin of S. pneumoniae and severity of pneumonia have been inconclusive due to selection bias in recruitment of participants and incomplete recording of clinical outcomes. With the emergence and spread of the drug-resistant strains of S. pneumoniae clinicians are worried about the clinical efficacy of penicillin in pneumonia patients.

Although there are suggestions that the emergence of drug-resistant pneumococci may result in treatment failures, no prospective study has been conducted to evaluate the impact of drug-resistant S. pneumoniae on the clinical outcome of pneumococcal pneumonia in Latin America. Most of the reports on drug resistance available in the Region are derived either from laboratory surveillance systems or from retrospective analysis of non-representative sampling from hospitalized patients.

**Objective(s):**
1. To investigate the relationship between in vitro penicillin resistance of S. pneumoniae and the clinical outcome of current recommended therapy for severe pneumonia as defined by the standard ARI case management.
2. To generate data to guide ARI therapy policy for the countries of the PAHO region.

**Description:**
1. A proposal development workshop to be held to develop a protocol to study this question.
2. In a multi-centre (18 hospitals in five countries) observational study of hospitalized children with severe pneumonia on injectable penicillin treatment will be observed.
3. Blood cultures will be obtained in all patients to identify and document the resistance patterns of S. pneumoniae.

**Expected Outcomes, Results and Progress Indicators**
1. To better understand the relationship between in vitro resistance to penicillin and antimicrobial clinical
efficacy in the management of severe pneumonia.
2. To support or improve current IMCI guidelines for treatment of severe pneumonia.
3. This activity will build capacity in epidemiological and microbiologic research.

**Progress Indicators:** A proposal finalization workshop was held in Santo Domingo, Dominican Republic and participants from five Latin American countries participated; Initiation of data collection.

**Country(s)/Regions:**
*Argentina:* Hospital Pedro de Elizalde Buenos Aires, Hospital Durand Buenos Aires, Hospital Sor Ludovica La Plata, Hospital Notti Mendoza; *Brazil:* Hospital das Clínicas/UFMG, Belo Horizonte, Instituto Materno Infantil, Recife, Inst Ped. Pueri. M. Gesteira, Rio de Janeiro, Hospital Universitário, Salvador, Hospital Aliança, Salvador, Hospital Santa Casa, São Paulo, Hospital Darci Vargas, São Paulo; *Columbia:* Hospital La Misericordia Bogotá, Clínica Colsubsidio Bogotá, Hospital Universitário Cali, Hospital San Vicente de Paúl Medellin; *Peru:* Instituto de Salud del Niño; *Dominican Republic:* Hospital Robert R. Cabral Santo Domingo, Hospital de Los Mina Santo Domingo.

**Partners:** Pan American Health Organization (PAHO) and WHO/CAH will jointly fund and co-ordinate this research activity. PAHO will have the primary responsibility of co-ordination. However, monitoring activities will be conducted by WHO. Applied Research for Child Health (ARCH), Harvard Institute of International Development (HIID), Harvard University, Cambridge will also co-fund (for a small amount) this large multi-centre study. Requested budget will be WHO’s share towards this activity. Finally, the technical expertise for quality control will be provided by the Canadian International Agency (CIDA). The requested funds would support the clinical, microbiology work, monitoring and data analysis.

**Results to Date:** Data collection in this large, multi-centre study has been completed and a data analysis workshop is scheduled to take place in Sao Paolo from 30-31 August 2001. Results of this important study will be presented at the IUATLD World Conference on Lung Health to be held in Paris (France) from 1-4 November 2001.

### 2.9 Investigation of the Impact of Antimicrobial Agent, Dose, and Treatment Duration on Carriage of Resistant Respiratory Tract Pathogens

**Implementing Organization:** CDC/NCID

**Status:** On-going (Funded: FY1998; Expected Completion: FY2002)

**Rationale:** Antibiotic use has been shown to be a significant risk factor for carriage of and infection with resistant pathogens. However, the importance of antibiotic dose, treatment duration, and the impact of non-compliance with therapy have not been evaluated for common outpatient pathogens. Assessing the importance of these factors is crucial in developing interventions to prevent the spread of resistance.

**Objective(s):** Assess the impact of antibiotic dose, agent and noncompliance with therapy on nasopharyngeal (NP) carriage of nonsusceptible respiratory pathogens.

**Description:** This evaluation was conducted through a prospective randomized trial in an outpatient clinic in the Dominican Republic. Children aged 6 - 59 months and requiring antibiotics for respiratory illness were eligible for inclusion in the study; those enrolled were randomized to receive routine or high-dose therapy with cotrimoxazole or amoxicillin. Impact of the different treatment courses on NP carriage of nonsusceptible pathogens was assessed by culture before and after therapy. Compliance was evaluated
by history and pill count and those data were incorporated along with drug and dose in a model with resistant carriage as an outcome.

**Countries/Regions:** Dominican Republic

**Partners:** Fundacion Dominicana de Infectologia

**Results to Date:**
1) The risk of penicillin nonsusceptible pneumococcal carriage and trimethoprim-sulfamethoxazole nonsusceptible pneumococcal carriage were each significantly lower in the short-course, high-dose group compared to the standard course group at 28-days post-enrollment.
2) The protective effect of short-course, high-dose therapy was stronger in households with at least three children.
3) Adherence to treatment was higher in the short-course, high-dose group.
5) Provision of evidence base in support of benefits on controlling antimicrobial resistance via shorter treatment regimens.

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<th>2.10 Impact of Fansidar Use on Cotrimoxazole Resistance</th>
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**Implementing Organization:** CDC/NCID

**Status:** Discontinued because suitable site could not be identified (Funded: FY1998)

**Rationale:** With the spread of chloroquine resistant falciparum malaria, fansidar (pyrimethamine sulfadiazine) has become first line therapy for malaria in many parts of the world. Because this agent and cotrimoxazole both affect folic acid biosynthesis, use of one agent may increase resistance to the other. In a study conducted in Malawi, use of fansidar was shown to significantly increase the proportion of children who carried cotrimoxazole resistant pneumococci at 28 days after therapy. These data suggest that widespread use of fansidar may increase transmission of cotrimoxazole resistant respiratory tract pathogens and increase the overall rate of resistance in the community. If this occurred, it could have important implications on the use of cotrimoxazole to treat bacterial infections or may indicate a need to modify malaria case management recommendations to decrease fansidar use and reduce selective pressure for resistance.

**Objective:** Assess the impact of fansidar use on NP carriage of cotrimoxazole resistant respiratory tract pathogens and on rates of cotrimoxazole resistance in the community.

**Description:** Two approaches could be taken in this investigation; which is optimal would depend on the specific characteristics of the study area. The first approach is to identify two malaria endemic areas: one where chloroquine remains the recommended therapy for malaria and another where fansidar is being introduced as therapy. In the fansidar use area, NP carriage of cotrimoxazole resistant respiratory tract pathogens will be assessed before and after therapy for children who receive fansidar versus those who receive no antimicrobial. In addition, longitudinal NP swab surveillance, according to guidelines developed in the above surveillance proposal, will be conducted in the fansidar and the control areas to
determine whether trends in cotrimoxazole resistance differ between the two areas, controlling for
cotrimoxazole use in each area. A second approach would be to perform cross sectional surveys in areas
with different rates of malaria (e.g., holoendemic, seasonal, and no malaria) and compare rates of
cotrimoxazole resistance controlling for differences in cotrimoxazole use.

**Expected Outputs, Results and Progress Indicators:** Results of this study will confirm an impact of
fansidar on cotrimoxazole resistance on an individual level and determine whether there also is an effect at
the community level. Results of this study will be presented at international meetings and a manuscript
submitted to a peer reviewed journal. In addition, results may be used by WHO to revise
recommendations for case management and for surveillance of resistance.

**Countries/Regions:** The most likely site for this study is Sub-Saharan Africa where fansidar is being
introduced in many areas due to the prevalence of chloroquine resistance. CDC has previous experience
and study sites in Malawi and in Kenya that may be appropriate for this study.

**Partners:** We would seek collaboration in the laboratory aspects of this project from the South African
Institute for Medical Research which provided collaboration for the previous study in Malawi.

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### 2.11 Advocacy and Information to Combat Antimicrobial Resistance

**Implementing Organization:** WHO/HTP/EDM

**Status:** Completed (Funded: FY1998; Completed: FY2000)

**Rationale:** Antimicrobial resistance is a growing problem worldwide, with major implications for the cost
and effectiveness of pharmacotherapy. The Essential Drugs Monitor was established in 1985 and is
published by the WHO/HTP/EDM on a twice yearly basis in English, French, Spanish and Russian. The
latest print run totalled 21,000 English, 6,000 French, 4,300 Spanish and 3,000 Russian copies. A
readership questionnaire survey, has shown that each copy is read by 8 people. The total readership
therefore is estimated as being some quarter of a million made up of policy makers, health practitioners,
academics, development workers in over 160 countries. Distribution has been mainly to individuals who
have personally subscribed through interest and the current numbers have accumulated on that basis; a
certain proportion go to libraries. It is an influential advocacy and information medium which reaches an
unusually large spectrum (both geographically and professionally) of people involved in the pharmaceutical
sector. Contributors are drawn from a wide range of organizations and individuals. The latest edition (No
24) whose theme is “Networking for Action” has articles from Acción Internacional por la Salud (AIS
Bolivia), African Drug Regulatory Authorities (AFRDRAN), Appropriate Health Resources and
Technology Action Group (AHRTAG), Action for Rational Drugs in Asia (ARAD), Alliance for the
Prudent Use of Antibiotics (APUA), BUKO Pharma-Kampagne (Germany), the Cochrane Collaboration,
E-Drug, Health Action International (HAI), International Clinical Epidemiology Network (INCLEN),
International Network for the Development of Pharmacotherapy Teaching (INDEPTH), International
Network for Rational Use of Drugs (INRUD), International Society of Drug Bulletins (ISDB), The
Network, Association for Rational Use of Medication in Pakistan, Medical Lobby for Appropriate
Marketing (MaLAM), La Revue Prescrire, Scottish Intercollegiate Guidelines Network (SIGN), as well as
from WHO divisions and others. The volume contains 21 book reviews.

A theme issue of the Essential Drug Monitor would have a pre-selected important and influential target
audience and result in increased global awareness of the problem of antimicrobial resistance.
**Objective(s):** The Essential Drugs Monitor is orientated towards developing countries. The objectives are (1) to increase awareness through focus on key topics in National Drug Policy; (2) to report on both descriptive and intervention research and country activities; (3) to present news items in the field of essential drugs; and (4) to provide a bibliography on aspects of pharmacotherapeutics (note: several pages are usually devoted to book reviews). A theme issue devoted to antimicrobial, produced in English, French, Spanish and Russian, will increase awareness of selected aspects of antimicrobial resistance and pharmaco-therapeutics, drawing on the opinions and experience of a wide range of organizations and individuals. It will also present some success stories and serve as a guide for further reading on the subject.

**Description:** WHO/HTP/EDM will develop and disseminate a theme issue of The Essential Drugs Monitor devoted to antimicrobial. WHO/HTP/EDM will select, commission, review, adapt, reject or accept material in the normal way, with full editorial control. The outcome of the November 1998 WHO meeting on the Global Strategy for the Containment of Antimicrobial Resistance will be covered. Clear terms of reference including time frames would be agreed with contributors. The issue will be translated and published in the usual four languages. Expanded distribution would be pursued through the WHO/HTP/EDM and WHO/CDS networks in addition to the WHO Regional Offices. The print run would be increased according to need.

**Expected Outcomes, Results, and Progress Indicators:** A theme issue of the Essential Drugs Monitor. Distribution of information to lead to improved knowledge of the causes and extent of the problem of antimicrobial resistance, how it is being tackled, and overviews of current research. A theme issue could be available in the first half of 1999.

**Progress indicators:** Designation of commissioning assistant editor; decisions on time frame; decisions on contents selection of contributors; commissioning of contributors with well defined terms of reference; review and editing of drafts; compilation; proof reading; printing; distribution.

**Countries/Regions:** 160 countries

**Partners:** WHO/HTP/EDM (Essential Drugs Monitor); other organizations would be selected from a wide range of organizations and individuals and the choice would be an editorial decision.

**Results to Date:** Special edition of Essential Drug Monitor that highlights the threat of AMR was published in 2000 (issue No. 28 & 29) and is available at http://www.who.int/medicines/library/monitor/EDM2829en.pdf

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**2.12 Training on the Rational Use of Drugs for Pharmacy Undergraduates**

**Implementing Organization:** WHO/HTP/EDM

**Status:** On-going (Funded: FY1999; Expected Completion: FY2003)

**Rationale:** Much work has been done to improve undergraduate medical curricula. There is a great need to do the same for pharmacy undergraduate curricula in developing countries. A core curriculum for pharmacy in developing countries is needed, which includes drug management issues and the role of the pharmacist to prevent antimicrobial resistance, including promoting rational use of antimicrobials, and infection control.
Objective(s): To prepare training materials for undergraduate pharmacy students, with the intention to transfer to them the knowledge, skills and attitudes necessary to prevent antimicrobial resistance.

Description: Regional workshops with heads of pharmacy schools in Asia, Latin America and Francophone Africa; development of a document with core curriculum and practical recommendations how to review/adapt any existing curriculum; field testing of the document; production of a WHO core curriculum with relevant training materials. This is a project which will require 2-3 years to complete.

Expected Output, Results and Progress Indicators:
Outputs include a WHO document with a core pharmacy curriculum, and key training materials for undergraduate pharmacy training for developing countries in English, French, Spanish and Russian.
Indicators: 1999, collecting existing training materials; developing core curriculum and training materials; 2002, field testing of materials in at least three pharmacy schools in developing countries; 2003, finalizing, editing, translating, and printing of materials in English, French, Spanish and Russian.

Countries/Regions: Global.

Partners: WHO Collaborating Centre on Research and Training in Pharmacy Practice, Aberdeen, Scotland; International Pharmacy Federation (FIP); pharmaceutical professional associations in developed and developing countries.

Results to Date: (Information not provided)

### 2.13 AMR 'Toolkit' for Information and Education

Implementing Organization: WHO/CDS

Status: On-going (Funded: FY1999; Information not provided on expected completion date)

Rationale: Effective containment of antimicrobial resistance will require the coordination and collaboration of many different stakeholders who have different levels of knowledge and understanding of antimicrobial resistance. Simple and more in-depth information, making reference to different stakeholder groups and packaged in a visually-attractive, user-friendly format can be a valuable tool for individual and group learning about resistance and ways in which it can be contained. Such a tool can also be used as a basis for advocacy.

Objective(s): To develop a multi-media tool to provide a basis for dissemination of information and advocacy about antimicrobial resistance.

Description: Communication with international partners to identify existing materials; preparation of appropriate new materials; collaboration with external technical expert to develop video and CD-ROM and to package toolkit.

Expected Output, Results and Progress Indicators:
Outcomes include a tool for information, education and advocacy to: (a) rapidly inform non-specialists of key information; and (b) cover each topic more comprehensively for more specialist educational uses.
Indicators include: feedback from interested parties; new needs identified and materials prepared; and
toolkit prepared and assembled.

**Countries/Regions:** Not applicable.

**Partners:** None.

**Results to Date:** A short video has been prepared on the problems of drug resistance. In addition, electronic slides are also being prepared based on the WHO Global Strategy and the available information on AMR prevalence. These materials—along with the Global Strategy, the technical reviews, and other supporting documents—will ultimately be disseminated on a CD-ROM.

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**2.14 Investigation of the Impact of Repeated Mass Azithromycin Prophylaxis on Antimicrobial Resistance in Countries Initiating Trachoma Control**

**Implementing Organization:** CDC/NCID

**Status:** On-going (Funded: FY1999; Expected Completion: FY2002)

**Rationale:** Mass chemoprophylaxis with azithromycin is the cornerstone of a global initiative to eliminate trachoma, a leading form of preventable blindness. Recent evidence suggests that blindness caused by the bacteria *Chlamydia trachomatis* can be prevented by a simple regimen of azithromycin along with improved hygiene. A number of African countries with high trachoma burden are planning to implement trachoma control programs in collaboration with donor agencies (e.g. the International Trachoma Initiative, the Carter Center, the Proctor Foundation of UCSF, Helen Keller International) and industry partners (Pfizer, Inc.). Control programs consist of repeated mass chemoprophylaxis of entire villages [or sub-populations of villages, as with the Proctor Foundation’s approach of administering prophylaxis to all children under ten, and also treating the families of infected children], along with educational campaigns about hygiene, surgery and environmental changes.

In communities with limited health care access, repeated mass exposure to macrolide antibiotics may reduce the incidence of bacterial diseases in addition to trachoma, such as group A streptococcal pharyngitis, skin infections and acute rheumatic fever. However, antibiotic prophylaxis may also have the adverse effect of increasing antimicrobial resistance in both *C. trachomatis* and other bacterial pathogens. Measuring antibiotic resistance in *C. trachomatis* is technically challenging; however, there is suggestive evidence that some strains have reduced sensitivity to macrolide antibiotics. For the case of other bacterial pathogens, a study in an Aboriginal Australian population found that azithromycin treatment to control trachoma resulted in an increased prevalence of macrolide-resistant *Streptococcus pneumoniae* that persisted for months following treatment. *S. pneumoniae* is one of the leading bacterial causes of acute respiratory infections in children in the developing world. Although macrolide antibiotics are not a standard treatment for respiratory illness in developing countries, resistance to macrolide antibiotics in *S. pneumoniae* is often associated with resistance to other antimicrobial classes commonly used in these settings, such as sulfa and penicillin. This raises the concern that mass treatment programs may reduce the burden of trachoma but increase the burden of antimicrobial resistance in common respiratory tract pathogens.

**Objective(s):**

1) Determine the impact of mass azithromycin prophylaxis on the prevalence of antimicrobial resistant pneumococcal carriage and invasive disease
2) Institute surveillance for potential benefits of community prophylaxis by monitoring the incidence of skin infections and acute respiratory infections.

Description: Three geographically separate regions were selected for inclusion in the study on the basis of their exposure to azithromycin prophylaxis: one had received no past treatment at baseline, one had received treatment six months prior, and one had received two treatments, one each six and eighteen months prior to baseline; only the region with no prior exposure received azithromycin in the course of this study. Each child 6 months – 10 years of age had the nasopharynx swabbed at baseline (day 0) before they received azithromycin to determine the baseline carriage of antimicrobial resistant *S. pneumoniae*, the same protocol was followed in regions not receiving the azithromycin. A follow-up swab survey on study participants was conducted ten days later and then again at a six months following baseline. Additionally, interviews were conducted to assess the rates of acute respiratory infections (ARI) and diarrhea, and photographs taken for a masked evaluation of the prevalence of impetigo. Oropharyngeal (OP) swabs were also collected to measure carriage of group A streptococci (GAS).

A possible add-on study in the follow-up period would involve examining the susceptibility patterns of *C. trachomatis* by collecting eye swabs. It is not certain we will be able to include this component of the study due to logistical concerns, such as necessity for dry ice / liquid nitrogen, as well as the challenge of performing susceptibility tests in *C. trachomatis*. To date (2001), we have not been able to perform this component of the investigation.

Expected Outputs, Results and Progress Indicators: Results of this study will help clarify whether mass antibiotic treatment leads to increased antimicrobial resistance in the common bacterial respiratory pathogen *S. pneumoniae*. In addition to this central question, the study will also determine whether mass antibiotic therapy acts to reduce the incidence of health problems unrelated to trachoma, such as impetigo, diarrhea and ARI. This will help countries with endemic trachoma assess the costs and benefits of initiating trachoma control programs, as well as impact future decisions regarding the overall risks and benefits of mass treatment with a broad-spectrum antibiotic. We hope to contribute to a general framework for evaluating the impact of mass treatment programs that can be used when future antibiotic prophylaxis interventions are proposed.

Countries/Regions: Nepal

Partners: Geta Eye Hospital, Nepal; Proctor Foundation (University of California, San Francisco); Nepalese Society for Comprehensive Eye Care (NNJS).

Results to Date:
1) No azithromycin-resistant pneumococci were isolated from any of the 345 children in the currently-treated (no prior exposure) or single-previous-exposure groups at any time point, while azithromycin-resistance was found in 4.3% of those with 2 previous exposures (p<0.001, vs. the other 2 groups).
2) Azithromycin treatment was significantly associated with a decrease in the prevalence of impetigo and diarrhea 10 days after treatment, though this effect was not sustained at 180 days.
3) The absence of macrolide-resistant pneumococci after one mass treatment with azithromycin in Nepal is encouraging. We found short-term benefits in addition to the known effectiveness of trachoma control.
4) The findings of azithromycin-resistance after 2 mass treatments suggest the need for resistance monitoring when multiple rounds of antimicrobial are given.
5) A manuscript summarizing findings has been submitted to *The Lancet* (draft enclosed).
6) Findings were presented at a WHO-sponsored international workshop for trachoma program implementers and the International Trachoma Initiative. [Fry AM, Jha HC, Chaudary JPS, Elliott J,
AMR Component 3: Developing Methods to Detect Resistance

3.1 Comprehensive Laboratory Manual for Isolation, Identification, and Susceptibility Testing of Common Outpatient Pathogens

Implementing Organization: CDC/NCID

Status: On-going (Funded: FY1998; Expected Completion: FY2002)

Rationale: Within developing countries, surveillance for antimicrobial resistance will require that hospital or reference laboratories can appropriately isolate, identify and test the susceptibility of common community acquired pathogens. There is currently no single, technically appropriate source that includes this information.

Objective(s):
1) Integrate, update and supplement existing pathogen and syndrome-specific manuals to include information on isolation, identification and susceptibility testing for *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, *Salmonella typhi*, *Shigella dysenteriae* and *Vibrio cholerae*.
2) Field test, assess the appropriateness of and modify the newly developed laboratory manual.

