Community-Based Surveillance of Antimicrobial Use and Resistance in Resource-Constrained Settings

Report on five pilot projects

World Health Organization

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Abbreviations

Abbreviations used throughout the text

ABM	Antibacterial medicine
AMR	Antimicrobial resistance
ATC	Anatomical Therapeutic Chemical (Classification System)
DDD	Defined daily dose
DSPRUD	Delhi Society for Promotion of Rational Use of Drugs
EARSS	European Antimicrobial Resistance Surveillance System
EDL	Essential drugs list
ESAC	European Surveillance of Antimicrobial Consumption
ESBL	Extended-spectrum beta-lactamase
GP	General practitioner
INRUD	International Network for the Rational Use of Drugs
MDR	Multi-drug resistance
MIC	Minimal inhibitory concentration
OP	Out-patient
OPD	Out-patients department
PHC	Primary health care
SOP	Standard operating procedure
STG	Standard treatment guidelines
STI	Sexually transmitted infection
TSI	Triple sugar iron (agar)
UTI	Urinary tract infection

ATC codes

Aminoglycosides (J01GA)
Amphenicols (J01BA)
β-lactamase-resistant penicillins (J01CF)
β-lactamase-sensitive penicillins (J01CE)
Cephalosporins (J01DA)
Combination of sulfas with trimethoprim (J01EE)
Fluoroquinolones (J01MA)
Macrolides (J01FA)
Penicillins with ES (J01CA)
Tetracyclines (J01AA)

Abbreviations used in graphs

Aminglyc	Aminoglycoside
Ampi	Ampicillin
AmCl	Amoxicillin Clavulanic Acid
Amik	Amikacin
BLRP	β-lactamase-resistant penicillins (cloxacillin and flucloxacillin)
BLSP	β -lactamase-susceptible penicillins (penicillin V and G)
Ceftx	Cefotaxime
Ceph	Cephalosporin
Cephal	Cephalexin
Cefur	Cefuroxime
Cipro	Ciprofloxacin
Chloro	Chloramphenicol
Cotrim	Cotrimoxazole
Eryth	Erythromycin
ESP	Extended-spectrum penicillins (amoxicillin, ampicillin)
Flquin / FQ	Fluoroquinolone
Genta	Gentamicin
Macro	Macrolides
Metro	Metronidazole
Nal	Nalidixic acid
Nalidix	Nalidixic acid
Norflox	Norfloxacin
Nitfur	Nitrofurantoin
Pen	Penicillin
Rifam	Rifampicin
Tetra	Tetracyclines

How this report is organized

This is a report on activities associated with the implementation of five pilot projects for the community-based surveillance of antibacterial medicine (ABM) use and antimicrobial resistance (AMR) in resource-constrained settings. The five pilot projects were conducted at two sites in South Africa and three sites in India. This report will be of interest to a variety of stakeholders involved in efforts related to the emergence and control of AMR and ABM use in developing countries. This will include those planning or implementing similar surveillance projects and those interested in the data, such as agencies involved in developing interventions to reduce ABM use.

The report covers two main aspects: details of issues related to the planning and implementation of such projects, and the actual data collected. This information is provided as eight chapters.

The first chapter describes the general structure of the overall project and the rationale for the choice of methodologies used. Chapters 2 to 6 contain the reports on each of the pilot sites. These chapters give details of the methods used, the results obtained, and commentary on the problems encountered at each site. Chapter 7 provides a summary of findings from different sites and places these in the context of the available literature. The final chapter explores the common problems experienced and draws lessons from the pilot projects.

Executive summary

In 2001, the World Health Organization (WHO) published a report entitled "*Global strategy for containment of antimicrobial resistance*". It dealt with the scale of the challenge posed by increasing resistance to antibacterial medicine (ABM) and the strategies that might be adopted to contain this threat. Antimicrobial resistance (AMR) has the potential to limit the effectiveness of many ABMs used widely in both developed and developing countries. Inappropriate therapy due to antimicrobial resistance has been identified as a significant reason for treatment failure. Infections due to resistant bacteria not only contribute to increased mortality and poor quality of life of affected individuals, but also increase the financial cost of treatment, the strain on health systems, and the risk of such infections spreading. Increasing AMR, together with inadequate infection control in hospitals and public health measures to control infections in the community, are continuing to evolve as a major global public health challenge. The effects are likely to be more pronounced in low-income countries where the burden of infection is high and antimicrobial choices are limited.

A World Health Assembly Resolution of 1998 urged Member States to develop measures to: encourage appropriate and cost-effective use of antimicrobials; prohibit the dispensing of antimicrobials without the prescription of a qualified health-care professional; improve practices to prevent the spread of infection and thereby the spread of resistant pathogens; strengthen legislation to prevent the manufacture, sale and distribution of counterfeit antimicrobials and the sale of antimicrobials on the informal market; and reduce the use of antimicrobials in food-animal production. Countries were also encouraged to develop sustainable systems to detect resistant pathogens, to monitor volumes and patterns of use of antimicrobials and the impact of control measures. A further World Health Assembly Resolution of 2005 urged Member States to "ensure the development of a coherent, comprehensive and integrated national approach to implementing the strategy for containment of antimicrobial resistance" and to "monitor regularly the use of antimicrobial agents and the level of antimicrobial resistance in all relevant sectors".

WHO highlights the establishment of effective, epidemiologically sound surveillance of ABM use and AMR among common pathogens in the community, hospitals and other health-care facilities as one of the key public health priorities. The available means to implement these surveillance tasks are currently unsuitable for resource-constrained settings. The best examples of such systems are from highly developed countries (such as Sweden) and from highly industrialized regions (such as Europe). It was therefore planned to assess the feasibility of establishing community-based surveillance systems to continually monitor trends in AMR and use of ABM in different geographical areas. This assessment would form phase 1 of a series of activities planned to contain AMR in resource-constrained settings. The data thus generated could help in quantifying the burden due to AMR and in developing and evaluating locally relevant interventions to promote rational ABM use. The data could also serve to stimulate a sense of urgency to act. In the long term, such data could help to better understand trends in AMR and ABM use, as well as the temporal associations between them. Initiation of an integrated surveillance system would help to build the

required liaison between different stakeholders, as well as the capacity to tackle the problem of AMR.

Pilot surveillance projects were established in five different sites – three in India and two in South Africa - with the aim of developing a model for undertaking community based surveillance in resource constrained settings and generating baseline data. The sites were chosen on the basis of existing capacity for surveillance and therefore were all attached to large hospitals in urban areas. The methodology used in each area aimed to collect AMR data and ABM use data from the same geographical area over time, but was modified to suit the particular characteristics of each site. Ethical approval was obtained from the WHO Ethics Review Committee and also from the respective institutions. Informed consent was obtained from all participants.

AMR data were collected using *E. coli* as the indicator organism at four sites and using potential respiratory pathogens at one site. All sites testing *E. coli* performed disc diffusion tests, while the single site focusing on respiratory pathogens determined minimum inhibitory concentrations. *E. coli* was obtained from urine at three sites, two of which differentiated the isolates into commensals and pathogens. The fourth site tested commensal *E. coli* isolated from faecal samples.

ABM use data were collected from multiple facilities, both from the public and private sectors, from which people living in the geographical area might obtain ABM for ambulatory use. Three sites used patient exit interviews and two sites used facility-retained prescription records to obtain data on ABM use. ABM use was expressed as the percentage of prescriptions containing specific ABMs, as well as the defined daily dose (DDD) of a specific ABM prescribed per 100 patients visiting the facility. In addition, two sites collected purchase or sales/dispensing data from records maintained by the facilities.

Data were collected over one year at three sites and over two years at the other two sites. Useful information was generated for understanding the current situation of AMR and ABM use in the areas and for developing interventions to promote rational use of ABMs. However, challenges were encountered at all sites.

AMR rates among *E. coli* were high at all sites. At all sites, the highest AMR rates were observed for those ABMs that have been in longest use, i.e., cotrimoxazole, ampicillin, tetracyclines and nalidixic acid. Resistance to newer antibiotics such as fluoroquinolone was present in all areas, with the rates being particularly high in India. Resistance to third-generation cephalosporins was also seen in isolates from all sites. Resistance among *S. pneumoniae* isolates was observed for cotrimoxazole and among *H. influenzae* to both cotrimoxazole and ampicillin. No significant monthly variations in resistance rates during the period of study were seen, although it must also be noted that the monthly numbers of isolates were often inadequate. Data were also inadequate to understand reliably any differences that might have been present between locations and between facilities within a site. Where AMR rates among commensals and pathogens were studied separately, the AMR rates were generally lower among commensals.

Although ABM use appeared to vary between the sites, any differences should be interpreted with caution. The legal systems and their application vary significantly between these sites. Two sites in India showed a much higher percentage of ABM-containing prescriptions compared to sites in South Africa. The usefulness of expressing ABM use in DDD terms was demonstrated, particularly with reference to the fluoroquinolones. These ABMs seemed to be used more in the private sector at all sites. However, in both India and South Africa, the difference was shown even more starkly when use was expressed as DDD prescribed per 100 patients. In general, inexpensive ABMs, e.g., cotrimoxazole, were used more widely in public sector settings, whereas the newer ABMs were more widely used in the private sector.

Since measurable AMR changes take several years to develop, no associations between ABM use and AMR were looked for during the pilot stage.

The following achievements were noted:

1. Pilot projects were carried out at sites in South Africa and India to ascertain the feasibility of undertaking long-term surveillance of AMR and ABM use in communities in these areas.
2. Data on ABM use and AMR were collected from all sites for a minimum period of 12 months. From some sites data were collected over two years.
3. The information gathered will be useful to start locally relevant interventions. The cooperation established with the sites will help in pilot testing such interventions.
4. Useful information on methods to study ABM use and AMR in communities was generated.
5. Several issues related to long-term surveillance logistics were identified and practical solutions suggested.
6. Recommendations could be made for expanding such systems in the future.
7. Involving several types of health-care facility at the community level for data collection in itself increases awareness of the issue of growing resistance to antibacterial therapy and its relation to ABM use.

Detailed lessons learnt were extracted from the experiences at each site, and the following general recommendations are made.

1. Community-based surveillance of AMR and ABM use is possible in resource-constrained settings, and the doing of it enables the development of multidisciplinary expertise for future AMR containment programmes. It is recommended that future surveillance projects be better integrated into existing routine systems, with sufficient long-term technical support to ensure adherence to standard operating procedures.

2. For ABM use, prescription data (especially that for calculating the percentage of ABM-containing prescriptions) is probably the most reliable. However, since data on DDD prescribed per 100 patients help to provide insight into ABM use, efforts must be made to collect these data and to improve their quality. Bulk use data may help in assessing ABM use, but unless issues concerning quality and reliability are addressed, they are probably not worth collecting.
3. For AMR surveillance, *E. coli* is a suitable indicator bacterium. There are different options for obtaining specimens that could yield *E. coli* isolates. Disc diffusion testing is probably better than minimal inhibitory concentration (MIC) testing, at least in resource-constrained settings.
4. A multidisciplinary approach is required to set up and maintain the project and to interpret data. Each site should have a qualified pharmacist/pharmacologist, microbiologist, community health personnel and a person competent in computerized data management. Training for data collectors, those collecting samples and managing data is essential. A standardization workshop for the investigators dealing with different aspects would be beneficial.
5. Standard operating principles (SOPs) acceptable and practical at all sites are needed for all aspects of data collection, both for AMR and ABM use. Quality assurance schemes need to be robust.
6. Database entry programmes for ABM use and AMR need to be developed to allow uniformity in standards to assure quality of surveillance data. The design of such databases should be done in consultation with experts in statistics, in order to enable appropriate analyses for time trends and measurement of impact. There should also be an in-built mechanism for assuring the quality of data collected and entered into the database.
7. Methods for ensuring adherence to protocols should be included in the overall programme. Frequent, more intense regular monitoring, starting in the first month of data collection and then continuing at least every six months by contracted long-term consultants, is necessary to identify problems early and rectify them more effectively.
8. The feasibility of integrating surveillance systems into existing systems, as well as the means of incorporating data generated into each country's health information systems, need to be explored.
9. For long-term sustainability, the commitment of local stakeholders is essential. Issues requiring attention include funding and human resource development. It is worth strengthening the microbiological laboratories in order to systematically collect routine AMR data on specific pathogens in the area and to use these data to guide therapy and monitor trends among pathogens. Strengthening pharmacoepidemiology expertise in pharmacology/pharmacy departments would help in sustainable monitoring of ABM use.

1. Background, aims and general methods

1.1 Background and justification

Although the discovery of penicillin and other antibiotics allowed for the effective and safe treatment of several bacterial infections, this was followed, within a few decades, by the emergence of increasing antimicrobial resistance (AMR). This has the potential to limit the effectiveness of many antibacterial medicines (ABMs) used widely in both developed and developing countries. Inadequate infection control in hospitals and the lack of effective public health measures to control infections in the community are factors that are contributing to this problem, particularly in developing country settings where the burden of infection is high and the choices for therapy limited [1,2]. Lack of antibacterial effectiveness due to AMR is associated with increased patient mortality[3] and morbidity, which have serious economic consequences in terms of more costly second- or third-line drugs, more frequent and longer hospital stays, etc.[4, 5].

AMR is a natural consequence of exposure to antimicrobials and is not a new phenomenon. Even with appropriate antimicrobial use, the rates of AMR can increase[6]. The progress, however, is likely to be more rapid when there is inappropriate use. Some hospital-based reports have shown associations between use and resistance[7]. There have also been a few reports on associations between quantity of use and AMR rates at a community level. A report on data from 20 countries showed penicillin and macrolide resistance in *S. pneumoniae* to be associated with specific ABM use[8]. In Chile, following legislation on ABM sales, the use of these agents fell significantly[9]. Hospital data from a limited numbers of centres in Chile suggested a decrease in AMR rates among *E. coli* causing infections[10]. In Finland, after nationwide reductions in the use of macrolides for outpatient therapy, the frequency of erythromycin resistance among group A streptococci causing infections declined over a few years[11]. In most cases, however, resistance is likely to be slow to reverse or even irreversible following reduction in use. The realistic outcome of reducing ABM use could, therefore, be just a slowing in the rate of increase in AMR.

In 2001, WHO summarized the nature of this global challenge and proposed various strategies for addressing the problem[12]. The following excerpts from the WHO's *Global strategy for containment of antimicrobial resistance* summarize the basic message:

- "Resistance costs money, livelihoods and lives and threatens to undermine the effectiveness of health delivery programmes. It has recently been described as a threat to global stability and national security. A few studies have suggested that resistant clones can be replaced by susceptible ones; in general, however, resistance is slow to reverse or is irreversible."
- "Antimicrobial use is the key driver of resistance. Paradoxically this selective pressure comes from a combination of overuse in many parts of the world, particularly for minor infections, misuse due to lack of access to appropriate treatment and underuse due to lack of financial support to complete treatment courses."

- "Resistance is only just beginning to be considered as a societal issue and, in economic terms, as a negative externality in the health-care context. Individual decisions to use antimicrobials (taken by the consumer alone or by the decision-making combination of health-care worker and patient) often ignore the societal perspective and the perspective of the health service."

The WHO Global Strategy noted that a 1998 World Health Assembly (WHA) Resolution had urged Member States to: 1) develop measures to encourage appropriate and cost-effective use of antimicrobials; 2) prohibit the dispensing of antimicrobials without the prescription of a qualified health-care professional; 3) improve practices to prevent the spread of infection and thereby the spread of resistant pathogens; 4) strengthen legislation to prevent the manufacture, sale and distribution of counterfeit antimicrobials and the sale of antimicrobials on the informal market; and 5) reduce the use of antimicrobials in food-animal production. Member States had also been encouraged to develop sustainable systems to detect resistant pathogens, to monitor volumes and patterns of use of antimicrobials and the impact of control measures.

A further World Health Assembly Resolution (WHA58.27) in 2005 reinforced this message, urging Member States to "ensure the development of a coherent, comprehensive and integrated national approach to implementing the strategy for containment of antimicrobial resistance" and to "monitor regularly the use of antimicrobial agents and the level of antimicrobial resistance in all relevant sectors".

Together, these Resolutions provided the impetus for this project. Surveillance systems are required to understand trends in AMR and ABM use, as well as the long-term temporal associations between these two in different areas. Data generated from these systems could also help in quantifying the burden due to AMR on society and health systems and for developing and evaluating locally relevant policies and guidelines for ABM use. Data could also stimulate a sense of urgency to act. Improving ABM use is the key feature in efforts to contain AMR[12]. Strategies for interventions to reduce ABM use have to be prioritized and customized based on existing local realities[12]. Data from surveillance could help in identifying priorities and processes and in documenting a baseline for monitoring effects of interventions.

Available data on the factors determining the use of antimicrobial agents in developing countries has been summarized by Radyowijati and Haak[13, 14]. They found multiple determinants of antibiotic use involving prescribers, dispensers, community members and health system factors and concluded that further research was needed to explore in-depth the sociocultural rationality of antibiotic usage in order to develop effective interventions to improve use. Intervention strategies that have proven to be effective in developing world contexts have also been reviewed by Management Sciences for Health[15]. This review concluded that educational strategies with supervision and/or group process strategies, such as peer review, could improve antibiotic usage by 20% or more, but that the distribution of printed materials, such as clinical guidelines, alone consistently failed to improve use.

In a number of developed country settings, extensive programmes have been developed to track patterns of AMR and ABM use over time However, the ability to undertake such surveillance is lacking in resource-constrained countries. An example of such an extensive

programme is the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA), which has demonstrated the ability not only to track AMR over time, but also to reduce antimicrobial use without adversely affecting health status[16]. This has been done by using the AMR and ABM use data for priority-setting of areas for intervention, which have included clinical guidelines, training of prescribers, consumer education, implemented through regional groups and coordinated by a national steering committee. The European Surveillance of Antimicrobial Consumption (ESAC) project has not only tracked consumption over time, but also developed quality tools to help guide more rational use of antimicrobials[17, 18]. This has been complemented by the European Antimicrobial Resistance Surveillance System (EARSS), which has also been able to document trends over time[19, 20]. Such systems can stimulate local action at the national level, as has been shown in Ireland[21]. The SENTRY Antimicrobial Surveillance Program has also sought to track resistance patterns, using a network of sentinel laboratories. While initially restricted to North America, the SENTRY Program has expanded considerably to include 22 countries, and has produced many reports. Recent reports have covered resistance patterns across many countries, including some from the developing world[22, 23, 24].

Nonetheless, currently it is nearly impossible in low-income countries to quantify the effects of AMR on the individual or the community, because of the lack of availability of good quality data in sufficient quantities. Most developing countries do not have systems for routinely monitoring AMR or its consequences[2]. Measuring AMR rates on the basis of hospital isolates, as is presently mostly done, is inadequate for understanding the burden of increasing AMR on the community. No standardized and universally acceptable, but cost-effective, method for routine community surveillance of AMR and the use of specific ABMs in resource-poor settings has yet been developed. Therefore, developing validated, reproducible and sustainable surveillance methodologies to quantify AMR and ABM use in the community, to measure the association between use and evolution and/or spread of resistance, and to inform the development of interventions and evaluate their impact, is a priority.

1.2 Aims and objectives

The overall, long-term aim was to carry out a series of activities that would contribute to knowledge on how to stem the rising trend in AMR. The activities were conceptualized in different phases:

- The aim for phase 1 was to set up pilot community-based surveillance systems to continually monitor trends in AMR and use of ABM in different geographical areas, in order to inform the development of a model for such activities.
- The aim for phase 2 was to use these established community-based surveillance systems to better characterize the relationship between ABM and AMR in different geographical areas, and to investigate and understand reasons for prevailing practices, in order to develop interventions to contain ABM misuse and the spread of AMR.
- The aim of phase 3 was to implement and evaluate the impact of interventions on ABM use and AMR, using established community-based surveillance systems.
- The aim of phase 4 was to advocate at the national level for the adoption of community-based surveillance systems, using the findings of phases 1-3.

Containment of AMR requires a multidisciplinary approach and it was hoped that the initiation of linked and integrated community-based surveillance, the development and implementation of interventions and the use surveillance data to evaluate the interventions, would all help to build the required liaison between disciplines and the capacity to tackle the problem in the long term.

Several specific objectives were thus identified for phase 1:

1. To develop and pilot test methodologies for integrated surveillance of AMR and ABM use in communities in resource-poor settings, by establishing pilot projects in five different areas in two developing countries.
2. To collect community-based surveillance data on AMR in indicator bacteria at each site, as monthly data points to facilitate time series analyses.
3. To monitor monthly ABM use, measured using data from prescriptions or bulk sales/purchase or both, in each site, as monthly data points to facilitate time series analyses.
4. To analyse these data to understand current trends in AMR and ABM use in each site.
5. To reflect on the issues and problems related to the methods used in each site.
6. To identify issues and problems related to the implementation of community-based surveillance systems for AMR and ABM use in resource-constrained settings.

Each site was also to be supported to use the data generated to develop interventions to reduce irrational use of ABM, with a view to subsequently documenting the impact of such interventions. This report covers only the surveillance aspects of the project during phase 1.

1.3 Methods followed and rationale

The intent was to establish pilot projects in five different sites. It was felt that multiple centres would be needed to capture geographical and demographic differences in AMR and ABM use, and also to increase the power to identify evolving issues and their risk factors. A request for expression of interest was issued to various countries and organizations with proven interest in the issue of bacterial resistance to antibiotics. Since multi-disciplinary efforts were considered essential for the success of the surveillance projects, sites were required to have proven expertise in microbiology, drug use measurement, data management and analysis. Once expressions of interest were received, visits were made to these sites to assess capacity to do microbiology laboratory work and infrastructure to collect community level data. Those sites with the necessary capacity were then requested to submit full proposals for establishing a community-based surveillance system.

The sites subsequently selected were in urban areas and attached to large hospitals, as these were the only sites able to meet the requirement for existing capacity, in particular to do microbiological investigations. Pilot projects were established in two low/middle-income countries: India and South Africa.

These two countries have quite different health systems. In India, over-the-counter sales of prescription-only medicines, such as antibiotics, although not permitted by law, happens

often. It is probable that ABMs are also used by practitioners of alternative forms of medicine, such as traditional healers. ABMs are also extensively used in veterinary practice and for agricultural use in a fairly unregulated manner. In South Africa, over-the-counter sale of prescription-only medicines, such as antibiotics for systemic use, is minimal. Although antimicrobials are used extensively in veterinary practice and in agriculture, this occurs in a fairly regulated manner. Both countries have a mixed system of health-care funding. In South Africa, while only about 15% of the population has access to health insurance, many uninsured patients also seek care in the for-profit private sector. In India, it is estimated that about 70% of the population obtains health-care services in the private sector. In addition, it is estimated that up to 80% of health-care services in India are paid for by patients at the time of obtaining these services (out-of-pocket expenditure). In South Africa, primary health-care services are free at the point of care for all non-insured citizens. Those with medical insurance may be required to make some co-payments, whereas uninsured patients mostly pay cash for services obtained in the private sector.

People living in the urban and peri-urban/rural areas included in the pilot projects could procure ABMs through different agencies, mainly government hospitals and clinics, private practitioners and clinics, and pharmacies. It was expected that ABM use in these different facility types could differ widely. Therefore, each site was required to gather data from a number of facilities belonging to as many of these different types as was feasible. This would also help in targeting subsequent interventions for different groups. It was expected that data would be collected every month for 12 to 24 months, thus allowing time series analyses for trends. A preference was expressed for continuous collection of data, rather than cross-sectional studies at widely spaced intervals. This approach was felt to be more feasible, and thus sustainable, and would allow for time series analysis to evaluate the impact of any future interventions. Each site was asked to propose a methodology for collecting AMR data and ABM use data, based on feasibility. It was important to learn from the differing experiences, as this would aid in making recommendations for future strategies in relation to site recruitment, AMR and ABM use measurements, sample collection, and testing systems and monitoring.

The following basic principles were established in relation to the methodology chosen.

1.3.1 AMR data

AMR rates can vary not only between bacterial species, but also between commensals and pathogens, between community and nosocomial pathogens, in different parts of the world, between time periods, between facility types in the same area, and between areas in the same facility, such as hospital wards and intensive care units. Since the aim was to pilot surveillance systems that could measure trends in AMR and ABM use in communities (and, in the long term, measure the effects of interventions), data needed to be collected on the resistance profiles of bacteria circulating in the community.

1.3.1.1 Choice of surveillance method

The most common method used for monitoring trends in AMR rates is by collating available results from tests done in clinical microbiology laboratories on pathogens isolated from patients visiting health-care facilities[10]. This method is inexpensive, as the data is a free by-product of routine testing and generates information on all local pathogens to provide locally

relevant treatment guidance. However, this generally results in an over-representation of nosocomial pathogens, since specimens will be collected mainly from patients in hospitals who fail to respond to first-line treatment. In addition, in resource-constrained settings, microbiology tests may seldom be done on a routine basis. Furthermore, access to retrospective data on the results of tests done may not be accessible in such settings. In order to partially address the expected over-representation of nosocomial data, some systems have sought to monitor AMR rates in isolates only from blood cultures or otherwise only species-specific rates in certain target bacteria, such as *S. pneumoniae*, *H. influenzae*, *N. gonorrhoeae* and *E. coli,* obtained from either institutional or community settings. Some of these bacteria, e.g., *S. pneumoniae* and *H. influenzae*, are not only the causative organisms in common and serious community-acquired infections but can also be part of the normal bacterial flora of the upper respiratory tract.

An alternative approach is to undertake AMR surveillance in indicator bacteria carried by the healthy population who have not recently been exposed to ABM. This reflects general baseline levels of resistance in commensal bacteria in a region and can allow for the detection of trends over time and between regions. It may also be possible to use this in the long term to measure the impact of community-based interventions. The resistance levels detected are not, however, representative of the picture in bacteria causing infections in that area, and so cannot be directly used to develop or alter treatment guidelines. Although the number of samples required for reliably understanding changes in AMR rates can more easily be obtained using commensal bacteria (as compared to pathogens), this method is resource intensive.

1.3.1.2 Choice of indicator bacteria

The choice of indicator bacterium is important. For example, *E. coli* is a commensal bacterium with the potential to cause many different types of infections requiring antibiotic therapy both in the community and in hospitals. It is the most frequent cause of urinary tract infections (UTI), a condition for which antibiotics are prescribed frequently in the community. *E. coli* has acquired resistance to many different groups of antimicrobials, and the prevalence of AMR in *E. coli* varies in different geographical areas. *E. coli* can act as a reservoir of resistant genes, which can be transferred to other bacteria belonging to the same species or others. It also has other practical features in its favour. It is not fastidious and can be easily handled in basic laboratories. The time taken for transportation of a sample, which is inevitably variable under field conditions, is not likely to seriously affect the viability of this organism. These features have made it a popular indicator target for AMR surveillance[25, 26, 27].

S. pneumoniae, H. influenzae and Moraxella spp. have also been used by other workers to document AMR trends, as they represent the causes of common and serious community acquired infections[28, 29, 30]. These bacteria are rapidly developing resistance to several antimicrobials used for therapy, and prevalence rates vary. Infections caused by these bacteria, antimicrobials used for therapy, mechanisms of resistance, transfer, etc., are different from those of *E. coli*. Thus, including these organisms would help to understand aspects not covered using *E. coli*. Just as *E. coli* is a normal part of intestinal bacterial flora, so may *S. pneumoniae, H. influenzae* and Moraxella spp. also be part of the normal bacterial flora

of the upper respiratory tract. However, unlike *E. coli,* these organisms are fastidious and collecting the required numbers of isolates for meaningful analyses could be difficult.

1.3.1.3 Exclusion criteria

Whichever method of acquiring the target organism is used, effort must be made either to exclude isolates from subjects who have received ABM in the recent past or to collect information on this issue. Furthermore, understanding AMR in relation to ABM use, with a view to developing containment programmes, requires that bacteria collected come from the same community as that where ABM use is being surveyed. Therefore, it was required that isolates from patients living outside the defined community be excluded. Lastly, it was required that duplicate isolates from the same patient be excluded to ensure that there was no bias of the data from duplicate isolates coming from patients supplying multiple specimens.