Description: Laboratory manuals dealing with isolation, identification and/or susceptibility testing of some of the pathogens listed above have been developed by CDC in conjunction with the World Health Organization (WHO), but the manuals have published separately and are not all currently available or up to date. In addition, susceptibility testing methods are not included in all the manuals and the methods included until now have not addressed the appropriate use of antimicrobial gradient strips for rapid and accurate MIC testing. Under this project, CDC microbiologists have worked to develop new chapters and made necessary revisions and additions to pre-existing manuals, and this has all been integrated into a single manual with a common format for each of the pathogens. After assessing the resources that a laboratory implementing the standardized procedures enumerated in the manual would require, it was determined that the appropriate target audience was reference laboratories.

Expected Outputs, Results and Progress Indicators: An integrated laboratory manual appropriate for developing country settings.

Countries/Regions: Global
Partners: WHO, PAHO.

Results to Date:
1) The newly developed manual was field tested in one developing country setting with the laboratory capacity for but without a current comprehensive system of isolation, identification and susceptibility testing of common pathogens of public health concern.
2) Following a ‘wet workshop’ in Zimbabwe, modifications were made to the format and content of the draft document. Since that time, microbiologists working in Ghana, Bangladesh and South Africa have reviewed the document to gauge the readability and practicality of the format.
3) The draft document has undergone final review by technical experts in several countries as well as by WHO.
4) The current document will be included on CD-ROM with other World Health Organization antimicrobial resistance surveillance tools in early FY2002; WHO will be responsible for its distribution.
5) The final version of the first edition of the “Manual” will be available for translation, production and distribution in FY2002.
6) The expected output is an integrated laboratory manual appropriate for use in regions with limited resources, available in English, French, and Spanish.
7) The “Manual” is to be incorporated as a key training tool for developing country laboratory capacity-building in the new WHO Laboratory Training Facility in Lyon, France.

3.2 Standardized Sampling Methods for Assessment of H. influenzae and S. pneumoniae Antimicrobial Resistance

Implementing Organization: JHU/FHACS

Status: On-going (Funded: FY1998; Expected Completion: FY2002)

Rationale: Antimicrobial resistance in disease causing bacteria has increased throughout the world in recent years. Although standard laboratory methods for performing antimicrobial susceptibility on bacterial isolates have been developed, no standard sampling methods have been developed by national or international agencies. Sampling methods for determining the incidence and prevalence of antimicrobial resistance have varied considerably in studies published to date, making comparisons between populations and geographic areas difficult. Antimicrobial susceptibility testing is technically difficult, expensive, and not generally available in most developing country settings. It is not necessary or practical to set up expensive laboratory facilities and test every bacterial isolate in order to estimate the incidence of resistant bacteria in every population. A simplified sampling method would allow valuable data to be collected with the least expenditure of resources.

A similar situation existed with regard to assessment of immunization coverage rates before the standardized EPI cluster sampling method was developed and implemented. Public health officials had great difficulty in assessing and comparing the effectiveness of programs in different populations. EPI cluster sampling has proven to be an important tool providing standardized assessment for evaluation of immunization coverage in developing countries throughout the world. A similar standardized methodology would be invaluable for comparison of antimicrobial resistance patterns and trends in different population as the epidemic of antimicrobial resistance increases and as interventions are developed to try to control this problem.
Objective(s): To develop a standardized sampling method for assessing antimicrobial resistance in defined populations.

Description: We will evaluate several industrial sampling methods as candidates for a standardized sampling method to determine the prevalence of antimicrobial resistant *Haemophilus influenzae* and *Streptococcus pneumoniae* in different populations including asymptomatic children in the general community, outpatients and hospitalized patients. We will evaluate nasopharyngeal cultures in all populations and evaluate isolates from normally sterile sites (blood, cerebrospinal fluid, pleural and joint fluid from sick outpatients and hospitalized patients.

Data from laboratory records from studies that have already been completed will be reviewed to develop models that can be used to compare different sampling industrial sampling methods.

The simplest approach would be a plan with a fixed \( n \) determined on the basis of the magnitude of change that is to be detected and the risk of failing to detect the change. If the sample is to be taken from several populations (hospitals), a somewhat more complex design would be needed as an adaptation of the EPI approach to account for the “design” effect.

Depending upon the specific situation, four industrial sampling designs might be considered. The first is a double sampling method that starts with a small \( n \) to determine whether conditions are clearly so “good” or “bad” that a decision can be made on the basis of limited evidence. If conditions are in the “gray” area, a second sample is taken, and the decision is based upon the aggregate information.

Sequential sampling represents a further refinement of this technique. In that case certain formulas are applied to establish bounds of experience. Every child would be tested and results plotted in chronological order, until the chart takes you above or below the two boundary lines. At that point it is possible to stop sampling and make a definitive judgment. Obviously, this needs to be explained by means of a diagram. The point, however, is that you continue sampling only until the precise moment when you have enough information to draw appropriate conclusions.

Another method calls for the sampling of every \( k \)th product (child) until trouble is found. Thereafter, every child would be tested until the trouble is corrected. I am not sure that your situation is such that “trouble” arises and is corrected, so that you can return to “normal” surveillance, but some modification of this approach might be relevant.

Finally, there is the normal-tightened-reduced sampling procedure. This begins with a designated “normal” sample size and criteria for decision making. If conditions are found to be “suspect” according to predetermined rules, a more stringent sample design is introduced. In contrast, if a predetermined period of time without difficulty elapses, a reduced, less costly sampling procedure is triggered.

In the second year of the project, sampling methodologies will be field tested in several developing country settings. Optimal culture methods will be used including selective media if appropriate in the surveys.

Expected Outputs, Results, and Progress Indicators: This project will develop a standardized sampling methodology that can be utilized for assessment of antimicrobial resistance in different populations. We will develop a first draft of a manual that can be field tested in other populations. As with other field methods, we anticipate the need for careful validation in multiple settings before the methodology is finalized.
Countries/Regions: Data from sentinel surveillance performed in Guatemala and on site studies will be conducted in year 2.

Partners: We will set up collaborate with CDC investigators, the World Health Organization and other organizations addressing this problem in countries throughout the world. CDC has developed standardized methodologies for laboratory testing that will be used in all studies. We will seek their assistance in applying the sampling methods to data sets that they have developed and coordinate our activities with the global efforts.

The study will be conducted at the three major referral hospitals in Guatemala City, Guatemala: Hospital General San Juan de Dios (HGSJD), Hospital Roosevelt (HR) and the General Hospital of the Institute of Guatemalan Social Security (IGSS). These three hospitals provide care to over 90% of all children with infectious disease problems in the city.

Results to Date: The study is underway and data collection has been completed in Las Pampas and is nearing completion in Iquitos.

3.3 Evaluation of Nasopharyngeal Swab Surveillance for Antimicrobial Resistance Among Respiratory Tract Pathogens

Implementing Organization: CDC/NCID

Status: Completed (Funded: FY1998; Completed: FY2000)

Rationale: CDC and WHO have developed a manual for surveillance of respiratory tract pathogens that recommends testing susceptibilities of \textit{S. pneumoniae} isolates obtained from nasopharyngeal (NP) swabs of children with pneumonia. Since these recommendations were developed, NP surveillance studies have been conducted in at least eight countries in Africa and Asia. Although each study used NP isolates for surveillance, they differed substantially in who was enrolled (some studies included children with upper respiratory infections or no illness), and in the duration of surveillance (ranging from two weeks to a several month “pneumonia season”). The impact of variations in surveillance methods on the results obtained by NP surveillance is unclear. Moreover, reaffirming the usefulness of this approach relative to other surveillance methods (e.g. using isolates from normally sterile sites like blood or CSF) would help countries and international organizations develop appropriate surveillance systems.

Objective(s):
1) Develop agreement among investigators and other experts regarding the optimal approaches to surveillance for resistance among respiratory tract pathogens using NP isolates and the usefulness of NP swab surveillance relative to other methodologies.
2) Disseminate findings of review with international partners.

Description: Meetings with investigators from sites where surveillance has been conducted using NP isolates and with other experts were held in order to summarize results from investigations with data both published and unpublished. Furthermore, the meetings allowed for assessment of the impact of different approaches to study enrollment and varying durations of surveillance on the results of the studies. Finally, the team of investigators evaluated the impact of variations in surveillance methods on the results obtained by NP surveillance in order to synthesize optimal surveillance methodology.
Expected Output, Results, and Progress Indicators: Results of the surveillance data analysis and the deliberations and consensus of the group will be presented in a report. In addition, the recommendations for epidemiological methods of surveillance included in the CDC/WHO manual will be revised to reflect the consensus optimal methodology.

Countries/Regions: Global.

Partners: WHO; Investigators who have conducted NP swab surveillance for resistant respiratory tract pathogens; experts who would be influential in gaining global acceptance of such a system.

Results to Date:
1) Findings were presented at an international meeting and used to inform and guide NP-swab specimen sampling approaches for public health investigators around the globe.
2) Results of the surveillance data analysis and the deliberations and recommendations of the group have been compiled as a manuscript and submitted for publication.

3.4 In Vivo Detection of N. gonorrhoeae Resistance

Implementing Organization: WHO/CDS

Status: Delayed (Funded: FY1998)

Rationale: At present, the detection of antimicrobial resistance requires the collection of specimens from patients, isolation of the pathogen and determination of its antimicrobial susceptibility in the laboratory (in vitro). Thus detection of resistance is severely limited by availability of necessary resources and technical skills. In addition, the relationship between resistance detected in vitro and clinical outcome has been questioned for some infections, notably those of the respiratory tract. Therefore alternative cost-effective methods to detect resistance in the clinic setting are needed. One approach to this, which has been applied in the field to detect resistance to antimalarials, is through analysis of treatment failures in a cohort treated according to prevailing treatment guidelines.

Objective(s): To establish, as a first model, in vivo method to detect antimicrobial resistance in Neisseria gonorrhoeae, the causative agent of gonorrhoea. This infection is chosen as a model because resistance detected in vitro appears to correlate well with clinical failure.

Description: Establishment (in collaboration with the WHO Office of HIV/AIDS and Sexually Transmitted Diseases, AD) of study design, based on lot quality assurance, to detect gonorrhoea resistant to antimicrobial treatment. Critical review of study design with experts in the WHO Gonococcal Antimicrobial Surveillance Programme (GASP). Field test in parallel with laboratory tests to detect resistance in vitro. Laboratory tests will be carried out in one or more of the laboratories participating in GASP and will provide the opportunity for strengthening techniques in these laboratories.

Expected Outcomes, Results and Progress Indicators: In-vivo method for detection of resistance in gonorrhoea, evaluated in the field.

Progress indicators in 1998: Establish, in collaboration with WHO/AD and GASP coordinators, a study design and costing; Identify a study site with suitable field and laboratory facilities; Identify a study team.
Countries/Region(s): The field study will be carried out in southern Africa in partnership with the South African Institute for Medical Research, Johannesburg, South Africa.

Partners: WHO/CDS; Gonococcal Antimicrobial Surveillance Programme (GASP) Collaborating Centres; South African Institute for Medical Research, Johannesburg, South Africa.

Results to Date: Collaboration with the local partner has so far not occurred. It may be necessary to redesign the activity or discontinue it.

### 3.5 Using Clinical Treatment Failures to Monitor Antimicrobial Resistance in *S. pneumoniae* and *H. influenzae*

**Implementing Organization:** WHO/CAH

**Status:** On-going (Funded: FY1998; Expected Completion: FY2002)

**Rationale:** Surveillance of antimicrobial resistance has been of little practical use to monitor the clinical efficacy of oral cotrimoxazole as the first line of treatment for children with WHO defined pneumonia. Data show that even in the presence of high rate of in-vitro antimicrobial resistance to cotrimoxazole, this antimicrobial is clinically effective. On the other hand, recent reports of increasing penicillin resistance have raised concerns about its clinical efficacy. At present there is very little data indicating that penicillin or cotrimoxazole resistance leads to clinical failure in pneumonia. At the same time there is limited information available about the effect of prior use of antimicrobial on clinical outcome and antimicrobial resistance.

**Objective(s):**
1. To study whether trends in the number of clinical failures in non-severe and severe pneumonia can be used to monitor the prevalence of antimicrobial resistance.
2. To study the effect of prior antimicrobial use on clinical outcome of WHO defined pneumonia and antimicrobial resistance.

**Description:**
1. A study, conducted in the community as well as in the hospital, will determine the relationship between treatment failures assessed clinically and prevalence of antimicrobial resistance to the first line antimicrobial determined on nasopharyngeal swab isolates of *S. pneumoniae* and *H. influenzae*.
2. A detailed history of prior antimicrobial use will be obtained at the beginning of therapy with special reference to the antimicrobial recommended by WHO ARI standard case management guidelines e.g. cotrimoxazole, amoxicillin, chloramphenicol etc.

**Expected Outcomes, Results and Progress Indicators:**
1. Development of a tool to monitor trends in antimicrobial resistance by monitoring clinical efficacy of first line antibiotics recommended for the management of pneumonia.
2. Better understanding on the relationship between prior antimicrobial use, clinical efficacy and antimicrobial resistance.

**Progress indicators:** development of the research protocol; initiation of data collection.

**Country(s)/Regions:** Pakistan.
Partners: Not applicable.

Results to Date: Research is in progress in 14 first-level health facilities in Chitral, Pakistan to evaluate a monitoring tool to identify clinical treatment failures in children with non-severe pneumonia. It is expected that data collection will be completed in the third trimester of 2001 and results will be available by late 2001.

3.6 Magnitude and Trends of Resistance in Priority Infectious Diseases

Implementing Organization: WHO/CDS

Status: On-going (Funded: FY1999; Information not provided on expected completion date)

Rationale: The data that exist on the magnitude and trends of AMR are seriously lacking in quantity, quality and comparability. Furthermore there are very few studies showing trends in resistance over time, or linking in-vitro resistance to antimicrobial use or clinical outcome. For some infectious diseases (such as tuberculosis) progress has been made in establishing internationally-accepted methods for data gathering. For other diseases there is still much to do in the area of standardisation of methods. Furthermore external quality assurance is essential to the collection of valid data.

The combination of these activities for several different diseases under one project will facilitate the synergy between projects and the sharing of learning about different resistance challenges.

Objective(s):
1. To measure the magnitude and monitor trends in resistance in tuberculosis (including MDR-TB), malaria, and other priority bacterial infections;
2. To develop national capacities, provide technical assistance for resistance monitoring, and maintain international networks of reference laboratories for external quality control;
3. To disseminate information on magnitude and trends of AMR.

Description:
1. Expand and continue to implement projects for monitoring MDR-TB in high priority countries;
2. Prepare and evaluate DRS protocols following standardised methodological guidelines. This will include technical advice, site visits and quality assessment;
3. Organise a meeting to review the data collected through monitoring of drug-resistant malaria by determining therapeutic efficacy of anti-malarial drugs;
4. Strengthen monitoring of gonococcal resistance and improve the epidemiological basis of the data collection;
5. Provide guidelines and training to enable the building/strengthening of networks to monitor other priority bacterial infections;
6. Maintain and expand as required networks of reference laboratories for quality assurance of antimicrobial susceptibility testing (incl. MDR-TB and DR-malaria)

Expected Output, Results and Progress Indicators:
1. Accurate and representative resistance data and trends in MDR-TB from 15-20 new projects validated by reference laboratories and sound epidemiological methods;
2. Report of meeting and recommendations to countries for monitoring drug resistant malaria (pending outcome of clinical trials of combination therapy);
3. Gathering of accurate and representative resistance data on drug resistance in malaria initiated and first
report complete;
4. Networks for AMR monitoring in other bacterial infections strengthened in 10 countries;
5. Data sharing on AMR optimised;
6. Reports from external quality assurance schemes.

Countries/Regions: To be determined.

Partners: These activities will be carried out in close collaboration with all other relevant groups in WHO/CDS cluster, especially Dept. of Control and Prevention, Dept. of Research and Development (TDR) and Roll Back Malaria, and with the STI/UNAIDS Working Group, with WHO Regional Offices and with the IUATLD and other external partners in public health and academic institutions around the world.

Results to Date: A database of national surveillance networks (disease-specific and non-specific) and a linked database of antimicrobial resistance data (http://oms2.b3e.jussieu.fr/arinfobank/) collected by these networks has been evaluated after one year of activity and revealed the lack of data and lack of consistency in AMR surveillance. A paper will be submitted for publication in 2001.

AMR Component 4:
Responding to Data on Antimicrobial Resistance and Drug Use

4.1 Model Prescribing Information -- Drugs Used in Bacterial Infections

Implementing Organization: WHO/HTP/EDM

Status: On-going (Funded: FY1998; Expected Completion: FY2001)

Rationale: It is generally believed that over prescribing or irrational prescribing of antimicrobials, is a major factor in the development of resistance to antimicrobials.

Objective(s): To produce a manual of treatment guidelines for prescribers on the rational use of antimicrobials to complement the WHO Model List of Essential Drugs. These guidelines will contain independent, scientific, non-biased and practical information. It is the intention to provide up-to-date source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, treatment guidelines for antimicrobials, drug compendia and similar material.

Description: The first draft of this manual is almost completed. It now needs to be reviewed and edited by an infectious disease specialist before being subjected to a broad consultative procedure including review by the relevant technical divisions within WHO, national Drug Regulatory Authorities, scientists, relevant non-governmental organizations including the International Society of Chemotherapy, International Union of Pharmacology and the International Federation of Pharmaceutical Manufacturers Associations. Relevant parts of the manual on establishing a national programme on promotion of rational drug use and antimicrobials in particular (see activity 4.3: "Guidelines for Establishing a National Programme...".) will be included and frequent cross referencing made.
Dissemination of the manual to all national regulatory authorities and the relevant non-governmental organizations is routine. Additional dissemination will be undertaken as appropriate by HTP/EDM and CDS.

**Expected Outputs, Results, and Progress Indicators:** The publication of a manual of WHO Model Prescribing Information "Drugs used in Bacterial Infections". This will be in two phases: (1) Development and review of draft material; and (2) A consensus consultation on the draft will be held. In year 1, a consultation would be held to finalize the draft text on drugs used in bacterial infections. The text will be edited and published by WHO in 2001.

**Country/Regions:** The six Regional Offices of WHO will be involved in the consultative procedure.

**Partners/Collaborating Institutions:** All relevant technical divisions within WHO, National Drug Regulatory Authorities, non-governmental organizations including the International Society of Chemotherapy, International Society of Infectious Diseases (ISID), International Union of Pharmacology and the International Federation of Pharmaceutical Manufacturers Associations and relevant Professional Associations will be involved in both the review and the consensus meeting.

**Results to Date:** The manuscript has undergone extensive editing and is now in the second proof stage. It will be published in English in March 2001. Translation into French is underway and will be completed in 2001.

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4.2 **Guidelines for National Policy Makers and Health Administrators on the Containment of Antimicrobial Resistance (linked to activity 5.1)**

**Implementing Organization:** WHO/HTP/EDM

**Status:** On-going (Funded: FY1998; Expected Completion: FY2001)

**Rationale:** It is recognized that there are practices for containment of resistance to antimicrobials, supported by scientific evidence, which in order to be implemented efficiently at national level need to be transmitted to policy makers and health administrators.

**Objective(s):** To develop a briefing document for policy makers and health administrators. This will be a policy and advocacy document detailing the roles of Ministries of Health, training institutions, health institutions, professional associations, industry and consumer organizations in the task of containing antimicrobial resistance.

**Description:** A skeleton outline has been prepared. This will be developed in consultation with all relevant technical divisions within WHO, national drug regulatory authorities, scientists, relevant non-governmental organizations, including the International Society of Chemotherapy, International Union of Pharmacology, the International Federation of Pharmaceutical Manufacturers Associations and the Consumers Union, and relevant professional associations.

Dissemination of the manual to all national regulatory authorities and the relevant non-governmental organizations is routine. Additional dissemination will be undertaken as appropriate by HTP/EDM and CDS:
Expected Outputs, Results, and Progress Indicators: Preparation of a briefing document (with consultation at the draft stage) containing consolidated information on resistance mechanisms, health impact, and practical action for national policy makers and in-country healthcare education programs. The document will be used in the "WHO Country Intervention Packages" (see activity 5.1: "Integrated Country Programmes forContainment of AMR").

Country/Regions: The six Regional Offices of WHO will be involved in the consultative procedure and a meeting to discuss the draft document.

Partners/Collaborating Institutions: Partners include all relevant technical divisions within WHO; National Drug Regulatory Authorities; non-governmental organizations including the International Society of Chemotherapy; International Society of Infectious Diseases (ISID); International Union of Pharmacology; the International Federation of Pharmaceutical Manufacturers Associations; and the Consumers Union. The relevant Professional Associations will be involved in both the review and the consensus meeting.

Results to Date: (see Activity 5.1)

### 4.3 Guidelines for Establishing a National Programme to Promote Rational Drug Use, and Rational Use of Antimicrobials in Particular (linked to activity 5.1)

Implementing Organization: WHO/HTP/EDM

Status: On-going (Funded: FY1998; Expected Completion: FY2001)

Rationale: Irrational use of antimicrobials is considered a major contributing factor in the development of antimicrobial resistance and one third of prescriptions in developing countries are for antimicrobials. The evidence on the efficacy of various types of interventions to promote rational drug use is incomplete and not easily accessible. It is very necessary for governments to have a briefing document from WHO with practical advice on how to design and implement a cost-effective programme to promote rational drug use, particularly the rational use of antibiotics.

Objective(s): To make existing knowledge on efficacious interventions accessible to decision makers through provision of guidelines to design and implement cost-effective programmes to promote rational drugs use, with emphasis on the containment of antimicrobial resistance

Description: Commission an analysis of current evidence based interventions available to promote rational use of drugs (special emphasis on cost effectiveness and antimicrobials). The draft report of this analysis will be used as the basis for a review by a global panel of experts on implementation of such interventions at national level. The draft document produced will be field-tested before finalization. Activities will be undertaken with INRUD and the School of Public Health in Boston, and other experts as needed. Relevant parts of the national guidelines on containing antimicrobial resistance (see activity 4.1: "Model Prescribing Information -- Drugs Used in Bacterial Infections") will be included in this manual and frequent cross referencing made. The final document would be complementary to that proposed in activity 4.1. The final version of the manual would be disseminated to ministries of health, national regulatory authorities, essential drug programmes, researchers and trainers in rational drug use as well as appropriate relevant non-governmental organizations by HTP/EDM and CDS.
Expected Outputs, Results, and Progress Indicators:  A WHO manual on how to establish and implement a national program to promote rational drug use, within the scope of a national drug policy, with a special chapter on promoting the rational use of antibiotics and containing antimicrobial resistance.