1.3.1.4 Sampling

The sites were required to provide an indication of the feasibility of the proposed method. This would also have implications for any subsequent intervention studies. For example, in order to detect a change of 20% over 24 months, with 80% power and 5% level of significance, a minimum sample of 960 isolates would have to be obtained in one year.

1.3.1.5 Antibiotic susceptibility testing

Determination of AMR was expected to conform with the relevant National Committee for Clinical Laboratory Standards (NCCLS-CLSI). Microbiology laboratories were also expected to have routine quality assurance systems for susceptibility testing. All sites testing *E. coli* used disc diffusion, whereas for *S. pneumoniae* and *H. influenzae*, MIC was determined.

Resistance was tested only to those ABMs commonly used for treatment of infections in the community. The following antimicrobial discs were used for susceptibility testing of *E. coli*. All discs were not used at all sites.

- β-lactam: Ampicillin 10μg; Amoxicillin/clavulanic acid 20/10μg; Cefuroxime 30μg; Ceftriaxone 30μg; Cefotaxime 30μg; Cephalexin 30μg
- Aminoglycoside: Gentamicin 10 μg
- Quinolones: Nalidixic acid 30 μg, Ciprofloxacin 5μg
- Trimethroprim/sulfamethoxazole 1.25/23.75μg
- Chloramphenicol 30μg, Tetracycline 30μg
- Nitrofurantoin 300 μg

Zone sizes were measured and interpreted as susceptible, intermediate or resistant based on NCCLS (CLSI) guidelines. Only one isolate from an individual was included in the study to avoid testing of duplicates.

1.3.1.6 Surveillance methods chosen in the sites

In one of the South African sites, AMR data on *E. coli* isolated from women with suspected community acquired UTI were collected, while from the other site data on three pathogens causing community-acquired respiratory infections were collected, again from patients with suspected infection. However, data collection was done specifically for the surveillance project.

In all three sites in India, commensal *E. coli* was used as the indicator organism. One site obtained this from faecal samples while the other two obtained it from urine contaminated with bowel flora. The latter two sites also collected data on *E. coli* causing UTI. The distinction was made primarily to provide appropriate treatment to those pregnant women with UTI. It could also help in understanding differences between infecting and commensal *E. coli*, if any. Pregnant women were studied in two sites since they represent healthy population from the community and access to this group is easier since they routinely visit clinics.

1.3.2 ABM use

ABMs are used by various different actors and facilities within the health system and in communities, and this use can vary enormously between and within countries. Thus, data needed to be collected on ABM use by the different health facilities and actors within the community from where bacterial isolates were being collected.

1.3.2.1 Choice of surveillance method

The options for ABM use surveillance would depend largely on the type of facilities and the availability of records, which could be sales records or prescriptions records. The legal requirements for such records vary between countries, as does the degree of compliance with such requirements. Other variables to consider would be the degree of computerization of records and the quality and extent of such records. In many developing countries, ABMs are available from a variety of outlets, some regulated and others not. The records retained at such facilities are likely to be either incomplete or inaccessible.

Two basic approaches were considered: 1) prospective data collection by exit patient interviews conducted at health facilities; and 2) retrospective data collected from such facilities. The latter can be of two main types: prescription data and bulk sales/purchase data.

In order to understand the use of ABM in the community as a whole, data needed to be collected from several types of facilities, in both the private and public sectors. It was accepted that the proportion of ABM use contributed by each facility type would vary. The pilot sites were therefore required to justify both the type and number of facilities to be included, based on healthcare service provision, feasibility and the ability to obtain consent. Sites were also allowed to collect data from the same facilities during the entire period of the pilot study, or to rotate between facilities that agreed to participate. Given the technical nature of the task, it was expected that data collection would be done by pharmacists or by field workers specifically trained for this task. Among the data points to be collected monthly were:

- the number of prescriptions with an ABM;
- the type of ABM used (allowing allocation to an ATC code) [31];
- dose and quantity of the ABM use (allowing for the calculation of the number of DDD prescribed)[31];
- data on the appropriateness of choice, where available.

All ABMs other than those used specifically for tuberculosis and leprosy were to be considered as ABM. Some flexibility was allowed in relation to the status of metronidazole, some sites considering it as an ABM while others did not. ATC codes were used to categorize ABM. Where bulk purchase data were used, it was assumed that the same amount purchased by the facility was sold/dispensed to patients in the period under consideration.

1.3.2.2 Measurement of use

The quantity of data to be collected was based on the WHO/INRUD methodology for investigating drug use in health facilities [32]. According to this method, 30 prescribing encounters per facility from 20 facilities are required to measure drug use indicators in a representative group of facilities. For the purposes of the pilot study, it was suggested that each site would aim to collect 30 ABM-containing prescriptions from each facility every month. ABM use can be expressed in two complementary ways. The first, drawing on the WHO/INRUD methodology, is the percentage of prescriptions containing a specific ABM. While this indicates the prevalence of ABM use, it does not provide much information on the extent of use, and in particular on the quantity of ABM used. This latter factor is expected to be important in determining the degree of ecological pressure exerted, which will inevitably result in AMR.

A more specific measure of utilization is therefore provided by the number of DDDs prescribed per unit of population. The challenge in settings where only a sample of prescriptions/sales can be measured is to decide on an appropriate denominator for this calculation. The total number of patients seen in the time required to generate the ABM-containing prescriptions captured can be used. Utilization is therefore expressed as the number of DDDs of a specific ABM prescribed per 100 patients seen, at a particular point in time. Data presented in this way cannot be compared with data based on the total population, as they are based only on those persons attending the health facilities in question. In most resource-constrained settings, populations are highly mobile and access services from a variety of facilities and facility types. Obtaining both appropriate numerator and denominator data for the whole population in such areas is simply impossible. It was suggested that each site should include both types of measures, so as to generate the maximum amount of data and allow for comparison of the results obtained and consideration of their positive and negative characteristics.

ATC and DDD data were obtained from the web site of the WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atcddd/)[31]. The DDD of a specific ABM prescribed per 100 patients was calculated as follows:

Step 1: Total dose in grams per patient

= Unit strength x no. of units per day x no. of days prescribed

Step 2: Number of DDD of specific ABM per patient

$$= \frac{\text{Total dose of specific ABM (in grams) per patient}}{\text{DDD for the specific ABM}}$$

Step 3: DDD of specific ABM prescribed per 100 patients per period

$$= \frac{\text{Sum of no. of DDDs per patient for a period x 100}}{\text{Total no. of prescriptions examined during that period}}$$

1.3.2.3 Surveillance methods chosen in the sites

In both sites in South Africa, retrospective data were collected monthly from prescriptions or clinic records. It was intended that data be collected from public sector primary health-care facilities, private general practitioners and pharmacies in both sites. While both succeeded in collecting data from public sector facilities, only one site managed to collect data from private general practitioners (GPs) and pharmacies.

In all three sites in India, prospective data were collected monthly by interviewing patients as they exited from facilities. In two of the sites, data were collected from public sector facilities, private general practitioners and private pharmacies. In the third site, due to resource constraints, data were collected only from private pharmacies. In addition, two sites collected bulk purchase data, one site measuring the number of DDD of specific ABM purchased per 100 patients attending the facility, and the other measuring the number of DDD of specific ABM purchased per 1000 population.

1.3.3 Comparison with larger-scale, network programmes

The pragmatic approach taken in these pilot studies can be contrasted with the very extensive infrastructure required for the larger scale, network programmes that have been instituted in Europe and elsewhere. For example, the ESAC programme was developed by a "multidisciplinary management team (a chief microbiologist plus three full-time equivalents in pharmacoepidemiology, medical sociology, pharmacoeconomics and administrative assistance)", which recruited a "network of dedicated national representatives (predominantly microbiologists), collaborating on a voluntary basis"[17]. National data on ABM use was obtained, "based on reports from the pharmaceutical companies, wholesalers, pharmacies or market research companies". Denominator data were collected "on the mid-year population of the country for ambulatory care, and on the number of bed days for hospital care, to calculate population-based measures of antibiotic exposure".

The EARSS report from 2002 explained that "to assess the comparability of susceptibility test results, a quality assurance exercise was performed in September 2000 among 482 laboratories from 23 countries participating in EARSS"[19]. The data flow was described in these terms: "Laboratories send standardized data to the national EARSS data manager, who checks data contents and ensures conformity with the EARSS data format. In collaboration with WHO, an export module from the laboratory-based software WHONET was developed

for EARSS. Every quarter, data are forwarded to the central database at the National Institute of Public Health and the Environment (RIVM), Bilthoven, the Netherlands, where the project is coordinated".

The Swedish Strategic Programme Against Antibiotic Resistance (STRAMA) is a decentralized nationwide organization operating through county medical officers to implement the national plan to prevent resistance to antibiotics. It was founded in 1995 and has been funded by the government since 2000. Through the programme, nationwide surveillance of AMR and ABM is undertaken and a package of interventions aimed at improving prescribing and reducing consumer demand has been implemented. Antibiotic use has significantly decreased since the programme started and AMR rates are low. Details on the STRAMA project can be obtained at the English language web page of the project (http://en.strama.se/dyn//,84,2.html).

1.4 Approval for the study

Ethical approval for the pilot study as a whole was obtained from the WHO Ethics Review Committee. Approval was also obtained from the respective institutions for collecting samples for testing. Informed consent was obtained from all subjects and facilities participating in the pilot studies.

2. Delhi, India

2.1 Background information on the site

Delhi is the capital city of India and is divided into 134 municipal wards for administrative purposes. Both ABM use and AMR surveillance data were collected from five such municipal wards in west Delhi (Patel Nagar, Rajinder Nagar, Karol Bagh, Inderpuri and Rajouri Garden). The total population of these five municipal wards was estimated to be approximately 900,000. The population is considered to be highly mobile. There are a large number of pharmacies in this area: 42 in Patel Nagar, 22 in Rajinder Nagar, 79 in Karol Bagh, 16 in Inderpuri and 42 in Rajouri Garden. Health-care services are also provided through public sector (government) hospitals and clinics (sometimes referred to as dispensaries), and through both private medical practitioners and private hospitals.

AMR data were collected through the Microbiology Department of Sir Ganga Ram Hospital, a large private hospital situated roughly at the junction of central and west Delhi. While a good proportion of the women attending antenatal services at this hospital come from the 5 west Delhi municipal wards targeted, the hospital caters for patients from other areas as well. ABM use data were collected through the Delhi Society for Promoting the Rational Use of Drugs (DSPRUD).

2.2 Methods

2.2.1 AMR Surveillance

This pilot site chose to use *Escherichia coli* as an indicator organism.

2.2.1.1 Sample collection

E. coli was isolated from mid-stream urine specimens obtained from consecutive pregnant women with symptoms of urinary tract infection (UTI) attending antenatal services at Sir Ganga Ram Hospital. Specimens were collected from women reporting that they were from areas within a 10km radius of the hospital. The samples were transported to the laboratory immediately on collection. Only one isolate per person was used.

Where *E. coli* was isolated in colony counts of $\geq 10^5$/ml or isolated in pure growth in colony counts of 10^3-10^5/ml with ≥ 10 pus cells/ml, these isolates were considered to be pathogens. Where *E. coli* was isolated in colony counts of $< 10^5$/ml, with pus cells <10/ml, these isolates were considered to be commensals.

2.2.1.2 Identification of bacteria and susceptibility testing

The samples were plated on sheep blood agar and MacConkey agar (BioMerieux/Hi Media) using a 0.001 ml loop. Identification was done using a battery of biochemical tests, including sugar fermentation using triple sugar iron (TSI) agar, tests for indole production, the methyl red test, urease production and citrate utilization. Susceptibility testing was done by disc diffusion test on Mueller Hinton agar (Hi Media/BioMerieux), following the

recommendations in NCCLS/CLSI 2002. The discs were obtained from Hi Media or BD. Internal quality control was done daily using *Staphylococcus aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *Pseudomonas* (ATCC 27853). The site also participates in the general quality assessment programme for microbiology laboratories, under the auspices of the Indian Association of Medical Microbiologists (IAMM), operated by Christian Medical College, Vellore, India.

In the last two months of the study, when it became apparent that insufficient numbers of isolates were being obtained, a modification was made to the methodology. About 0.5 ml of each urine sample showing no growth after overnight incubation was inoculated into 2-3 ml tryptic soya broth (TSB), incubated at 37 °C overnight, and then sub-cultured to get an additional yield of *E. coli.* These were also classified as commensals.

2.2.2 ABM use

ABM use data were obtained by two methods, as recommended.

2.2.2.1 Facility selection

Data were collected monthly from a sample of 30 private sector retail pharmacies in the 5 municipal wards in west Delhi. The pharmacy located in the Sir Ganga Ram Hospital was included in the sample, as well as 7 in Inderpuri, 3 in Karol Bagh, 5 in Patel Nagar, 6 in Rajinder Nagar and 9 in Rajouri Garden. All 30 pharmacies were considered to operate in the private sector. The same facilities were used throughout the study period to collect data, and prior consent was obtained from each pharmacy. Facilities were not selected randomly but on their willingness to cooperate.

2.2.2.2 Bulk purchase data

Purchase data were extracted from the purchase bills (records) maintained by each facility. Data were collected on a proforma, designed to contain the names of all ABMs and the different strengths available for each. Each pharmacy was visited every 15 days to capture purchase data. It was not possible to differentiate between the quantity of ABM supplied to the hospital wards for use by in-patients at Sir Ganga Ram Hospital and the quantity of ABM dispensed to out-patients from that pharmacy. The total population of each municipal ward was used as the denominator, although the sample chosen did not represent every pharmacy in each ward, and the population from one municipal ward could visit pharmacies in other municipal wards. The population of each municipal ward studied was as follows: Karol Bagh, 123,610; Rajinder Nagar, 72,093; Patel Nagar, 150,058; Inderpuri, 87,239; and Rajouri Garden, 469,963. Analysis was done at the level of the cluster (the ward).

2.2.2.3 Patient exit interviews

ABM use data were also collected by pharmacists who conducted exit interviews with patients leaving each pharmacy. Exit interviews were done every 15 days at each pharmacy, on the same day as purchase records were examined. Exit interviews were used to identify those patients who had purchased ABM for out-patient use. Data were collected on the name of the ABM(s) purchased, the dose, the duration prescribed and the quantity actually purchased, using a pre-designed format. Approximately 15-25 exit interviews were performed in each pharmacy each month. The number of patients presenting a prescription

during the time taken to collect the desired number of ABM-containing prescriptions was recorded at each visit. These data allowed for the calculation of the percentage of prescriptions with an ABM, and with a specific ABM. ABMs were categorized using ATC codes, and the number of DDDs prescribed for each ABM per 100 patients visiting the facility was calculated. In this case, the denominator was the number of patients who visited the pharmacy whether purchasing an ABM or not, during the time of data collection. The data collection process and data capture instruments were piloted before the actual survey commenced.

2.2.3 Data management

Data on both AMR and ABM were captured using a locally developed data-entry programme in FoxPro software and exported into Microsoft Excel 2003 for analysis. All data were double entered to check for errors.

2.3 Findings

AMR data were collected from November 2003 to December 2004 and ABM use data from December 2003 to December 2004 at this site.

2.3.1 AMR in *E. coli*

2.3.1.1 AMR in commensals and pathogens

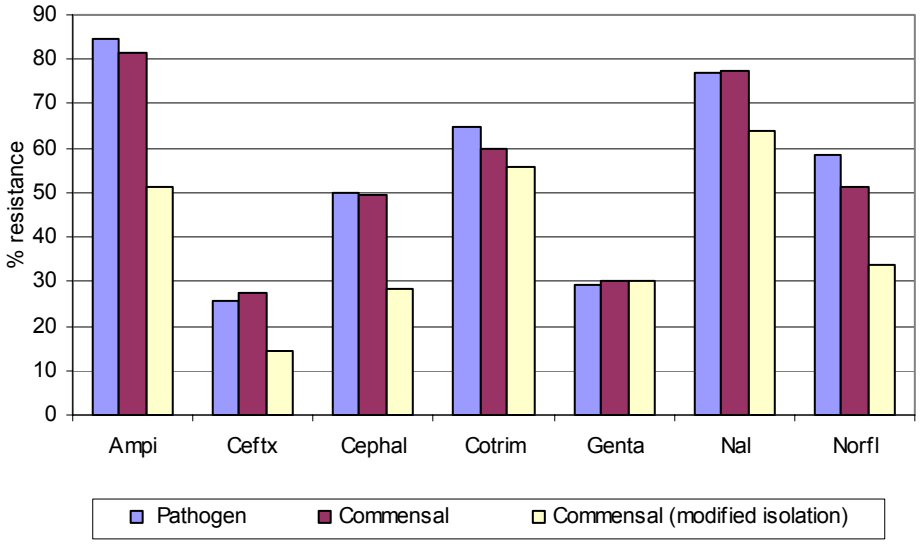
All samples were collected from women suspected of having UTI. Data on AMR was available from 603 isolates collected over a period of 14 months, from November 2003 to December 2004. The overall AMR pattern is shown in Table 2.1 and Figure 2.1. Resistance rates among pathogens and commensals were high to all ABM tested. The rates were above 70% for ampicillin and nalidixic acid. Over 50% of isolates were resistant to fluoroquinolones and more than 20% resistant to third-generation cephalosporins. Cross-resistance to ampicillin, nalidixic acid and cotrimoxazole was shown in 117 (51.1%) pathogens and 158 (42.5%) commensals, and high levels of resistance to each of these ABMs was also demonstrated.

Table 2.1: AMR in *E. coli* isolated during the period November 2003 to December 2004*

	Pathogens			Commensals		
	No. tested	No. resistant	% resistant	No. tested	No. resistant	% resistant
Amikacin	222	35	15.8	245	29	11.8
Ampicillin	227	192	84.6	376	267	71.0
Cefotaxime	227	58	25.6	372	86	23.1
Cephalexin	225	112	49.8	374	157	42.0
Ciprofloxacin	215	123	57.2	249	126	50.6
Cotrimoxazole	223	145	65.0	376	217	57.7
Gentamicin	224	66	29.5	375	112	29.9
Nalidixic acid	227	175	77.1	373	269	72.1
Norfloxacin	225	132	58.7	375	168	44.8

* The values for % resistance of commensals relate to *all* commensals. These values therefore lie in between the values shown in Figure 2.1 for commensal from normal isolation and those from modified isolation.

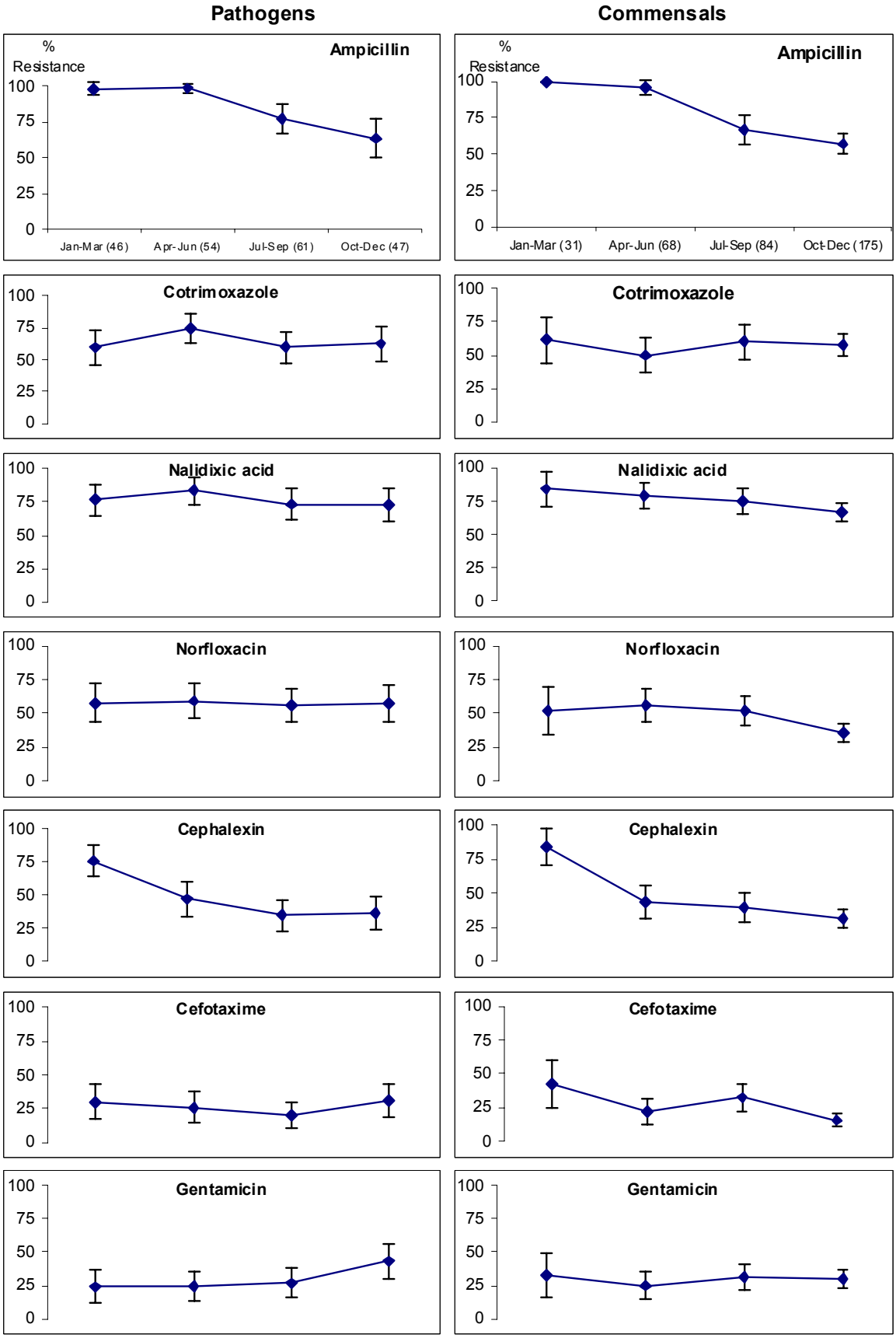
Fig.2.1: Annual percentage AMR rates in *E.coli* (November 2003 to December 2004)



2.3.1.2 Monthly trends in AMR

A high degree of month-to-month variability was seen with some AMR rates. For example, initially there were very high rates of resistance to ampicillin and cephalexin, and these later declined sharply. The numbers of isolates tested per month were small, especially in the early part of the pilot study, and this may explain the degree of variability seen during this period. After introducing the modification in method for isolating commensal *E. coli*, the numbers of isolates obtained increased significantly. An average of 19 isolates per month was obtained during the initial 10 months, compared to an average of 72 isolates each month during the last two months of the pilot study. Lower rates of resistance rates to most ABMs were found in commensals obtained by modification compared to pathogens and commensals obtained without modification, as seen in Figure 2.1. Urine can select out pathogenic *E. coli* and can be inhibitory to commensal *E. coli.* The modification introduced, where urine was diluted with culture broth, probably helped in isolating commensal bacteria preferentially, while the commensals isolated from urine directly could possibly have been *E. coli* able to colonize the lower urinary tract. Quarterly AMR rates show less variability, and are depicted for both pathogens and commensals (Figure 2.2). While the results obtained are reported, it must be noted that the NCCLS/CLSI guidelines do not recommend testing *E. coli* for cephalexin susceptibility.

Fig.2.2: Quarterly percentage AMR rates in *E. coli* (January to December 2004)



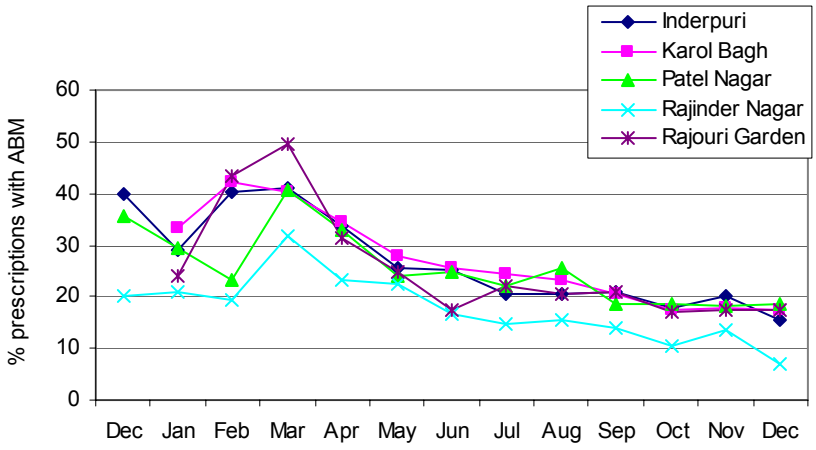
Numbers in parenthesis in the first set of graphs indicate total numbers tested.
Error bars indicate confidence intervals.

2.3.2 ABM use

2.3.2.1 Prescription data

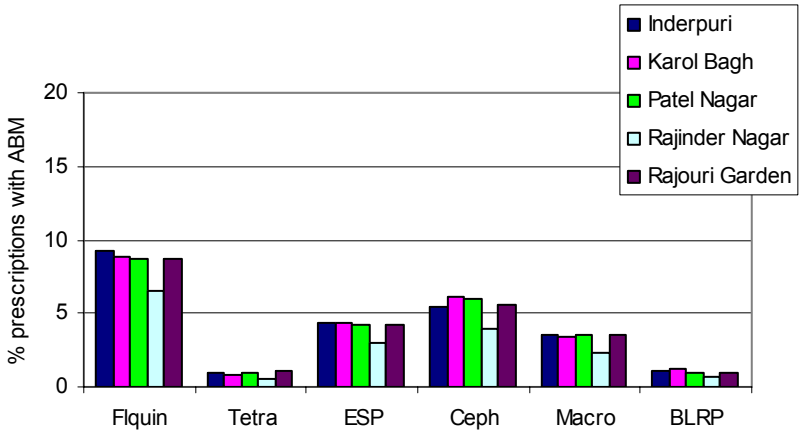
A total of 6772 AMB-containing prescriptions was examined during exit interviews, out of a total of 31,571 patients visiting pharmacies at the same time. Overall, therefore, 21.5% of all prescriptions were recorded as containing at least one ABM prescription. Figure 2.3 shows the monthly trend in the percentage of prescriptions containing any ABM. Although a high percentage of ABM-containing prescriptions was shown in the early months of the pilot study (February – March), this could not be confirmed as a seasonal trend, based on a single year of data only. It may well be that ABM consumption measured by this indicator is higher during the change of season, associated with an increased occurrence of acute respiratory tract infections (ARI). However, this trend may also reflect the challenges of data collection in the early stages of a pilot study, where data collection involves a number of personnel working in a number of different sites. That this may be a more feasible reason is shown by the fact that the denominator recorded (the total number of patients visiting the pharmacies in the time taken to identify the ABM-containing prescriptions) increased steadily during the duration of the study, from less than 500 in the first month of the study to more than 3000 in the last month.

Fig.2.3: Percentage of prescriptions with ABM in pharmacies (December 2003-December 2004)



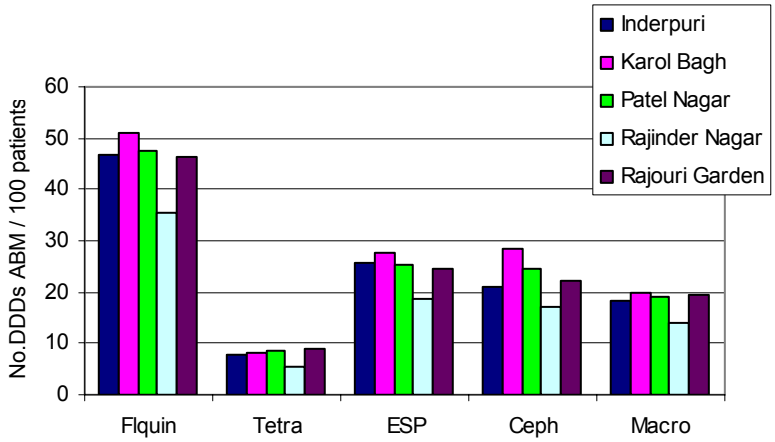
The relative use of major classes of ABMs (fluoroquinolones, extended-spectrum penicillins, cephalosporins, macrolides and beta-lactamase-resistant penicillins) per municipal ward over the entire study period, as shown by the percentage of all prescriptions that were for each class, is shown in Figure 2.4. By this measure, fluoroquinolones were the most used ABM class, followed by cephalosporins, extended-spectrum penicillins, and macrolides. No major differences between use patterns in the five municipal wards could be detected.

Fig.2.4: Annual use of ABM as percentage of prescriptions with specific ABM: exit interviews (December 2003 to December 2004)



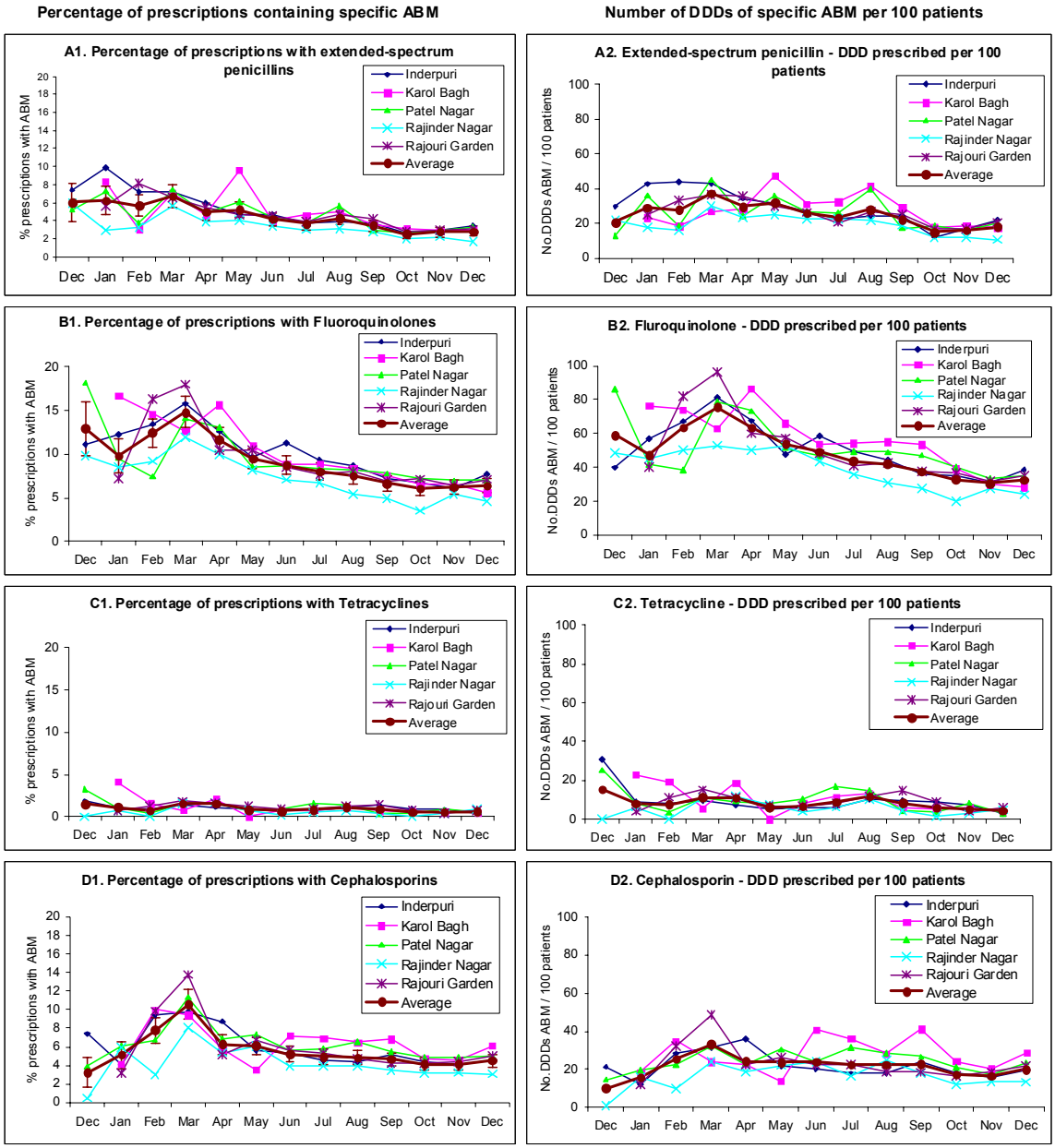
The same data were also represented as the annual use in DDD per 100 patients per municipal ward, as shown in Figure 2.5. By this measure, fluoroquinolones were the most used ABM class, followed by cephalosporins, then extended-spectrum penicillins and macrolides.

Fig.2.5: Annual use of specific ABM as DDD prescribed per 100 patients: exit interviews (December 2003 to December 2004)



Although not depicted in this report, detailed data showed that several newly introduced ABMs were being used extensively. In contrast, very little cotrimoxazole was being used in this area, at least by patients who obtained their medicines from private pharmacies. Monthly usage of the major ABM classes, expressed as the percentage of all prescriptions and as DDD per 100 patients, is shown in Figure 2.6. The possible problem with calculation of the denominator data in the first months of the study is evident.

Fig.2.6(A-D): Monthly use of specific ABM from December 2003 to December 2004 measured using exit interviews



2.3.2.2 Purchase data

ABM use, as measured from purchase records, needs to be interpreted with caution, especially when a denominator is used. The annual quantities of the major ABM classes, expressed as DDD per 1000 population per municipal ward are shown in Figure 2.7. Although the fluoroquinolones appear to dominate, the high quantity purchased per 1000 population in Rajinder Nagar is probably affected by the presence in this municipal ward of the Sir Ganga Ram Hospital pharmacy. However, it could also be that the purchase data provided by the other facilities was not complete. The combined monthly purchases of the major ABM groups, across all five municipal wards, are shown in Figure 2.8. With the exception of the fluoroquinolones, monthly total purchases seemed stable over time.

Fig.2.7: Annual bulk purchase of specific ABM in pharmacies: No. DDDs per 1000 population (December 2003 to December 2004)

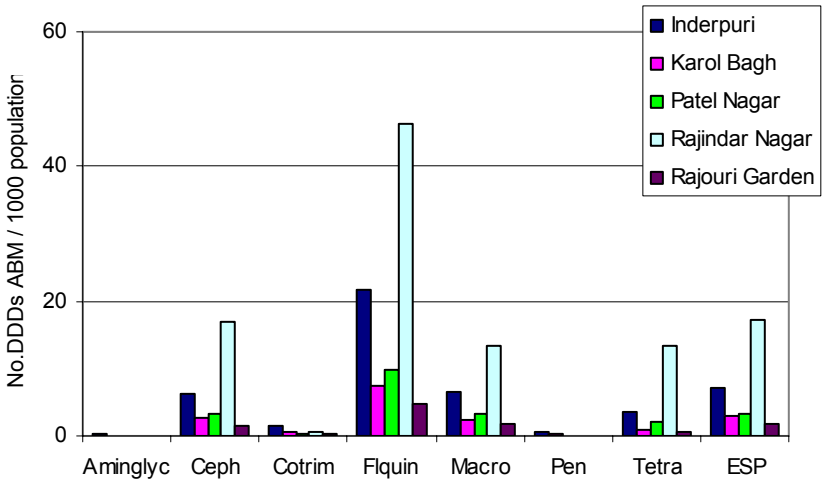
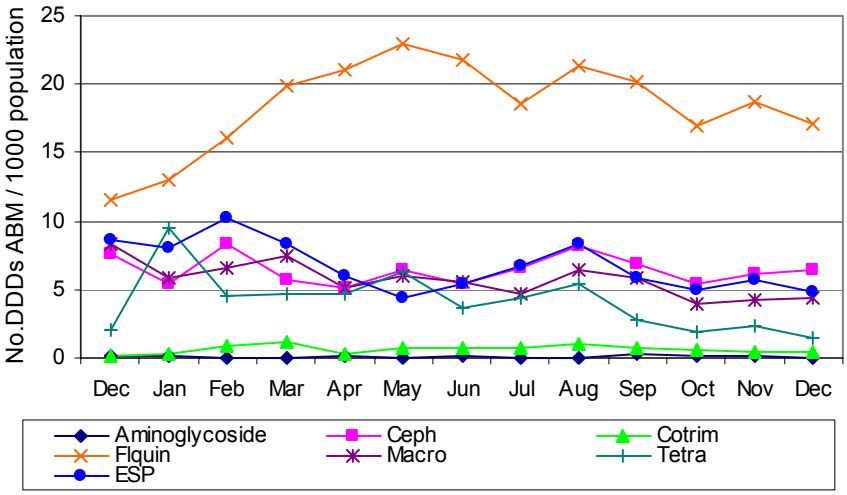


Fig.2.8: Monthly trends in bulk purchase of specific ABM in pharmacies: No. DDDs per 1000 population (December 2003 to December 2004)



2.3.3 Effect of ABM on AMR

While the intent of the pilot study was not to show any effect of ABM use (or changes in use) on AMR (or trends in AMR), some general comments could be made on the basis of the data collected. In general, it was shown that levels of resistance were higher for those ABMs that had been in use for a longer period, such as ampicillin, nalidixic acid and cotrimoxazole. However, it was also noted that more recently launched ABMs, such as the fluoroquinolones and cephalosporins, also showed high levels of consumption and resistance rates. Some of the older ABMs, such as cotrimoxazole and nalidixic acid, were not widely used in these settings. It should be noted that, although aminoglycosides would not be expected to be widely used in ambulatory practice, about 30% of *E. coli* isolates were resistant to these agents.

2.4 Lessons learnt from this site

2.4.1 AMR

This site demonstrated the usefulness of using *E. coli* from urine as an indicator organism. The method allowed the collection of both commensals and pathogens, the former being used for surveillance and the latter being of direct clinical benefit to patients and prescribers. Obtaining urine samples from pregnant women is also practical, as they routinely visit health facilities that have access to laboratory services. They are also not likely to be receiving ABM, but can be questioned about such use when providing the sample. However, as shown in the early months of the study, the yield of isolates may still be lower than expected.

2.4.2 ABM use

At this site, measures of trends in ABM consumption based on the percentage of prescriptions with an ABM and those on the DDD prescribed per 100 patients correlated to a great extent. Determination of the former measure is far easier, and the chances of calculation error are much lower. The amount of data to be recorded and captured is also far less. However, if some of the interventions to be assessed are dependent on reducing the quantity of ABM prescribed (for example, advocating short-course ABM for UTI in otherwise healthy women), then measures that take quantity into account (such as DDD per 100 patients) will be important. However, care must be taken to:

- examine sufficient numbers of prescriptions to obtain sufficient ABM-containing prescriptions;
- determine the total number of patients seen in the time required to obtain sufficient exit interviews from patients receiving ABM;
- define the correct DDD for combination products, such as those containing both ampicillin and cloxacillin, and in capturing all ABM prescribed for a single patient.

Although appealingly simple, measuring consumption on the basis of purchase records may be misleading. What is purchased may not be consumed or may be consumed months after purchase. Such methods are also challenging in terms of the denominator to be applied, if DDD per 1000 population is to be used as the measure of exposure. Since different denominators were used, no comparison could be made between consumption measured according to bulk purchase data and exiting patient interviews.

This site utilized only one type of facility (private pharmacies), and so no comparison with other settings or types of prescribers (such as public sector clinic personnel) could be made.

3. Vellore, India

3.1 Background information on the site

Vellore, a rapidly growing town in the state of Tamil Nadu, southern India, situated between Chennai and Bangalore, was designated as a city in August 2008. Two sites in this geographical area were used for the pilot study. One was within the town of Vellore itself, with a population of about 400 000, and the other a rural area (KV Kuppam, population about 100 000), located some 30km from the town. The population of Vellore district, in which both are located, is about 3.5 million people. The population is considered to be highly mobile.

Surveillance data were collected by different departments of Christian Medical College Hospital (CMC), a private sector not-for-profit organization. The CMC hospital, situated in Vellore town, and its rural unit (the RUHSA hospital), situated in KV Kuppam, provide primary care (including routine antenatal care) and secondary care primarily to the population of Vellore district. The hospital also provides advanced tertiary care to people from different parts of India. There is also a district level government hospital, a number of smaller private hospitals and many private practitioners in the town area. The rural KV Kuppam area is served by four government-run primary health care (PHC) clinics and a number of private practitioners, in addition to the RUHSA unit. ABMs are therefore dispensed by the CMC hospital, government and private hospitals, PHC clinics and privately-owned pharmacies. There are approximately 175 pharmacies in the town and 12 in the KV Kuppam area.

3.2 Methods

3.2.1 AMR surveillance

This pilot site chose *E. coli* as the indicator organism.

3.2.1.1 Sample collection

All pregnant women attending the antenatal service at either the CMC hospital or the RUHSA unit were eligible for recruitment. Samples were collected on two days per week from each centre. All women included in the study had a nitrate reductase dipstick test performed on a small sample of urine. In symptomatic and/or dipstick-positive women, midstream urine was collected aseptically in a sterile container, and culture was carried out to identify the infecting organism and its susceptibility. Asymptomatic and dipstick-negative women were instructed to collect deliberately contaminated urine. Without prior cleaning of the genitalia, urine was collected into a sterile container. The women then swabbed the perineal area themselves with pre-supplied sterile tissue and this was placed into the collected urine. *E. coli* isolated from unclean urine samples was taken to represent the commensal gut flora. From the CMC hospital, samples were transported immediately on collection to the laboratory. From the rural area, the samples were transported so as to reach

the laboratory within 3-4 h after collection. During this transit time, they were stored under cool conditions (initially in a refrigerator and then in cold bags while in transit).

In patients with suspected UTI, *E. coli* isolated in pure growth and in counts above 1000 colony-forming units/ml was counted as an infecting strain (pathogen). All isolates of *E. coli* from deliberately contaminated urine were counted as commensals. Approximately 80 isolates (40 from each centre) were collected every month.

3.2.1.2 Identification of bacteria and susceptibility testing

Urine samples were plated on both blood agar and MacConkey agar in 0.01ml amounts. The isolates were identified as *E. coli* on the basis of colony morphology, negative oxidase test, reaction on triple sugar iron (TSI) agar, mannitol fermentation, ability to produce indole from peptone water, and inability to utilize citrate or split urea.

Susceptibility testing was performed on Mueller Hinton agar (Hi Media, India) following NCCLS/CLSI 2002 criteria (2002). Discs for testing were either obtained from Hi Media (India) or prepared in the laboratory. Reference strains were tested, as recommended by NCCLS/CLSI, every time susceptibility testing was performed. Readings for the test strains were taken only if the results for each antibiotic with the reference strains were acceptable. The site also participates in the quality assessment programme for microbiology laboratories under the auspices of the Indian Association of Medical Microbiologists (IAMM), which is operated by CMC Vellore, India.

Data on AMR were maintained in dedicated laboratory registers and also entered into study questionnaires.

3.2.2 ABM use

3.2.2.1 Facility selection

ABM use data were obtained from three types of facilities: 1) hospitals or PHC clinics (including not-for-profit and for-profit hospitals in the urban area and public sector PHC clinics and a not-for-profit hospital in the rural area); 2) private sector pharmacies; and 3) private sector general medical practitioners' practices. A sample of five urban and five rural facilities from each type (30 in total) was made, and ABM use data were obtained from these facilities each month. The CMC Hospital and the RUHSA hospital (both not-for-profit mission hospitals) were included in the urban and rural samples, respectively. However, patient exit interviews were not conducted at CMC Hospital. Private sector pharmacies, general practitioners and hospitals were not selected randomly but on their willingness to cooperate. All the government PHC facilities in the rural area were included in the sample. All facilities were situated in the same locations as the antenatal patients, from whom samples for AMR purposes were obtained, were living.

ABM use data were obtained from bulk sales/purchase records and also from exit interviews conducted by pharmacists from facilities in the same area.

3.2.2.2 Patient exit interviews

To obtain the patient exit interview data, patients leaving each sampled facility were interviewed until 30 ABM-containing prescriptions could be obtained per facility in each month. The total number of prescriptions examined was then taken to be the denominator for that facility, as this represented the total number of patients seen during the time period of observation. The forms used to gather prescription data in exit interviews were pilot-tested prior to use.

3.2.2.3 Purchase data

Bulk sales/purchase data could only be obtained from those facilities that sold or dispensed ABMs. Such data were thus only collected from some not-for-profit hospitals and all pharmacies, and not from private general practitioners or private (for-profit) hospitals. In the urban area, such data could therefore only be collected from the five selected pharmacies and in the rural area from the five selected pharmacies, the RUHSA hospital and four public primary level clinics. In the private sector pharmacies, data could be extracted from either purchase bills or from dispensing records. In the RUHSA hospital and the four public clinics, data could only be obtained from the dispensing registers maintained by the facility. The same source of data were used in each facility throughout the study. Purchase/sales volumes were converted to DDDs per 100 patients, with the denominator being the total number of patients visiting the facility per month, calculated as follows.

- For government and CMC facilities the total number of patients attending each working day was obtained from the registers and then added up for that particular month;
- For pharmacies, the total number of patients coming to the facility during the time taken to conduct patient exit interviews was noted. This number was then extrapolated for the total operating (opening) time of the pharmacy and the number of working days, and expressed as an estimated total for the month.

3.2.3 Data management

All AMR and ABM data were captured using locally developed FoxPro data entry software, and double entry was performed to check for errors. Data were exported into SPSS and Microsoft Excel 2003 for descriptive analyses.

3.3 Findings

AMR and ABM data were collected at this site in two time periods, from August 2003 to July 2004 (phase 1a) and from January to December 2005 (phase 1b).

3.3.1 AMR in *E. coli*

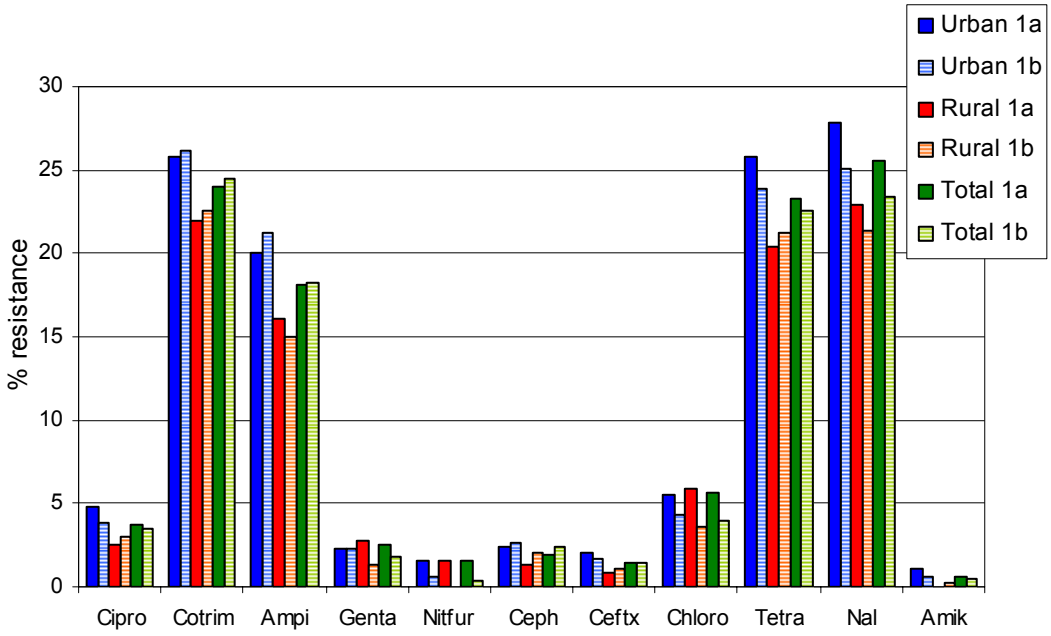
3.3.1.1 AMR in urban and rural areas

In total, over both phases 1a and 1b, 2024 *E. coli* isolates from contaminated urine specimens were obtained and tested for susceptibility. In phase 1a, 1095 isolates (585 from the urban hospital and 510 from the rural hospital) were identified, while in phase 1b a total of 929 isolates (490 urban and 439 rural) were identified. The overall resistance pattern for these commensal *E. coli* is shown in Table 3.1 and Figure 3.1. There was no statistically significant difference in resistance between the urban and rural settings.

Table 3.1: Resistance patterns of commensal *E. coli* isolated during phases 1a and 1b

ABM	Phase 1a			Phase 1b		
	Urban n (%)	Rural n (%)	Total n (%)	Urban n (%)	Rural n (%)	Total n (%)
Ampicillin	118 (20.0)	81 (16.0)	199 (18.0)	104 (21.1)	66 (15.0)	170 (18.3)
Cotrimoxazole	151 (26.0)	112 (22.0)	263 (24.0)	128 (26.1)	99 (22.6)	227 (24.4)
Cephalexin	14 (2.4)	7 (1.4)	21 (1.9)	13 (2.7)	9 (2.1)	22 (2.4)
Gentamicin	12 (2.0)	14 (3.0)	26 (2.0)	11 (2.2)	6 (1.4)	17 (1.8)
Chloramphenicol	31 (5.0)	30 (6.0)	61 (6.0)	21 (4.3)	16 (3.6)	37 (4.0)
Tetracycline	153 (26.0)	103 (20.0)	256 (23.0)	117 (23.9)	93 (21.2)	210 (22.6)
Nalidixic acid	165 (28.0)	119 (23.0)	284 (26.0)	123 (25.1)	94 (21.4)	217 (23.4)
Ciprofloxacin	27 (5.0)	13 (3.0)	40 (4.0)	19 (3.9)	13 (3.0)	32 (3.4)

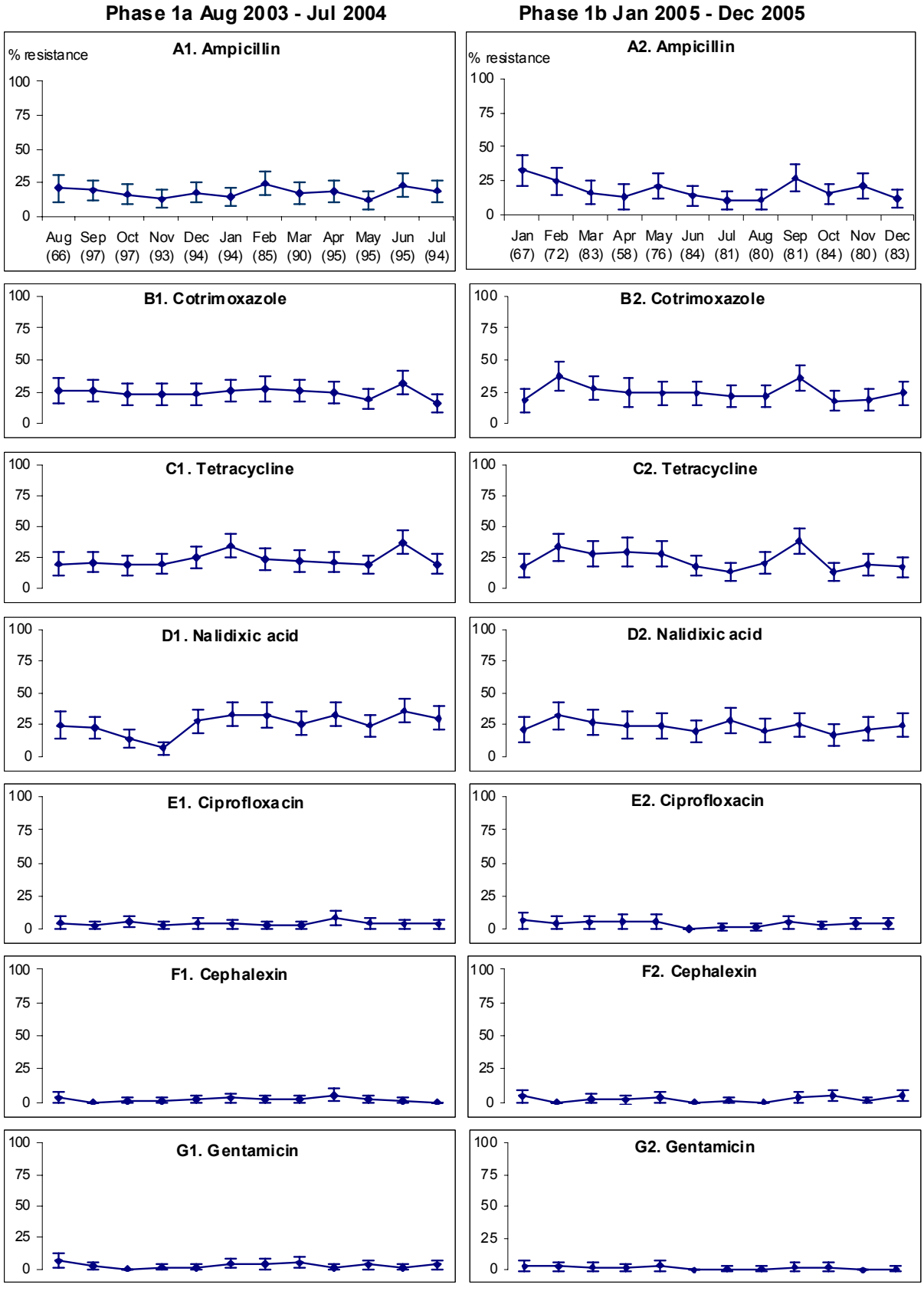
Fig.3.1: Percentage AMR rates in *E. coli* during phases 1a (2003-4) and 1b (2005)



3.3.1.2 Trends in AMR over time

In phase 1a, 463 (42%) of these commensal isolates showed resistance to one or more ABMs. Similarly, 364 (39.1%) commensal isolates in phase 1b showed resistance to at least one of the ABMs tested. As might have been expected, a higher proportion of isolates was resistant to those ABMs that had been used for longer periods of time, such as ampicillin, cotrimoxazole, nalidixic acid and tetracyclines. Cross-resistance to the three ABMs most commonly used to treat UTIs (ampicillin, cotrimoxazole and nalidixic acid) was seen in 92 isolates (8.4%) in phase 1a and 79 (8.5%) in phase 1b. This was the most common multidrug-resistant phenotype observed. Aminoglycoside and cephalosporin resistance was observed in both time periods in isolates resistant to one or more of the three ABMs mentioned above. Only 1.5% and 0.3% isolates, respectively, were resistant to nitrofurantoin. No differences between the two phases were statistically significant. Monthly trends in resistance among commensal *E. coli* during the two time periods for selected ABMs are shown in Figure 3.2. There were variations but none were significant, as can be seen from the overlapping confidence intervals.

Fig.3.2 (A-G): Monthly percentage AMR rates in commensal *E.coli*



The error bars indicate confidence intervals.
The numbers within brackets are the total tested each month.

While the results obtained are reported, it must be noted that the NCCLS/CLSI guidelines do not recommend testing *E. coli* for cephalexin susceptibility.

3.3.1.3 AMR in commensals and pathogens

Only a small number of pathogenic *E. coli*, adjudged to be causing a clinical UTI, were isolated. The prevalence of resistance in these 29 isolates identified in phase 1a and 15 in phase 1b is shown in Table 3.2.

Table 3.2: Resistance patterns of *E. coli* causing UTI during the two periods of study

ABM	Phase 1a (n =29)		Phase 1b (n = 15)	
	Number	%	Number	%
Ampicillin	15	48	8	53
Cotrimoxazole	11	34	9	60
Cephalexin	5	17	2	13
Gentamicin	4	10	2	13
Chloramphenicol	6	21	3	20
Tetracycline	10	34	8	53
Nalidixic acid	18	59	9	60
Ciprofloxacin	10	31	4	27

Resistance was significantly higher in infecting strains compared to commensal strains in both years for all ABMs ($p \leq 0.005$), as shown in Table 3.3. By disc approximation test (NCCLS 2002), 18 (1.6%) commensal *E. coli* and 3 (10.3%) infecting strains ($p < 0.001$) were found to be ESBL producers in phase 1a. Only four (19%) of these isolates were from a rural ($p < 0.05$) area. This trend also continued in phase 1b, with 13 (1.4%) commensal *E. coli* being resistant to third-generation cephalosporins compared to 2 (13%) pathogens.