Year 1: Current funding would allow: commissioning of an analysis of current evidence based interventions available to promote rational use of drugs (special emphasis on antimicrobials); production of a draft report on the analysis; review of report by global panel of experts on implementation of interventions at national level;

Year 2: Further funding would be required for field testing of the draft document at country level; finalization of document to become a WHO manual (see activity 4.2: "Guidelines for National Policy Makers and Health Administrators on the Containment of AMR"); publication dissemination as for the activities 2.4 ("Measuring, Understanding and Changing Irrational Drug Use") and 4.2.

Country/Regions: WHO/HTP/EDM in Geneva

Partners/Collaborating Institutions: International Network for the Rational Use of Drugs (INRUD); Prof. Richard Laing of the School of Public Health of Boston University; WHO/CDS.

Results to Date: (see Activities 4.4 and 5.1)

4.4 Guidelines for Containing Antimicrobial Resistance at Hospital Level ("Hospital Package")

Implementing Organization: WHO/HTP/EDM; WHO/CDS


Rationale: There is a great need to promote rational drug use (RDU), and especially rational antimicrobial use, in hospitals because they represent a large proportion of the drug use in most countries and because they set an example through their teaching functions. Likewise, it is important to emphasise the need for high standards of infection control to prevent spread of resistant strains in the hospital environment, from patient to patient, or from patient to health care worker and vice versa. In developed countries the organizational structures that promote rational drug use and infection control procedures are Hospital Drugs and Therapeutics Committees (HDTCs) and Infection Control Committees (ICCs). These are rarely operational in developing countries. Thus guidelines that combine the formation and strengthening of these committee structures and the provision of guidance for RDU and infection control, with particular reference to containing antimicrobial resistance, should be beneficial.

Objective(s): To develop practical guidelines to assist hospital staff to effect a reduction in the emergence and spread of antimicrobial resistance at hospital level.

Description:
1. Review of available guidelines on establishment and function of HDTCs and ICCs;
2. Modification of guidelines if required for developing country conditions;
3. Development of draft text on RDU (see Review, AMR Component 1) and infection control to be incorporated into guidelines [note - these guidelines are incorporated into a manual on drugs and therapeutics committees that is written and now being edited (2001). The manual is being made consistent with an international training course that has been developed by MSH];
4. Pilot in at least two developing countries and evaluate changes in actual prescribing of antimicrobials;
5. Review text with global consultation;
6. Issue document and disseminate through Ministries of Health and university teaching hospitals,
   essential drug projects, RUD projects, and appropriate non-governmental agencies.

**Expected Outputs, Results, and Progress Indicators:** This is a multi-year project whose final outcome
should be: establishment and greater understanding of the value of HDTCs and ICCs; improved
antimicrobial prescribing in hospitals where HDTCs are operative; improved infection control where ICCs
are operative.

**Progress indicators** include: (1998) available guidelines on establishment and function of HDTCs and ICCs
reviewed and modified as necessary; review (see AMR component 1) completed; (2001) draft text prepared
for RDU (based on Review) and infection control sections to be incorporated into guidelines; completed
draft text prepared for pilot study; (2002) pilot countries identified and field testing initiated.

**Country/Regions:** Zimbabwe.

**Partners/Collaborating Institutions:** WHO Action Programme on Essential Drugs; AIHA; School of
Public Health, Boston University; International Federation of Infection Control (IFIC); public sector;
church-related and private hospitals in the pilot countries.

**Results to Date:** A WHO consultant facilitated a meeting in Zimbabwe in early 2000 with Drug and
Therapeutic Committee (DTC) members of eight hospitals and a draft manual on “Establishing an
Effective Drug and Therapeutics Committee: the Zimbabwe Experience” was finalized. Each of the
hospitals also made a final presentation of their drug utilization review projects, six of which related to
antimicrobials. The consultant concluded that the DTCs can be powerful channels for conducting
interventions to promote more rational use of drugs, including antimicrobials, but that they only worked if
there was sufficient continuity of staff within a hospital. Thus, it was found that such committees worked
well in the mission hospitals, but not the government ones, where continuity of staff and motivation were
lower.

All eight hospitals conducted a survey of drug-use indicators for inpatients. In addition, individual
hospitals conducted the following projects related to antimicrobials:

- Evaluation of a single dose regimen (1 gm amoxyccillin) versus a 5-7 day course of amoxyccillin
  prophylaxis in cesarean section. The intervention was well implemented and there was no increase in
  infection rate or length of stay in the hospital, but there was a decrease in cost.
- Evaluation of intramuscular versus intravenous quinine for cerebral malaria. The study showed no
difference in outcome.
- Reduction of inappropriate amoxyccillin use through and educational intervention in a staff meeting.
  Amoxyccillin use was reduced by 20%, but there was an increase in the use of cotrimoxazole,
  doxycycline, and erythromycin.
- Slight reduction in the use of ceftriaxone through a regulatory intervention whereby approval of the
  medical superintendent was necessary prior to use. However, there are some evidence that
  chloramphenicol use and mortality increased slightly.

A contract was issued for a two-year project in Ghana (Noguchi Memorial Institute for Medical Research)
to conduct research on interventions to improve antibiotic prescribing habits of doctors in a teaching
hospital.
The second draft for the WHO DTC Manual was completed and sent out for review. WHO will collaborate with MSH on the further development and field testing of this manual in conjunction with the development and running on an international course on DTCs. One international course will be conducted and technical support will be provided for two regional workshops on DTCs during 2001. A longer-term goal (extending beyond 2001) is to build on contacts made through the 2001 training activities to conduct an extended program for technical support (of several year duration) to a group of hospitals in several developing counties.

**AMR Component 5:**

*Preventing and Slowing the Spread of Antimicrobial Resistance*

5.1 Integrated Country Programs for Containment of Antimicrobial Resistance

**Implementing Organization:** WHO/CAH; WHO/CDS; WHO/HTP/EDM

**Status:** On-going (Funded: FY1998; Information not provided on expected completion date)

**Rationale:** Although containing the emergence and spread of antimicrobial resistance is complex, multifactorial and not completely understood, it is believed that measures can be initiated in countries in a coordinated and integrated manner. These include:

- **Surveillance:** Quality data from laboratory-based surveillance of antimicrobial resistance in key bacterial pathogens can be used to improve patient care and infection control/outbreak containment practices at the local level and to raise local awareness of resistance problems. Establishment of national surveillance networks can provide data to support policy development, develop resistance containment strategies and make projections of future priority health issues. In addition, for diseases such as respiratory infections, in which the correlation between in vitro antimicrobial resistance and clinical outcome is questioned, systems to monitor treatment efficacy will have to be established.

- **Education and training:** Education on the causes of antimicrobial resistance, interventions that are effective for its containment and particularly on the rational use of antimicrobial agents raises awareness of resistance and improves antimicrobial prescribing practices. Pre-service and continuing in-service training in the clinical diagnosis and the proper management of infection, using simplified assessment and treatment algorithms such as the ones developed for the Integrated Management of Childhood Illness (IMCI), improves the accuracy of diagnosis and the appropriateness of treatment.

- **Guidelines and Policies:** All countries have some regulatory mechanisms in place. These need to be strengthened to include specific measures to assure strict regulation of quality and availability of antimicrobial, and ethical standards of promotion. Many countries also have in place an essential drug policy to promote the rational use of drugs. This should be expanded to include a specific section on the problem of antimicrobial resistance.

**Objective(s):** To establish processes for the introduction a model package of interventions to contain antimicrobial resistance and to demonstrate the efficiency and benefit of an integrated approach to resistance containment at national and local levels.

**Description:** The package will contain a series of activities to be initiated, together with indicators of
efficiency and benefit, in the selected countries.

1. **Situation analysis**: Surveillance studies to determine the prevalence of priority infectious diseases, prevailing antimicrobial resistance patterns and knowledge of antimicrobial use. (Disease surveillance will be coordinated with other Divisions in WHO).

2. **Activities in laboratory-based surveillance**:
   
   2.1. Provision of laboratory-based training in microbiological diagnosis and detection of resistance and analysis of resistance data, and laboratory capacity strengthening;
   
   2.2. Training trainers in order to enable sustainable in-country technical training in lab-based resistance detection;
   
   2.3. Assistance to countries to establish external quality assurance schemes for antimicrobial susceptibility tests;
   
   2.4. Assistance in initiating a national surveillance network.

3. **Activities in education and training**:
   
   3.1. Development of continuing education programmes for laboratory technologists, prescribers and other healthcare professionals;
   
   3.2. Public education programmes;
   
   3.3. Development of training modules for health workers in the use of assessment and treatment algorithms, such as the ones developed and used in the IMCI;
   
   3.4. Development of a core undergraduate medical and pharmacy curriculum for training in the rational use of drugs particularly antimicrobials.

4. **Activities in guidelines and policy formulation**:
   
   4.1. Organization of workshops to bring together policy-makers, physicians, pharmacists, laboratory staff, nurses and community health workers to review national antimicrobial resistance data and current antimicrobial use practices, to identify constraints in information flow and to develop national plans of action for the surveillance and containment of resistance;
   
   4.2. Assistance in development of national antimicrobial use guidelines and drug use indicators relevant for antimicrobial use. These activities will, as far as possible, be integrated within the scope of a national policy to promote rational drug use.

**Expected Outputs, Results, and Process Indicators**: This is a multi-year project and the outcomes therefore represent ultimate outcomes.

- Knowledge of the pattern of prevalent infectious diseases, prevailing resistance patterns and patterns of antimicrobial drug use;
- Improved laboratory surveillance of antimicrobial resistance, including facilities for monitoring resistance of common bacteria;
- Mechanisms for better information flow between surveillance information, national treatment guidelines, essential drug lists, supply and training;
- Pre- and in-service training for health workers;
- A raised public awareness of the problem of antimicrobial resistance;
- A national policy to promote the rational use of antimicrobials, including specific chapters on rational use antibiotics in humans, animals and agriculture;
- National treatment guidelines for the public and private sector;
- A national voluntary code for ethical drug promotion.

**Indicators**:

- Agreement with pilot countries to initiate project;
- Report of situation analysis available within 3 months of initiation;
- Training activities initiated within 6 months of start;
- Quality assured surveillance data available within 12 months;
• Public information package prepared and initiated within 6 months;
• Continuing education package prepared and initiated within 12 months.

Outcomes:
• Package of materials prepared and collated;
• Baseline data available on antimicrobial resistance in priority bacterial diseases;
• National policy to promote rational use of antimicrobials in force;
• Voluntary code for ethical drug promotion in force.

Countries/Regions: Three pilot developing/transition countries will be identified by WHO. Criteria for inclusion to be considered will include: (1) existence of national drug policy; (2) existence of an essential drug programme with a rational use of drugs component; (3) existence of suitable microbiology laboratory facilities; (4) existence or experience of WHO projects including IMCI; (5) political willingness to be involved in a project.

Partners/Collaborating Institutions: WHO divisions CHD, CDS, HTP/EDM, ASD/STD; WHO/UNAIDS working group; Gonococcal Antimicrobial Surveillance Program, (GASP); American International Health Alliance; International Society for Infectious Diseases; International Clinical Epidemiology Network; Alliance for the Prudent Use of Antibiotics (APUA); RPM/MSH; U.S. Pharmacopeia; Ministries of Health and universities in three developing countries.

Results to Date:
• In 2001, two short briefing documents will be produced for policy makers on the subjects of (1) national strategies to promote rational use of drugs (including antibiotics) and (2) containing AMR. With further experience, such briefing documents may be expanded. Since a integrated country program must necessarily incorporate the promotion of rational use of antimicrobials in all sectors, it is anticipated that Activity 5.6 (promoting rational use of antimicrobials in the private sector) will be incorporated into Activity 5.1.
• Surveillance Standards for Antimicrobial Resistance are in final draft and have been incorporated in proposals for field testing (see below).
• A workshop on the integration of data on antimicrobial usage and AMR was held in March 2000.
• Discussions were held with MSH and ARCH to develop a process to foster operational research related to community-based interventions to promote the rational use of antimicrobials. A workshop was held in Bangkok (November 29-December 8, 2000) to further develop the 10 best (out of 20 submitted) community-based proposals to promote rational use of antibiotics at the household level. Five of the proposals included surveillance of AMR as an additional endpoint for monitoring the effect of the various interventions. The proposals were adjusted in accordance with the final draft of the Manual of Surveillance Standards for Antimicrobial Resistance and it is hoped that the proposals can serve as preliminary field tests.

5.2 APUA Chapter Development

Implementing Organization: Alliance for the Prudent Use of Antibiotics

Status: Completed (Funded: FY1998; Completed: September 1999)

Rationale: APUA is an independent, grassroots organization whose mission is to promote public health through education and research concerning antibiotic resistance and the prudent use of antibiotics around the world. Founded in 1981, with members in over 100 countries, APUA provides a network that
facilitates international exchange of information and supports country-based efforts to curb antibiotic resistance. APUA proposes to keep pace with the escalating emergence of antibiotic resistance worldwide by expanding its network of foreign affiliated chapters and by increasing the package of chapter services as a model for more aggressive local intervention. The goal is to create a global network of highly specialized experts working in a more coordinated way to attack the antibiotic resistance problem at country and global levels.

APUA national chapters facilitate global planning to curb antibiotic resistance by performing these vital functions: raising awareness about the problem of resistance within a country and the dangers of incorrect antibiotic usage and faulty prescription; communicating information on proper antibiotic usage; conducting related research and educational projects; allowing for a multidisciplinary approach to interventions; fostering practically applicable and scientifically sound solutions; affording a local platform for input and feedback into any global planning effort; and providing local leaders with regular international networking opportunities to enhance their knowledge and effectiveness at the local level.

The APUA chapter also provides a natural link between data and action within the country. As research findings are documented in country and through the international APUA chapter network, they will be conveyed to clinicians and policy makers. The APUA affiliation empowers chapter members through support of their own research efforts and an international affiliation to enable them to act as more effective advocates for more prudent use of antibiotics in their country.

Last but not least, the APUA chapter can also act as an early warning and intervention system. By increasing understanding of the resistance problem within the country, and encouraging implementation of more prudent antibiotic usage policy and practice, an APUA chapter can be influential in containing an emergent resistant pathogen before it spreads to the rest of the world. The APUA network publicizes and encourages replication of successful local antibiotic resistance interventions, many of which have been spurred by the APUA chapter and membership network.

Objective(s): APUA chapters will further the global effort to curb antibiotic resistance by addressing the following critical objectives:

- To establish and mobilize local networks to raise public and professional awareness and advocate for national programs and policies to curb antibiotic misuse and resistance;
- To develop in-country leadership and capacity to advocate and intervene in order to curb antibiotic resistance by linking researchers to the international scientific community;
- To act as a grassroots early warning source regarding resistance problems;
- To foster national and regional coordination of antibiotic resistance research and surveillance and intervention activities;
- To increase the understanding of key governmental and other decision makers about the problem of antibiotic resistance and the need for prudent antibiotic use;
- To increase the number and quality of local surveillance and research efforts related to antibiotic resistance and use; and
- To improve local scientific and clinical practice through publicizing and developing standards and guidelines on prudent antibiotic use and antibiotic resistance surveillance.

Description:
A. Development of New Chapters
- Identification of qualified leaders in appropriate professional societies and government and non-governmental organizations through APUA scientific advisory board and other partners’ contacts;
- Preparation of introductory packets;
- Initial telephone contacts and mailings of APUA chapter information and background packet to 100-200 potential members;
- Explaining of chapter guidelines and agreement;
- Gaining agreement on contract and chapter representation;
- Organization of initial chapter meeting;
- Identification of chapter technical support needs;
- Establishing initial link with other chapters;
- Mailing of APUA newsletters;
- Assistance with outline of chapter goals and objectives.

B. Support of Established Chapters
- Identification of local chapter needs and provision of technical assistance;
- Assistance with development of local work plans, priority objectives and activities reflecting both local needs and those relating to the global planning effort;
- Establishment of electronic and other links with other APUA chapters and the larger scientific community dealing with antibiotic resistance;
- Annual chapter surveys: develop, conduct, compile and disseminate results;
- Organization of local workshops regarding antibiotic research and education;
- Dissemination of educational and membership materials: newsletter, video, relevant publications and materials to key authorities and professional groups;
- Compilation and dissemination of standards and guidelines on antibiotic resistance surveillance and antibiotic use;
- Providing technical assistance to country to advise on research and training needs;
- Development of guidelines for review of chapter small grants proposals;
- Providing small grants for local research, surveillance and educational programs;
- Translation of APUA educational materials into Spanish and wide distribution of them;
- Encouraging and editing original research from chapters for inclusion in the APUA newsletter;
- Publishing and disseminating APUA newsletter to chapter members and relevant contacts;
- Collecting and disseminating chapter success stories;
- Assistance with development of local guidelines for surveillance and antibiotic use;
- Conducting mentoring and international networking and exchange programs;
- Development of model training sessions;
- Development of press packages.

**Expected Outputs, Results, and Progress Indicators:**
1) New chapters developed;
2) increase in membership for new and existing chapters; 3) key organizations contacted, aware of and/or involved in chapter activities; 4) number of APUA newsletters distributed; and number of educational materials translated and disseminated; 5) original research findings submitted from chapters to APUA; 6) documentation of local resistance trends; 7) chapter research and educational programs, meetings, publications; 8) educational materials and research findings distributed to appropriate professional, policy groups and donors; 9) local and regional networking training sessions for relevant local practitioners, researchers and policy makers; 10) regional and international networking meetings for chapter leaders (teleconferencing, email, chat groups, in person); 11) other evidence of collaborations, including number of exchanges among scientists; 12) number of speakers provided from the international office to local meetings; 13) media coverage of chapter activities and issues; 14) model chapter programs to track and curb resistance identified and disseminated; 15) surveys of chapters and compilation and dissemination of findings.
Countries/Regions: Argentina, Colombia, Dominican Republic, Venezuela, and other countries in Latin America that were developed before this grant.

Partners/Collaborating Institutions: To maximize impact, APUA will work with other organizations including PAHO, WHO, RPM, and INRUD to implement a logical division of labor and minimize duplication. APUA will collaborate with national and global authorities to coordinate training and dissemination of information to help ensure that chapter activities impact national drug policies. In order to foster sustainability and cost sharing, APUA will work with chapters to help secure funding from appropriate sources to support activities.

Results to Date: Establishment of four new chapters and support of existing chapters on outputs #1, 2, 3, 4, 5, 7, 8, 10, 11, 12 and 13. Less progress made with the established chapters on outputs #6, 9, 14 and 15 because of limited resources.

5.3 Antimicrobial Drug Booklet for Pharmacists and Drug Sellers

Implementing Organization: USP

Status: Completed (Funded: FY1998; Expected Completion: FY2002)

Rationale: Although national drug policies usually prohibit pharmacists and drug sellers from dispensing antimicrobials without a prescription, it has been documented that a large percentage of antibiotics are taken through self-medication, with the antibiotics often being made available by untrained PHC workers or retail drug sellers. Through USP’s experience in Nepal, it has been observed that training requirements to become a licensed drug seller are minimal and no "refresher" training is required. Drug information available to the retailer comes almost exclusively from the pharmaceutical industry. Current, unbiased information is required for appropriate dispensing and for advising consumers about side-effects and how to take their medicines. Studies have shown that 68% of retailers in Nepal have no qualifications to sell drugs, let alone to prescribe. In one study, a therapeutically-appropriate full course of antibiotic treatment was received less than 25% of the time in retail shops.

Objective(s): To decrease the amount of inappropriate dispensing of antimicrobial drugs by private sector retailers and to improve their consumer counseling practices.

Description: Using Nepal ID funding, USP will research the antimicrobial drug knowledge and consumer counseling practices of drug sellers in Nepal in cooperation with the NCDA. Emphasis will be placed on antimicrobials used to treat high priority diseases such as pneumonia, Shigella and sexually transmitted infections. A template for a booklet for pharmacists and drug sellers (which can be adapted by other countries) will be completed using the Nepal research results and USP’s patient information database, appropriately adapted for Nepal. In addition, information relating to appropriate counseling techniques will be included based on USP’s patient counseling guidelines, again, adapted for Nepal. Nepal ID funds will allow the booklet to be tested in Nepal. Core funds will be used to develop the template, disseminate the booklet outside of Nepal as a model and to assist other countries with adapting/ translating the model for local use through a sub-agreement mechanism. Core funds will also be used to develop a facilitator’s guide for use by trainers of retailer-groups.

Expected Outputs, Results, and Progress Indicators:
Output: Booklet for pharmacists and drug retailers to use to improve dispensing and to counsel
consumers on the proper use of antimicrobial drugs.

**Progress Indicators:** Research methodology and tools developed, e.g., number of surveys completed, number of focus groups held, etc., amount and quality of data collected and analyzed, format for booklet developed, drugs to be included identified, general AM information developed, drug-specific information developed, draft template developed.

**Countries/Regions:** Nepal

**Partners/Collaborating Institutions:** NCDA, USAID-Nepal, MSH, DINoN

**Results to Date:** Research has been completed on the antimicrobial (AM) drug knowledge and consumer counseling practices of drug sellers in Nepal. Development of the booklet on AM drugs has been delayed until the training intervention described under 5.24 could be field tested and evaluated. The field test and evaluation have now been completed and results will be used to guide the development of the booklet so the format will be useful to the drug sellers, but also for nurses and physicians in rural areas. It will be published in the Nepali language with Nepal ID funds. The booklet is envisioned as a tool for the training intervention, but also as a stand-alone product that can be adapted for other countries with core funds.

### 5.4 Training Modules for Drug & Therapeutics Committees and Antibiotics Sub-Committees

**Implementing Organization:** RPM/MSH

**Status:** On-going (Funded: FY1998; Expected Completion: FY2002)

**Rationale:** The First International Conference on Improving Use of Medicines identified the need to develop guidelines and performance indicators for Drug and Therapeutics Committees (DTC), a key structural component of an effective pharmaceutical management system. Although these committees have been in existence for many decades in both advanced industrialized and developing countries materials are unavailable to assist in capacitating committee members to effectively carry out their roles. Relative to an antimicrobial focus, there is a need to develop relevant skills to select appropriate (effective, safe and economic) antimicrobials for national or local formularies and promote their appropriate use. DTC members do not receive prior training to develop such skills.