Table 3.3: Resistance patterns of *E. coli* causing urinary tract infection compared to that of commensals

	Pathogenic *E. coli* (n =44)		Commensal *E. coli* (n = 2024)		Significance
	Number	%	Number	%	
Ampicillin	23	52.3	369	18.2	p <0.001
Cotrimoxazole	20	45.5	490	24.2	p 0.001
Cephalexin	7	15.9	43	2.1	p <0.001
Gentamicin	6	13.6	43	2.1	p <0.001
Chloramphenicol	9	20.5	98	4.8	p <0.001
Tetracycline	18	40.9	466	23	p 0.005
Nalidixic acid	27	61.4	501	24.8	p <0.001
Ciprofloxacin	14	31.8	72	3.5	p <0.001

3.3.2 ABM use

3.3.2.1 Prescription data

A total of 10,800 ABM-containing prescriptions were captured in both phases of study, as planned. Overall, 41.3% of prescriptions in phase 1a and 40.5% of prescriptions in phase 1b contained at least one ABM. The proportion of ABM-containing prescriptions per facility type and by setting (urban and rural) over the two phases is shown in Table 3.4. More than one ABM was prescribed in 736 (2.9%) prescriptions in phase 1a and in 847 (3.2%) in phase 1b. The most commonly used combinations were ampicillin with cloxacillin and ampicillin with gentamicin. Monthly trends in the percentage of prescriptions containing at least one ABM per facility type and according to phase are shown in Figure 3.3. No obvious seasonal trends were observed.

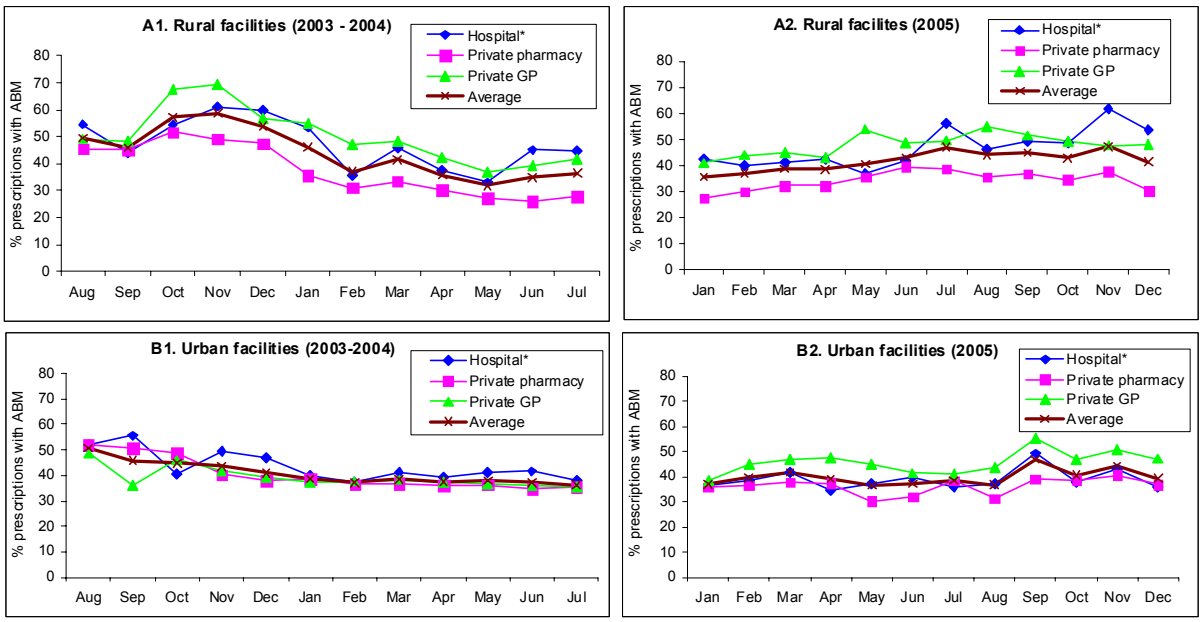
Table 3.4: Summary of prescription data

	Phase 1a		**Phase 1b**	
Urban	**Total prescription**	**Number with ABM (%)**	**Total prescription**	**Number with ABM (%)**
Private Pharmacies	4554	1800 (39.5%)	5000	1800 (36 %)
Hospitals*	4195	1800 (42.9%)	4665	1800 (38.6%)
Private GPs	4634	1800 (38.8%)	3971	1800 (45.3%)
Total urban	13,383	5400 (40.3%)	13,636	5400 (39.6%)
	Phase 1a		**Phase 1b**	
Rural	**Total prescription**	**Number with ABM (%)**	**Total prescription**	**Number with ABM (%)**
Private Pharmacies	5091	1800 (35.4%)	5314	1800 (33.9%)
Hospital/PHCs**	3935	1800 (45.7%)	3937	1800 (45.7%)
Private GPs	3721	1800 (48.4%)	3771	1800 (47.7%)
Total rural	12,747	5400 (42.4%)	13,022	5400 (41.4%)
Urban + Rural	26,130	10,800 (41.3%)	26,658	10,800 (40.5%)

* For-profit and not-for profit hospitals

** 4 government PHCs and 1 not-for-profit hospital

Fig. 3.3 (A-B): Percentage of prescriptions containing any ABM in rural and urban areas in phases 1a and 1b (2003-2005)

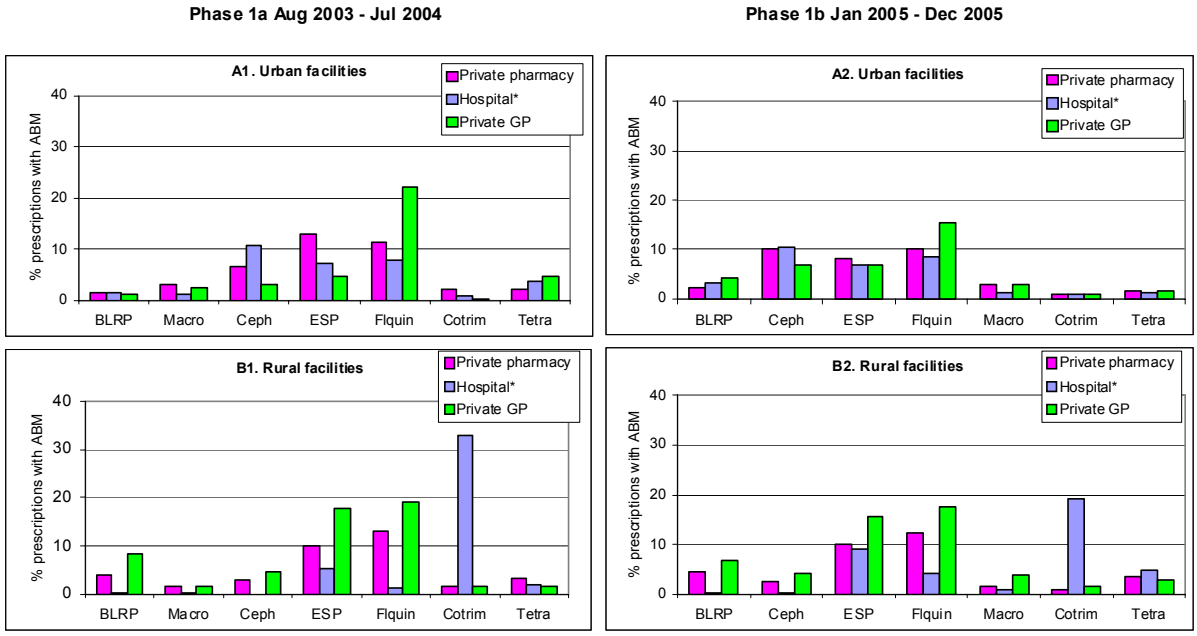


* Not-for-profit and for-profit hospitals in the urban area; public sector primary health care clinics and a not-for-profit hospital in the rural area

3.3.2.2 Specific ABM use over time

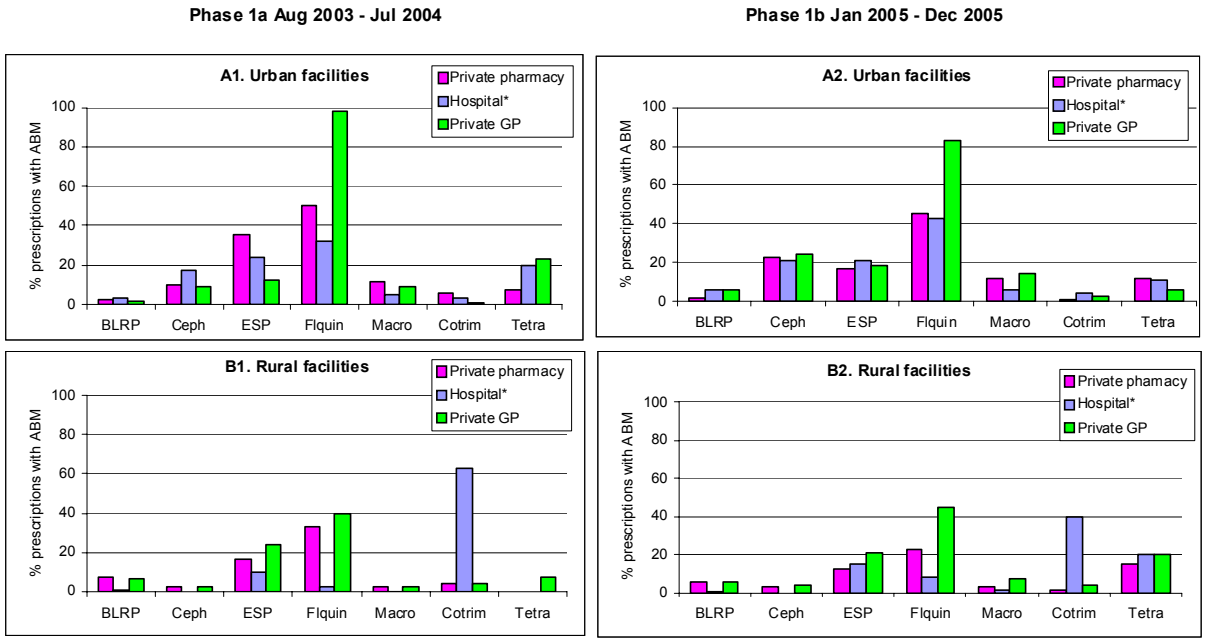
Data showing the use of major ABM classes are represented in Figures 3.4 and 3.5, as measured by the percentage of prescriptions containing an ABM from that class as well as expressed as DDD per 100 patients seen. Both measures show high levels of use of fluoroquinolones and extended-spectrum penicillins (or cephalosporins), particularly in urban settings, but also high levels of cotrimoxazole use in the public sector PHC clinics and RUHSA mission hospital in the rural area. Prescriptions filled in private sector pharmacies also reflect the prescribing habits of private medical practitioners in the area. Marked differences in ABM choice were seen between private practitioners and the government clinics and mission hospital. By using both measures of ABM use, it is possible to see differences in the scale of exposure. For example, although the percentage of prescriptions including a fluoroquinolone was similar in the rural and urban private practice settings, the number of DDD per 100 patients seen was much higher in the urban areas, reflecting differences in the doses and quantities prescribed.

Fig. 3.4 (A-B): Annual use of ABMs by facility type measured as percentage of prescriptions containing a specific ABM



* Not-for-profit and for-profit hospitals in the urban area; public sector primary health care clinics and a not-for-profit hospital in the rural area

Fig. 3.5 (A-B): Annual use of ABMs by facility type measured as no.DDDs of specific ABM prescribed per 100 patients



* Not-for-profit and for-profit hospitals in the urban area; public sector primary health care clinics and a not-for-profit hospital in the rural area

When the use of selected classes of ABMs is represented on a monthly basis, by either the percentage of prescriptions containing one ABM from the class (Figure 3.6) or the DDD per 100 patients seen (Figure 3.7), very little variation was discernible in either of the time periods studied.

Fig. 3.6 (A-D): Monthly use of ABM expressed as percentage of prescriptions with specific ABM during phases 1a and 1b (2003-2005)

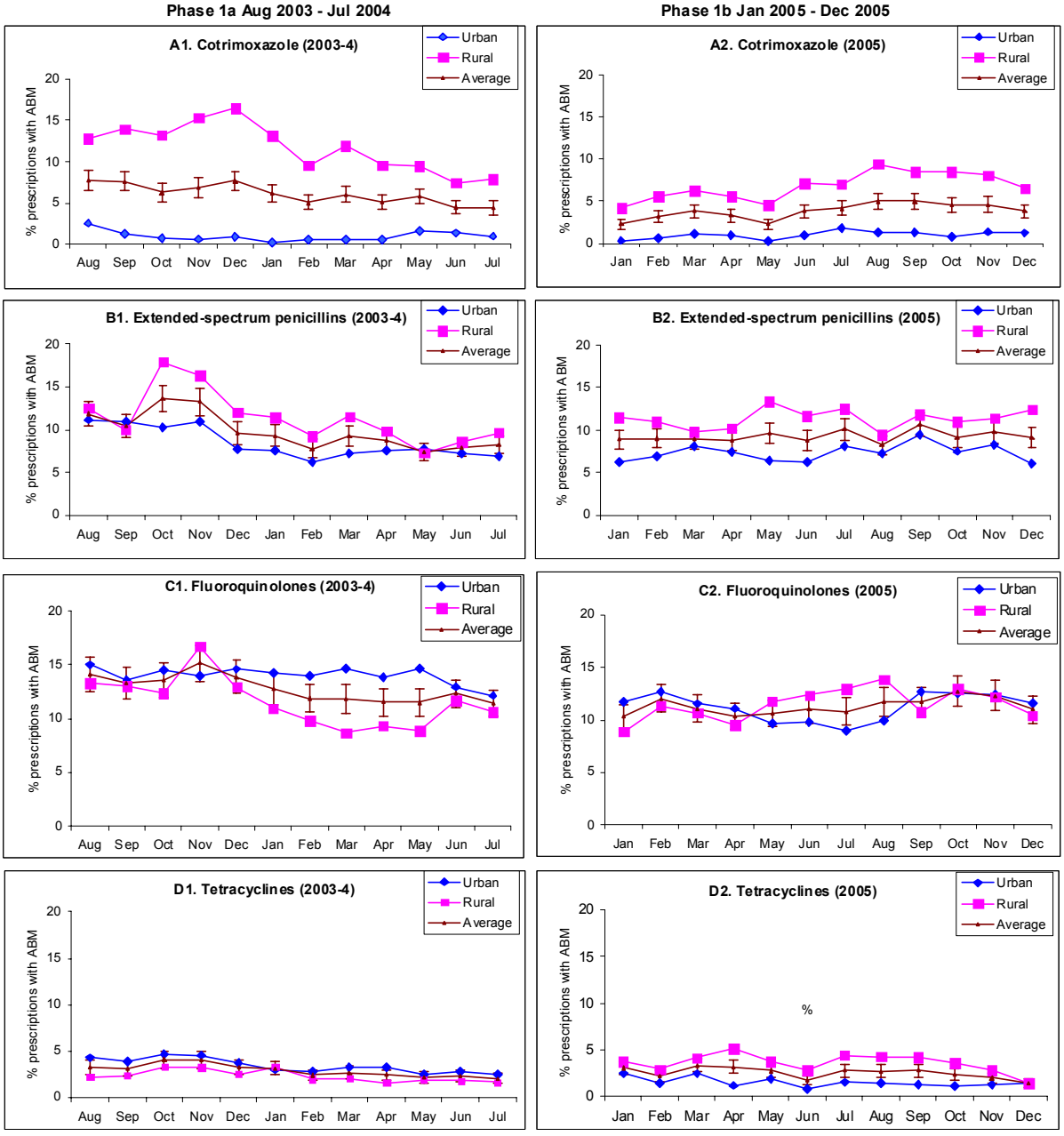
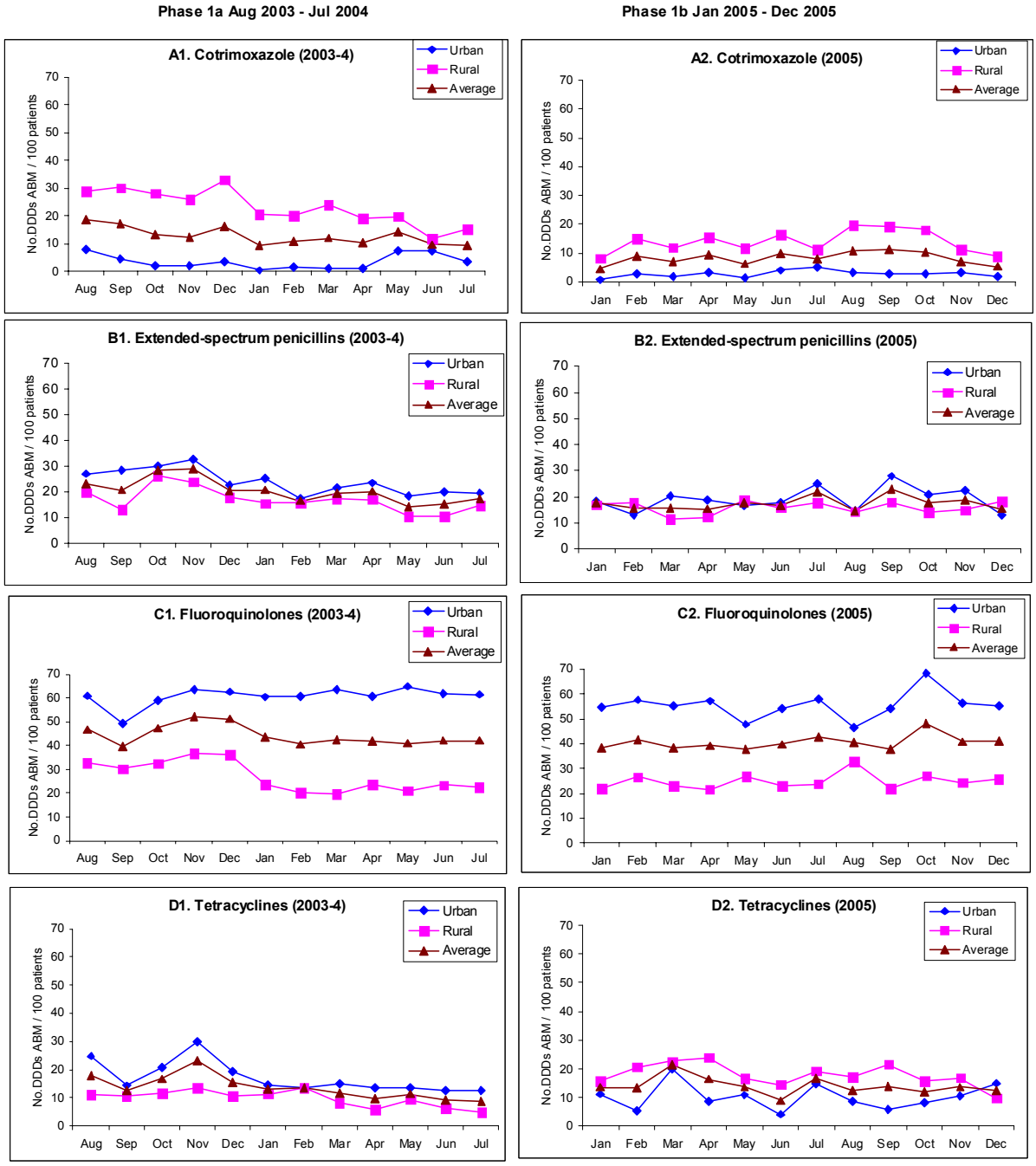


Fig. 3.7 (A-D): Monthly use of ABM expressed as number of DDDs of specific ABM prescribed per 100 patients during phases 1a and 1b (2003-2005)

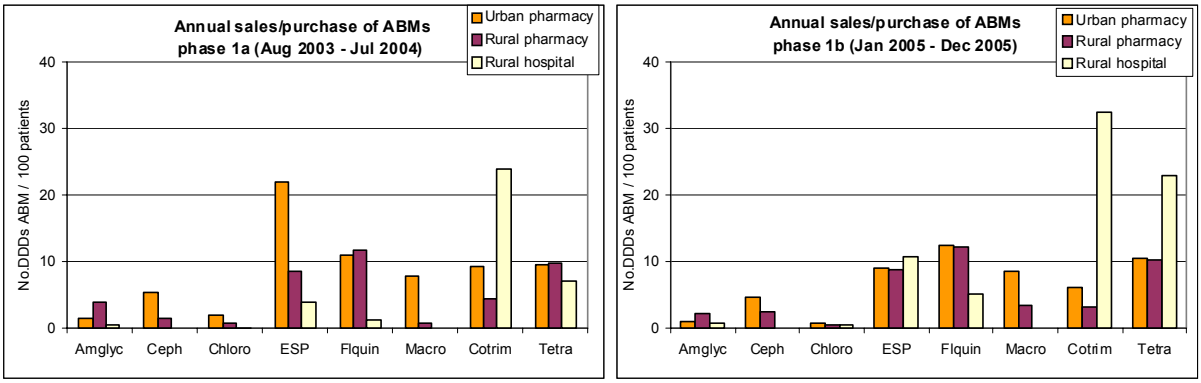


3.3.2.3 Purchase and sales data

Figure 3.8 shows annual use and Figure 3.9 monthly use of major ABM classes by facility type and urban/rural, respectively. Bulk purchase/sales data need to be interpreted with caution, as the sources used varied in type and potential accuracy. Such data could also not be obtained from all of the facility types surveyed by exit interviews. In facilities where data were obtained, it came from dispensing records in public facilities and some private pharmacies and from purchase data in other private pharmacies. Where sales data expressed per 100 patients seen is far greater than that determined from examination of prescriptions

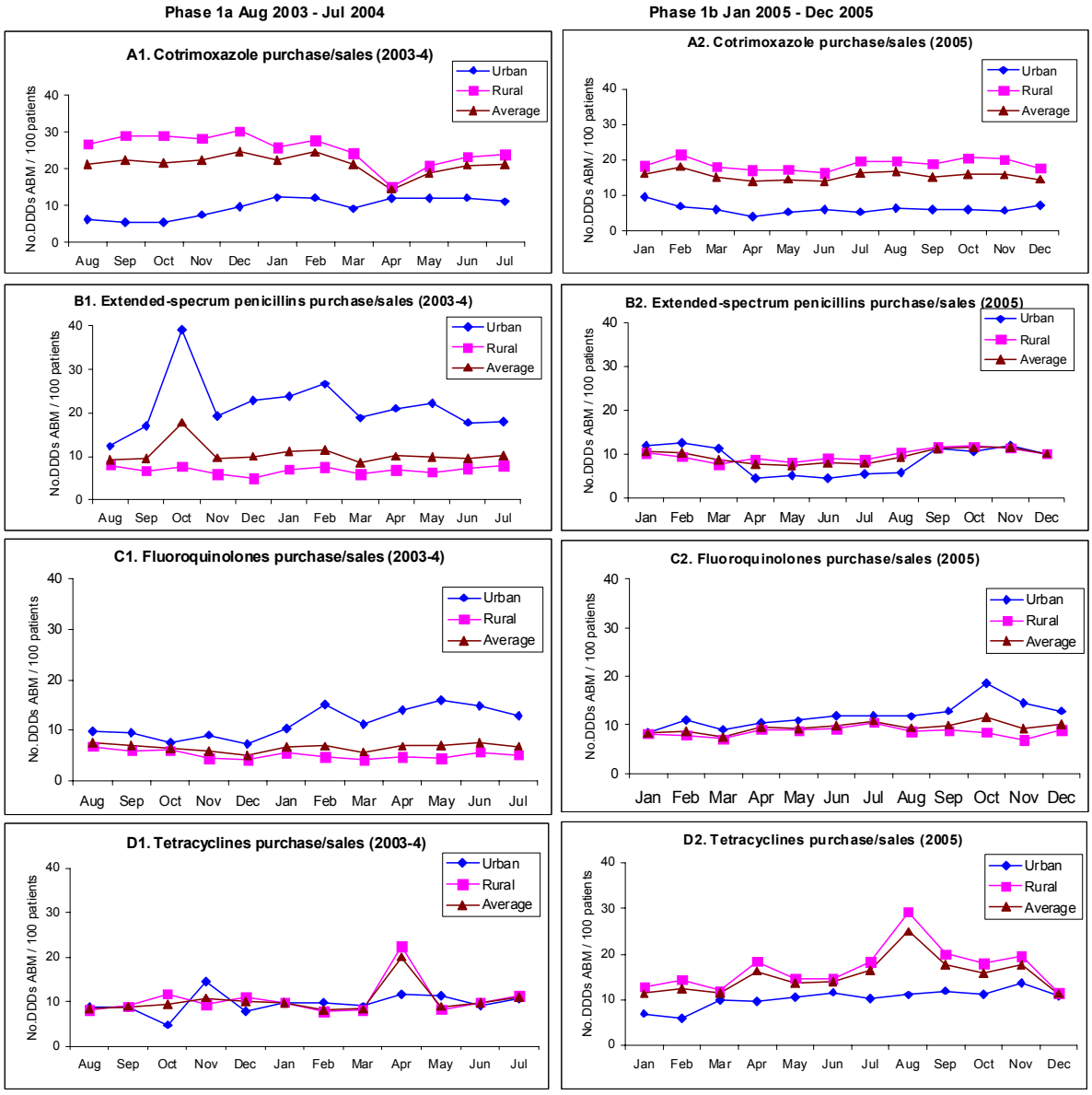
by exit interviews, the difference may reflect over-the-counter sales. However, this was not seen at this site, where differences in consumption, measured by exit interviews (Figure 3.5) and based on purchase data (Figure 3.8), should be interpreted with caution, as the denominators used were markedly different.

Fig. 3.8 Annual sales/purchase of ABMs by facility expressed as number of DDDs of specific ABM prescribed per 100 patients during phases 1a and 1b (2003-2005)



Where unexpected differences over time are shown, this may reflect purchasing patterns and not use patterns. An example is provided in Figure 3.9, showing the bulk purchase/sales data for extended-spectrum penicillins over time, expressed as DDD/100 patients seen. The marked differences in urban pharmacies in phase 1a may be an artefact of purchasing patterns, but this cannot be confirmed from the data collected.

Fig. 3.9 (A-D): Monthly sales/purchase of ABMs by urban/rural areas across facility types expressed as number of DDDs of specific ABM per 100 patients during phases 1a and 1b (2003-2005)

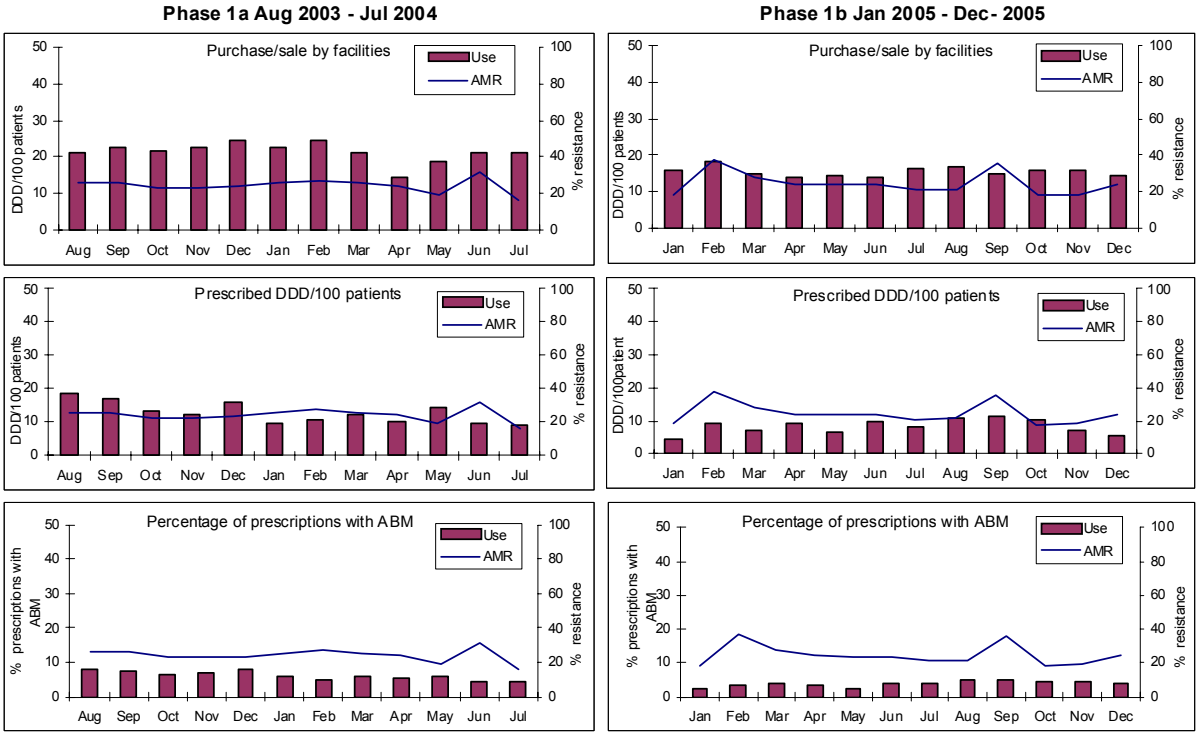


3.3.3 Effect of ABM on AMR

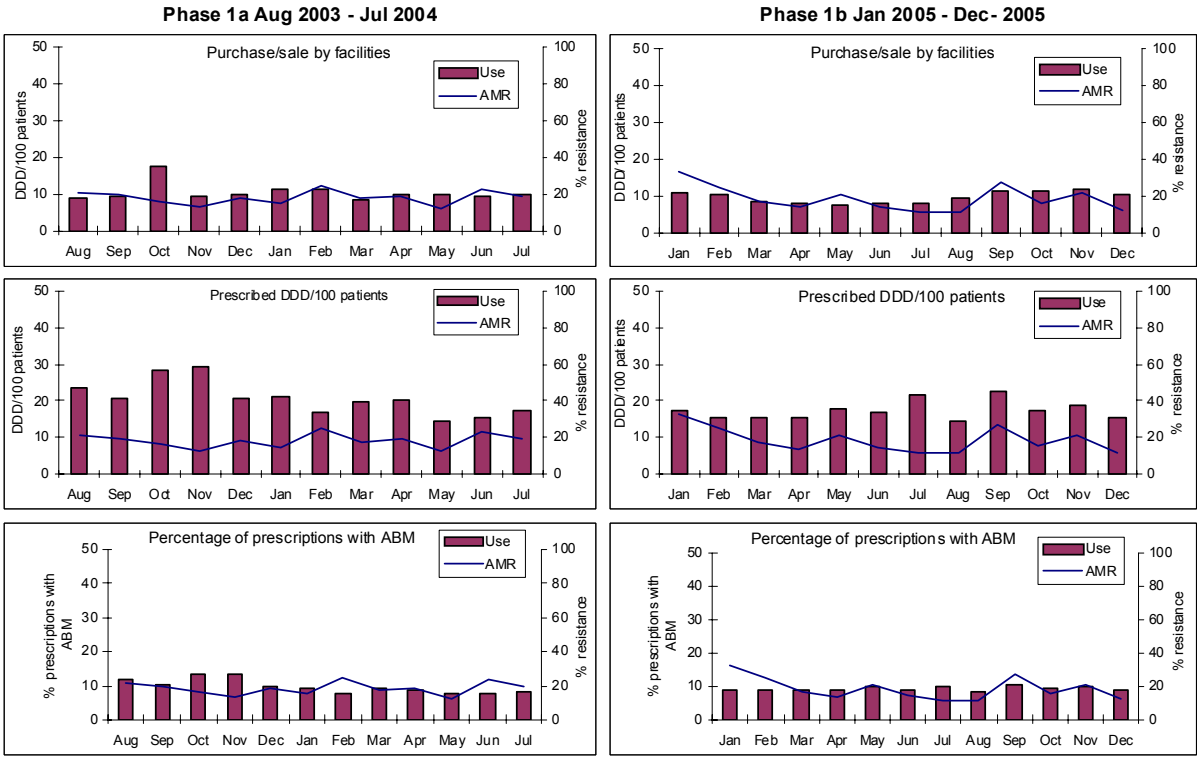
No changes in AMR trends would be expected over the short period of time included in this study. Figure 3.10 shows how use and resistance data can be expressed to demonstrate any relationships that may emerge over time, or under the influence of any interventions. Only the data for four ABM classes, using ABM data from the exit interviews, are depicted as examples. The ABM use shown here is an estimated "average" across all facilities calculated at the level of the individual prescription. Bearing in mind the selection of facilities used in this study, this "average" reflects use by a patient population where more than 80% use the private sector. This may or may not be similar to the usage pattern of the local population. In order to better compare ABM exposure and AMR in a community, more consideration would have to be given to selecting the number and type of health facilities in the proportions as used by the general population.

Fig. 3.10 (A-D): ABM use versus AMR during phases 1a and 1b (2003-2005)

A. Cotrimoxazole use versus resistance

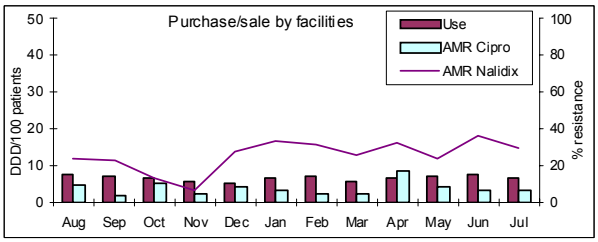


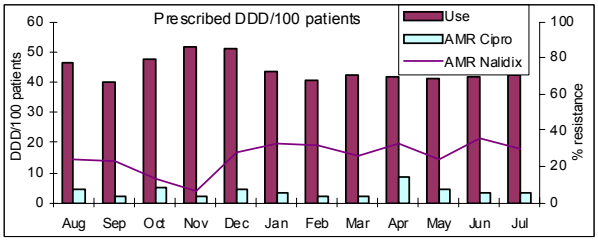
B. Extended-spectrum penicillins use versus ampicillin resistance

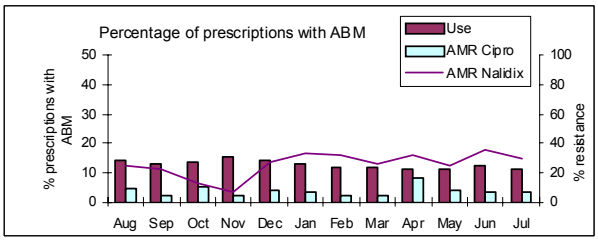


C. Fluoroquinolones use versus nalidixic acid and ciprofloxacin resistance

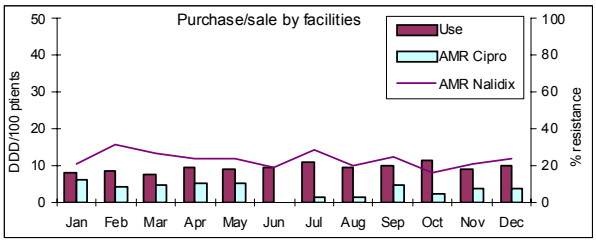
Phase 1a Aug 2003 - Jul 2004

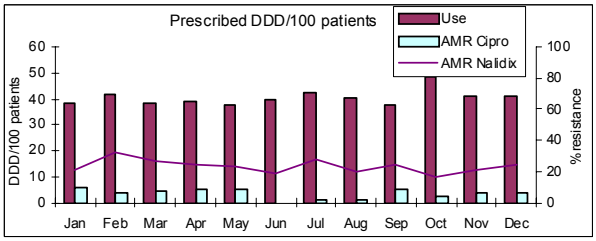


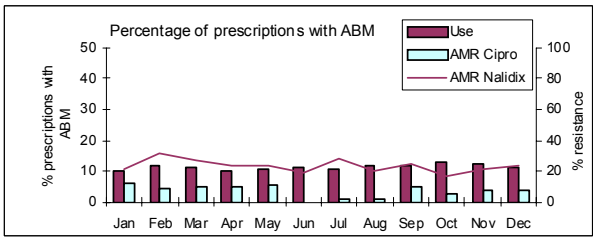




Phase 1b Jan 2005 - Dec- 2005

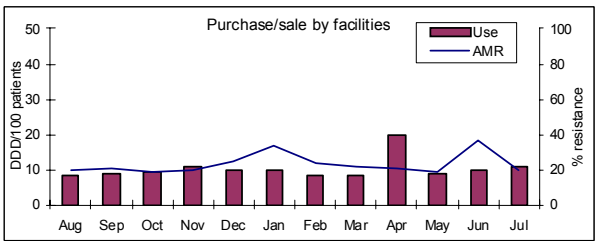


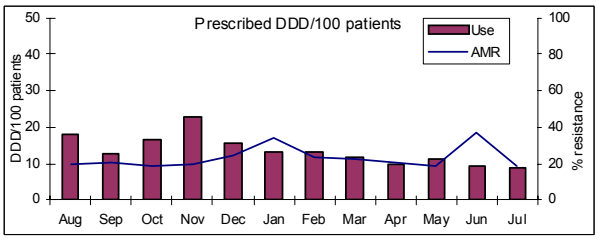


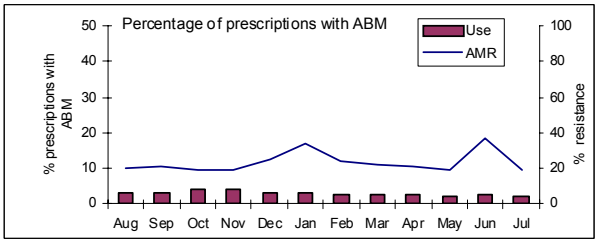


D. Tetracyclines use versus resistance

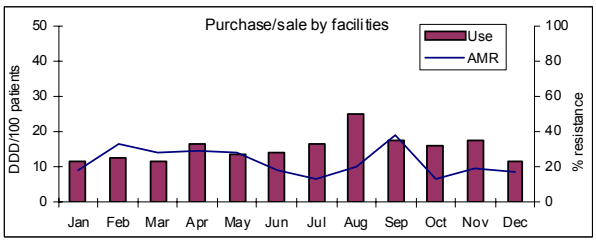
Phase 1a Aug 2003 - Jul 2004

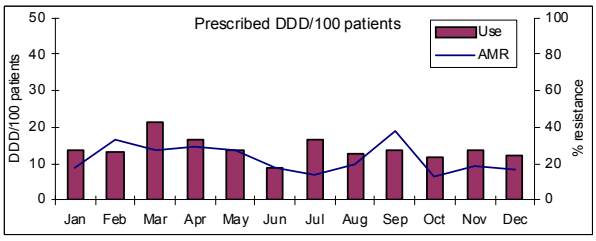


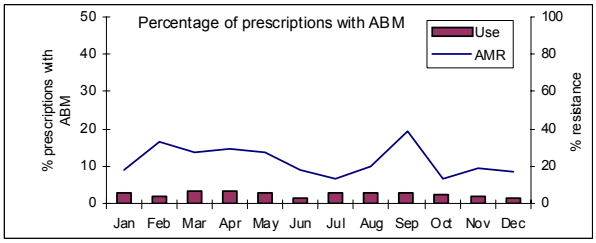




Phase 1b Jan 2005 - Dec- 2005







Only for graphic representation of monthly AMR and ABM use
Not for data interpretation

3.4 Lessons learnt from this site

3.4.1 AMR

This site demonstrated the usefulness of using *E. coli* as an indicator organism. Perianal swabbing was both an acceptable and practical method for obtaining *E. coli* from pregnant women. Such women are healthy representatives of the community, and may be less likely to be taking an ABM. They are also accessible when making use of antenatal care facilities. This method, however, has the potential to select for pathogenic *E. coli*, since urine can be inhibitory to commensal *E. coli.* This should not limit its usefulness for surveillance to monitor changes over time. This pilot study also showed that minimal screening procedures could be used to identify patients with UTI or asymptomatic bacteriuria, allowing AMR data to be collected on both commensals and pathogens. However, the yield of pathogenic isolates may be lower than expected.

This pilot study expended considerable resources to obtain AMR data from both an urban and a rural setting. Given the modest differences seen, this may not always be necessary. In addition, the AMR data capture instrument collected far more data than were needed for the analysis presented. This can lead to errors.

3.4.2 ABM use

Although multiple sources of ABM use data were tried, in order to allow for triangulation, the usefulness of the bulk purchase/sales data obtained was questionable. While some reflected purchases, others reflected sales records. There was also no way of differentiating, from purchase records, which stock was used for in-patient care and which for out-patient care. There is also sometimes reluctance on the part of private pharmacists to share such information. Obviously, medicines purchased in a particular period (especially if as short as a month) may not be dispensed or sold in the same period. If collected consistently, data gathered for longer periods of time may be useful for tracking trends. Bulk purchase/sales data also present particular challenges in the choice of a suitable denominator. Data provided on the total number of patients visiting a facility cannot easily be verified. Population data are also not suitable, unless bulk data for all facilities dispensing or selling ABMs in the area can be included.

Expressing ABM use both as a percentage of prescriptions containing at least one ABM (or an ABM from a particular class) as well as by DDD per 100 patients seen is useful, as differences in the intensity of exposure can be revealed in this way.

Any surveillance system should try to track behaviour in all types of facilities. Although the majority of the facilities used in this pilot study were from the private sector, differences between facility types (public/private, pharmacies, general practitioners, clinics, hospitals) were discernible. While including a large number of facility types is resource intensive, this may be necessary in the early stages of any surveillance exercise, and can also help to identify appropriately targeted interventions.

4. Mumbai, India

4.1 Background information on the site

Mumbai is a major metropolitan city in India. The metropolis is administratively divided into 24 municipal wards. This pilot study was conducted in municipal ward "E", which has an estimated population of about 450 000. Health services in the municipal ward "E" area are provided by 3 public sector municipal hospitals, 115 private general medical practices, 75 pharmacies, 12 public sector municipal PHC facilities (referred to as dispensaries) and 6 health posts.

AMR and ABM data were collected from the general medicine and paediatric out-patient departments of the BYL Nair Hospital (a tertiary level municipal hospital), 10 private general medical practitioners, 9 public sector municipal PHC facilities (dispensaries) and 10 pharmacies in the area of Mumbai each month. About 800-1200 patients, from municipal ward "E" only, attend the out-patient clinics of the hospital per week. It was estimated, from records (in the municipal PHC facilities) and observation (at pharmacies and general medical practices), that about 400-700 patients attended each of the other facilities used per week.

4.2 Methods

4.2.1 AMR surveillance

This pilot site chose *E. coli* as the indicator organism.

4.2.1.1 Sample collection

Stool samples were collected from consenting patients or their attendants visiting the general medicine and paediatric out-patient departments of the BYL Nair Hospital, municipal PHC facilities and private general practitioners. No stool samples were collected in pharmacies. Any person residing in the study area was eligible for recruitment, irrespective of age and regardless of whether they had presented with diarrhoeal disease or not. Consenting participants were issued with a sterile container and asked to return the collected stool on the following day. On the designated day, samples were collected and transported to the laboratory of the BYL Nair Hospital for processing.

4.2.1.2 Identification of bacteria and susceptibility testing

Stool samples were plated on MacConkey agar plates and isolates were identified as *E. coli* based on lactose fermentation on MacConkey agar, motility and ability to produce indole. Only one isolate per person was included and all isolates were considered to be commensals. Susceptibility testing was done on Mueller Hinton agar (Hi Media, India) following NCCLS/CLSI 2002 criteria. Discs for testing were obtained from Hi Media, India. *E. coli* ATC 25922 was tested, as recommended by NCCLS/CLSI, every time susceptibility testing was performed. Readings for the test strains were taken only if the results for each ABM with the reference strains were acceptable. The site also participated in a general quality assessment

programme for microbiology laboratories run by the Indian Association of Medical Microbiologists (IAMM).

AMR data were maintained in dedicated laboratory registers and also entered into study questionnaires.

4.2.2 ABM use

4.2.2.1 Facility selection

ABM use data were collected by exit interview from four types of facilities in the municipal ward "E" area each month: the general medicine and paediatric out-patients departments (OPDs) of the BYL Nair Hospital (treated as one facility in the data), 10 private general medical practitioners (GPs), 9 municipal PHC facilities (dispensaries), and 10 private sector pharmacies. The same OPDs and 9 municipal PHC facilities were used every month. However, a sample of 10 private sector GPs and 10 private sector pharmacies was selected each month, from a set of 90 GPs and 55 pharmacies that had consented to participate, i.e., there was a rotation of these facilities each month.

4.2.2.2 Exiting patient interviews

Sufficient prescriptions were examined by exit interviews, conducted by trained research staff, to obtain approximately 300 ABM-containing prescriptions per month from each of the participating facility types. In each exit interview, data were recorded on the ABM purchased, the dose and duration. All ABMs were categorized using ATC codes. The data were used to calculate the percentage of prescriptions containing at least one ABM (or specific class of ABM), as well as the DDD prescribed per 100 patients seen. The denominator applied was the total number of prescriptions examined to obtain the required number of ABM-containing prescriptions.

The data capture instruments were pilot tested prior to use in the actual study.

Although a target of 300 ABM-containing prescriptions per facility type per month was set, this target was not achieved in many months during the latter part of the study.

4.2.3 Data management

All AMR and ABM data were captured and analysed using Microsoft Excel 2003.

4.3 Findings

AMR and ABM use data were collected for two consecutive years, from October 2002 to September 2003 (phase 1a) and from October 2003 to September 2004 (phase 1b).

4.3.1 AMR in *E. coli*

4.3.1.1 Trends in AMR over time

A total of 3294 isolates were tested, of which 819 (24.9%) were obtained from municipal PHC facilities, 904 (27.4%) from GP practices and 1571 (47.7%) from the OPDs of the tertiary level hospital. The overall resistance patterns found in phases 1a and 1b are shown in Table 4.1. The highest rates of resistance were observed for those ABMs historically in longest use, namely tetracycline, nalidixic acid, ampicillin and cotrimoxazole. Although use of nalidixic acid was minimal, fluoroquinolones were used in all facilities and this would have maintained the high resistance levels to nalidixic acid.

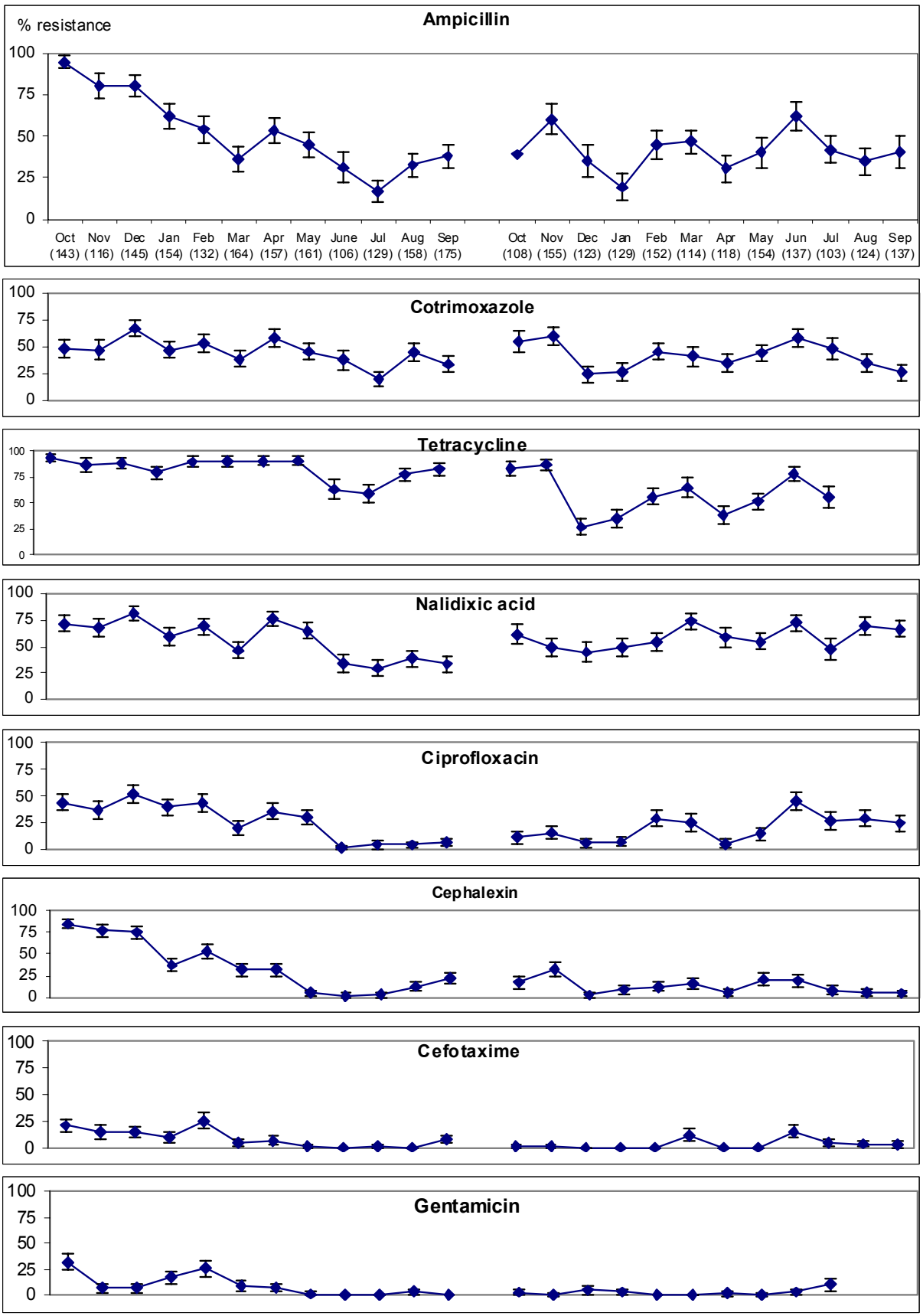
Table 4.1: Resistance pattern of faecal *E. coli* during the period of study

	Phase 1a (n= 1740)		Phase 1b (n =1554)*		Total (n= 3294)	
	Number	%	Number	%	Number	%
Ampicillin	897	51.6	648	41.7	1545	46.9
Cephalexin	619	35.6	203	13.1	822	25.0
Cefotaxime	147	8.5	47	3.0	194	5.9
Nalidixic acid	971	55.8	904	58.2	1875	56.9
Ciprofloxacin	458	26.3	310	19.9	768	23.3
Cotrimoxazole	782	44.9	647	41.6	1429	43.4
Tetracycline	1446	83.1	749	57.9*	2195	72.4
Gentamicin	157	9.0	32	2.5*	189	6.2

* Only 1293 isolates (not 1554) were tested for resistance against tetracycline and gentamicin in phase 1b and percentages were calculated on this basis

Although the overall levels of resistance are somewhat different between phase 1a and phase 1b, detailed monthly figures showed even greater variability. This was particularly evident in relation to resistance to ampicillin, cephalexin and ciprofloxacin, as could be seen in Figure 4.1 showing monthly variation. This was interpreted as suggestive of a technical problem in the early stages of the study. However, the patterns seen may reflect the true situation. As a result, only the AMR data from phase 1b are presented in more detail.

Fig. 4.1: Monthly variations in percentage AMR rates during phase 1a and 1b (2002 - 2004)



The numbers within brackets indicate total numbers tested and the error bars indicate confidence intervals.

4.3.1.2 AMR in patients from different facility types

The overall rates of resistance among isolates from the three facility types during phase 1b are shown in Table 4.2 and Figure 4.2. AMR rates to cephalosporins and ciprofloxacin were significantly lower in isolates from municipal PHC facilities than in those isolated from patients visiting private GPs or the tertiary hospital OPDs.

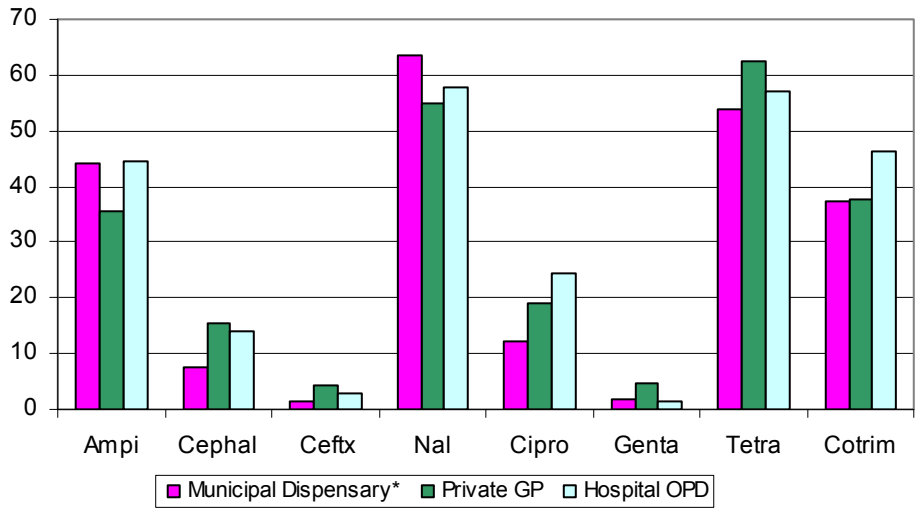
During phase 1b, 1246 (80.2%) isolates were resistant to one or more of the ABMs tested. During this phase of the study, 334 (21.5%) isolates were shown to be resistant to all four of the following ABMs: tetracycline, nalidixic acid, ampicillin and cotrimoxazole.

Table 4.2: AMR rates in different facility types (phase 1b)

	Public Municipal Dispensary* n = 350		Private General Practice n = 476		Public Hospital Outpatient Department n = 728	
	Number	%	Number	%	Number	%
Ampicillin	154	44	169	35.5	325	44.6
Cephalexin	27	7.7	74	15.5	102	14.0
Cefotaxime	5	1.4	21	4.4	21	2.9
Nalidixic acid	222	63.4	261	54.8	421	57.8
Ciprofloxacin	43	12.3	90	18.9	177	24.3
Gentamicin*	5	1.8	18	4.6	9	1.5
Tetracycline*	150	53.8	246	62.4	353	56.9
Cotrimoxazole	131	37.4	179	37.6	337	46.3

* Public facility delivering PHC

Fig. 4.2: Resistance rates in different facilities studied during phase 1b (October 2003 to September 2004)



4.3.1.3 AMR in patients with and without prior ABM use

Based on information collected from participants, 457 (29.4%) had received no ABM in the recent past. The resistance patterns for isolates from previously ABM-treated patients,

compared with those from patients who had not received recent ABM treatment, are shown in Table 4.3. The only significant difference noted was in relation to susceptibility to ampicillin, where resistance was higher with prior ABM use.

Table 4.3: AMR rates based on prior ABM use (phase 1b)

	No prior ABM use n = 457		Prior ABM use n = 1097	
	Number resistant	% resistant	Number resistant	% resistant
Ampicillin	162	35.5	486	44.3
Cephalexin	62	13.6	141	12.9
Cefotaxime	15	3.3	32	2.9
Nalidixic acid	261	57.1	643	58.6
Ciprofloxacin	87	19.0	223	20.3
Gentamicin*	10	2.7	22	2.4
Tetracycline*	203	55.2	546	59.0
Cotrimoxazole	180	39.4	467	42.6

* 71, 82 and 108 isolates from municipal dispensaries, private GPs and hospital OPD clinics, respectively, were not tested for these two ABMs.