**Objective(s):** Develop and test a set of training modules aimed at members of DTCs and Antibiotics Sub-committees of local hospital and national levels

**Description:** The materials will include, minimally, sessions on (1) the role and functions of a DTC, (2) criteria for antimicrobial drug selection, (3) economic analyses for antimicrobial drug selection, (4) the appropriate use of in vitro antimicrobial susceptibility testing, (5) how to evaluate the clinical literature on drug efficacy and safety, (6) how to conduct analyses to target drug use interventions, (7) a framework to improve the use of antimicrobial drugs, (8) effective strategies to improve antimicrobial drug use, (9) sources of reliable information on antimicrobial drugs, and (10) effective communication skills and teamwork.

Tasks include a review of relevant literature and a selective survey of these committees to gather information to design the training modules. RPM intends to prepare (1) a discussion paper on the role of these committees and the need for skills development in developing countries and (2) a draft outline of
modules, stating the rationale, objectives, key content, and a preliminary list of suggested readings for each module, that will be reviewed before actual drafting of modules. Once the modules are drafted, an alpha course will be organized and conducted in collaboration with interested partners.

Once the alpha course has conducted, availability of materials will be announced in electronic and print fora (E-drug, INRUD News, Essential Drug Monitor). Field test results may be published in the INRUD News, Essential Drugs Monitor and a peer-reviewed journal. Subsequent course may be organized through INRUD, WHO, or other interested organizations for regional or national level training of trainers.

**Expected Outputs, Results and Progress Indicators:**

**Outputs:** list of key references on DTCs; compilation of key readings on DTCs; discussion paper on role of DTCs; a set of training modules for DTCs; report on field test of training modules.

**Results:** set of training modules available and field tested; core group of trainers trained.

**Progress indicators:** literature review completed; key readings compiled; training modules drafted; training modules (alpha course) field tested.

**Countries/Regions:** Africa or Asia (to be determined)

**Partners/Collaborating Institutions:** INRUD country core group members are expected to collaborate in technical review of modules; WHO/HTP/EDM is expected to collaborate in technical review of modules; USP staff and advisory panelists will be asked to provide technical review; potential partners who may provide support for participants to attend the alpha course may include Danida, NORAD, SIDA, WHO HTP/EDM, WHO country programs, and World Bank field projects.

**Results to Date:** The DTC training material was completed and alpha tested in Bangkok in June 2000 under RPM. Under RPM Plus the material was modified from the Bangkok experience and sent out for external review to four reviewers. A collaboration was developed between WHO for RPM Plus to produce the training material and WHO to produce a complementary manual. The modified material was tried in a country workshop in the Philippines in April and then in an International workshop in Indonesia in June 2001. Forty-two participants from 24 countries attended. Each participant agreed on plans for follow on activities. These will be monitored with necessary technical assistance by E-mail. A further regional course is planned for Kenya in October 2001. The material is being translated into Spanish for a course in Latin America in the autumn of 2001.

There are plans to incorporate an infection control module and a module on drug information and drug information centers to the DTC training materials. These additional modules are expected to be developed during the summer of 2001. In addition, there are plans to develop an infection control quality improvement process for hospitals in developing countries.

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**5.5 Improving the Use of Antimicrobials through Interventions Aimed at Health Professionals, Drug Sellers and Community Health Workers**

**Implementing Organizations:** BU/ARCH and RPM/MSH

**Status:** On-going (Funded: FY1998; Expected Completion: FY2002)

**Rationale:** Inappropriate antimicrobial use in primary care settings is widespread. This is felt to be a major force driving the spread of community-acquired antimicrobial resistance. Numerous studies have
documented both over-prescribing as well as inappropriate selection and dosing of antibiotics by health care providers, unfettered access to antimicrobials by consumers, and a failure to adhere to clinically desirable treatment regimens.

Antibiotic therapy is a mainstay of hospital therapy. Antibiotics typically are both the most frequently used, and by far the most expensive, category of drugs in a hospital budget. Although unnecessary use of antibiotics in hospitals appears to be as widespread as in primary-care settings, even appropriate use can drive the rapid development of resistance because of the intensity of pressure in a self-contained ecosystem. There has been very little documented experience from developing countries in how best to improve the use of antibiotics in hospital settings.

In 1997, the First International Conference on Improving Use of Medicines (ICIUM) was held in Chiang Mai, Thailand. It was co-sponsored by the CIH/ARCH, INRUD, RPM, USP, and WHO/HTP/EDM. The conference identified key topics for research on improving prescribing and dispensing practices, improving community use of medicines, and developing effective pharmaceutical policies and regulations. In line with these priority areas, the partner organizations (RPM, INRUD, CIH/ARCH, and WHO/HTP/EDM) issued a joint call for proposals emphasizing the most important gaps in experience that were identified at ICIUM. Areas highlighted in the call for proposals were the need for innovative interventions to improve malaria case management, and the scarcity of well-designed interventions in hospital and private sector settings. In response to the call for submissions, 88 pre-proposals for intervention research were submitted from Africa, Asia, and Latin America. They were reviewed and ranked by a panel from amongst the collaborating partners. The partners assisted the researchers, using a structured process, to develop completed proposals and to implement and analyze their research.

Objective(s):
- Strengthen capacity to develop, conduct, analyze and disseminate effective interventions to improve the use of antimicrobial drugs
- Support intervention research to improve the use of antimicrobial drugs

Description: The drug use research portfolio includes several studies proposing innovative approaches to behavior change among health workers, including small interactive group discussions with drug sellers, or the use of local hospital specialists as educational leaders to facilitate change among primary health care physicians.

In addition, a number of studies target the use of antibiotics in hospitals. Their focus ranges from teaching hospitals to district hospitals; public to private to mission institutions; neonatal intensive care units to pediatric outpatient departments; specialists to general medical officers. A number of studies focus on improving and expanding the role of Pharmacy and Therapeutics Committees, the mainstay in many developed countries of efforts to improve the quality of prescribing.

The fifteen (15) top-ranked research pre-proposals that address antimicrobial drug use were submitted by investigators in Asia and Africa (one in Mexico), reviewed, approved and funded. They include:
- Ghana: An Intervention to Improve Antibiotic Prescribing Habits of Doctors in a Teaching Hospital – Ofori-Adjei
- Indonesia: Reducing the Use of Expensive Antibiotics for Acute Respiratory Tract Infections (ARI) in Children Utilizing a Small Group Face-to-Face Intervention - Rustamadji
- Indonesia: Small Group Discussion Among Paramedics at the Health Centre Level to Improve Compliance to Standard Treatment Guidelines for Acute Respiratory Tract Infections(ARI) - Hidayati
- Kenya: Study to Assess the Effect of an Educational Intervention to Influence Cost-Effective Prescribing
in the Use of Antibiotics in the Treatment of Non-Pneumonia ARI and Malaria in 10 Mission Hospitals in Kenya – Gitau

- **Mexico**: Effectiveness of An Educational Strategy, Based on Critical Analysis of Clinical Practice, to Improve Appropriateness of Treatment of Common Diseases in Family Medicine Clinics – Reyes/Morales

- **Nepal**: Test of Strategies for Implementing Standard Treatment Schedules in Improving Use of Drugs - Kafle.

- **Philippines**: Improving Private Physicians’ Prescribing Patterns in the Diagnosis and Treatment of Uncomplicated Urinary Tract Infection through Clinical Practice Guidelines - Saniel

- **Philippines**: The Effect of an Educational Activity on the Dispensing Practices of Drug Store Clerks - Galang

- **Philippines**: The Effect of an educational Intervention on the Drug Purchasing Practices of Local Officials in the Philippines – Sia

- **Tanzania**: Improving Appropriate Dispensing Practices of Antimalarials and Antimicrobial Agents in Treating Malaria and Diarrhea in Dar-es-Salaam, Tanzania – Nsimba

- **Thailand**: Improving Economic Rationality of Antibiotic Prescribing in a Teaching Hospital through an Educational Strategy to Promote Generic Prescribing – Anansakunwatt

- **Uganda**: Improving Rational Drug Use by Private Physicians in Uganda: An Educational Intervention Study – Ogwal-Okeng

- **Uganda**: Improving the Dispensing of Drugs for Treatment of Acute Respiratory Tract (ARI) Infections in Children Under Five Years of Age by Private Pharmacists and Dispensers in Kampala District, Uganda by Using Small Group Face-to-Face Intervention - Tumwikirize

- **Uganda**: The Impact of Decentralization on Utilization of Health Services, Use and Availability of Drugs in Apac and Lira District Hospitals, Uganda - Anokbonggo

- **Vietnam**: Improving Community Drug Use Focusing on Hospital Out-Patients through Peer Review and Implementation of Guidelines – Dung

- **Zambia**: The Effect of an Intervention to Promote Correct Use of Antimalarial Drugs at Household Level in Nakonde District, Northern Province, Zambia - Kaona

Each partner of the Joint Research Initiative on Improving the Use of Medicines (JRIIUM) plans to contribute their intellectual labor through the structured proposal development and data analysis workshops and on-going field technical support to implement selected studies. The JRIIUM will also fund participants to attend the workshops and selected studies. The first proposal development workshop was hosted by the WHO Collaborating Centre for Clinical Pharmacology and Drug Policy Studies in Indonesia, secretariat for the Indonesia INRUD Country Core Group, in May 1998. The second proposal development workshop was hosted by the secretariat for the Uganda INRUD Country Core Group, in September 1998. ARCH and RPM continue to provide technical support to selected researchers who are carrying out the study protocols developed at these workshops. RPM has provided financial support for one intervention study, and ARCH has supported eleven studies. An Asia Data Analysis and Policy Paper Workshop was recently concluded in Hanoi, Vietnam from July 7 – 17, 2001 for the eight teams who participated in the Proposal Development Workshop that was held in Indonesia in May 1998. An Africa Data Analysis and Policy Paper Workshop will be held in Kampala, Uganda in late 2001/early 2002 for the seven African research teams.

**Expected Outputs, Results, and Progress Indicators:** The principal outputs of this component are a set of intervention research studies aimed at behavior change among health providers, their analysis, and the dissemination of the results to the global and national programs responsible for infectious disease case management. Researchers and policy makers concerned with slowing the spread of antimicrobial resistance will also benefit from these research results.
By the end of the Policy Paper and Data Analysis Workshop, each team is expected to produce the following: a draft manuscript, a policy paper from the study incorporating the analyses completed by the researchers during the workshop and a short oral presentation of research results to workshop participants. Manuscripts will be reviewed by ARCH and RPM technical staff and external reviewers. Technical support will be provided to facilitate publication in appropriate journals. Every six months researchers are required to submit scientific updates to the JRIIUM’s scientific secretariat at the ARCH Project to assess progress. These reports provide details of project status, problems, presentations made or papers written. The study will be deemed completed only when the research team has submitted a final scientific report to ARCH and USAID. Once the study has been funded, ARCH and RPM project staff provide technical assistance and monitoring of the research which includes site visits, formation of safety and/or data monitoring committees, financial management oversight and other related activities.

At the end of this process, capacity to undertake and disseminate intervention research to improve antimicrobial drug use will also have been strengthened in developing countries.

Countries/Region: Asia, Africa, and Latin America (see Description for countries)

Partners/Collaborating Institutions:
- INRUD/MSH will co-fund workshop activities, provide technical support to researchers, and fund selected studies; some INRUD country core group members will participate in research proposal development and data analysis workshops as technical resource persons and others may participate as participants/researchers
- WHO/HTP/EDM will co-fund workshop activities, provide technical support to researchers, and fund selected studies.

Results to Date: (Information not provided)

5.6 Promoting Rational Use of Antimicrobials in the Private Sector

Implementing Organization: WHO/HTP/EDM

Status: On-going (Funded: FY1998; Information not provided on expected completion date)

Rationale: In most developing countries 50-90% of antimicrobial drugs are purchased directly in the private sector, often without prescription. About half of the customers buy less than one day’s supply at a time. Improving the rational use of antimicrobials in the private sectors needs to be a mixture of regulatory approaches towards drug promotion, continuous education through professional associations, consumer education and active dialogue with the pharmaceutical industry.

Objective(s): To establish and document functional mechanisms to improve rational use of drugs in general and antimicrobials in particular in the private sector to act as a model for other countries.

Description:
- Assist 3 developing countries in developing a national strategy and action plan to promote rational use of antimicrobial drugs in the private sector to include: (1) strengthening regulatory control over sales and drug promotion; (2) working with professional associations to encourage rational use of antimicrobials; (3) working with consumer groups active in the wider community; and (4) working with industry
associations on development and enforcement of self-regulatory codes.

- Based on the experience in these countries prepare a draft manual with guidelines on developing and implementing such a plan.
- Production and dissemination of the guideline to all national regulatory authorities, ministries of health and the relevant non-governmental organizations. Additional dissemination will be undertaken as appropriate by WHO (HTP/EDM, and CDS).

**Expected Outputs, Results, and Progress Indicators:** More rational use of drugs in general, and antibiotics in particular in three countries; a WHO guideline on how to promote rational use of drugs, including antimicrobials in the private sector, tested in several developing countries.

**Progress indicators:** Depending on the countries chosen and their national drug policies and plans, organise a national survey on the use of antibiotics; develop and update antimicrobial use guidelines; investigate legal and regulatory situation; integrate training programmes through professional associations and continuing medical education, making links with ongoing activities with the public sector and the national essential drug programme.

**Countries/Regions:** Philippines.

**Partners/Collaborating Organizations:** WHO/CDS; INRUD; IFPMA; FIP; non-governmental organizations; international networks.

**Results to Date:** (Information not provided)

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### 5.7 Development of an Intervention to Improve Compliance with Antimicrobial Therapy using IMCI Drug Counseling Guidelines

**Implementing Organization:** JHU/FHACS

**Status:** Completed (Funded: FY1998; Completed: FY2001)

**Rationale:** The integrated management of childhood illness (IMCI) approach developed by WHO and UNICEF is being adopted by an increasing number of developing countries as their primary intervention to improve facility and community-based management of sick children. The prescription of antimicrobials for sick children with bacterial infections is a key element of the IMCI approach. The IMCI clinical algorithm recommends oral antimicrobials and home treatment for sick children with clinical diagnoses of non-severe pneumonia, malaria, dysentery, and acute ear infections. The effectiveness of the IMCI drug counseling guidelines on compliance with antimicrobial therapy in the home has not been evaluated. This is a key programmatic issue. If sub-therapeutic treatment doses are being given in the home, then there is an increased risk of the development of antimicrobial resistance and an increased risk of mortality for the individual child. This study will determine the impact of IMCI counseling guidelines on compliance with antimicrobial therapy in the home, develop programmatic interventions to improve compliance and test the effectiveness of these interventions.

**Objective(s):**

- To evaluate the impact of the IMCI treatment counseling guidelines on compliance with antimicrobials for sick children in the home
- To identify barriers to compliance with antimicrobial treatment in the home following IMCI treatment counseling
To develop and test the effectiveness of interventions using the IMCI approach to improve compliance with antimicrobial treatment for sick children in the home.

Description:

**Phase 1 (3 months)** Data collected in this phase will be used to design locally-appropriate instruments for subsequent phases.

- **Semi-structured interviews with service providers and officials.** To examine institutional factors that facilitate or obstruct adherence to treatment recommendations, a series of 15 interviews will be conducted with officials of the IMCI program of the Ministry of Health, district health officials and health facility personnel at the hospital, dispensary and health post level. The interviews will cover obstacles encountered in implementing the IMCI approach in Uganda, factors limiting adherence to treatment recommendations, suggestions (methods or specific questions) for data collection on treatment-seeking, and perceptions of the antimicrobial resistance problem in Uganda.

- **Semi-structured interviews on knowledge and perceptions of medications.** A sample of 30 parents of young children will be administered a 30 minute semi-structured interview on knowledge and perceptions of medications. Topics will include free-listing of types of medications, pile sorting (classification) of locally-available medications for children, and local names for medications.

- **Direct observation of provider-patient interaction.** Activity in the waiting room and patient-provider interaction in health facilities will be directly observed in facilities which have and have not implemented the IMCI approach. Approximately 2 days of observation will be conducted in each facility selected.

- **Exit interviews.** Exit interviews will be conducted with parents of young children upon leaving the health facility. Respondents will be administered a brief survey about how long they waited, what happened in the appointment, what treatment they were told to take, etc., in order to assess the degree to which people understand the information they are being given.

**Phase 2 (3 months)**

- **Evaluation of compliance with treatment recommendations.** In the districts chosen for the study, lists of facilities that are performing "gold standard" IMCI [applying the 3 components of treatment counseling; explain, demonstrate, verify comprehension] and of facilities that have not yet implemented IMCI will be compiled. Children receiving outpatient care at the two types of facilities will randomly be selected for follow-up. The IMCI clinical classification of all children will be determined by trained observers. Children selected for follow-up will be <5 years of age and have a clinical diagnosis of pneumonia, malaria, dysentery or acute ear infection. Children will receive the nationally recommended first-line antimicrobial agent for their clinical diagnosis. All children will be followed-up in the home after 5 days. The two groups will be compared on compliance with treatment. Serum samples may be collected on a sub-sample of children to correlate compliance histories with serum levels of antimicrobials. Qualitative and quantitative data will be collected from compliers and non-compliers with antimicrobial therapy. Areas of particular interest will include the formulation of the medicines, the type of illness, perceived severity of illness, perceived quality of the counseling received, and the role of other family members on treatment practices. It is unlikely that the mortality outcome for the two groups will be able to be compared due to the large sample sizes that would be needed. Barriers to compliance with a full course of antimicrobials will be identified.

**Phase 3 (3 months)**

- **Intervention development.** Data from the second phase will be analyzed. Data on barriers to antimicrobial...
compliance will be used to develop an intervention or interventions that can be implemented at the time of the facility visit. These interventions will be developed with local health staff and program managers. An emphasis will be placed on developing interventions that are feasible using local resources, acceptable to local staff and communities, and time efficient. Potential interventions will be pre-tested.

**Phase 4 (3 months)**
A design similar to Phase 2 will be implemented. Facilities already implementing "gold standard" IMCI counseling will be randomized to continue with existing counseling, or to implement an improved counseling approach based on the results of the preceding phases. A costing element will be added to estimate the cost of adding the intervention(s) to routine outpatient practice. All children will be followed up in the home at 5 days and compliance with treatment will be assessed. The same variables will be evaluated. Qualitative and quantitative methods will again be used to assess compliers and non-compliers. The effectiveness and cost-effectiveness of the intervention(s) to improve antimicrobial compliance will be determined.

**Expected outputs, results and progress indicators:**
**Outputs:** a cost-effective intervention(s) to improve compliance with antimicrobial therapy given to sick children at health facilities using the IMCI approach.
**Results:** a reduction in the number of sub-therapeutic doses of antimicrobials given to sick children and a slowing in the development of antimicrobial resistance to common childhood pathogens; a reduction in overall mortality for sick children managed as outpatients with antimicrobials.
**Progress indicators:** data from phases 1 and 2 analyzed and presented: Barriers to compliance with antimicrobial therapy at home following counseling at outpatient health facilities; intervention to improve compliance with treatment recommendations developed and pre-tested; intervention implemented and evaluated.

**Countries/Regions:** Uganda was selected as the site for the following reasons: 1) High morbidity and mortality amongst children <5 from lower respiratory tract infections and malaria; 2) Commitment by the ministry of health to use IMCI as its primary child health strategy; 3) Active implementation of IMCI in the country and availability of trained health workers; 4) Strong JHU links with ministry of health staff and research institutions in the country; and 5) Availability of highly trained local research counterparts.

**Partners/Collaborating Institutions:** Ministry of Health in Uganda and the Ugandan Institute of Public Health (research expertise); the protocol will be developed in collaboration with WHO/CAH which is coordinating the global IMCI initiative. CHD has identified compliance with antimicrobial therapy as a key research area. Coordination with WHO in Uganda will allow locally trained staff to be identified. CHD will be involved with the interpretation and dissemination of results; participation will be critical if wider recommendations for improving antimicrobial compliance are to be made. Collaboration with INRUD will be sought for the development of methods to investigate the behavioral aspects of compliance with antimicrobial therapy.

**Results to Date:** Study completed and results presented at a community IMCI conference in Baltimore (January 2001).

5.8 Clinical Efficacy of Short Course Treatment with Ceftriaxone for Bacterial Meningitis

**Implementing Organizations:** JHU/FHACS and WHO/CAH
**Status:** On-going (Funded: FY1998; Expected Completion: FY2003)

**Rationale:** Early identification and prompt antibiotic therapy have been crucial in reducing the mortality and morbidity from meningitis over the last 40 years. Recently the treatment of meningitis has been complicated by the emergence of high rates of *Streptococcus pneumoniae* resistant to penicillin, and the increase in *Haemophilus influenzae* type b (Hib) strains resistant to ampicillin and chloramphenicol. Third generation antibiotics (ceftriaxone and cefotaxime) have become the standard drugs for initiating antibiotic treatment of meningitis in most developed and some developing countries. The optimal duration of therapy for bacterial meningitis is not clear and recommendations have varied in different countries. In the United States, the recommended duration of treatment has been 7-10 days for meningitis due to Hib, 10-14 days for *S. pneumoniae* meningitis, and 7 days for *Neisseria meningitidis*. Antibiotic treatment courses as short as 3-to-5 days have been shown to be highly effective in children and adults with meningitis due to *N. meningitidis*.