4.3.2 ABM use

4.3.2.1 Prescription data

During phase 1a of the study, 12,294 (36%) prescriptions with at least one ABM were obtained from 34,180 patients identified in exit interviews. During phase 1b, 9119 (40.4%) prescriptions of 22,548 examined contained at least one ABM. More than one ABM was prescribed in 2679 (4.7% of total) prescriptions. In this pilot study, metronidazole was considered to be an ABM.

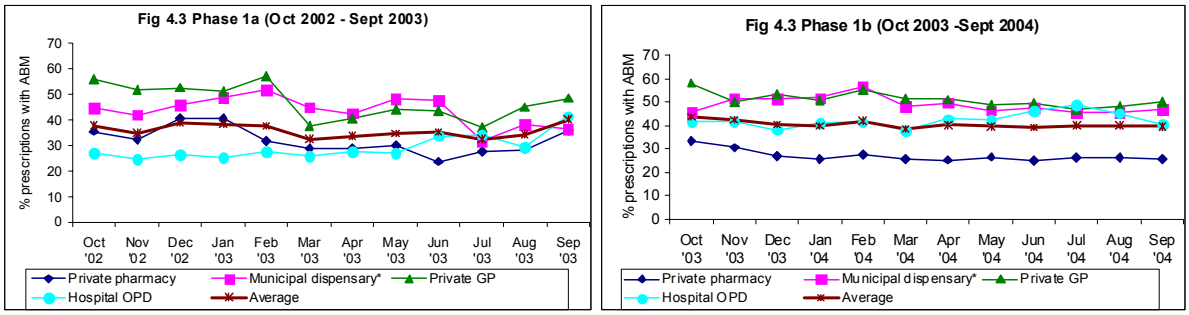
The percentage of patients interviewed who had received at least one ABM per facility type is shown in Table 4.4, for both phases 1a and 1b. During both periods of study, patients interviewed on exit from GP practices showed the highest level of ABM use by this measure. Small but statistically significant increases in the percentage of patients receiving an antibiotic were apparent between phase 1a and phase 1b in the data from PHC facilities, GPs and the hospital OPDs.

Table 4.4: Summary of ABM prescriptions according to facility types

	Phase 1a			Phase 1b		
	Total patients	With ABM	Number of ABM	Total patients	With ABM	Number of ABM
Pharmacy	8598	2765 (32.2%)	3301	7253	1946 (26.8%)	2199
Municipal dispensary	7545	3276 (43.4%)	3483	5117	2489 (48.6%)	2577
Private GP	6186	2904 (46.9%)	3486	4399	2252 (51.2%)	2663
Hosp OPD	11,851	3349 (28.3%)	3710	5779	2432 (42.1%)	2794
Total	34,180	12,294 (36.0%)	13,980	22,548	9119 (40.4%)	10,233

Monthly rates of the percentage of prescriptions containing at least one ABM by facility are shown in Figure 4.3. There was relatively little monthly variation, although ABM use did appear to be greater in the winter months, particularly by the PHC facilities and GPs.

Fig. 4.3: Monthly percentage of prescriptions containing any ABM by facility type in phases 1a and 1b (2002 - 2004)

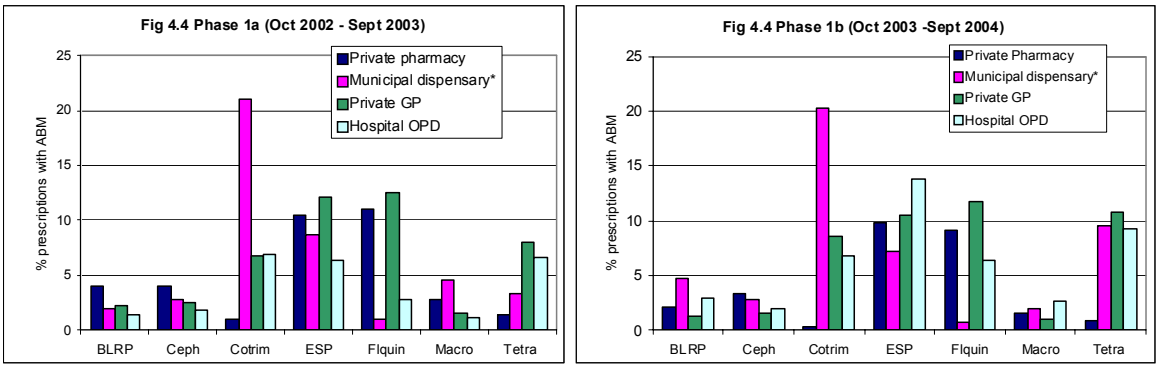


* Public facility delivering primary health care

4.3.2.2 Specific ABM use

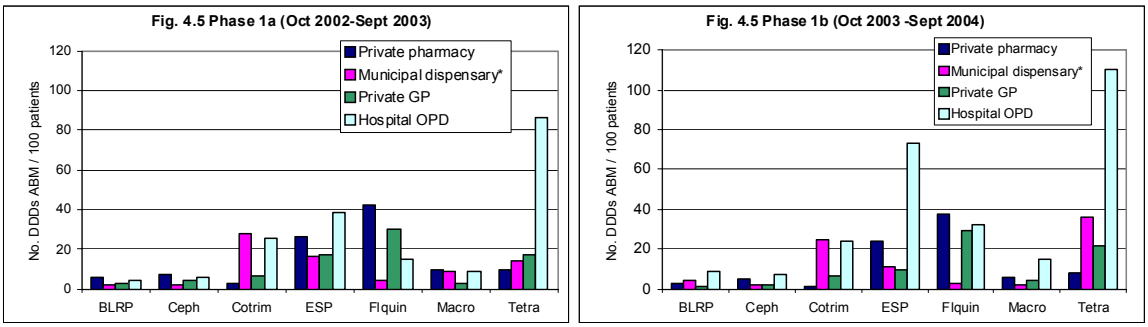
The use of selected classes of ABM, expressed both as the percentage of prescriptions containing at least one example from that class and as DDD per 100 patients seen, per facility type is depicted in Figures 4.4 and 4.5, respectively. Overall, the most used ABMs were the extended-spectrum penicillins, cotrimoxazole, tetracyclines and fluoroquinolones. Cotrimoxazole was extensively used in the municipal PHC facilities, but was rarely seen in prescriptions filled in pharmacies. Fluoroquinolone use was also minimal in the municipal PHC facilities, but often identified in prescriptions screened in pharmacies and GP practices. While patterns of specific ABM use are similar when expressed by the two measures shown in Figures 4.4 and 4.5, there were certain notable differences. Thus, tetracyclines contributed the highest number of DDDs per 100 patients in both phases 1a and 1b even though a greater percentage of prescriptions contained penicillins. While the percentage of prescriptions containing tetracyclines and penicillins appeared similar for GP practices and the hospital OPD, the number of DDDs of tetracycline and penicillin used was much greater in the OPD than in the case of GP practices, suggesting that GPs were using much smaller doses of these ABMs.

Fig. 4.4: Annual percentage of prescriptions containing specific ABM by facility type in phases 1a and 1b (2002 - 2004)



* Public facility delivering primary health care

Fig. 4.5: Annual use of specific ABM by facility type measured as DDDs per 100 patients in phases 1a and 1b (2002 - 2004)

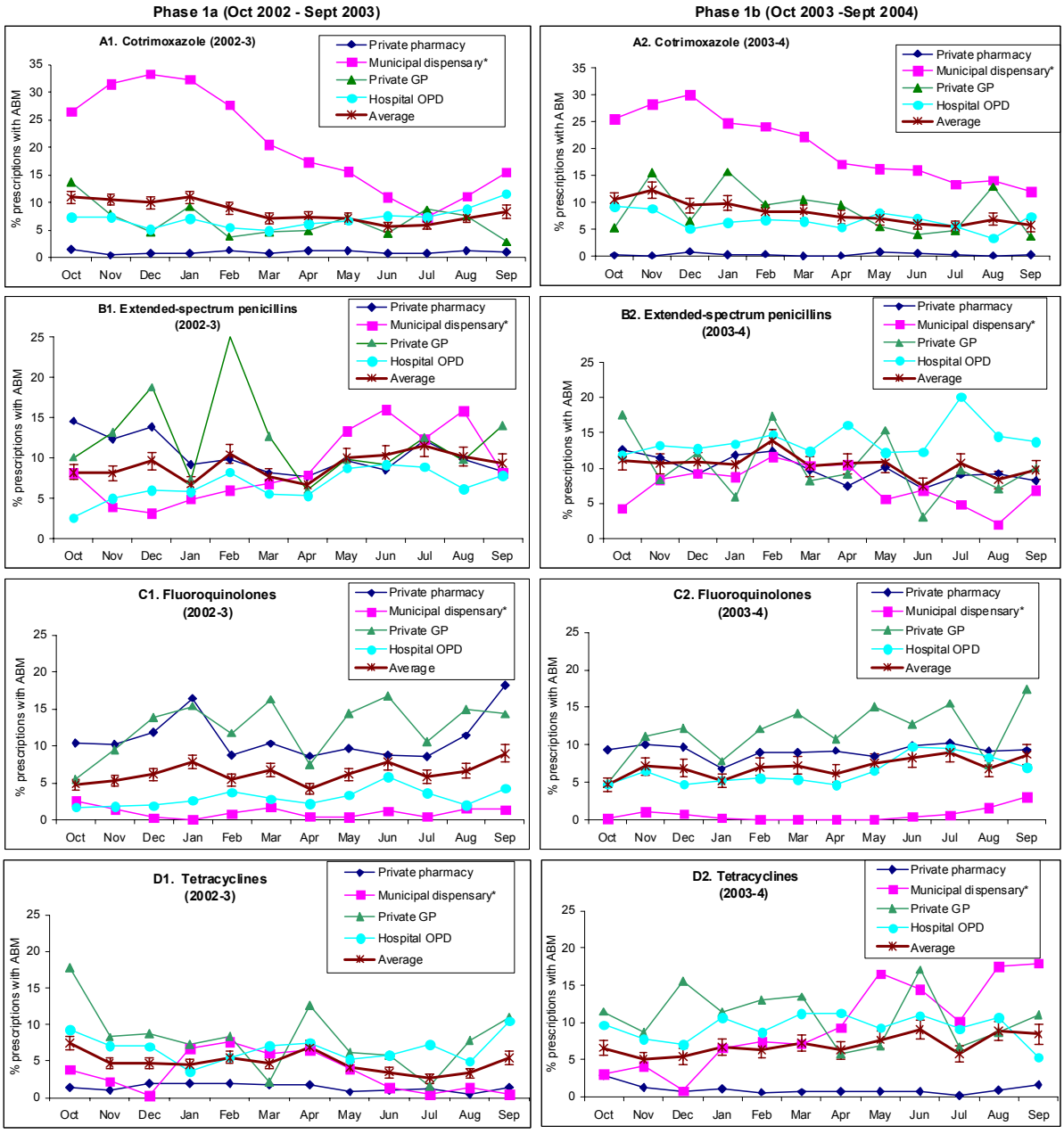


* Public facility delivering primary health care

4.3.2.3 Monthly trends in specific ABM use

Monthly ABM use data for selected classes are depicted in Figure 4.6 (percentage prescriptions containing an ABM) and Figure 4.7 (DDD of ABM per 100 patients). It would appear that at least one consistent seasonal trend was apparent. The percentage of prescriptions containing cotrimoxazole was higher during October to March of both years in the municipal PHC facilities, and this was also apparent when expressed in DDD per 100 patients seen. Fluoroquinolone use was observed to be higher in GP practices and pharmacies throughout the year by both measures. Tetracycline use was observed to be much higher in the hospital OPD throughout the year when expressed at DDD per 100 patients, but not when expressed as a percentage of prescriptions. This suggests that long courses of tetracyclines were being prescribed to a number of patients in the hospital OPD compared to the other facility types.

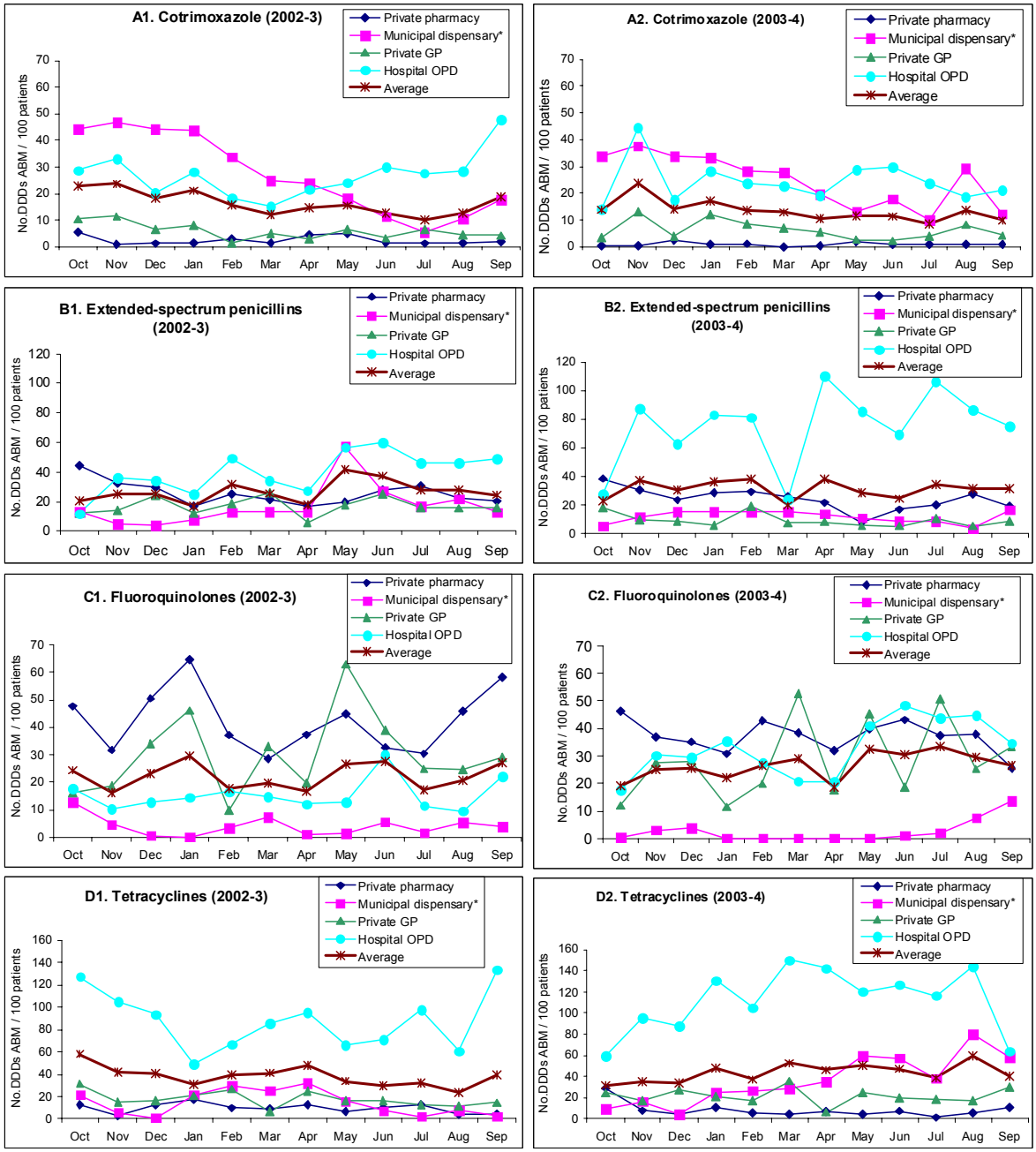
Fig. 4.6 (A-D): Monthly percentage of prescriptions containing specific ABMs by facility type in phases 1a and 1b (2002 - 2004)



Error bars indicate CI

* Public facility delivering primary health care

Fig. 4.7 (A-D): Monthly use of specific ABM measured as DDDs per 100 patients by facility type in phases 1a and 1b (2002 - 2004)



* Public facility delivering primary health care

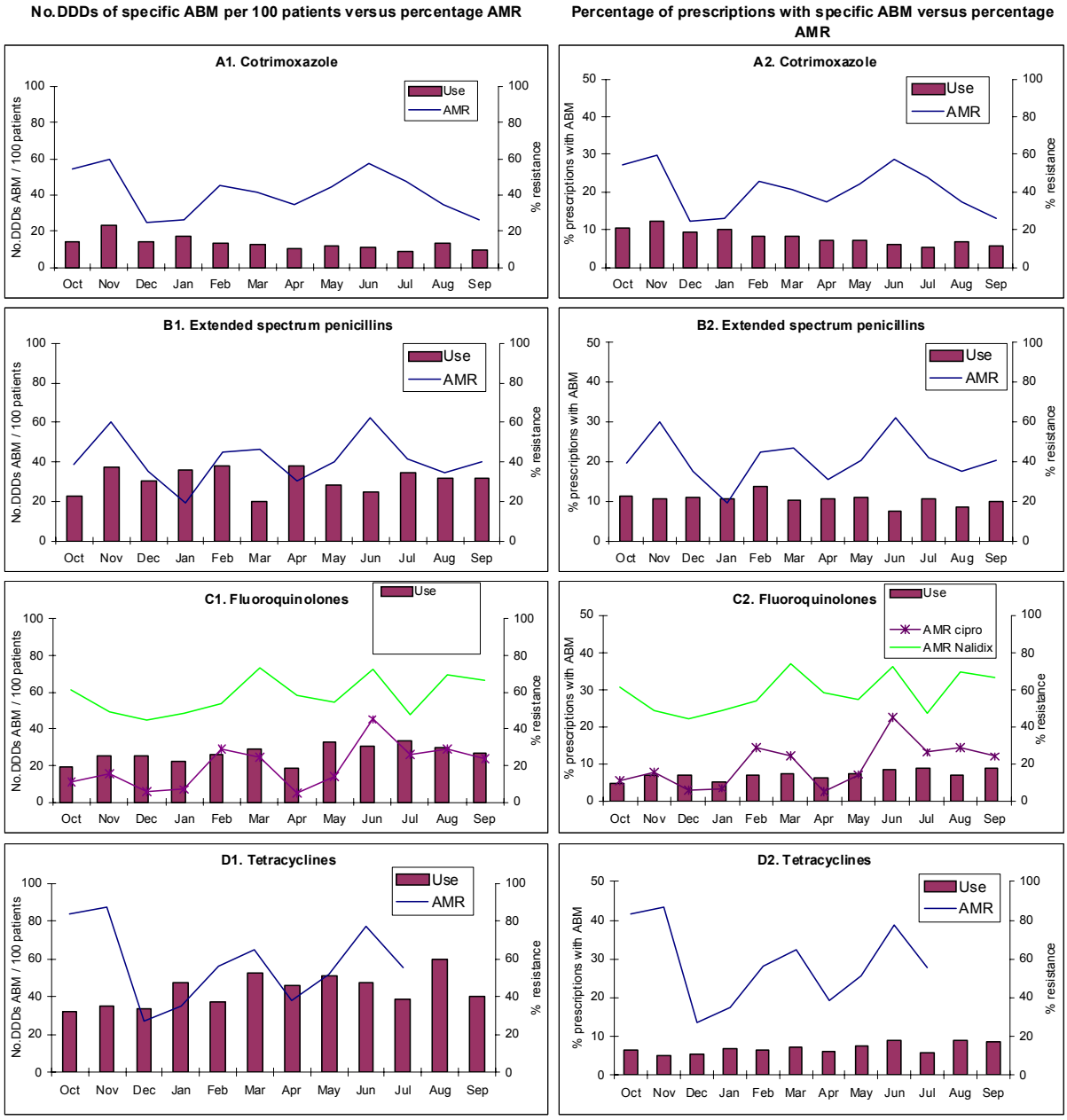
There appeared to be a much wider monthly variation of ABM use when data were expressed as DDDs of ABM per 100 patients, as compared to when expressed as percentage of prescriptions containing at least one ABM. This may be due to the differing availability of the concerned ABM, so impacting on doses used, but could also be due to error in data handling.

4.3.3 Effect of ABM on AMR

Although no associations between AMR and ABM were expected in the short time surveyed in this pilot study, data for both elements are presented in Figure 4.8. The ABM use shown

here is the estimated "average" across all facilities calculated at the level of the individual prescription. Bearing in mind the selection of facilities used in this study, this "average" reflects use by a patient population where about 40-50% use the private sector. This is likely to be less than use of the private sector by the general population and thus the levels of ABM use shown in Figure 4.8 are likely to biased towards public sector usage patterns.

Fig. 4.8 (A-D): ABM use (measureed two ways) versus percentage AMR rates during October 2003 - September 2004



These graphs are presented as examples only and not for understanding associations
Inferences on associations cannot be drawn from this data for reasons discussed in text

4.4 Lessons learnt from this site

4.4.1 AMR

This pilot study demonstrated the utility of stool samples as a source of commensal *E. coli*, to serve as an indicator organism for AMR. This has the advantage of being non-invasive, but has the disadvantage of requiring the participant to return the sample to the health facility at a later time point. This may be inconvenient to many participants and result in a large proportion of samples not being returned. However, as only one sample is provided per participant, duplicates are easily avoided. Obtaining such samples from a setting where patients are seeking health care services (many curative) also results in a large proportion having had recent exposure to an ABM.

Stool specimens were collected from different facilities and the AMR rate was found to vary according to the facility type. Collection of specimens from different facilities is more costly and time consuming but may be necessary in the early phases of any surveillance in order to pick up differences in levels of AMR in different sectors of the community.

4.4.2 ABM use

This pilot study also demonstrated the usefulness of including a number of different facility types, as differences in ABM use were evident. The data generated could also be used for developing targeted interventions. Although the decision to rotate certain facilities (GP practices and pharmacies) might have helped to avoid fatigue in participating facilities, its effect and necessity cannot be decided on the basis of the data collected.

Obtaining the required number of ABM-containing prescriptions from the facilities targeted also proved difficult at times. Measuring ABM use using both the percentage of prescriptions method and the DDD per 100 patients seen also provided different insights, and was useful. The latter method may be affected by availability of stock (as the quantity supplied may vary), but this would accurately depict community exposure to the agent in question. Calculating DDDs does require more data collection and manipulation, and thus incurs a greater possibility of error.

5. Brits, South Africa

5.1 Background information on the site

Brits is a town in the Madibeng District in the North West Province of South Africa. The town is located 28 kilometres from the Pretoria campus of the Medical University of South Africa (MEDUNSA). The district has an estimated population of 419 681 people, of whom 42% are estimated to be unemployed. While most would therefore be expected to access health care from public sector facilities, some may also access services in the private sector. The public sector provides health-care services from a single district hospital and 21 PHC clinics.

AMR and ABM data were collected from seven PHC clinics and the Brits district hospital. Of the PHC clinics utilized, six are operated by either the provincial government or local authorities. One PHC clinic is operated by a non-governmental organization.

5.2 Methods

5.2.1 AMR surveillance

This pilot site chose *E. coli* as the indicator organism.

5.2.1.1 Sample collection

Mid-stream urine specimens were collected from women with symptoms of UTI and also from pregnant women visiting four antenatal clinics (located in the Bapong, Lethlabile, Majakaneng and Oukasie PHC clinics) if they had positive dipstick tests for leucocytes or nitrites on routine urine testing. Patients younger than 13 years, patients with recurrent UTI, patients who were hospitalized in the past month, patients on treatment for bacterial infections in the past month, and patients with a vaginal discharge or genital ulceration were excluded. Repeated specimens from the same patient were also excluded.

Specimens were stored in the clinic refrigerator until they were collected by the National Health Laboratory Services (NHLS) driver every day.

5.2.1.2 Identification of bacteria and susceptibility testing

Specimens were plated on blood agar (BA) and MacConkey agar plates. On BA, a quantitative method of streaking, with a 0.04 mm diameter inoculating loop, was done to determine the colony count. Lactose broth with phenol red, SIM (sulfide, indole, motility) medium, TSI agar slopes, urease slopes, SSM (semi-solid mannitol) agar tubes and citrate plates were used for identification. Isolates that were motile and fermented lactose, sucrose, mannitol and glucose, produced gas with glucose fermentation, did not utilize urease and citrate and gave positive reaction in the indole test were identified as *E. coli*. Mueller Hinton (Oxoid) agar plates were used for susceptibility testing, according to NCCLS/CLSI 2003 guidelines.

The site participated in two external quality assessment programmes: the National Quality Assessment Scheme (NEQAS) of the United Kingdom, and the Quality Assurance Programme of the National Health Laboratory Services (formerly the South African Institute for Medical Research). A Quality Control Section managed by a chief medical technologist under the supervision of a consultant microbiologist carried out the internal quality assurance. Media and susceptibility testing were evaluated once a week, using *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *Klebsiella pneumoniae* ATCC 700603 as reference strains.

5.2.2 ABM use

5.2.2.1 Facility selection

Retrospective data on ABM use were collected from the out-patient files at Brits Hospital and from clinic records at 6 PHC clinics (Bapong, Bertoni, Lethlabile, Madibeng, Majakaneng, and Oukasie). Of these, only Bertoni clinic is run by a non-governmental organization. Initially it was planned to collect ABM use data from five private general medical practitioners, five private sector pharmacies and a mine clinic in the same area. The private sector pharmacies withdrew their agreement to participate, and logistic difficulties prevented the other facilities from being included.

5.2.2.2 Prescription examination

The aim was to examine sufficient prescriptions to obtain at least 30 ABM-containing prescriptions per month per facility. The denominator was thus the total number of prescriptions examined to obtain the required ABM-containing prescriptions. A predesigned data capture instrument was used to record details of the diagnosis, the ABM(s) prescribed, the dosage form, strength, dose frequency and duration, and the quantity issued. ABMs were then assigned to ATC codes and DDDs calculated. Metronidazole and antituberculosis drugs were also considered as ABMs.

5.2.3 Data management

Data were captured and analysed using Microsoft Excel 2003.

5.3 Findings

Data were collected from this site for 12 months, from April 2004 to March 2005.

5.3.1 AMR in *E. coli*

A total of 707 urine specimens (ranging from 15 to 103 per month) were collected to obtain 558 (79%) samples for processing. Of these 212 (38%) yielded *E. coli.* The isolates are likely to be a mixture of uropathogens and commensals. The number of monthly isolates varied from 4 to 38, with the lowest number achieved in December 2004 when data collectors were not available due to the summer holiday break.

The overall resistance among *E. coli* is shown in Table 5.1 and Figure 5.1. Only 46 (22%) isolates were susceptible to all the ABMs tested, while 112 (53%) isolates were resistant to at least two ABMs tested. Resistance to both ampicillin and cotrimoxazole was shown in 91 (43%) of the 210 isolates tested. Resistance to ampicillin could be overcome in about 75% of the isolates by the addition of clavulanic acid. This suggests β-lactamase production as the

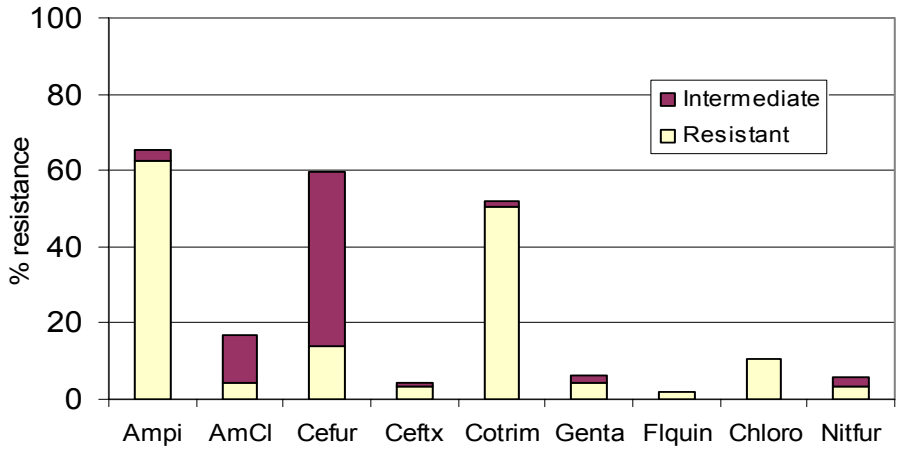
most prevalent mechanism of resistance. Only 2% were non-susceptible to fluoroquinolones and 4.5% to ceftriaxone. Of the six ceftriaxone-resistant isolates tested for extended-spectrum β-lactamase (ESBL) production, one was positive.