Recommendations for duration of treatment for meningitis caused by Hib and *S. pneumoniae* were derived from clinical case series of meningitis conducted primarily in the 1960's with antibiotics that are not as effective as the new cephalosporins. For example, relapses appear to be more frequent following chloramphenicol therapy, which is bacteriostatic for many bacteria, and organisms are killed relatively slowly. In contrast, third generation cephalosporins are rapidly bactericidal resulting in sterilization of the cerebrospinal fluid within 48 hours in almost all patients who have meningitis due to susceptible organisms. Recent studies have demonstrated that 6-to-7 days of ceftriaxone therapy can cure meningitis due to Hib and *S. pneumoniae* without increased rates of relapse or neurological sequelae. Maintaining intravenous infusions over a 10-day period can be difficult and tax the limited resources available in many developing country hospitals. A 5-day treatment course would make the use of these more expensive antibiotics feasible and cost-effective. If a shorter treatment course is proved to be efficacious, it would have profound implications for the treatment of bacterial meningitis all over the world. This would have special implications for IMCI in the developing countries. It is also expected that short (5 days) course of injectable third generation cephalosporin (ceftriaxone or cefotaxime) is less likely to cause antimicrobial resistance as compared to the 10 days course in treatment of bacterial meningitis.

**Objective(s):** To compare the safety and rates of bacteriologic cure, relapse, deafness and other sequelae in children with acute bacterial meningitis due to *H. influenzae* type b, *S. pneumoniae* and *N. meningitidis* who receive 5 vs. 10 days of therapy with ceftriaxone.

**Description:** A multi-centre study will be set up in developing countries. Bacterial meningitis cases among children will be randomized to two treatment groups. One group will receive 5 days of injectable third generation cephalosporin (ceftriaxone or cefotaxime) followed by 5 days placebo in a blinded manner and the other group will be randomized to injectable third generation cephalosporin (ceftriaxone or cefotaxime) for 10 days. Cerebrospinal fluid and blood isolates will be obtained before treatment and after 24-48 hours of treatment to see the persistence of bacteria in the cerebrospinal fluid or blood. Facilities for CSF cultures and basic susceptibility testing will be developed where they are not available.

**Expected Outputs, Results, and Progress Indicators:**
- Antimicrobial resistance rates for common bacteria causing bacterial meningitis will be documented;  
- It will provide information that will help the developing countries to decide whether to change the first line antimicrobial guidelines for the treatment of bacterial meningitis;  
- Short (5 days) course of injectable third generation cephalosporin (ceftriaxone or cefotaxime) is less likely to cause antimicrobial resistance as compared to the 10 days course in treatment of bacterial meningitis;
Short (5 days) course of injectable third generation cephalosporin (ceftriaxone or cefotaxime) is as efficacious as 10 days course for bacterial meningitis; Capacity building of the research institutions regarding clinical and microbiological work; Negotiations with the pharmaceutical industry to bring down the price of ceftriaxone.  

**Progress Indicators:** development of a research protocol; initiation of data collection.

**Countries/Regions:** Guatemala, Pakistan, South Africa, and Vietnam (a total of ten tertiary care hospitals). WHO will conduct studies in Pakistan and South Africa; JHU will conduct studies in Guatemala: Hospital General San Juan de Dios (HGSJD); Hospital Roosevelt (HR); and the General Hospital of the Institute of Guatemalan Social Security (IGSS). (The HGSJD will be the coordinating center.) To get adequate number of patients which are representative would require at least 4-5 sites. Bangladesh may be added in order to reach the desired sample size.

**Partners/Collaborating Organizations:** WHO will host a meeting to standardize methodologies (enrollment, treatment guidelines, outcome measures and patient assessment). JHU data from Latin America and WHO-sponsored data from Africa and Asia will complement each other and will be representative of all developing regions. A prospective meta-analysis of the data from both studies will be performed after completion.

WHO has approached Hoffmann La Roche Pharmaceuticals, Switzerland (manufacturers of ceftriaxone) for donation of ceftriaxone for the above mentioned studies. Negotiations have started and Roche is considering the request favourably. The study medicine cost (ceftriaxone) alone for both JHU and WHO supported studies could be as high as 300-350,000 US$. WHO is also in negotiations with Roche Pharmaceuticals, Switzerland for bringing down the price of ceftriaxone in order to make it more accessible to the needy patients in the developing countries.

**Results to Date:** The drugs for the study were finally donated by Medochemie (Malta) and were made available to the study sites in March 2001. Data collection was therefore started at all sites in April 2001 and is expected to last two years. Because of difficulties recruiting sufficient numbers of cases, the study may expand to also include Bangladesh.

**5.9 Development of a Clinical Prediction Instrument for Group A Streptococcal Pharyngitis (GRASP)**

**Implementing Organizations:** JHU/FHACS and WHO/CAH

**Status:** On-going (Funded: FY1998; Expected Completion: FY2003)

**Rationale:** Pharyngitis or sore throat is a common ailment the world over, and is especially common in children. Pharyngitis due to group A, beta-hemolytic *Streptococcus* assumes a special significance because of the risk of subsequent rheumatic fever (RF) and chronic rheumatic heart disease (RHD) in the infected host. RHD is a major public health problem in developing countries today, where it is the leading cause of cardiovascular morbidity and mortality in children and young adults. Besides the enormous economic burden of medical and surgical costs, these illnesses cause great suffering and hardship to the victims and their families, with repeated hospitalisations, disability and premature death.

In economically developed countries, RF and RHD are largely controlled, due to antibiotic treatment of streptococcal pharyngitis and improvements in living standards. However, antibiotic treatment of all
pharyngitis episodes is wasteful--since it means overtreatment of 70 - 80% of cases--and there are concerns about health costs, penicillin allergy, and alteration of normal throat flora. One of the major problems is that unnecessary antibiotic use for sore throat may result in emergence of drug-resistant strains of other pathogens especially *S. pneumoniae* and *H. influenzae* which has already been noted in some parts of the world.

In developing countries, these same problems exist and are compounded by other deficiencies. The prevalence of Group A streptococcal pharyngitis (GRASP) in these countries is largely unknown due to paucity of studies. Secondly, facilities for performing throat cultures levels and agglutination tests as well as determining antibody titres are not generally available. Lastly, because of lack of awareness, many patients do not seek medical care. Since it is not desirable to treat all pharyngitis with antibiotics and laboratory facilities are usually not available, it would be useful to have a clinical prediction rule for GRASP, especially for use in developing countries.

**Objectives:** To identify the optimal set of clinical findings in children between 24 months and 12 years of age that are predictive of GRASP as documented by positive throat culture and/or serology. Data from the study will be used to create clinical prediction instruments tailored to health care providers with different levels of training (physicians, mid-level practitioners and community health workers) in various clinical settings (outpatient departments, emergency departments, and rural and urban ambulatory practices). Based on study data, a cost-effectiveness analysis will be conducted to determine the appropriate threshold for treatment and throat culture in different settings.

Secondary objectives include describing: the prevalence of GRASP in children seeking care for the complaint of sore throat under different conditions (i.e., season, age) in different geographical areas; variations in serotypes, M-types and serologic response to Group A streptococcal infection in different geographical areas and the relationship of these markers to the clinical virulence of Group A streptococci causing pharyngitis; the frequency of secondary complications of GRASP in different countries; the patterns of developing of antimicrobial resistance in infected and uninfected patients following treatment with antibiotics; and the prevalence of the carrier state in non-symptomatic patients.

**Description:** In many developing countries it is not possible to obtain a throat culture needed for identification of GRASP prior to the prescription of appropriate antibiotics. This collaborative, multi-center study seeks to improve the diagnosis and management of streptococcal sore throat by determining the clinical findings that reliably predict GRASP using standardized laboratory protocols. The goal of the study is to help clinicians make more rational use of the clinical history and examination in determining the need for antibiotic therapy. A second goal is to reduce the unnecessary use of antibiotics in patients having a low probability of streptococcal pharyngitis. Local capacity will be built by standardizing methodology for culture and serology.

**Expected Outputs, Results, and Progress Indicators:**

**Outputs:** (1) uniform prospectively collected data on the prevalence of streptococcal pharyngitis in a variety of developing country sites; (2) uniform and prospectively collected information regarding the correlation of signs and symptoms in young children with the proven presence of streptococcal pharyngitis; (3) prospective data on the serology of streptococcal infections in selected sites; (4) prospective data on the prevalence rates of antimicrobial resistance for *S. pneumoniae* and *H. influenzae*.

**Results:** development of a clinical algorithm presumptive treatment of streptococcal pharyngitis for use in health clinics of developed countries.

**Progress indicators:** (1) development of a joint research protocol; (2) the number of sites (countries) in which activities are initiated; (3) number of studies completed; (4) number of children evaluated; and (5)
scientific presentations and papers.

**Country/Regions:** Brazil, Croatia, India, Latvia, Philippines, Thailand

**Partners:** INCLEN, University of North Carolina, Universidade Federal Do Rio De Janeiro, WHO Collaboration Centre for Reference and Research in Streptococci (Prof. E. Kaplan, University of Minneapolis), and others not yet identified.

**Results to Date:** Results of the pilot study supported by INCLEN and WHO to differentiate between sore throat due to viral infections from those needing antibiotic treatment were analyzed in a workshop held in Bangkok (Thailand) in October 2000. Following this analysis, a proposal for a larger study was finalized in the same workshop. This study will be a multi-centre study conducted in four countries (Brazil, Croatia, India and Latvia); patient recruitment is expected to start in late 2001.

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**5.10 A Multi-Center, Prospective, Observational Study of Clinical Outcome Following Amoxycillin Treatment of Non-Severe Acute Respiratory Infection**

**Implementing Organization:** BU/ARCH

**Status:** Completed (Funded: FY1998; Completed: FY2000)

**Rationale:** The widespread and inappropriate use of antibiotics in the treatment of simple pneumonia, which is often non-bacterial in origin, is potentially a major contributor to the development of antimicrobial resistance.

**Objective(s):** The main objective of the study is to strengthen the ARI research portfolio towards reducing the unnecessary use of antimicrobials for non-severe pneumonia. The goal of the first stage observational component of the study was to determine clinical failure rates using a standard case management approach. This observational data was used to determine the feasibility of conducting a second stage study to determine the safety and efficacy of a placebo controlled equivalency trial comparing no antimicrobials with the use of amoxycillin. These findings on the latter study would support the more restricted use of antibiotics in non-severe pneumonia and if adopted, would significantly reduce the pressure for the development of antibiotic resistance as well as the cost of care.

**Description and Countries/Regions:** This study will determine the feasibility of conducting a placebo controlled study of oral amoxycillin in the treatment of non-severe pneumonia. Specific aims sought will be the proportion of children with antibiotic exposure prior to presentation to the health facility, proportion with signs of consolidation on X ray and the failure rate of oral amoxycillin in the treatment of non-severe pneumonia. The research studies will be conducted in South Africa and Vietnam.

**Expected Outputs, Results, and Progress Indicators:** The principal output of this component is the conduct of the specified research studies, their analysis, and the dissemination of the results to the global and national programs responsible for ARI case management. Researchers and policymakers concerned with slowing the spread of antimicrobial resistance will also benefit from the research results.

**Countries/Regions:** South Africa and Vietnam.

**Partners/Collaborating Institutions:** All the activities will operate within well-functioning consortia
with WHO/CAH (see activity 5.13: "Increased Specificity of Treatment Guidelines for Non-Severe Pneumonia").

Results to Date: The study was completed in 2000. Because of a high degree of prior antibiotic exposure (up to 44%) and the presence of signs of consolidation on chest x-ray in more than 20% of cases, it was deemed that a placebo-controlled study (see 5.13) would not be feasible in these populations.

### 5.11 Efficacy of Short Course Treatment with Oral Amoxicillin for Non-Severe Pneumonia and its Relationship with Antimicrobial Resistance

**Implementing Organization:** WHO/CAH

**Status:** On-going (Funded: FY1998; Expected Completion: FY2001)

**Rationale:** At present WHO ARI Control Programme recommends oral antimicrobials for the treatment of non-severe pneumonia for five days. Cotrimoxazole is recommended two times a day as compared for oral amoxicillin, which is recommended three times a day. It is also known that the patients do not comply well with the recommended duration of therapy for five days and may take the antimicrobials for as little as 2-3 days. Similarly, often they may take oral medicines twice a day instead of thrice a day. There are two very important public health issues related to these problems. First, what are the implications of this "shorter" duration of antimicrobial use on development of antimicrobial resistance. Second, oral amoxicillin is three times more expensive than oral cotrimoxazole. If it were shown that a shorter duration (3 days) of oral amoxicillin is as efficacious as 5 days of therapy, it would have profound implications for the public health policy. It would reduce the cost of treatment and will also improve the patient compliance to treatment. There is a need to find out the effect of a shorter course of therapy on antimicrobial resistance for *Streptococcus pneumoniae* and *Haemophilus influenzae* and whether it is as efficacious as the normal five days course of oral amoxicillin for non-severe pneumonia. We expect that conducting a clinical efficacy trial by comparing the two regimens and collecting the antimicrobial resistance data can answer this question.

**Objective(s):** To study which duration (3 versus 5 days) is less likely to lead to the emergence of resistant strains of *S. pneumoniae* and *H. influenzae* and to test the efficacy of 3 days oral amoxicillin therapy as compared to five days therapy for non-severe pneumonia.

**Description:** The aim of this research is to optimize antimicrobial use for childhood diseases to slow the emergence and spread of antimicrobial resistance. In a multi-centre trial, non-severe pneumonia cases among children 2-59 month old will be randomized to two treatment groups. One group will be randomized to oral amoxicillin for 3 days followed by 2 days placebo in a blinded manner and the other group will be randomized to oral amoxicillin for 5 days. Nasopharyngeal isolates will be obtained before and after treatment to see the resistance levels of *S. pneumoniae* and *H. influenzae* to penicillin, cotrimoxazole, ampicillin etc.

**Expected Outputs, Results, and Progress Indicators:**

**Outputs:** a shorter course of oral amoxicillin is less likely to lead to the emergence of resistant strains of *S. pneumoniae* and *H. influenzae*, simplified IMCI treatment guidelines.

**Progress Indicators:** development of a research protocol; initiation of data collection.

**Countries/Regions:** Pakistan (total of 6 hospitals in Gilgit, Islamabad, Lahore, Multan, and Rawalpindi.)
Partners/Collaborating Institutions: CDC/Respiratory Diseases Branch is planning to conduct a study on the impact of compliance on development of antimicrobial resistance. Theirs is an observational study and they do not plan to do any intervention. We will collaborate with them so that there is no duplication of the data and both studies complement each other’s results.

Results to Date: Data collection was completed in April 2001. Analysis is underway and results will be available in September 2001 for presentation at the IUATLD World Conference on Lung Disease to be held in Paris (France), from 1-4 November 2001.

5.12 Efficacy of Short Course Treatment with Oral Cotrimoxazole in Treatment of Non-Severe Pneumonia and its Relationship with AntimicrobialResistance

Implementing Organization: WHO/CAH

Status: On-going (Funded: FY1998; Expected Completion: FY2003)

Rationale: At present WHO ARI Control Programme recommends oral antimicrobials for the treatment of non-severe pneumonia for five days. Cotrimoxazole is the first line antimicrobial recommended two times a day. It is also known that the patients do not comply well with the recommended duration of therapy for five days and may take the antimicrobials for as little as 2-3 days. There are two very important public health issues related to these problems. First, what are the implications of this "shorter" duration of antimicrobial use on development of antimicrobial resistance. Second, if three days treatment is as effective as five day therapy, it would reduce the cost of treatment and will also improve the patient compliance to treatment. There is a need to find out the effect of a shorter course of therapy on antimicrobial resistance for \textit{S. pneumoniae} and \textit{H. influenzae} and whether it is as efficacious as the normal five days course of oral cotrimoxazole for non-severe pneumonia. We expect that conducting a clinical efficacy trial by comparing the two regimens and collecting the antimicrobial resistance data can answer this question.

Objective(s): To study which duration (3 versus 5 days) is least likely to lead to the emergence of resistant strains of \textit{S. pneumoniae} and \textit{H. influenzae}, to study whether 3 days oral cotrimoxazole therapy is as efficacious as five days of therapy for non-severe pneumonia.

Description: The aim of this research is to optimize antimicrobial use for childhood diseases to slowdown the emergence and spread of antimicrobial resistance. In a multi-centre trial, non-severe pneumonia cases among children 2-59 month old will be randomized to two treatment group. One group will be randomized to oral cotrimoxazole for 3 days followed by 2 days placebo in a blinded manner and the other group will be randomized to oral cotrimoxazole for 5 days. Nasopharyngeal isolates will be obtained before and after treatment to see the resistance levels of \textit{S. pneumoniae} and \textit{H. influenzae} to penicillin, cotrimoxazole, ampicillin etc.

Expected Outputs, Results, and Progress Indicators: It is expected that shorter course of oral cotrimoxazole is less likely to lead to the emergence of resistant strains of \textit{S. pneumoniae} and \textit{H. influenzae}. Development of simplified treatment guidelines for non-severe pneumonia, for inclusion in the IMCI package.

Progress Indicators: development of a research protocol; initiation of data collection.
Countries/Regions: Bangladesh (Shishu Hospital) and Indonesia (Bandung)

Partners/Collaborating Institutions: None.

Results to Date: A protocol to investigate the efficacy of short course treatment with oral cotrimoxazole for non-severe pneumonia and its relationship with antimicrobial resistance has been finalized. Two sites, one in Bangladesh and one in Indonesia, have been identified. The study objectives are: (i) determine the clinical efficacy of a 3-day course of oral cotrimoxazole in the treatment of non-severe pneumonia compared to the standard 5-day course of oral cotrimoxazole; and (ii) monitor the emergence of resistant strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* in the two treatment groups. Delays have been experienced in gaining local ethical clearance. Data collection will begin in September 2001.

### 5.13 Increased Specificity of Treatment Guidelines for Non-Severe Pneumonia

**Implementing Organization:** WHO/CAH

**Status:** Discontinued (Funded: FY1998)

**Rationale:** In the past decade, resistance to commonly used antimicrobials among bacteria causing acute respiratory disease (ARI) in children has increased in prevalence. This has raised concerns about the current clinical management guidelines for non-severe pneumonia recommended by the World Health Organization (WHO) for use in the developing world. Many children with simple pneumonia treated according to the WHO guidelines are lost to follow-up, and many do not complete the recommended course of therapy because they may improve quickly. This may mean that the duration of an appropriate antimicrobial regimen may be too brief, and that any left over medicine may be used inappropriately in the future. Both of these behaviours are potential risk factors for the selection and amplification of drug resistance genes among respiratory pathogens. When the WHO ARI guidelines were first developed, it was recognized that many, if not the majority of children with so-called non-severe pneumonia may have non-bacterial infections and would not benefit from the use of antimicrobials. However, to maximize the number of children treated who really need antimicrobials, all children with fast breathing were recommended for antimicrobial treatment at the cost of also treating many children who did not need a drug. At that time, however, antimicrobial resistance was not common among the major lower respiratory tract bacterial pathogens. Because of increase in the antimicrobial resistance it has become essential to reduce unnecessary and inappropriate antimicrobial use, and increase the specificity of the WHO management guideline. If antimicrobial treatment for non-severe pneumonia can be shown to be of little benefit in some well defined cases, there would be a justification to revise the present clinical management guideline so that patients at low risk of bacterial infection would not receive an antimicrobial at the initial encounter.

**Objective(s):** To determine whether children 2 to 59 months of age with WHO defined non-severe pneumonia have an equivalent clinical failure rate when they are treated with oral amoxicillin compared to no amoxicillin; to improve the specificity of treatment guidelines for non-severe pneumonia.

**Description:** In a multi-center trial of non-severe pneumonia among children 2-59 month old cases will be randomized to two treatment groups. One group will be randomized to oral amoxicillin for 5 days and the other group will be randomized to oral placebo for 5 days. Blood cultures nasopharyngeal swabs for *S. pneumoniae* and *H. influenzae* and nasopharyngeal aspirates for RSV virus will be obtained in these children.
NOTE: The sample size needed to answer this question is much bigger study than what was anticipated before the proposal development workshop. It means that some sites would have to collect data for up to 18 months in order to get enough patients over two acute respiratory infection (ARI) seasons. It is expected that approximately one-third of this amount will be spent on microbiology and the rest on the clinical aspects of the study.

Expected Outputs, Results, and Progress Indicators:
- Development of revised recommendations for the management of WHO defined non-severe pneumonia, to be included in the IMCI case management guidelines;
- A research protocol has been developed in a proposal development workshop (Canberra, Australia) to answer this question;
- Oral amoxicillin is as effective as no oral amoxicillin in WHO defined non-severe pneumonia;
- Building research capacity regarding clinical, epidemiology and microbiology of the involved institutions.

Progress Indicators: development of a research protocol; initiation of data collection.

Countries/Regions: A descriptive study was conducted in Vietnam (Ho Chi Minh City) and South Africa (Durban).

Partners/Collaborating Organizations: This will be a large multi-center trial. BU/ARCH and WHO/CAH co-funded the proposal development workshop in Canberra, Australia and will co-ordinate the study together (see activity 5.10: "A Multi-Center, Prospective, Observational Study of Clinical Outcome Following Amoxicillin Treatment of Non-Severe Acute Respiratory Infection"). INCLEN also supported one researcher and one facilitator to attend the proposal development workshop.

Results to Date: The feasibility of conducting this study was dependant on the outcome of activity 5.10 (above) which was a preliminary observational cohort study of the failure rate and frequency of prior antimicrobial use in a population of children 2-59 months. The descriptive study to investigate the case management of non-severe pneumonia, with and without wheeze, was conducted in South Africa and Vietnam; data collection was completed and a preliminary analysis performed. Failure rate among children with non-severe pneumonia was considerably less than expected. In addition, the amount of antimicrobial use prior to presentation at the hospital was low in South Africa (11%), but quite high in Vietnam (44%). Preliminary findings from the data collected in these two sites indicate that children with non-severe pneumonia had chest X-ray evidence of pneumonia (75% in South Africa and 48% in Vietnam). The presence of chest X-ray findings on such a high proportion of the children enrolled in the study implies that a bacterial process was the underlying cause (or a complication) of many of the cases of WHO-defined pneumonia in the children enrolled into the study at these two sites. Given the high likelihood of the presence of bacterial infection in children presenting with non-severe pneumonia, it would not be appropriate to enroll children with non-severe pneumonia into a placebo-controlled trial, as originally conceived.

Results form this study will be presented at the IUATLD World Conference to be held in Paris (France) from 1-4 November 2001.

5.14 Increased Specificity of Treatment Guidelines for Children with Wheezing Diagnosed as WHO-Defined, Non-Severe Pneumonia
Implementing Organization: WHO/CAH and BU/ARCH

Status: On-going (Funded: FY1998; Expected Completion: FY2003)

Rationale: The ARI case management guidelines recommend use of oral antimicrobials for non-severe pneumonia, which is defined as cough or difficult breathing plus fast breathing. This is recognized to be a definition of pneumonia that is relatively imprecise, and results in the inclusion of substantial numbers of children that have bronchospasm due to asthma, RSV infection or hyper-reactive airway disease rather than pneumonia. A more precise definition of non-severe pneumonia would assist in patient care decisions and in efforts to minimize the inappropriate use of antibiotics.

If antimicrobial treatment can be shown to be of little benefit to children presenting with wheezing and inappropriately categorized as having non-severe pneumonia, there would be a justification to modify the present ARI case management guidelines so that these children do not receive an antibiotic.

In order to determine how to increase the specificity of ARI case management guidelines, WHO convened a meeting of members of the ARCH Project and six clinical researchers in the field of respiratory infections and wheezing to seek their opinions about this issue in December, 2000. This panel recommended that studies be undertaken to assess the efficacy of a new therapeutic approach for children with suspected non-severe pneumonia who present with wheezing. While the experts acknowledged the value of studying this through a randomized controlled trial (RCT), some recommended collecting more descriptive data before designing such a clinical trial.

In order to define the research question, the technical consultation discussed the methodological issues related to this research. Current published and unpublished data from India, Pakistan, Thailand, and Vietnam were reviewed with the intent of designing a study to refine the ARI case management guidelines concerning children presenting with difficulty breathing and wheezing. However, in discussing the characteristics of the study question (i.e., study population, intervention, effect of intervention and outcome) several limitations to the RCT were identified:

- A relatively small proportion of children with non-severe pneumonia have audible wheezing.
- Relatively large numbers of children presenting with cough or difficult breathing receive antibiotics before presentation to the hospital, thus enrolling patients who have not received antibiotics will be quite challenging.
- A fairly large number of patients, categorized as non-severe pneumonia with wheezing, will be required to address this issue.
- There are ethical concerns about the possibility of increases in mortality in non-severe pneumonia patients randomized to placebo.
- Data from a non-severe study in Vietnam suggested that the likely impact of antibiotic overprescription in cases categorized as non-severe pneumonia plus wheezing may be small, although these data did not include data from the RSV bronchiolitis 'season'.

The panel of experts was also concerned that health workers do not consistently recognize wheezing. Because wheezing is audible in only one-third of cases, many children with signs of pneumonia but inaudible wheezing may be inaccurately categorized as non-severe pneumonia, and inappropriately given antibiotics rather than a trial of bronchodilators.
It was concluded that available information was inadequate to design a RCT that was feasible and not prohibitively expensive. It was decided instead to conduct a study to model the likely impact of (i) improving the clinical recognition of wheezing, and (ii) more extensive use of rapid acting bronchodilators in this population of children. This information would be helpful in determining the feasibility of a RCT.

**Objective(s):** To determine the feasibility of conducting a RCT to assess the need for antimicrobial treatment of children 2-59 months of age who present with fast breathing and wheeze and to increase the specificity of treatment guidelines for children with wheezing diagnosed as WHO defined non-severe pneumonia.

**Description:** In a multi-center trial of children 2-59 month old with wheeze who are determined to be suffering from non-severe pneumonia will be observed for 5-7 days after treatment with oral bronchodilators for recurrence or treatment failure. Nasopharyngeal swabs for *S. pneumoniae* and *H. influenzae* and nasopharyngeal aspirates for RSV virus will be obtained in these children.

**Expected Outcomes, Results, and Progress Indicators:**
- Development of revised recommendations for the management of wheezing children, to be included in the IMCI case management guidelines;
- Determination of the feasibility of mounting a RCT of oral amoxicillin compared with placebo in children with wheezing assessed as WHO defined non-severe pneumonia;
- Building research capacity regarding clinical, epidemiology and microbiology of the involved institutions.

**Progress Indicators:** development of a research protocol; initiation of data collection.

**Countries/Regions:** The study will be conducted in Colombia, Egypt, Ghana, India, Pakistan, and Thailand.

**Partners/Collaborating Organizations:** This will be a large, multi-center trial. BU/ARCH and CHD/WHO co-funded the proposal development and will co-ordinate the study together (see activities 5.10 and 5.13).

**Results to Date:** Work progressed to increase specificity of treatment guidelines for children with wheezing diagnosed as WHO-defined, non-severe pneumonia. A model research proposal was developed, reviewed and finalized during a workshop held in Geneva in December 2000. A multi-centre study involving six countries (Colombia, Egypt, Ghana, India, Pakistan and Thailand) will soon be initiated. The main objectives of the study are to: (i) follow the clinical course of children 1-59 months presenting in the outpatient department (OPD) with wheeze along with cough and difficult breathing; (ii) define the clinical characteristics of children with wheeze; and (iii) determine how many children treated for wheeze relapse within 7 days.

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5.15 Clinical Efficacy of Oral Amoxicillin as Compared to Injectable Penicillin for the Treatment of Severe Pneumonia

**Implementing Organization:** BU/ARCH and WHO/CAH

**Status:** On-going (Funded: FY1998; Expected Completion: FY2002)

**Rationale:** At present for WHO defined severe pneumonia treatment with injectable benzyl penicillin is recommended after the child has been hospitalized. There are several issues, which are related to this
hospitalization. First is higher cost of therapy, hospitalization and other indirect costs. Second, risks associated with hospitalization such as nosocomial infections, risks of injectable therapy leading to hepatitis B and C, HIV and other viral infections. Finally, in some circumstances the referral to the hospital may not be possible due to economic or logistic reasons. In one study from Pakistan oral amoxicillin was found quite efficacious in children with WHO defined severe pneumonia. If these results were replicable in other settings, it would be possible to reduce the number of referrals and admissions for injectable therapy, which will in turn result in less nosocomial hospital infections. It is also expected that it is also less likely to lead to emergence of penicillin-resistant strains of \textit{S. pneumoniae} and \textit{H. influenzae}. This study has very important implications for the Integrated Management of Childhood Illnesses (IMCI) strategy. It will optimize antimicrobial use for childhood diseases to slowdown the emergence and spread of antimicrobial resistance.

**Objective(s):** To determine whether children 2 to 59 months of age with WHO defined severe pneumonia have an equivalent clinical failure rate when they are treated with oral amoxicillin compared to injectable penicillin.

**Description:** In a multi-centre trial, severe pneumonia cases among 3-59 months old will be randomized to either therapeutic regimen. One group will be randomized to oral amoxicillin for 7 days and the other group will be randomized to injectable benzyl penicillin for 7 days. Nasopharyngeal swabs will be obtained from all patients to assess penicillin-resistant strains of \textit{Streptococcus pneumoniae} and \textit{Haemophilus influenzae}. 

**NOTE:** The sample size needed to answer this question is more than 1700 severe pneumonia patients. This is a much bigger study than what was anticipated before the proposal development workshop. It means that some sites would have to collect data for up to 18 months in order to get enough patients over two acute respiratory infection (ARI) seasons. This funding will be used for both clinical and microbiology work planned for this study.

**Expected Outputs, Results, and Progress Indicators:**
- Development of revised recommendations for the management of severe pneumonia, to be included in the IMCI case management guidelines;
- A research protocol has been developed in a proposal development workshop (Durban, South Africa) to answer this question;
- Oral amoxicillin is as effective as injectable benzyl penicillin in WHO defined severe pneumonia;
- This study will improve the capacity for epidemiological and microbiological research in the institutions involved.

**Progress Indicators:** development of a research protocol; initiation of data collection.

**Countries/Regions:** The study will be conducted in South Africa (Departments of Paediatrics Child Health at University of Cape Town, Cape Town and University of Natal, Durban), Ghana (Kitampo Vitamin A Project (KIVAP), Kintampo), Zambia (Tropical Diseases Research Centre, Ndola), Colombia (Unidad de Epidemiologia Clinica, Facultad de Medicina, Pontifica Universidad Javeriana Carrera, Bogota), Mexico (Division de Investigacion Medica, Instituto Nacional de Pediatria, Mexico), and a few countries in Asia (India, Pakistan, and Vietnam).

**Partners/Collaborating Institutions:** BU/ARCH (WHO and ARCH co-funded the proposal development workshop in Durban, South Africa and will co-ordinate the study together).

**Results to Date:** The multi-centre clinical trial to compare the efficacy of injectable penicillin with oral amoxicillin in the treatment of severe pneumonia in children is progressing in seven of the original sites (Colombia, Ghana, India, Mexico, Pakistan, South Africa/Durban, and Vietnam), but not in South
Africa/Cape Town or Zambia, which has had decreasing patient enrollment. Interim analyses were performed in April 2000 and April 2001 by the Data Safety and Monitoring Board (DSMB) that confirmed the originally calculated sample size. So far, enrollment for this study has reached 75% of the projected sample size. Therefore, patient recruitment in this study will continue until December 2001.

5.16 Management of WHO-Defined, Very-Severe Pneumonia

Implementing Organization: BU/ARCH and WHO/CAH

Status: On-going (Funded: FY1998; Expected Completion: FY2003)

Rationale: WHO ARI case management guidelines categorize pneumonia in children 2-59 months old into non-severe, severe and very severe pneumonia. Children suffering from very severe pneumonia are referred for hospitalization and injectable chloramphenicol therapy. Although, pneumonia was recognized as the major killer of children under five years old, not much data was available for ideal treatment of these very sick children diagnosed as very severe pneumonia. A number of experienced paediatricians from developed and developing countries were consulted and taking into account efficacy and cost, they recommended chloramphenicol as the drug of choice for very severe pneumonia.

This recommendation needs to be re-visited. First, many of these children assessed as very severe pneumonia may in fact also have bacterial meningitis or septicemia. Symptoms and clinical signs overlap for these three conditions. Data shows that in presence of antimicrobial resistance, a number of these children with bacterial meningitis may not respond to injectable chloramphenicol. Second, there is limited data on the aetiology of very severe pneumonia cases. Data showed *H. influenzae* and *S. pneumoniae* to be the common bacterial organisms causing bacterial meningitis, non-severe and severe pneumonia cases. It is possible that for very severe pneumonia, some other bacteria are responsible which are less susceptible to chloramphenicol. Finally, many paediatricians do not believe chloramphenicol is the right treatment and use a combination of penicillin and gentamicin instead. There is lack of scientific data to support either choice.

Objective(s): Identify bacteria causing very severe pneumonia and document their antimicrobial resistance pattern; compare the clinical efficacy of injectable chloramphenicol with injectable penicillin plus gentamicin for very severe pneumonia cases in children less than five-year-old.

Description: In a clinical trial, very severe pneumonia cases among 2-59 months old children will be randomized to two treatment groups. One group will be randomized to injectable chloramphenicol for 7 days and the other group will be randomized to a combination therapy of injectable penicillin and gentamicin for 7 days. Blood cultures will be obtained to document the aetiology and susceptibility patterns of etiologic agents. Nasopharyngeal swabs would be obtained to document carriage and resistance rates in children with very severe pneumonia.

Expected Outputs, Results, and Progress Indicators:
- Development of revised recommendations for the management of children with very severe pneumonia, to be included in the IMCI case management guidelines;
- Better scientific data to improve treatment guidelines for very severe pneumonia cases, resulting in more appropriate antimicrobial use in the referral level facilities.

Progress Indicators: development of a research protocol; initiation of data collection.
Countries/Regions: Study sites include Bangladesh, India, Mexico, Pakistan, Yemen, and Zambia.

Partners/Collaborating Organizations: BU/ARCH coordinates this activity with WHO/CAH.

Results to Date: The study has been initiated in eight tertiary care hospitals in six countries (Bangladesh, India, Mexico, Pakistan, Yemen and Zambia). Enrollment for this study is approximately 35% of the desired sample size. It is projected to continue for another 12-18 months.

5.17 Epidemiological, Laboratory, and other Technical Assistance

Implementing Organization: CDC/NCID

Status: On-going (Funded: FY1998; Information not provided on expected completion date)

Rationale: Epidemiological, laboratory, and other technical expertise are important for the development and conduct of surveillance, for investigation of the factors contributing to the spread of resistance, and for the development and evaluation of intervention programs. Development of a global strategy for investigation and prevention of antimicrobial resistance is important so that activities can be focused on the highest priority areas and can be coordinated to achieve the greatest impact. In addition, promoting the goal of controlling antimicrobial resistance with USAID personnel and Ministries of Health may lead to more activities and support for this activity.

Objective(s):
1) Provide epidemiological and laboratory assistance to other organizations participating in activities to combat the spread of antimicrobial resistance.
2) Assist in the development of a global strategy to address the spread of antimicrobial resistance.

Description: CDC epidemiologists have considerable international experience in development and evaluation of surveillance, investigation and intervention programs. In addition, there is a long history of collaboration with WHO and other international organizations on issues related to child survival and antimicrobial resistance. Given this background and context, we propose CDC participates in the development of a global strategy to address the spread of antimicrobial resistance and, at USAID’s request, participate in the technical review of proposals and consultancies with other partners. Similarly, CDC laboratory personnel and epidemiologists can provide expert review and training at CDC or in the field.

Expected Outputs, Results, and Progress Indicators:
- Technical assistance to countries requesting laboratory and epidemiological consultations.
- Training of foreign scientists.
- Consultations with partners to help develop global strategy.

Countries/Regions: Argentina, Bangladesh, Brazil, Chile, Czech Republic, Dominican Republic, Ecuador, the Gambia, Ghana, Kenya, Mexico, Peru, South Africa, Uruguay, Zimbabwe, as well as Global activities via WHO, USAID, WHO/AFRO and PAHO.

Partners/Collaborating Institutions: WHO; other organizations requesting assistance

Results to Date:

2) Support of participation in international pneumococcal resistance meeting

3) Support of international researcher’s attendance to present on resistance at International Conference on Emerging Infectious Diseases (Atlanta, Georgia, USA).

4) Support of laboratory supplies and educational materials for training purposes

5) Participation in meetings sharing information with other international public health agencies to inform policy and practice.


7) Technical assistance with analysis of epidemiological and microbiological data.

8) Training of microbiologists from Bangladesh, Brazil, Chile, Czech Republic, Denmark, Dominican Republic and Mexico at the CDC Streptococcal Reference Laboratory (a WHO Collaborating Center for Streptococcal Research).

9) Facilitation of microbiologic testing of pneumococcal cultures from: Argentina, Brazil, Canada, Chile, Dominican Republic, Ecuador, Mexico, Nepal, Peru and Uruguay.

10) Support of coordinator for capacity-building, epidemiology and laboratory training activities.

11) Technical consultations to support development of country-level surveillance for antimicrobial resistance

12) Participation in meetings to develop global strategy to combat antimicrobial resistance and to boost laboratory and epidemiological capacity

5.18 Evaluation of the Impact of Pneumococcal Conjugate Vaccine on Antimicrobial Resistant Streptococcus pneumoniae

Implementing Organization: CDC/NCID

Status: On-going (Funded: FY1999; Expected Completion: FY2003)

Rationale: Streptococcus pneumoniae is the predominant cause of bacterial pneumonia and a major cause of meningitis, sepsis, and ear infections. This organism has become increasingly resistant to multiple classes of oral and parenteral antibiotics, complicating clinical management decisions and increasing the cost of caring for children in both developed and resource-poor countries. Protein-polysaccharide conjugate vaccines directed against 7, 9, or 11 pneumococcal serotypes are under investigation in several countries. A 7-valent formulation was shown to be efficacious against bacteremic disease, otitis media, and radiographically confirmed pneumonia with consolidation among infants studied in a Northern California managed care population. Preliminary studies suggest that pneumococcal conjugate vaccines reduce nasopharyngeal carriage of pneumococci due to serotypes included in the vaccine, but may increase carriage of other serotypes (non-vaccine types). To date, the majority of pneumococci associated with penicillin resistance are caused by serotypes included in the seven-valent protein-polysaccharide conjugate vaccine formulation. In the United States, where the vaccine was approved for use in early 2000 but has not yet been widely administered, data from the Active Bacterial Core surveillance (ABCs) system estimates the proportion of resistant invasive pneumococcal disease caused by vaccine-serotypes to be 77%. A study of a Northern California managed care population showed the 7-valent conjugate vaccine to be efficacious against bacteremic disease, otitis media and radiographically-confirmed pneumonia with consolidation among infants. Preliminary studies also suggest that pneumococcal conjugate vaccines may
reduce nasopharyngeal carriage of vaccine-serotypes and increase carriage of non-vaccine serotypes. Because the carriage of \textit{S. pneumoniae} in the nasopharynx is associated with its transmission, and because it is believed that the vaccine will effectively target those invasive serotypes that carry resistance, we hypothesize the conjugate vaccine may effectively function as an anti-resistance tool.

The potential for pneumococcal conjugate vaccines to reduce nasopharyngeal colonization and therefore transmission of drug resistant pneumococci is great. While large and small-scale studies of immunogenicity and effectiveness of pneumococcal conjugate vaccine are in progress, the focus of most of these is impact of vaccine on clinical endpoints (bacteremia, otitis media, pneumonia) rather than antimicrobial resistance. Quantifying the impact of conjugate vaccine on resistant carriage will provide important data for decision-makers trying to determine potential benefits of these new prevention tools. We propose a study to be located in a community with high-prevalence of drug-resistant pneumococci designed to assess the impact of widespread introduction of pneumococcal conjugate vaccine on carriage of drug resistant pneumococci. We will focus susceptibility testing on both beta-lactam agents (e.g., penicillin, amoxicillin, or cephalosporin) and trimethoprim-sulfamethoxazole, the first line therapeutic agents for respiratory infections in most developing countries. High-level penicillin-resistant organisms are considered to be markers for pneumonia treatment failures.

**Objective(s):**
1) Determine the impact of widespread introduction of pneumococcal conjugate vaccine on carriage of penicillin and trimethoprim-sulfamethoxazole nonsusceptible pneumococci in vaccinated infants and unvaccinated older children.
2) Determine the impact of widespread introduction of pneumococcal vaccine on carriage of susceptible pneumococci in vaccinated infants.

**Description:** Rates of pneumococcal disease are higher among the Alaska Native population than the general population of the United States, with rates of invasive pneumococcal disease similar to rates found in the developing world. This project involves sequential carriage studies in children before and at increasing community levels of uptake of pneumococcal conjugate vaccine.

Investigators use cluster design for sequential assessments of pneumococcal carriage and include collection of simple data elements regarding relevant confounders and/or risk factors for the carriage of resistant pneumococci. Characterization of the serotype will be performed to evaluate vaccine impact.

**Expected Outputs, Results, and Progress Indicators:** The output of the study will be a report comparing the proportion of children before and after the introduction of conjugate vaccine to the population who are colonized with nonsusceptible pneumococci. These data will fill a gap in understanding of the full impact of pneumococcal conjugate vaccines which in some areas will help overcome barriers to vaccine use. Progress indicators will include: (1) identification of partner organizations, research collaborators, and potential field setting for study; (2) development of protocol in concert with local investigators; (3) obtaining appropriate OPRR approved project assurance and IRB approvals (by local ethics committee, CDC IRB, and other partners as appropriate); (4) training of laboratory and field staff in study methods; (5) conduct vaccination and initial carriage study; (6) completion of laboratory studies on baseline carriage study; (7) analyze risk factors for resistant carriage at baseline; (8) complete follow-up carriage studies (likely to be two annual carriage studies); (9) analysis of epidemiologic and laboratory results from follow-up carriage studies; (10) presentation of study results to local authorities, research community, and partners; and (11) publication of final report of study results.
Countries/Regions: This study takes place in Anchorage, Alaska, but falls under the USAID International Antimicrobial Resistance Initiative as a result of population health disparities between the Alaska Native population and the rest of the United States. (Alaskan villages are a suitable setting because of the anticipated widespread introduction of conjugate vaccines in the United States before other sites in the world, the availability of baseline data on resistance, the availability of ongoing laboratory-based surveillance for invasive disease, and the fact that Alaskan villages reflect developing country settings with very high rates of respiratory and invasive pneumococcal diseases.)

Partners: Arctic Investigations Program (NCID/CDC); Alaska Native Medical Corporation.

Results to Date:
1) Two trips to Alaska by epidemiologists for collection of baseline data and collection of early post-vaccine exposure data.
2) Initial prevalence of cotrimoxazole resistance was very high (>75%); and 36% of isolates were nonsusceptible to penicillin.
3) At very early stages of vaccine uptake, overall resistance was unchanged although the clinic with the highest proportion of participants receiving at least one dose of vaccine showed a significant increase in overall carriage and a decrease in carriage of strains resistant to cotrimoxazole.
4) Preliminary results have been disseminated locally to clinicians and will be presented at the 2001 meeting of the Infectious Diseases Society of America.
5) Follow-up studies in 2002 are essential to evaluate impact of higher vaccination coverage on carriage of nonsusceptible and susceptible strains and the persistence of trends detected in 2001.

5.19 Studies to Evaluate Behavioral and Policy Interventions to Improve the Use of Antimicrobials at the Household and Community Levels

Implementing Organizations: BU/ARCH and RPM/MSH

Status: On-going (Funded: FY1999; Expected Completion: FY2004)

Rationale: The 1997 International Conference on Improving Use of Medicines (ICIUM) marked a major milestone in international efforts to promote quality use of medicines by health providers and consumers, and to develop rational pharmaceutical policies. For the first time, there exist a consensus about appropriate methodologies for implementing and assessing interventions in these areas, coherent summaries of previous experience, as well as an agreed agenda of priority policy implementation and intervention research topics. Four organizations (WHO/EDM, INRUD, RPM, and ARCH) have collaborated to advance this agenda through a joint intervention research initiative, including a series of research proposal development workshops and a subsequent research program.