Table 5.1: Antimicrobial resistance among *E. coli*

	No. tested	No. resistant	% resistant
Ampicillin	212	139	65.6
AmoxClav	211	35	16.6
Cefuroxime	211	126	59.7 (includes 45.9% intermediate)
Ceftriaxone	202	9	4.5
Cotrimoxazole	210	109	51.9
Gentamicin	212	13	6.1
Fluoroquinolones	211	4	1.9
Chloramphenicol	48	5	10.4
Nitrofurantoin	209	12	5.7

A large number of isolates tested intermediate for cefuroxime, as is depicted in Figure 5.1. A possible reason for this is that the interpretive break-points were close to the zone diameters of wild type *E. coli* in the area.

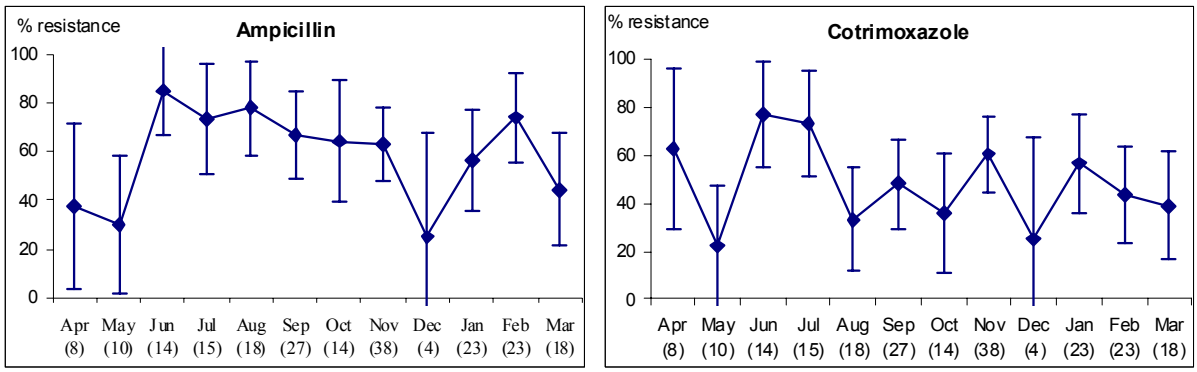
Fig. 5.1: Annual percentage AMR rates among *E. coli* (April 2004 to March 2005)



5.3.1.1 Trends in AMR over time

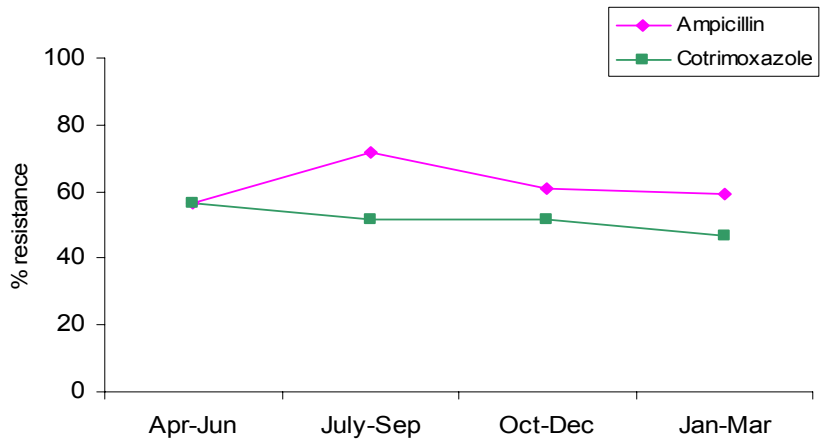
Given the small number of isolates obtained, analysis of monthly trends could only be attempted in relation to susceptibility to ampicillin and cotrimoxazole, as shown in Figure 5.2. On a quarterly basis, variability in susceptibility to these two ABMs was not seen over the duration of the pilot study (Figure 5.3).

Fig. 5.2: Monthly percentage AMR rates among *E. coli* (April 2004 to March 2005)



The numbers shown in parenthesis indicate total numbers tested.
Error bars indicate CI

Fig. 5.3: Percentage AMR rates in *E. coli* calculated quarterly (April 2004 - March 2005)



In general, higher AMR rates were observed in relation to ABMs historically in longest use, such as ampicillin and cotrimoxazole. Although low, resistance had appeared to fluoroquinolones and third-generation cephalosporins.

5.3.2 ABM use

5.3.2.1 Prescription data

Although the target was achieve 360 ABM-containing prescriptions per year per facility visited, this was only achieved in 2 of the 7 clinics. Data were collected by trained field workers provided by a community partner organization. Data for all 12 months was obtained from only 3 facilities. Data for only 5 months were available from the Lethlabile clinic, as this site was added later. Access to retrospective data was also complicated by the non-availability or incompleteness of facility-retained records.

Overall, at least one ABM was recorded on 2313 (25.5%) of the 9058 prescriptions or clinic registers examined. These 2313 prescriptions included 2970 ABMs, but the majority of patients (79%) received only one ABM. The data shown in Table 5.2 needs to be interpreted with caution, as antituberculosis drugs were included as ABMs, and this could have contributed to the high proportion of prescriptions for multiple agents.

Table 5.2: Number of antibacterial medicines prescribed per patient

Number per prescription	Number of patients	%
1 ABM	1826	78.95
2 ABM	318	13.75
3 ABM	168	7.26
4 ABM	1	0.04
Total number of patients	2313	

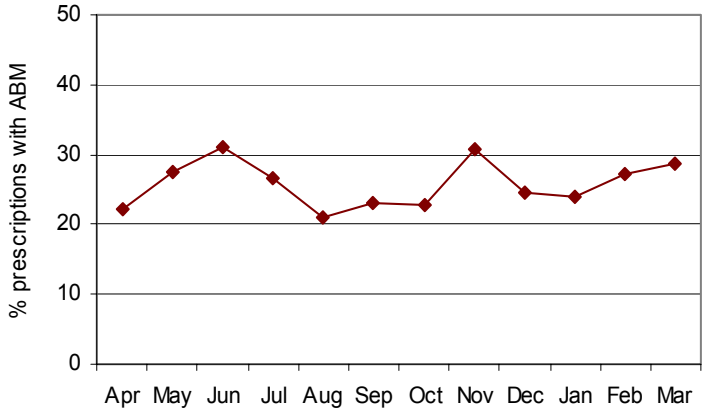
5.3.2.2 ABM use by facility

The percentage of patients prescribed an ABM in each of the facilities surveyed is shown in Table 5.3. While some differences were evident between the clinics, on a monthly basis between 20 and 30% of patients received an ABM (Figure 5.4).

Table 5.3: Prescriptions containing antimicrobials

Facilities	Patients screened	Prescriptions with ABM		Number of ABM prescribed
		Number	%	
Brits hospital	1477	480	32.5	661
Bapong	1276	310	24.3	390
Bertoni	952	360	37.8	453
Lethlabile	419	150	35.8	170
Madibeng	1245	330	26.5	434
Majakaneng	2317	353	15.2	438
Oukasie	1372	330	24.1	424
Total	9058	2313	25.5	2970

Fig. 5.4: Monthly trends in percent prescriptions with any ABM (April 2004 to March 2005)



5.3.2.3 Specific ABM use

The use of selected classes of ABM, as shown by the percentage of prescriptions containing an example from that class, and as expressed in DDD per 100 patients seen, is shown in Figures 5.5 and 5.6. By both measures, cotrimoxazole and the extended-spectrum penicillins were the most used, but for the other ABMs the order of use varied according to the measure

used. The difference in these two measures was well illustrated by the data on fluoroquinolones use. While a moderate percentage of prescriptions contained a fluoroquinolone, as the agent provided was restricted to single dose use in sexually transmitted infections, the number of DDDs per 100 patients seen was far more modest.

Fig. 5.5: Annual use measured as percent of prescriptions with specific ABM (April 2004 to March 2005)

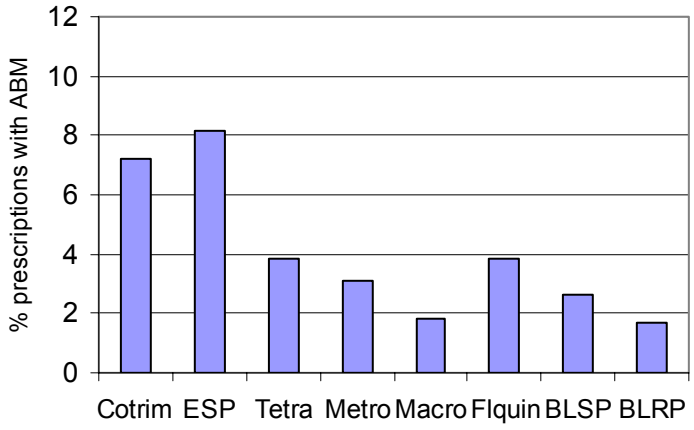
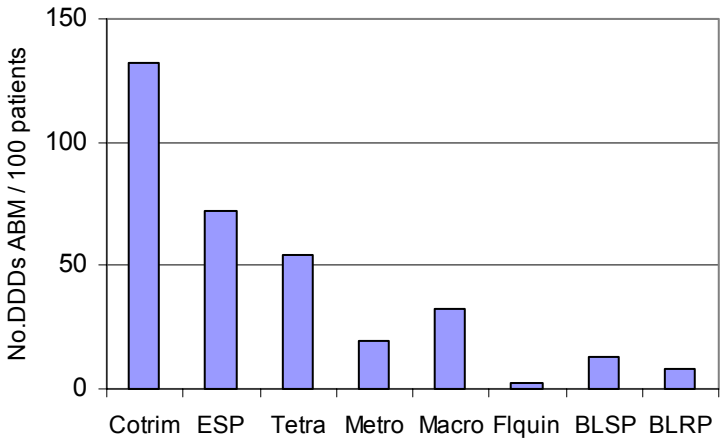


Fig. 5.6: Annual use measured as DDD of specific ABM prescribed per 100 patients (April 2004 to March 2005)



The same data is shown broken down by facility in Figures 5.7 and 5.8. This data shows that Lethlabile was by far the biggest user of cotrimoxazole by both measures of use, while Brits hospital was the biggest consumer of extended-spectrum penicillins. Such data can be helpful in targeting interventions to particular facilities. The wide variation between facilities also demonstrates the importance of including sufficient numbers of health facilities in the surveillance if one wishes to gain a truer picture of ABM use that is generalizable to a larger community.

Fig. 5.7: Percentage of prescriptions with specific ABM per facility in one year (April 2004 to March 2005)

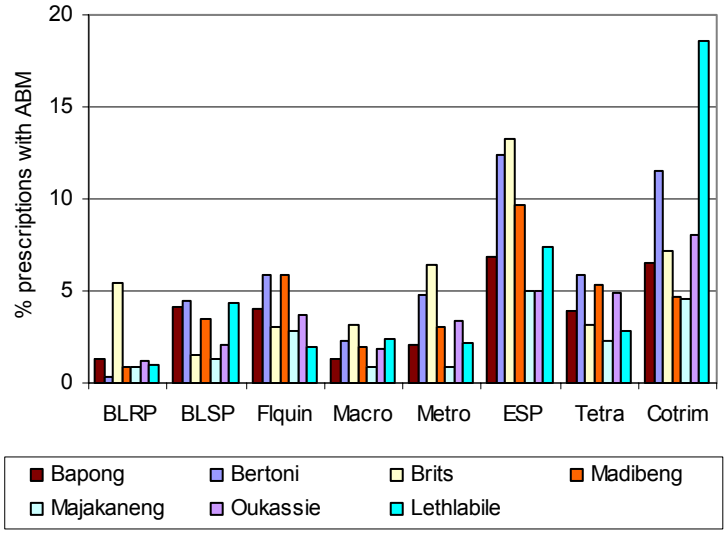
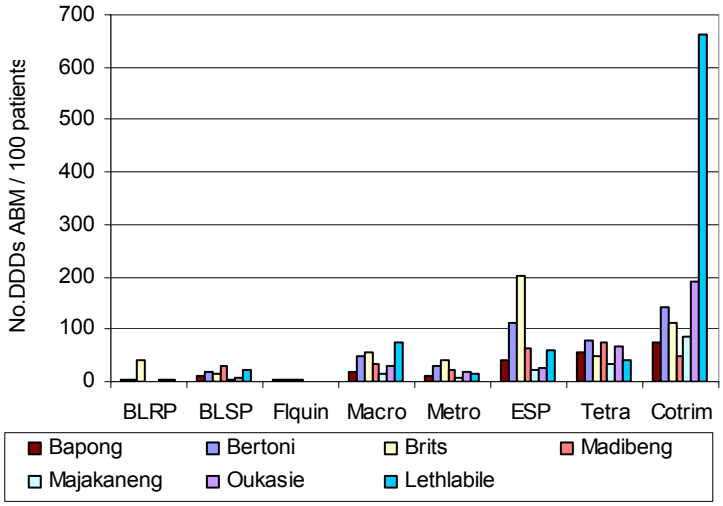


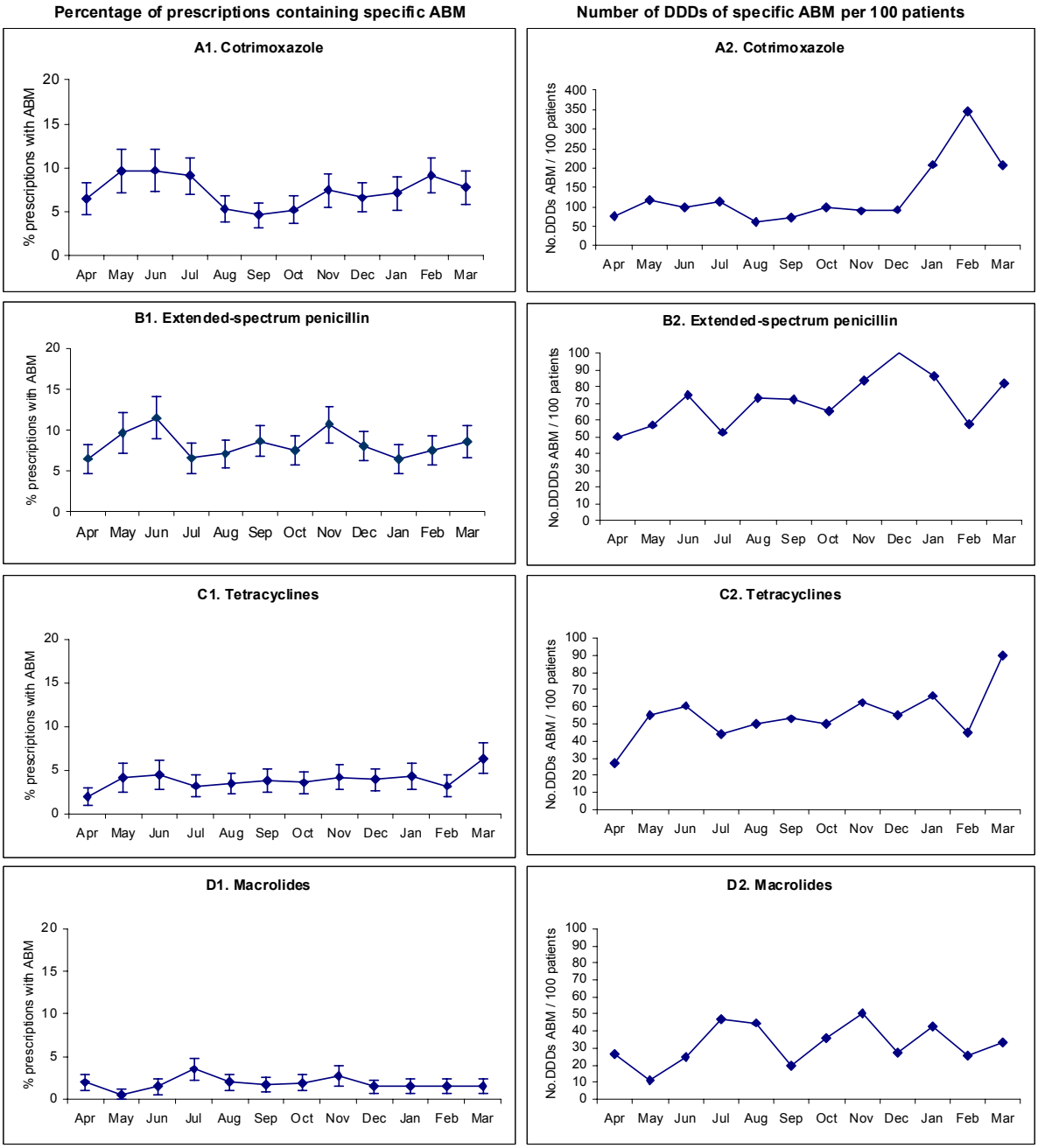
Fig. 5.8: No. DDD of specific ABM prescribed per 100 patients per facility in one year (April 2004 – March 2005)



5.3.2.4 Monthly trends in specific ABM use

Figure 5.9 shows the monthly use of specific ABMs. No obvious seasonal trends were seen when ABM use was expressed on a monthly basis. The increase in cotrimoxazole use noted in the latter part of the study (January, February and March, 2005) was mostly from a single clinic (Lethlabile), and could be seen most clearly when expressed in DDD per 100 patients seen. This was associated with the introduction of month-long provision of cotrimoxazole prophylaxis in patients with HIV infection.

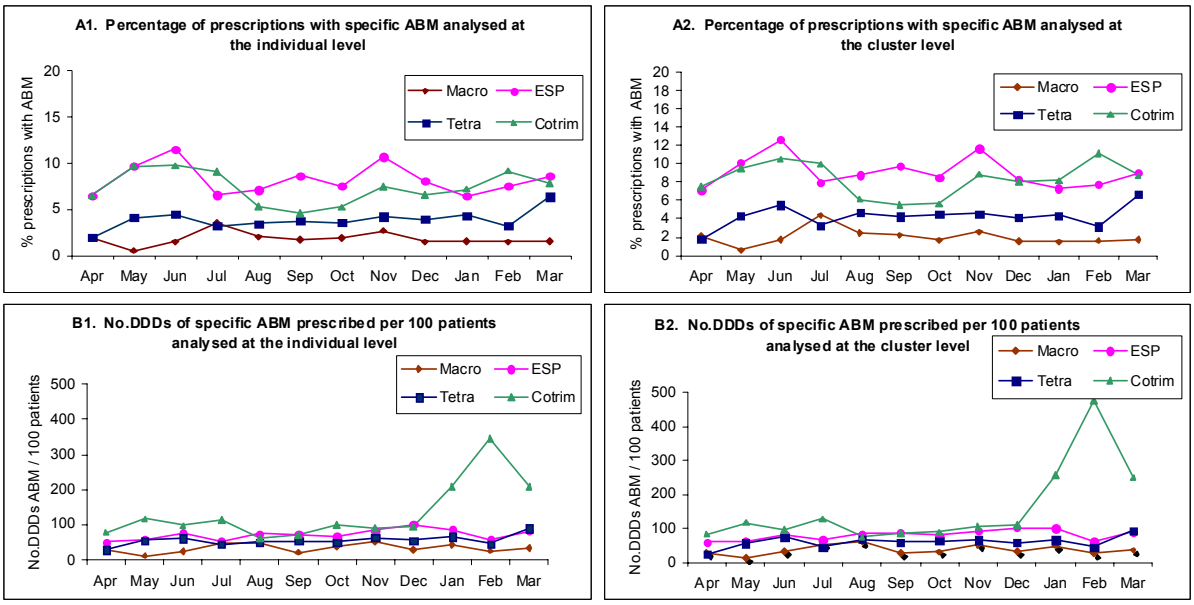
Fig. 5.9 (A-D): Monthly use of specific ABMs (April 2004 - March 2005)



The error bars indicate CI

Since the target monthly number of ABM-containing prescriptions was not achieved and prescription numbers examined varied widely between facilities, there is the possibility of bias of composite data across facilities by individual facilities in any analysis done at the individual prescription level. Thus the data analysed at the level of the individual prescription shown in Figure 5.9 was re-analysed at the level of the cluster, i.e., the health facility level. Figure 5.10 shows monthly trends estimated through analysis at the health facility (cluster) level. Comparison of Figures 5.9 and 5.10 show similar results with both analytical methods.

Fig. 5.10 (A-B): Monthly use of specific ABM calculated at the individual and cluster levels (April 2004 to March 2005)



5.3.3 Effect of ABM on AMR

No trends in AMR were expected to be seen, nor was it anticipated that these would be associated with any changes in ABM use during the duration of the pilot study.

5.3.4 Compliance with the Standard Treatment Guidelines

At this site, the investigators also assessed compliance with the relevant Standard Treatment Guidelines (STGs) included with the South African Essential Drugs List (EDL), applicable to PHC facilities in the public sector. As shown in Table 5.4, about one third of total prescriptions did not comply with STG/EDL guidelines for choice of therapy. Potentially inappropriate use was identified most commonly in relation to extended-spectrum and β-lactamase-resistant penicillins. Compliance was most common in relation to fluoroquinolone use. ABMs were prescribed for several indications, but most commonly for symptoms and signs related to respiratory infections. Of the 544 patients receiving ABM therapy for this indication, 334 reportedly had upper respiratory tract infections. Other diagnoses/presenting complaints recorded were sexually transmitted infections (in 534 patients), urinary tract infections (291), skin infections (203), retroviral disease (345), otitis media (84), gastrointestinal infections (93) and dental conditions (36). Several other indications were recorded and these included viral and fungal infections.

Table 5.4: Compliance with STG/EDL in choice of therapy

	Not compliant		No. of prescriptions with information available
	Number	**%**	
β-lactamase-resistant penicillin	59	44.4	133
β-lactamase-susceptible penicillin	48	25.1	191
Fluoroquinolones	26	10.0	259
Macrolide	44	33.6	131
Metronidazole	87	38.2	228
Extended-spectrum penicillin	281	47.7	589
Tetracycline	56	21.1	265
Cotrimoxazole	174	30.3	574
Total	**775**	**32.7**	**2370**

5.4 Lessons learnt from this site

5.4.1 AMR

This pilot site based its surveillance method only on women suspected of having a UTI, in order to obtain *E. coli* isolates. The feasibility of this method is in question, as it failed to deliver the required numbers to allow for time series analysis. The number of urine specimens collected was not enough to obtain the required number of isolates. It would have proven too costly to increase the number of specimens by incorporating more clinics and collecting specimens on a daily basis. Specimen collection was also dependent on the clinical acumen of the trained field workers, who might have included patients other than those with UTIs. The high rate of sexually transmitted infections in the population visiting the clinics also led to the exclusion of many such patients as being possible UTIs.

The investigators identified a number of other constraints that may be specific to the site, rather than the method, including:

- difficulties in negotiating collaboration from sites that have never before been included in any surveillance efforts;
- the involvement of community partners, which also required extensive and lengthy negotiations, but also resulted in a high turnover of data collectors;
- the long distances between the different facilities, some remote, and the lack of regular public transport;
- health management changes and sensitivity towards research, due to South Africa's social past, which significantly delayed the programme approval and start, and occasioned an initial retraction of support due to staff shortages.

5.4.2 ABM use

Some differences were seen in the ABM use in the PHC clinics and the OPD of the district hospital. This emphasized the need to obtain data from a range of facilities. Importantly, this site could provide no data on ABM use in the for-profit private sector. Data on

metronidazole and antituberculous drugs may be useful in assessing prescribing practice, but the usefulness of this data in the surveillance of ABM use and AMR is doubtful. Although more complex to calculate, expressing ABM use in terms of both the percentage of prescriptions containing an ABM and the DDD per 100 patients seen is useful, as it provides insights that would otherwise be lost, and which could misdirect those seeking to intervene in this arena.

The logistic problems encountered at this site made it difficult to comment on the utility of retrospective prescription data, drawn from patient's files at a hospital or from PHC clinic registers, as compared with prospective data. Exit interviews take far longer to do, and may, in the context of an intervention study, be subject to the Hawthorn effect (where the interviewer unintentionally influences the behaviour/comments of the interviewee).

6. Durban, South Africa

6.1 Background information on the site

The Durban metropolis (also referred to as the eThekwini metropolitan municipality) is a large city on the east coast of South Africa, in the KwaZulu-Natal province. The site for this pilot study was the Inner West area. In 1998, this area was estimated to contain about 14% of the city's population of more than 3 million people. Health care in this area is delivered through both private and public sector facilities. In the province as a whole, about 12% of the population has access to medical insurance, and accesses health-care services almost exclusively in the private sector. In general, those without insurance cover are more likely to go to public sector facilities for prescription medicines including ABM. However, a good proportion could also seek health-care services from dispensing medical practitioners in the private sector as well. The population is mobile and people from other areas also could access health care in this area.

Both ABM use and AMR data were collected from the Inner West area. The study was conducted by staff of the School of Pharmacy and Pharmacology and the Departments of Medical Microbiology and Therapeutics and Medicines Management at the University of KwaZulu-Natal.

6.2 Method

6.2.1 AMR

This pilot site chose to focus on *Streptococcus pneumoniae, Haemophilus influenzae* and Moraxella species in order to monitor AMR.

6.2.1.1 Sample collection

Sputum samples were collected from consecutive patients aged 12 years or older presenting at four study sites with a febrile illness and productive cough, in sterile sputum containers and inspected macroscopically. Patients producing poor quality sputum samples (i.e. mostly saliva) were excluded. The four sites were two PHC clinics, one dispensing medical practitioner practice and the OPD at a large regional public sector hospital (R K Khan Hospital). The sputum specimens were collected from patients identified by the field workers in a private area of the clinic.

Based on past experiences, the assumption was that approximately 50% of patients with suspected lower respiratory tract infection would have chronic lung disease and the other 50% acute infections. From the former group a culture positivity rate of 40% (*S. pneumoniae* to *H. influenzae* in the ratio 1:1) and from the latter a 10% rate (mostly *S. pneumoniae)* was expected. Therefore from 400 patients, 52 *S. pneumoniae* and 46 *H. influenzae* isolates were expected. To obtain 100 isolates per species, 1000 patients per month had to be recruited.

6.2.1.2 Identification of bacteria and susceptibility testing

Purulent parts of the sputum were plated onto a colistin-nalidixic acid agar plate with an optochin disc, a bacitracin chocolate agar plate and a non-selective blood agar plate. The identity of *S. pneumoniae* was confirmed by optochin susceptibility and bile solubility tests, and that of *H. influenzae* by NAD dependency and a negative porphobilinogen (PBG) test. Gram-negative diplococci growing at room temperature on chocolate agar and giving positive results for production of oxidase, DNA-ase and β-lactamase were identified as Moraxella species. All isolates were then stored at –70°C. Susceptibility testing was performed by determining minimum inhibitory concentration (MIC) by agar dilution. For *H. influenzae*, Mueller Hinton base with 0.5% blood and 10mg/l NAD was used, and for *S. pneumoniae* and Moraxella, Diagnostic Sensitivity Test (DST) agar with 5% blood was used. The antibiotic test panel included ampicillin, chloramphenicol, ciprofloxacin, cotrimoxazole, erythromycin, and rifampicin (Sigma-Aldrich). Data were interpreted using NCCLS/CLSI 2001 guidelines. For interpreting susceptibility to erythromycin, values for clarithromycin were used. Batches of culture media were tested for ability to support growth. Antibiotics were tested for inhibitory capacity using *E coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213. The Department of Medical Microbiology participated in the United Kingdom National External Quality Assessment Scheme for Microbiology (NEQAS).

In error, the susceptibility of *S. pneumoniae* isolates was tested to ampicillin and ciprofloxacin, instead of penicillin and one of the NCCLS recommended fluoroquinolones. As this is contrary to the relevant guidelines, the results from these tests are not included.