The overall goal of the post-ICIUM initiative is to increase the capacity for drug use intervention research and to stimulate a critical mass of research projects in the priority areas. The first phase of the joint initiative has focused on interventions targeting the practices of physicians, paramedics, and other health providers working in primary care, hospital, or retail pharmacy settings. A call for proposals on these topics by the sponsoring organizations resulted in 88 submissions that were reviewed and prioritized. The top-ranked 22 of the pre-proposals were invited to advance to the next stage of full proposal development, either independently or during one of two proposal development workshops that were held in 1998 in Yogyakarta, Indonesia and Kampala, Uganda. These projects are either already underway or nearing completion.
USAID has been an active participant both in ICIUM and in the growing drug use intervention research initiative through its support to WHO/EDM and to the ARCH and RPM programs. Many of the priority topics for implementation and research identified at ICIUM are in areas of traditional USAID interest, such as improving pharmaceutical management of common childhood infections or reducing child and maternal mortality through more effective drug use in hospitals. In 1998, the USAID AMR Initiative enabled the expansion of the drug use portfolio to its current level by supporting the development and implementation of several proposals in the first phase that focused on antimicrobial use by health providers.

The second phase of the joint initiative will emphasize the two remaining research priority areas identified at ICIUM. First, proposals have been sought in the areas of improving patient compliance with antimicrobial therapy and improving patterns of antibiotic use within households or in the wider community. Participants at ICIUM recognized the critical need to inform and empower patients and consumers, who are the ultimate decision-makers in the use of medicines. Although consumer organizations and health educators have tried individual education and media-based approaches to modify patient and community behavior, few have been adequately evaluated. Effective patient and consumer education about antibiotic use is a neglected area that requires focused research to identify promising strategies, and much greater advocacy.

Secondly, there will be a call for proposals for studies evaluating policies that affect the way antibiotics are used in the community. Studies that critically examine the impacts of common economic and pharmaceutical sector policies on use of antimicrobials are conspicuously lacking, despite the fact that these policies are widely employed. The topics and methods for these analyses could be diverse. Studies might examine, for example, the impacts of including or excluding a particular antimicrobial on a formulary or national essential drug list; a change in national or district-level policy regarding the antibiotic of choice for treating pneumonia; the impact of decentralization and local purchasing on appropriate use on antimicrobials; or the effects of increased patient cost-sharing for brand name or reserve antibiotics.

As emphasized at ICIUM, both community-focused and policy-analytic studies frequently require the use of multiple research methodologies, quasi-experimental designs, and longitudinal analyses. Practical examples of such methods and designs in developing countries are quite limited. This set of studies will add to experience in this area, and result in tools and approaches that can be employed in future studies.

Objective(s):
- To identify practical methods and tools for evaluating community-oriented interventions or policies that seek to improve antimicrobial use;
- To facilitate the design, implementation, and evaluation of at least four intervention studies that aim to improve household and community drug use;
- To develop capacity to conduct and evaluate interventions or to evaluate policies intended to improve community use of antimicrobials.

Description: This activity will follow the model for research capacity building and successful proposal development that has been employed by ARCH/ADDR for many years, and which formed the basis for the work in the first phase of the drug use intervention initiative (see section 5.5).

During the first year, a request for proposals was circulated through the research networks of the partners and other related organizations. Twenty-two (22) pre-proposals were reviewed independently by each partner, and priorities for support were made based on the collective results of these reviews. Ten (10)
research teams were invited to attend a proposal development workshop in Bangkok, Thailand from November 29 – December 8, 2000 in Bangkok, Thailand at which the research ideas were clarified and developed into full proposals. These proposals are in the process of being reviewed by a panel consisting of the workshop facilitators and external reviewers, revised according to their comments, and, when acceptable, approved for funding.

It is envisaged that at least four (4) studies will be implemented by the research teams by early FY 2002. The typical study of this type will be two years duration. Technical support will be provided as required during the process of study implementation, with at least one visit per year by technical experts to each study team.

During the third year, research teams will be invited to participate in a data analysis workshop. Initial analyses of data will be completed, and research teams will prepare policy briefs for disseminating results of their studies at a local and national level. Their final reports will be revised for publication in national and international scientific journals in order to maximize the value of the lessons learned.

**Expected Outputs, Results and Progress Indicators:** It is expected that this activity will result in the design, funding, and initiation of at least 4-6 investigator-initiated studies on the priority topics by the end of FY 2002; completion of the interventions and collection and cleaning of outcomes data by the end of FY 2003; and completed data analyses, study reports, and policy dissemination by the end of FY 2004.

**Countries/Region:** Countries will be determined by the results of a competitive review of submitted proposals. Currently, Nigeria, Ghana, Uganda and South Africa from Africa; Philippines, Thailand, Vietnam, India and Nepal from Asia and Moldova from Eastern Europe are represented in the proposals under review.
Partners: WHO/EDM; INRUD; CHANGE Project; RPM/MSH

Results to Date: These partners agreed on a framework for the Phase II studies — Appropriate Drug Use for the Treatment of Infectious Diseases at the Household and Community Level. In addition to the community intervention, the framework specified two things: (1) the research is to focus on improving antimicrobial use (antibiotics and/or antimalarials) due to the growing problem of resistance and widespread consumer misuse of this class of drugs; and (2) the interventions to be tested are to encompass all relevant suppliers of medicines at the community level, including mobile drug vendors, drug retail shop owners, community health workers, health center personnel, and private practitioners.

The partners sent requests to 20 research teams around the world asking them to submit letters of interest (LOIs) to improve a critical problem in their context and, if possible, to combine an antimicrobial resistance surveillance component. To qualify, the teams had to have close links with community organizations. From the received LOIs, 10 teams were chosen and asked to submit preproposals, which they all did; these 10 groups were then invited to a proposal development workshop in Bangkok from November 29 to December 8, 2000. The 10 research teams came from Ghana, India, Moldova, Nepal, Nigeria, the Philippines, South Africa, Thailand, Uganda, and Vietnam. Seven teams worked on proposals for community interventions that addressed drug use for acute respiratory infections (ARI) in rural and urban slum environments. The other teams developed proposals on drug use for malaria, tuberculosis, and antibiotic use in general. The researchers made significant progress in drafting the proposals, and final versions were expected during the first quarter of this year. No funding for any project was assured at this stage. However, it is expected that the final proposals will be strong enough to attract the required support for implementation.

A similar process for assessing policy interventions will be started later in 2001.

5.20 Home Management of Neonatal Sepsis by Village Health Workers and the impact on Neonatal Mortality and Colonization with Antibiotic-Resistant Bacteria

Implementing Organization: JHU/FHACS

Status: On-going (Funded: FY1999; Information not provided on expected completion date)

Rationale: Neonatal mortality rates remain unacceptably high in developing countries. Almost half of neonatal deaths in developing countries are associated with infection, and 60% of deaths occur during the first week of life. Limited understanding of the causes of neonatal mortality in developing countries is based on studies of hospitalized infants that may not reflect causes of neonatal mortality in the community.

In a recent study in Gadchiroli District, Maharashtra, India, Bang et al. trained village health workers (VHWs) to diagnose and manage sepsis in newborns and to provide perinatal and neonatal care. The net percent decline for neonatal mortality was 62% and for infant mortality 46%. The mortality due to sepsis was reduced by 76%. Although promising, the use of antibiotics in the community to reduce neonatal mortality must be shown to be effective in other settings, and the impact on the prevalence of antibiotic-resistant bacteria assessed.

Objective(s):
1. Evaluate the impact on neonatal mortality of management of neonatal sepsis by VHWs
2. Evaluate the impact on colonization with antibiotic-resistant bacteria of home administration of antibiotics by VHWs to neonates with suspected sepsis
3. Evaluate the cost-effectiveness of a community-based approach to neonatal care and the management of neonatal sepsis

**Description:** The project will be conducted in two countries. In each country, communities will be randomized to control or intervention arms. Criteria for study sited selection include high rates of infant mortality and home delivery, poor access to health care, availability of VHWs and a minimum of 6000 live births per year. With a baseline neonatal mortality rate of 50/1000, an individually-randomized study with 1605 newborns in each group would be sufficient to detect a reduction of 40% in the intervention arm. As this is a community-randomized trial, doubling the sample size should be sufficient to account for between-community variability. We anticipate enlisting 10-15 communities, and 3210 newborns, for each study arm in each country.

Baseline data to be collected during the first year will include: 1) neonatal mortality rates; 2) causes of neonatal deaths based on verbal autopsy reports; and 3) newborn care practices. VHWs from the intervention community will be trained in neonatal care, including the recognition and management of neonatal sepsis. To further improve neonatal survival, VHWs and Trained Birth Attendants (TBAs) in the intervention community will be instructed in: 1) the recognition and management of complicated pregnancy; 2) appropriate hygiene during delivery and the immediate post-partum period; 3) neonatal resuscitation; and 4) newborn warming.

After completion of the baseline data collection and training, VHWs will perform regular home visits in the intervention community on days 1, 3, 7, 14, 21 and 28. If the birth weight is less than 2500 grams, home visits will take place daily until one month of age. VHWs will be trained to diagnose neonatal sepsis using the following criteria: 1) temperature greater than 38 C or less than 36 C; 2) poor feeding; 3) lethargy; 4) erythema and tenderness around the umbilicus; 5) a combination of diarrhea, vomiting and/or abdominal distention; and 6) severe pneumonia. Parents of infants diagnosed with sepsis will be encouraged to take the child to the nearest hospital. If not feasible, the VHW will initiate antibiotic therapy. The antibiotic regimen will be parenteral ampicillin and gentamicin, or oral cotrimoxazole and parenteral gentamicin. The VHW will maintain a record of the daily clinical status and outcome for each infant diagnosed with sepsis. VHWs will visit newborn infants in the control community within 24 hours of birth. If the infant weighs less than 2,500 grams, the mother will be advised to take the infant to the nearest hospital or health care facility. The VHW will visit the home and weigh the infant again at one month of age. A trained health care worker will perform a verbal autopsy to determine the cause of death for all infants who die.

Colonization with antibiotic-resistant bacteria will be assessed in a sub-sample of one month old infants during the baseline data collection period and at the end of the intervention. Nasopharyngeal and stool/rectal swabs will be obtained from one month old infants and cultured for penicillin-resistant *Streptococcus pneumoniae* and ampicillin-resistant *Escherichia coli*. Costs will be recorded during the training and intervention periods, and categorized as service costs or research costs. Anticipated costs include training, equipment, wages, incentives, drugs, supplies and transportation.

**Expected Outputs, Results and Progress Indicators:** Cause-specific neonatal mortality rates and rates of colonization with antibiotic-resistant bacteria during the pre-intervention and intervention periods will be compared for each community, and between the control and intervention groups. The cost-effectiveness of community-based neonatal care will be evaluated.

**Countries/Regions:** Bangladesh
Partners: ICDDR,B

Results to Date: (Information not provided)

### 5.21 Impact of IMCI Counseling Guidelines on Compliance with Antimicrobial Therapy in the Home

Implementing Organization: JHU/FHACS

Status: On-going (Funded: FY1999; Information not provided on expected completion date)

**Rationale:** The integrated management of childhood illness (IMCI) approach developed by WHO and UNICEF is being adopted by an increasing number of developing countries as their primary intervention to improve facility and community-based management of sick children. The prescription of antimicrobials for sick children with bacterial infections is a key element of the IMCI approach. The IMCI clinical algorithm recommends oral antimicrobials and home treatment for sick children with clinical diagnoses of non-severe pneumonia, malaria, dysentery, and acute ear infections. The effectiveness of the IMCI drug counseling guidelines on compliance with antimicrobial therapy in the home has not been evaluated. This is a key programmatic issue. If sub-therapeutic treatment doses are being given in the home, then there is an increased risk of the development of antimicrobial resistance and an increased risk of mortality for the individual child. This study will determine the impact of IMCI counseling guidelines on compliance with antimicrobial therapy in the home, investigate barriers to compliance. This study will complement another study now being conducted in Uganda with USAID AMR funds by Johns Hopkins University and Institute of Public Health, Kampala, Uganda.

**Objective(s):**
1. To evaluate the impact of the IMCI treatment counseling guidelines on the number of sick children seen at Community Health Centers (CSCOM) that complete a full course of antimicrobial treatment at home.
2. To identify barriers to completing a full course of antimicrobial treatment in the home following IMCI Treatment counseling.

**Description:** The study will be conducted in sikasso Region, Bougouni District, Mali. For the purposes of this study, Bougouni District can be divided into 3 zones.

- **Zone 1:** This comprises two rural arrondissements and the commune (urban area) of Bougouni where Save The Children USA has implemented a USAID BHR/PVC Child Survival grant from September 30, 1995 to September 29, 1999. Activities implemented under the grant included immunization, improved case management of diarrhea and malaria in health centers and in the home, nutrition including Vitamin A distribution, family planning and maternal health. There were no specific intervention activities related to acute respiratory infections.
- **Zone 2:** This comprises 3 rural arrondissements where the Save The Children project will be expanding its activities through mission funding from USAID/ Bamako after the current child survival project in Zone 1 ends.
- **Zone 3:** This comprises 6 other rural arrondissements that are not included in either of the Save The Children projects.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 1</td>
<td>M</td>
<td>I</td>
<td>M</td>
</tr>
</tbody>
</table>
Zone 2    M   I   M
Zone 3    M

I=Intervention: Personnel in Health Centers receive a modified IMCI training course including the complete IMCI training on counseling of parents on how to administer the drug to the sick child.
M= Measurement: Measurement of reported doses of antimicrobials given in the home will be conducted. For children receiving antimicrobials for diarrhea or ARI at health facilities, home visits will be made after 5 days. Completion of the course of antimicrobials will be assessed by history and by counting antimicrobials remaining after 5 days. Exit interviews will also be conducted with a sample of parents of young children upon leaving the health facility. Respondents will be administered a brief survey about how long they waited, what happened in the appointment, what treatment they were told to take, etc.

Comparisons:
1) Comparison of Zone 2 at Times 1 and 2 and Zones 2 and 3 at Time 2 will show how much IMCI training of health personnel improves compliance in health facilities that had not otherwise been upgraded.
2) Comparison of Zones 1 and 2 at Time 2 will show how much better IMCI training is than the routine training implemented as part of many PVO child survival projects that include diarrhea and malaria case management.
3) Comparison of Zone 1 at Times 2 and 3 will show how much improvement results from IMCI training in facilities that have already had some upgrading.

Other data collection methods: A sample of 30 parents of young children will be administered a semi-structured interview on knowledge and perceptions of medications.

Countries/Regions: Save The Children USA is just completing a four year Child Survival Project (CS XI) (September 30, 1995 to September 29, 1999) in Bougouni District, Sikasso Region, Mali. Save The Children has developed local capacity to carry out operations research, and is eager to build on existing activities. While not providing funds, Save The Children will make some project resources available for the study.

Partners: Ministry of Health and Population Services (MSSP), Mali.

Results to Date: Study underway.

5.22 Assessing The Effectiveness of Client-Based Job Aids to Support Compliance with Antibiotic Treatment Regimens

Implementing Organization: Quality Assurance Project II

Status: On-going (Funded: FY1999; Expected Completion: FY2001)

Rationale: This study examined the effectiveness of a set of client and provider job aids to improve adherence to antibiotic regimens for the treatment of children with pneumonia. The study was conducted in Niger, West Africa. The development of antimicrobial resistance (AMR) has increased the worldwide threat of infectious disease. The study focused on two strategies to curb the development of antimicrobial resistance; improving patient counseling and improving antibiotic regimen adherence through the use of job aids.
**Objective(s):** To develop and evaluate the effectiveness of client and provider job aids to enhance caretaker adherence to antibiotic regimens (specifically oral cotrimoxazole) for the treatment of pneumonia in children.

**Description:** The study was conducted in two phases. Phase 1 utilized a qualitative methodology to assess parental knowledge about common respiratory infections, medications (specifically antibiotic therapy), traditional remedies, health seeking behavior, cultural beliefs about wellness and illness, traditional dissemination of information, and the appropriate way to deliver a message to caretakers of children. Observation of health center activities included patient counseling, counseling materials, and the number and duration of antibiotic stock outs.

Based on the results from Phase 1, several interventions were developed to improve adherence with the antibiotic regimen. Low cost packaging of oral cotrimoxazole was designed depicting the antibiotic regimen (dose, frequency and number of days). Images of mothers giving their child the antibiotic were drawn by a local artist to convey messages on proper administration and storage, and completion of the entire 5-day course. These images were combined in a counseling card and poster for the health worker. A training program for health workers on interpersonal communication and use of the envelopes, counseling card and poster was developed by the Niger Ministry of Public Health.

Phase 2, an efficacy trial of the above interventions was then completed. A sample of 675 caretakers of children with pneumonia (348 in the experimental group and 327 in the control group) from 8 health centers (4 experimental and 4 control) were visited at home 4 to 5 days after the initial consultation. The dependent variable, adherence to the antibiotic regimen, was measured with a pill count on day 4 or 5 after the clinic consultation. Two measures were calculated with these data; 1) the proportion of caretakers who adhered to the antibiotic regimen, and 2) a ratio of observed pills to expected pills.

**Expected Outputs, Results and Progress Indicators:**

*Phase 1 results:* Pneumonia was considered a serious childhood illness, however there were constraints to seeking care at health centers. The cost of the visit, usually borne by the father, and the availability of cheap medicines in the market, coupled with occasional drug stock outs at the health centers, combined to impede care seeking at health centers. Cotrimoxazole (40 mg trimethoprim and 200 mg sulphamethoxazole), the drug of choice for treating non-complicated pneumonia in Niger, was considered by parents to be effective, was well tolerated by children, but difficult to dissolve in water. We found that only 2 or 3 days of the full 5-day course of cotrimoxazole were dispensed at the first visit. Parents are advised to return for the rest of the treatment at a follow-up appointment.

Little counseling by health workers was observed during the baseline study. Parents were given the antibiotic in unmarked paper cones. Medication was improperly stored in the home and most parents did not make sure that the infant swallowed the entire dose.

*Phase 2 results:* There were no significant differences between the experimental and control groups for the child’s characteristics (age, birth order, sex) nor the mother’s characteristics (age, educational level, marital status). However, household characteristics and characteristics of the health center visit did differ significantly. The size of the household was larger in the control group (9.3 vs. 7.4 persons) and households in the experimental group had more radios (68% vs. 44%). The control group lived farther from the health center than the experimental group (2.9 vs. 2.3 km) and the caretaker stated that improvements were needed in care at the health center more often in the experimental group (75% vs. 42%). In addition to cotrimoxazole, more children were prescribed aspirin in the control group (49% vs.
36%) however more children were prescribed chloroquine in the experimental group (93% vs. 63%).

In the initial results (Table 1), the experimental group had greater adherence to the antibiotic regimen than the control group, even if a full 5 day course of medication was dispensed at the initial visit. Further analysis, hierarchical linear modeling, using a nested design, will be completed to assess the effect of the individual clinic on patient adherence.

Table 1. Description of differences in experimental and control group for dependent variables (patient adherence, follow-up appointment, maternal knowledge, child’s health, medication storage and preparation)

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Experimental Group</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient adherence (% who adhered to regimen)</td>
<td>76%</td>
<td>90%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patient adherence (ratio of observed to expected pill count)*</td>
<td>.929</td>
<td>.980</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>3 days of medication received initially</td>
<td>.920</td>
<td>.980</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>5 days of medication received initially</td>
<td>.952</td>
<td>.979</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Kept follow-up appointment (% yes)</td>
<td>58%</td>
<td>79%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Maternal knowledge (% correct)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of pills</td>
<td>99%</td>
<td>99%</td>
<td>NS</td>
</tr>
<tr>
<td>Number of times per day</td>
<td>97%</td>
<td>93%</td>
<td>.01</td>
</tr>
<tr>
<td>Number of days</td>
<td>98%</td>
<td>99%</td>
<td>NS</td>
</tr>
<tr>
<td>Child’s health (Mother’s perception, % yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved completely</td>
<td>35%</td>
<td>47%</td>
<td>.002</td>
</tr>
<tr>
<td>Improved a little</td>
<td>65%</td>
<td>53%</td>
<td>.002</td>
</tr>
<tr>
<td>Still has a cough</td>
<td>46%</td>
<td>38%</td>
<td>.03</td>
</tr>
<tr>
<td>Still has a fever</td>
<td>25%</td>
<td>13%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Still has nasal discharge</td>
<td>42%</td>
<td>28%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Medication storage (% correct)</td>
<td>87%</td>
<td>91%</td>
<td>.04</td>
</tr>
<tr>
<td>Used clean water to mix medication (% correct)</td>
<td>73%</td>
<td>94%</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

* Note: ratio closer to 1 indicates greater adherence

These results will be discussed with our collaborators at the Ministry of Public Health in Niger in June 2001. Recommendations for the use of the job aids in Niger will be forthcoming. We would also like to propose that this methodology be used to develop job aids to increase adherence to treatment regimens for other diseases or in the private drug sector to improve adherence for caretakers who choose to seek care outside of the health center.

Countries/Regions: Niger (Boboye District)

Partners: Ministry of Public Health, Niger

Results to Date: (Information not provided)

5.23 Improving Knowledge of Primary Care Physicians and Medical Students to Enhance Rational Prescribing of Antimicrobials through the Use of Established Drug Information Centers and Networks

Implementing Organization: USP

Status: On-going (Year Funded: FY1999; Information not provided on expected completion date)
Rationale: It is generally accepted that the misuse of antimicrobial drugs, resulting in part from a lack of appropriate drug use information, contributes to antimicrobial resistance. Based on the state of the art technical review of antimicrobial drug information in Russia, Nepal, Peru, and Ghana, USP has found that, in general, physicians lack concise up-to-date information on the use of antimicrobials, especially information on basic use, pharmacokinetics, pediatric and geriatric use, drug interactions, and treatment of side effects. In addition, more information is needed on appropriate perioperative infection prophylaxis; recommendations for adjustment of treatment regimens, e.g., parenteral to oral therapy, as the patient improves; and practical comparisons among antimicrobial agents, in particular within families of drugs. This review also found that there is very little drug information included in disease-specific standard treatment guidelines and that these guidelines tend to be poorly disseminated within countries.

Many countries, both developed and developing, have existing mechanisms for disseminating drug and therapeutics information. In most cases, the mechanism takes the form of drug information centers and networks. In fact, in research conducted by USP, it was found that the number of drug information centers in developing countries was increasing at a significantly faster rate than was the case for developed countries. The presence of these information centers and networks offers a unique opportunity to build grassroots efforts in educating health care professionals and students about the problem of antimicrobial resistance and in providing information to improve rational prescribing and use of antimicrobials.

Objective(s): To develop and evaluate prototype programs and materials for primary care physicians and medical students that would improve access to and understanding of information relating to the appropriate prescribing of antimicrobial agents.

Description: The proposed activity takes advantage of the ongoing USP activities in the Russian Federation and Moldova that relate to the provision of unbiased drug information. Specifically, the activities will build on the Russian translation/adaptation of the USP DI database and the establishment of the 12-member All-Russia Drug Information Network (ARDIN) and the Moldovan Association DRUGS. USP will work with members of ARDIN and the Moldovan Association DRUGS in the development of strategies for improving access to unbiased information about antimicrobial agents and in the creation of a training module for educating practitioners and students about their appropriate use. Concurrently, USP will work with PHARMEDINFO to publish a subset of the translated/adapted USP DI antimicrobial information monographs as an inexpensive reference for clinicians. The information will be condensed from the full monographs included in the Russian USP DI translation/adaptation. The format for the monographs will be developed through consultation with MOH officials and medical specialists, with input from ARDIN and DRUGS members. Where appropriate, local adaptations of the information will also be included in those materials developed for use in a specific geographic area. This process will not only serve to develop relevant, useful information but it will also raise awareness of the problem of antimicrobial resistance and build demand for appropriate training and the handbook. PHARMEDINFO will publish up to 20,000 copies of the handbook (depending on costs) and make them available for use in the training initiatives. It is anticipated that PHARMEDINFO will also make copies available at a subsidized rate for other clinical health care providers and will make the information available via electronic means, such as the Internet. The information will also serve as a resource for articles published in local and regional newsletters and bulletins that are developed by the drug information centers. Local and regional ARDIN members will coordinate use and evaluation of the teaching modules in their respective areas. After appropriate evaluation and revision, through a “training-the-trainers” approach, ARDIN members and the Association DRUGS will work to involve other information centers and institutions in Russia, Moldova, and potentially other Eastern Europe/Eurasia countries in effectively using the training module in their respective populations.
Expected Outputs, Results and Progress Indicators:

**Outputs** include a strategy for improving access to unbiased information about antimicrobial agents; training module for teaching practitioners and students about the appropriate use of antimicrobial agents; prototype of handbook (Russian language) for clinicians on proper use of antimicrobial drugs; newsletter/bulletin articles.

**Results** include:
- Increased availability of and access to unbiased information on appropriate use of antimicrobials;
- Increased number of DIC inquiries and responses relating to antimicrobial agents;
- Increased number of educational encounters relating to appropriate antimicrobial drug use;
- Increased recognition of the importance of appropriate use of antimicrobial agents in an attempt to decrease antimicrobial resistance;
- Increased knowledge among practitioners on appropriate antimicrobial prescribing.

**Progress indicators** include:
- Availability of training module;
- Availability of antimicrobials handbook;
- Number of articles published in newsletters/bulletins;
- Number of continuing education programs/participants;
- Number of inquiries to DICs;
- Improved prescribing of antimicrobials as determined by DUR.

**Countries/Regions:** Russia, Moldova, and other Eastern Europe/Eurasia countries as determined appropriate and feasible; potential for replication in other developing countries.

**Partners:** PHARMEDINFO, ARDIN, Association DRUGS.

**Results to Date:** Antimicrobial Textbook and Training Modules were developed by 39 Russian scientists under coordination of USP and its primary partner in Russia, PHARMEDINFO. Fifty five thousand copies of the Textbook and one thousand copies of the Training Modules were published. They were distributed, free of charge, throughout Russia and the Newly Independent States by PHARMEDINFO. Full text of the Textbook is available on WWW at www.antibiotic.ru/ab

- A total of 34,790 copies of the Antimicrobial Textbook were distributed throughout Russian Oblasts, including 7,200 to medical and pharmacy schools.
- NIS countries received 1,850 copies, with at least 100 copies distributed to each country.
- More than 2,000 copies were distributed in response to individual requests from health care professionals.
- Approximately 1100 copies were sent with Farmatsia medical journal.
- Over 16,000 copies were distributed at professional workshops and conferences, including the Man and Drugs Conference, as well as among authors.

The Antimicrobial Textbook includes two monographs on TB. The first on drugs used in treatment of TB. It includes information on ftivazide, isoniazid, metazide, opiniazide, rifampicin, streptomycin, pyrazinamide, ethambutol, kanamycin, amikacin, rifabutin, cycloserin E, capreomycin, ethionamide, prothionamide, ciprofloxacin, ofloxacin, lomefloxacin, sodium para-aminosalicylate, and thioacetazon.

The second provides information on the rational treatment of TB. It includes information on various regimes and schemes of therapy, including Directly Observed Therapy (DOT); therapy of multi-resistant TB; TB therapy in patients with HIV/AIDS; and therapies in children; during pregnancy; in patients with kidney and liver problems; and others.

Seven RPM-sponsored antimicrobial courses took place in various Russian and NIS regions (Pskov, Vladivostok, Tomsk, Saint Petersburg, Ryazan, and Novgorod regions of Russia, as well as in Moldova). The courses were conducted by ARDIN drug information centers together with local medical and pharmacy faculties. More than 1,000 health care professionals have participated in the courses. All participants received a copy of the Antimicrobial Textbook. The book received high praise from students and from teachers delivering lectures. All lectures were based on book materials. A number of medical and
pharmacy school faculty members said that they would use the Antimicrobial Textbook in education of students, and they requested additional copies.

Two questionnaires (25-30 questions each) were developed to evaluate a level of knowledge before and after the training course. The results of testing showed a dramatic increase in the percentage of correct answers. For example, among 136 participants in Novgorod before courses, 35% had a “low level of knowledge” (less than 25% of correct answers) and only 0.8% had “excellent level of knowledge” (more than 80% of correct answers) about the topics presented. After school, only 0.7% were “low level,” whereas 37% scored as having an “excellent level” of knowledge. The percent of “good level of knowledge” (70 – 80% of correct answers) increased from 4% to 33%.

After the first successful course, the Health Care administration of Saint Petersburg Region asked the local DIC staff to conduct additional courses for health care professionals of the region and agreed to provide financial support. The second course was conducted in Novgorod with the financial support of local Evangelical Church.

Saint Petersburg DIC staff has been conducting a study to examine the effects of these courses. This study, which is ongoing, began in 1999. During this study, 584 case histories before the initiation of the courses and 96 case histories after the initiation of the courses in outpatient health care facilities were analyzed. The findings include these pertinent facts:

- Use of gentamicin in patients with pneumonia has decreased from 10.9% to 3.1%.
- Use of fluoroquinolones in patients with pneumonia has decreased from 19.8% to 10.4%. This is a positive fact for Russia since only second generation fluoroquinolones are registered there. The second-generation fluoroquinolones have a low effect on Gram-positive cocci, including S. pneumoniae, which is a main cause of pneumonia. Their application as monotherapy can promote selection of the resistant strains and development of resistance to fluoroquinolones.
- The percentage of injections given has decreased from 64.4% to 58.6%, indicating that the preferred method of medicating, oral antibiotic therapy, is increasing in use.

5.24 Improving Patient Counseling and Dispensing Skills of Private Drug Retailers

Implementing Organization: USP

Status: On-going (Year Funded: FY1999; Expected Completion: FY2002)

Rationale: Most people in Nepal receive antimicrobial drugs directly from a private drug seller or chemist, usually without a prescription. Through USP’s experience in Nepal, it has been observed that training requirements to become a licensed drug seller are minimal and no “refresher” training is required. Studies have shown that 68% of retailers in Nepal have no qualifications to sell drugs, let alone to prescribe. In one study, a therapeutically-appropriate full course of antibiotic treatment was received less than 25% of the time in retail shops. Using Nepal Infectious Diseases funding, USP has researched the antimicrobial drug knowledge and consumer counseling practices of licensed private sector drug sellers in Nepal in cooperation with the Nepal Chemists and Druggists Association (NCDA). Based on the results of this research the RPM project is developing a training intervention to improve patient counseling and dispensing of antimicrobial drugs used to treat the most common infectious diseases in Nepal. It is anticipated that the training intervention will become institutionalized as a part of the new legal requirements for becoming a licensed drug retailer currently being enacted by the Dept. of Drug Administration, HMG-Nepal and later rolled out to reach the majority of drug sellers in the country.
**Objective(s):** To reduce the spread of resistance to antimicrobial drugs used to treat the most common infectious diseases in Nepal (tuberculosis, malaria, STI’s, pneumonia, diarrheal diseases, and kala-azar) by improving the skills of the major provider of antimicrobial drugs: private retailers.

**Description:** *Progress to date* includes research that has been done with the private sector retailers on the dispensing of and patient counseling for antimicrobials during FY 99 using funds from the 1998 allocation of ID money. The Manoff Group was contracted to develop a research plan, manage data collection and analysis and present findings and recommendations for an appropriate intervention. Manoff has worked in collaboration with New Era, a local Nepali research group. Preliminary results of the research show that:

- Drug retailers dispense antibiotics for illnesses that do not necessarily call for antibiotic treatment;
- Drug retailers learn what antibiotics to dispense by observing what doctors prescribe for the same illness;
- Drug retailers do minimal, if any, labeling of medicines dispensed
- Drug retailers provide very little or no counseling to their clients when they dispense medicines to them;
- Drug retailers often sell less than the required/appropriate amount of antibiotics;
- To some extent, drug retailers see themselves as health care providers, not just businessmen;
- Drug retailers would welcome more training on drug selling;
- Drug retailers have very few, if any reference materials, and do not make effective use of those that they do have.

The findings from the qualitative portion of the research, which examines *why* the above findings are true, will inform the design and development of training and reference materials. For example, simple and easy-to-use reference materials on appropriate packaging and labeling may be indicated. In addition, support for drug retailers’ encouraging clients to follow a full course of antibiotic treatment, instead of taking the medicine just until they feel better, may be appropriate.

**In process:** A training intervention has been developed and field-tested in collaboration with RPM/MSH. Core funds are being used to develop the draft training materials which can be adapted by other countries.

**Planned for FY 2000:** Core funds will also be used to develop a facilitator’s guide for use by trainers of retailer-groups. Nepal ID funds will be used to evaluate the field test and revise the intervention and materials for Nepal. Additional core funds are requested to disseminate the training materials outside of Nepal as a model and to assist other countries with adapting/translating the model for local use through a sub-agreement mechanism. During FY 2000, the intervention will be evaluated and a rollout implementation phase will be planned. The group of drug sellers who go through the field-test training will be compared to a group of untrained drug sellers three months after the training. At the end of the field test, measures such as decreased AM drug sales, changes to more appropriate products, increases in repeat customers, improved patient/consumer counseling, will be used to evaluate impact. The DDA has already agreed, in principle, to include the training in the new requirements for drug retailer licensing being established now in Nepal.

**Expected Outputs, Results and Progress Indicators:**

- **Outputs:** Appropriate training materials developed which can be adapted for other countries.
- **Results:** DDA and NCDA staff trained to deliver the intervention and monitor improvement in drug retailer’s knowledge and skills through post-training tests and surveillance mechanism, e.g., mystery clients.
• **Indicators:** decreased sales of drugs which have become less effective due to increasing resistance; changes to more appropriate products; increases in repeat customers; improved patient/consumer counseling, e.g., more time spent with customer, accurate instructions provided on taking medicine, etc.

**Countries/Regions:** Nepal

**Partners:** Co-funders, USAID-Nepal and RPM/MSH; collaborating organizations, DDA, NCDA, DINoN, Manoff Group, and New Era.

**Results to Date:** The field test of the training intervention was implemented in May 2000, later than planned due to political turmoil within the Nepal Chemists and Druggists Association (NCDA). In FY 01, the field test was been evaluated using Nepal ID funding. The evaluation report is currently in the process of being edited. When finalized, the report will be shared with the USAID mission and all participating organizations. Revisions to the intervention will be made in and a rollout will be planned in FY 02. Training materials will be published and made available for adaptation with core funds, after revisions are made.

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**5.25 Methodology to Assess Malaria Drug Management in Developing Countries**

**Implementing Organization:** RPM/MSH

**Status:** On-going (Funded: FY1999; Expected Completion: FY2002).

**Rationale:** The increasing rate of resistance of Plasmodia to traditional first-line antimalarial drugs such as chloroquine has prompted WHO, CDC and other organizations to initiate global efforts to assess the effectiveness of alternate treatment regimens. However, developing country malaria decision-makers do not have ready access to sufficient information on which to base policy and programmatic decisions that can appropriately incorporate findings from these efforts. To the extent that current management policies and practices determine the availability and effective use of currently available antimalarial drugs, program managers need a mechanism to rapidly gather key information to assess and monitor the functioning of malaria drug supply. This information can be used to improve existing programs and policies and slow the emergence and spread of resistance, or to determine the need to switch to more effective treatment options.

**Objective(s):** Develop and test a rapid assessment methodology and indicators to assess and monitor the availability and use of antimalarial drugs in Developing Countries

**Description:** The rapid assessment methodology and indicators will build upon three existing RPM tools. The *Manual for Rapid Pharmaceutical Sector Assessment*, a tool for assessing the overall performance of a pharmaceutical sector, provided the foundation for the later development for the *Manual for Drug Management for Childhood Illness (DMCI)*. The latter was designed to assess the specific drug management concerns of countries considering implementing Integrated Management of Childhood Illness (IMCI) programs and for those with existing IMCI programs. The *DMCI* approach for assessing IMCI drug will be adapted to create a new tool for assessing the availability and the use of drugs to treat malaria. The third RPM tool that will be adapted for malaria drug management is the *Cost Estimate Strategy (CES)* tool. This tool, originally developed to assist Reproductive Health Programs, estimates drugs and commodities needs and corresponding costs, according to both actual and normative use patterns. The tool is particularly useful when considering expanding programs.
The Drug Management for Malaria (DMM) tool will follow the same developmental approach taken by the DMCI manual. The manual will discuss key drug management issues for the treatment of malaria, indicators for assessing the status of malaria drug management, their calculation, interpretation, and suggestions for follow-up actions. The assessment methodology will include a structured questionnaire instrument to be applied in both the public and private sectors to obtain data for conducting a cost comparison analysis, lead time analysis, availability of key drugs analysis, a review of prescribing, among others. The CES tool will be adapted to include the drugs and medical supplies required for the treatment of malaria as per existing national and international treatment guidelines, and will be incorporated into the assessment methodology. A comprehensive data collectors guide will be developed to accompany the manual.

The tool will be field tested in an appropriate setting. The purpose of the field test is to clarify concepts, language and presentation of the material, as well as finesse data collection issues. The field test will involve collaboration with local counterparts in the design, planning and implementation and follow-up review and analysis of preliminary results.

Expected Outputs, Results and Progress Indicators:

Output: a DMM Manual and Data Collectors Guide.
Results: field-tested malaria drug management assessment methodology and indicators available; team of malaria program managers trained to use the DMM tool; team of trained DMM data collectors.

Countries/Regions: South Africa

Partners: WHO/EDM; WHO/TDR; CDC; INRUD.

Results to Date: The Drug Management for Malaria Manual was developed by RPM and a completed draft published in July 2000. The Manual is currently being field tested in South Africa. The data collection for the field test has been completed and findings and an evaluation of the methodology are expected in August 2001. RPM will make revisions as recommended from the field test and publish the manual in 2002.

5.26 Methodology to Assess Tuberculosis Drug Management in Developing Countries

Implementing Organization: RPM/MSH

Status: On-going (Funded: FY1999; Expected Completion: FY2002).

Rationale: In the last decade, tuberculosis (TB) has re-emerged as a significant public health concern for many countries through the developing world and Eastern Europe/Eurasia. WHO’s Directly Observed Treatment Short-course therapy (DOTS) has been an important development in the management of TB. Despite this and other efforts to improve the treatment and prevention of TB, several factors may adversely affect their effective implementation. These factors include the emergence of multi-drug resistant strains, lack of adequate training and supervision of both providers and recipients, and unreliable or poorly managed drug supplies. TB program managers may benefit from a tool that can help them quickly assess TB drug supply in their programs; identify weaknesses in the system; and once appropriate interventions
are designed and implemented to improve it, monitor their impact.

**Objective(s):** Develop and test a rapid assessment methodology and indicators to assess and monitor the availability and use of TB drugs.

**Description:** This tool will build upon three existing RPM tools. The *Manual for Rapid Pharmaceutical Sector Assessment*, a tool for assessing the overall performance of a pharmaceutical sector, provided the foundation for the later development for the *Manual for Drug Management for Childhood Illness (DMCI)*. The latter was designed to assess the specific drug management concerns of countries considering implementing Integrated Management of Childhood Illness (IMCI) programs and for those with existing IMCI programs. The *DMCI* approach for assessing IMCI drug will be adapted to create a new tool for assessing the availability and the use of TB drugs. The third RPM tool that will be adapted for TB drug management is the Cost Estimate Strategy (CES) tool. This tool, originally developed to assist Reproductive Health Programs, estimates drugs and commodities needs and corresponding costs, according to both actual and normative use patterns. The tool is particularly useful when considering expanding programs.

The *Drug Management for Tuberculosis (DMTB)* tool will follow the same developmental approach taken by the *DMCI* manual. The manual will discuss key drug management issues for the treatment of TB, indicators for assessing the status of TB drug management, their calculation, interpretation, and suggestions for follow-up actions. The assessment methodology will include a structured questionnaire instrument to be applied in both the public and private sectors to obtain data for conducting a cost comparison analysis, lead time analysis, availability of key drugs analysis, a review of prescribing, among others. The CES tool will be adapted to include the drugs and medical supplies required for the treatment of TB, as per existing national treatment guidelines and as per internationally recognized guideline such as the WHO DOTS program, and will be incorporated into the assessment methodology. A comprehensive data collectors guide will be developed to accompany the manual.

The *DMTB* tool will be distributed for external peer review with structured feedback mechanisms. After revisions have been completed to the tool as per the feedback, the tool will be field tested in an appropriate setting. The purpose of the field test is to clarify concepts, language and presentation of the material, as well as finesse data collection issues. The field test will involve collaboration with local counterparts in the design, planning and implementation and follow-up review and analysis of preliminary results.

**Expected Outputs, Results and Progress Indicators:**

**Output:** *DMTB Manual and Data Collectors Guide*

**Results:** field-tested TB drug management assessment methodology and indicators available; team of TB program managers trained to use the *DMTB* tool; team of trained *DMTB* data collectors.

**Progress indicators:** *DMTB Manual and Data Collectors Guide* drafted; *DMTB Manual and Data Collectors Guide* field tested.

**Countries/Regions:** Tool development will take place in Washington, DC. One country in either Africa or the NIS (yet to be determined) will be selected to field test this tool.

**Partners:** WHO/EDM is expected to collaborate in technical review of the manual; WHO TB program is expected to provide input (need to identify the program); CDC may participate in the technical review of the manual.
Results to Date: Under RPM, the draft DMTB manual and data collectors guide were completed. They are awaiting field testing during 2001. The formation of a shorter assessment guide that includes a continuous monitoring component is being considered based on recent MSH assessments for the TB Global Drug Fund.

### 5.27 Increased Specificity for Treatment Guidelines for Clinical Overlap of Non-Severe Pneumonia and Malaria

**Implementing Organization:** WHO/CAH

**Status:** On-going (Funded: FY1999; Expected Completion: FY2003)

**Rationale:** Pneumonia and malaria are common conditions in young children and are leading causes of death. Both pneumonia and malaria are part of Integrated Management of Childhood Illness (IMCI) algorithm. In some countries, an overlap in the clinical presentation of pneumonia and malaria has been reported. Many children meeting pneumonia case definition (cough and fast breathing and or chest indrawing) have fever or history of fever and a significant number of children with fever will meet pneumonia case definition. At present there is no simple method to differentiate between pneumonia and malaria if a patient with fever fulfils the pneumonia case management criteria. Consequently, effective malaria therapy is often required in febrile children with pneumonia. A few countries recommend cotrimoxazole (sulphamethoxazole-trimethoprim) as the first-line antibiotic in non-severe pneumonia and first-line antimalarial as sulphadoxine-pyramethamine (Fansidar) due to chloroquine resistance. This use of both antibiotic and antimalarial drugs has implications for costs, development of antimicrobial resistance and toxicity if the two sulpha are used concurrently. Some diagnostic techniques have been developed to diagnose malaria quickly e.g., dip sticks etc. There is a need to test such technology to differentiate between clinical overlap of pneumonia and malaria. It is proposed that a study be designed to do that. A meeting on “Malaria diagnostics” will be held in Geneva in August this year. Results and recommendation from that meeting will be used to design this study.

**Objective(s):** To increase specificity of treatment guidelines for clinical overlap of pneumonia and malaria.

**Description:** The study will be designed and implemented in an area with significant clinical overlap of malaria and pneumonia. Children between 2 and 59 months old who present with fever and fit the case definition of pneumonia will be tested for malaria using simple and quick diagnostic tests. This test will be compared with the presence of malarial parasites in peripheral blood.

**Expected Outcomes, Results, and Progress Indicators:** Outcomes include: evaluation of the use of a simple malaria diagnostic test and its effect on reduction in the use of antimalarial drugs; strengthened local capacity in epidemiological research and microbiology; and strengthened local capacity to differentiate between pneumonia and malaria using simple technology. Progress indicators include: development of a research protocol; initiation of data collection for the study; and development of better differential diagnosis criteria between pneumonia and malaria.

**Countries/Regions:** Papua- New Guinea.
**Partners/Collaborating Institutions:** Communicable Disease Research and Development (CRD), Communicable Diseases (CDS) Cluster, WHO.

**Results to Date:** A preliminary proposal to investigate clinical overlap of malaria and pneumonia is being reviewed internally. If approved, the study will be conducted in Papua-New Guinea.