6.2.2 ABM use

6.2.2.1 Facility selection

ABM use data were collected from retrospective records of prescriptions given to patients visiting facilities in the same broad geographical areas as those used for AMR data. Retrospective records were examined in 20 health facilities belonging to three facility types - six public sector PHC facilities (operated by either the provincial Department of Health or local government authorities), seven private sector pharmacies and seven private sector dispensing medical practitioners. Although it was initially intended to obtain ABM use data from an additional PHC site (a large community health centre), this site was omitted when, even after repeated attempts, access to the necessary records could not be achieved.

The public sector PHC facilities were selected randomly from the 20 such facilities and permission was obtained from all six thus selected. The pharmacies were selected by random selection from 49 such practices listed in the South African Pharmacy Council register, and permission was obtained from all thus selected. ABMs dispensed at such facilities would be mostly for insured patients. Although random selection of private dispensing practitioners was attempted, the final set of seven was a purposive sample of those who agreed to participate, drawn from the membership of a single Independent Practitioners Association. Both insured and uninsured patients would be expected to obtain medicines from this group.

6.2.2.2 Prescription examination

Data were collected from each facility for one week every month by trained research staff. They used original prescriptions for collecting data from pharmacies, which were fully computerized. In the clinics, the data were extracted from daily statistical return sheets, or "tick registers". In dispensing practitioner settings the data were extracted from non-computerized clinical records. All prescriptions or patient records for the week prior to the visit were examined, and details for those containing ABM captured on a pre-designed form. When it became apparent that the required 30 ABM-containing prescriptions per month were not being attained in each pharmacy, the field workers returned to examine prescriptions for another week in each month. The identity of the ABM(s), dose and duration were recorded and used to calculate the DDD per 100 patients. For both this and the determination of the percentage of prescriptions containing at least one ABM, the denominator was the total number of prescriptions or records examined. The same facilities were used through out the study period. ABMs from the imidazole groups were included.

6.2.3 Data management

Data were captured and analysed using Microsoft Excel 2003.

6.3 Findings

Data from a total of 16 months, from October 2002 to January 2004, was available from this pilot site.

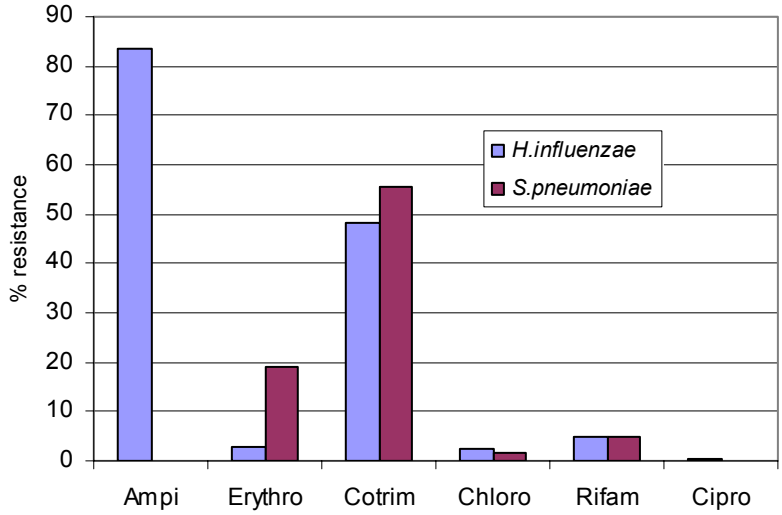
6.3.1 AMR in potential respiratory pathogens

In all, of 311 *H. influenzae*, 184 *S. pneumoniae* and 30 Moraxella spp. were isolated and tested for susceptibility by MIC determination during the study period of 16 months. The overall resistance pattern is shown in Table 6.1 and Figure 6.1. As was noted before, because of deviations from the relevant NCCLS/CLSI guidelines, susceptibility to penicillin and fluoroquinolones among *S. pneumoniae* isolates could not be reported. It was notable that nearly 84% of the *H. influenzae* isolates tested were reported to be resistant to ampicillin.

Table 6.1: Resistance pattern of bacteria tested

	***S. pneumoniae* (n=184)**		***H. influenzae* (n= 311)**		**Moraxella spp. (n=30)**	
	Number resistant	**% resistant**	**Number resistant**	**% resistant**	**Number resistant**	**% resistant**
Ampicillin			260	83.6	30	100.0
Erythromycin	35	19	9	2.9	9	30.4
Chloramphenicol	3	1.6	8	2.6	1	3.4
Cotrimoxazole	103	55.6	150	48.2	30	100.0
Ciprofloxacin			1	0.3	10	33.4
Rifampicin	9	4.9	15	4.8	2	6.7

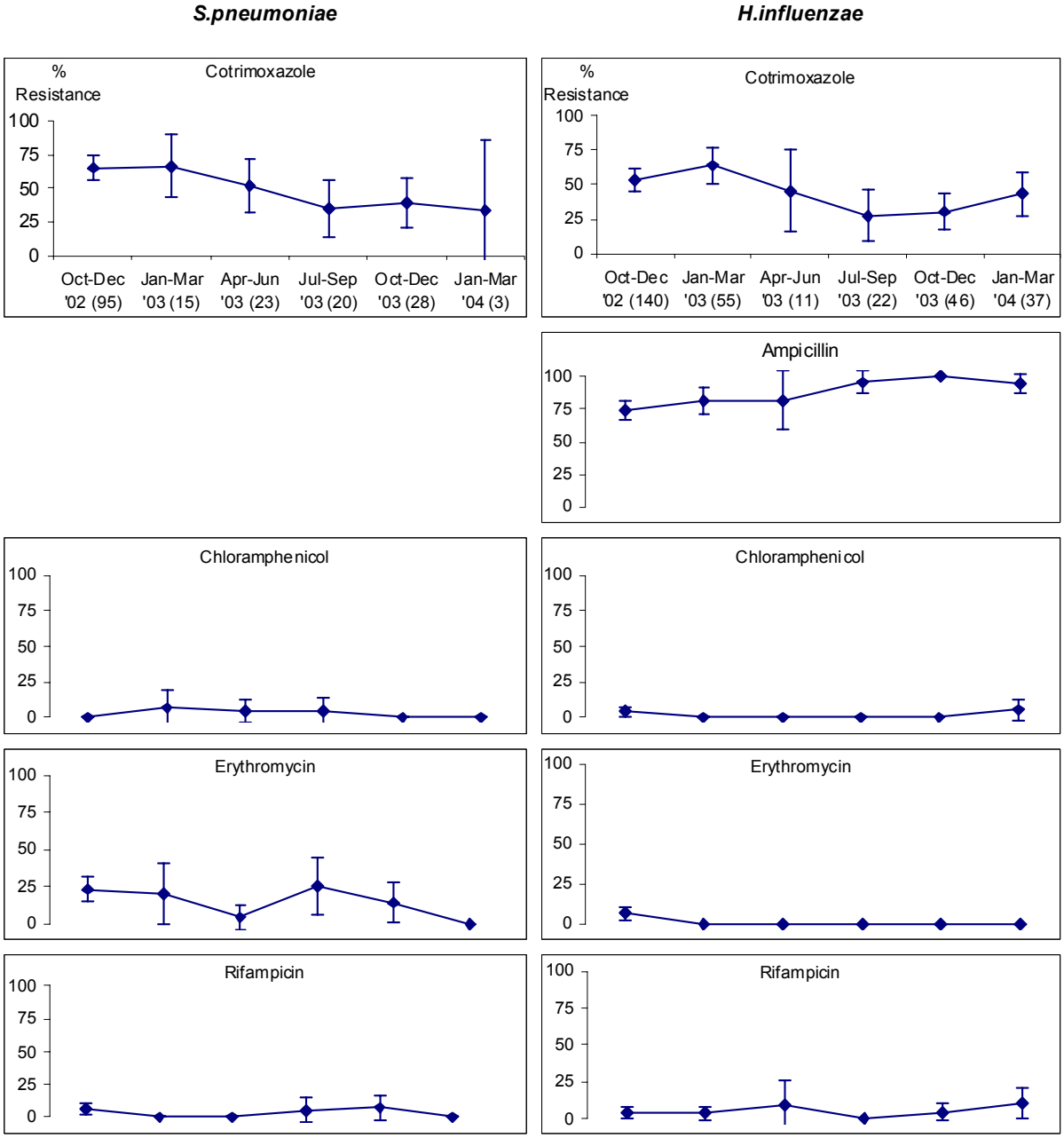
Fig. 6.1: Percentage of AMR in *H. influenzae* and *S. pneumoniae* between October 2002 to March 2004



6.3.1.1 Trends in AMR over time

Too few isolates were obtained to allow for analysis on a monthly basis, but quarterly trends for resistance in *H. influenzae* and *S. pneumoniae* isolates over time did not show any discernible trends, as depicted in Figure 6.2..

Fig. 6.2: Quarterly percentage AMR rates for *S. pneumoniae and H. influenzae*



Numbers within brackets indicate total numbers tested. Error bars indicate confidence intervals.

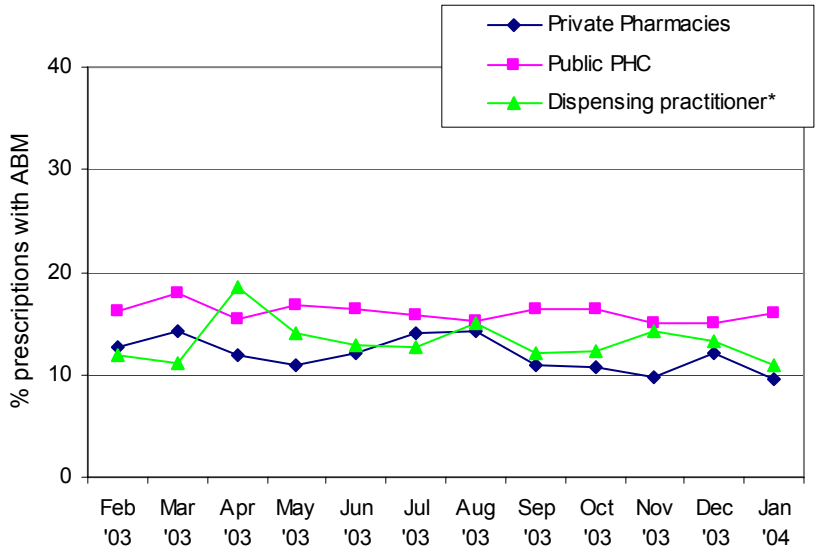
6.3.2 ABM use

6.3.2.1 Prescription data

Although collection of data started in October 2002, data from a full set of seven of dispensing practitioners could only be obtained from February 2003. During the 12 months beginning from February 2003 to January 2004, a total of 96,369 prescriptions were scrutinized, yielding 14,217 (14.8%) ABM-containing prescriptions. Of the 14,565 prescriptions scrutinized in pharmacies, 1723 (11.8%) contained at least one ABM. Of the 59,926 "tick register" records (equivalent to prescriptions) scrutinized in public sector PHC facilities, 9640 (16.1%) contained at least one ABM. Finally, of the 21,878 patients' records

(containing details of prescribed and dispensed medicines) scrutinized in dispensing practitioners' practices, 2854 (13.0%) contained at least one ABM. As can be seen in Figure 6.3, the only marked variability in the monthly trend for the percentage of prescriptions containing an ABM was seen among the dispensing practitioners. This may, however, have been an artefact of the low number of ABM-containing prescriptions seen in these settings. In several months of the study, the required number of 30 ABM-containing prescriptions per month per facility could not be obtained from a number of pharmacies and dispensing medical practitioners.

Table 6.3: Percent of prescriptions containing any ABM



* Private facility

6.3.2.2 Specific ABM use by facility type

The use of selected classes of ABMs, as measured by the percentage of total prescriptions containing an example from that class and also as expressed as DDD per 100 patients seen, is shown in Figures 6.4 and 6.5. By both measures, penicillins, mostly aminopenicillins, were the most commonly used ABMs. Cotrimoxazole and tetracyclines were used mostly in primary health clinics. The newer ABMs, such as co-amoxiclav and the cephalosporins, were used more frequently in the private sector, represented by data from both the dispensing practitioners and pharmacies.

Table 6.4: Annual use of ABM measured as percentage of prescriptions with specific ABM: February 2003 to January 2004

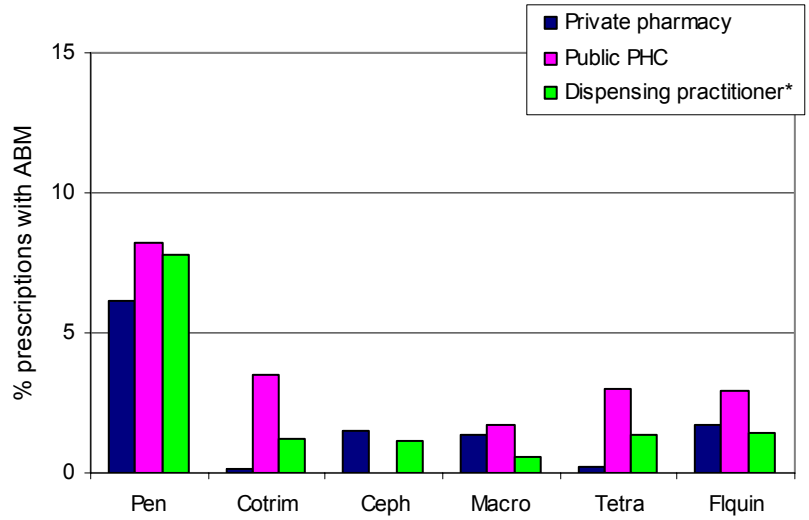
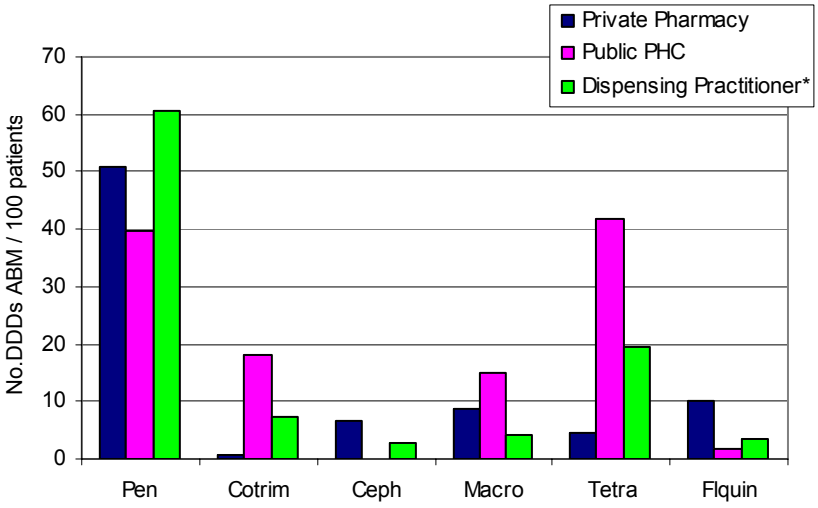


Table 6.5: Annual use of specific ABM measured as number of DDDs per 100 patients: February 2003 to January 2004



* Private facility

The use of both measures did allow for differences in practice to become apparent. For example, while the percentage of prescriptions containing a fluoroquinolone was higher in the PHC clinics compared to the pharmacies, total exposure measured as DDD per 100 patients was higher in pharmacies. The likely reason is that ciprofloxacin was, at that time, included as a single dose in the syndromic management protocols for certain sexually transmitted diseases, which were applied in the public sector PHC clinics.

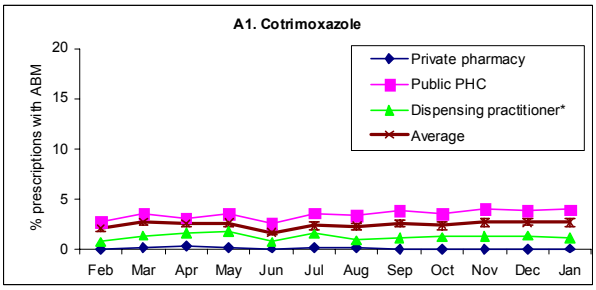
6.3.2.3 Trends in specific ABM use over time

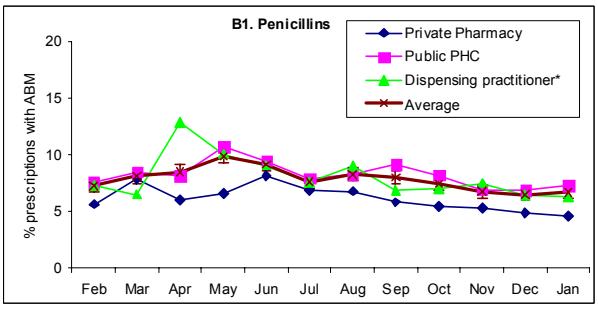
Monthly trends in the use of different ABMs per facility types are shown, using both measures, in Figure 6.6. Some evidence of an increase in cotrimoxazole use in PHC clinics could be seen towards the end of the study period, perhaps linked to the introduction of a

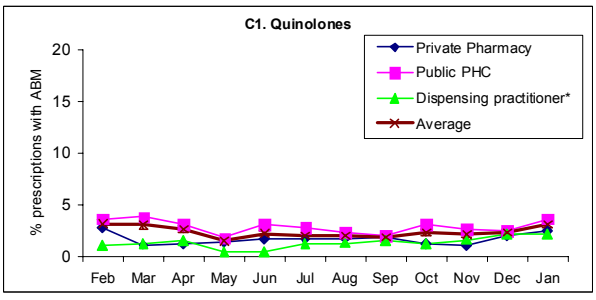
prophylaxis policy for *Pneumocystis jiroveci* in HIV-positive patients in the public sector. As individual patients would receive doses sufficient for use for a month, this would be reflected in the total DDDs prescribed.

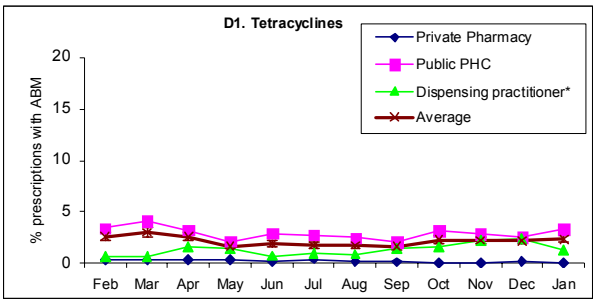
Table 6.6 (A-D): Monthly use of specific ABM from February 2003 to January 2004

Percentage of prescriptions containing specific ABM

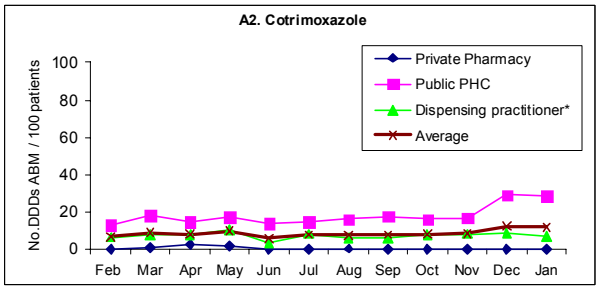


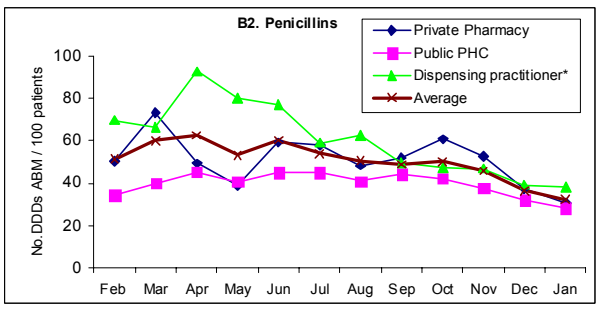


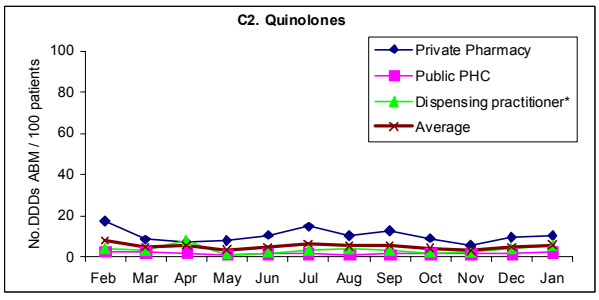


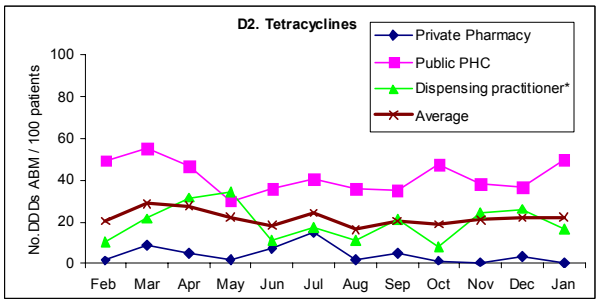


Number of DDDs of specific ABM per 100 patients









* Private facility

6.3.3 Effect of ABM on AMR

It was not expected that ABM use would be associated with any AMR changes over the period of the pilot study. Although based on scanty data, it was notable that AMR to cotrimoxazole appears to be high among both *H. influenzae* and *S. pneumoniae* isolates.

6.4 Lessons learnt from this site

6.4.1 AMR

This pilot site chose to collect data on AMR in three potential respiratory pathogens. However, there were difficulties in obtaining sufficient numbers of isolates. Patients may be reluctant or unable to provide sputa for no evident benefit. Poor quality sputa will also not yield viable organisms. The use of field workers who were not trained in health matters, rather than trained health personnel, to identify patients and obtain sputum specimens, may have contributed to the failure to obtain the expected number of good quality sputum specimens.

H. influenzae and *S. pneumoniae* are both fastidious in their requirements for survival and growth. Handling these organisms can be difficult and they may not therefore be the ideal choices for surveillance systems in resource-poor areas. This could be one of the reasons for the poor yield in numbers. Extending this system to other less equipped areas could be very difficult.

In addition, although the MIC method is universally accepted as an excellent method for determining susceptibility, strict adherence to guidelines while performing these tests is required to guarantee quality of data generated. Disc diffusion tests are currently well standardized and can provide reliable data that is comparable across centres. This latter option may be more practical in many settings.

6.4.2 ABM use

This pilot study showed differences in ABM use between the different types of facilities studied. Different types of facilities have to be sampled to understand ABM use in a given area and also in order to develop appropriately targeted interventions.

While the calculation of measures of ABM use using DDDs is more taxing, this method does provide insights that would otherwise be lost. The example of the fluoroquinolones demonstrated this well.

Although access to complete prescription records was easily attained in the private pharmacies and dispensing practitioners' practices, this was only possible in six of the original seven public sector facilities included. The greatest challenge seemed to be the low patient numbers seen in some pharmacies and dispensing practitioner settings, and hence the difficulty in attaining at least 30 ABM-containing prescriptions in one week. In addition, private dispensing practitioners were reluctant to participate in the study. It may be possible to access accurate bulk purchase/sales/dispensing data in some of these types of facilities, but this was not attempted at this site.

7. Summary of findings from all sites

AMR and ABM use data were collected from three sites in India and two sites in South Africa. For logistical reasons, the data collected in these pilot projects came mostly from urban communities around major hospitals. These are the facilities that have existing capacity to test AMR. In general, existing systems do not collect data on ABM use. Data were available for at least one year from all sites, and the periods of data collection varied but were between 2002 and 2005. Comparing data between sites was ***not*** an objective of the programme, and so methods used for collecting data at each site had some differences. The main aim of this chapter is therefore to summarize the data from all the sites and place the results obtained in the context of the available literature.

7.1 AMR

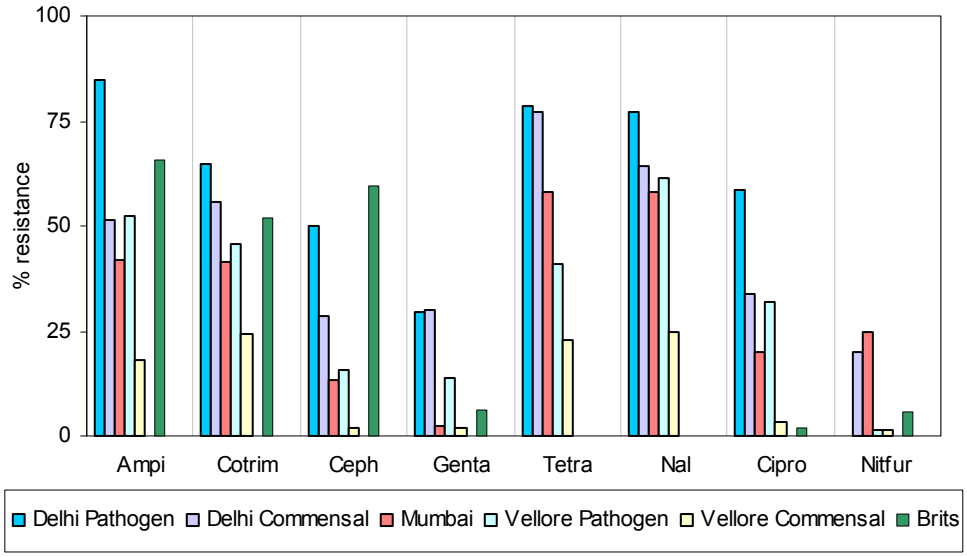
The susceptibility of *E. coli* was documented in four centres. Different methods were used at different sites to obtain the isolates and thus the *E. coli* isolates tested were either bowel commensals or pathogens causing UTI or a mixture of these two. The expected numbers required to understand monthly trends were obtained in only two sites. In spite of these limitations, the data collected provide usable information regarding prevailing AMR rates at these sites. These are summarized in Table 7.1 and Figure 7.1.

Table 7.1: AMR (% resistance) among *E. coli* at different sites

Site	**Brits, South Africa**	**Vellore, India**	**Mumbai, India (phase 1b)**	**Delhi, India**
Origin of isolates	**Commensal & pathogen**	**Commensal/ pathogen**	**Commensal**	**Commensal/ pathogen**
Ampicillin	65.6	18.2/52.3	41.7	51.5/84.6
Cotrimoxazole	51.9	24.2/45.5	41.6	55.6/65.0
Cefalexin/cefuroxime*	59.7	2.1/15.9	13.1	28.4/49.8
Gentamicin	6.1	2.1/13.6	2.5	30.1/29.5
Tetracycline		23/40.9	57.9	78.4/77..3
Nalidixic acid		24.8/61.4	58.2	64.1/77.1
Ciprofloxacin	1.9	3.5/31.8	19.9	33.6/58.7
Nitrofurantoin	5.7	1.5	25	20.2

* Cefuroxime was only tested in Brits, where cephalexin was not tested.

Table 7.1: Percentage of AMR in *E. coli* isolated from four centres



AMR rates among *E. coli* were high at all sites. At all sites, somewhat higher AMR rates were observed towards cotrimoxazole, ampicillin, tetracyclines and nalidixic acid, antibiotics historically in longer use and AMR rates to these ABMs were lower among commensal bacteria than among pathogens. Resistance to fluoroquinolones and third-generation cephalosporins was present in all areas, although the rates seemed to be much higher in India, especially among pathogens.

Although the detection of trends over time was not a primary objective in the pilot projects, it was noted that no significant monthly variations in resistance rates during the period of study were seen. However, it must also be noted that the monthly numbers of isolates were often inadequate. There were also inadequate data to reliably understand any differences that might have been present between locations and between facilities within a site. In general, where AMR rates among commensals and pathogens were studied separately, the AMR rates were lower among commensals.

There are very few reports on AMR rates among commensal *E. coli* and those causing community-acquired UTI, collected systematically over a period of time from developing countries. Data on the susceptibility of *E. coli* isolated from clinical samples submitted for routine examination have been reported from two large international data sets (SENTRY and MYSTIC)[33]. These revealed definite geographical differences, as summarized in Table 7.2. Non-susceptibility rates were generally higher in South Africa and Asia as compared to countries such as the USA and Canada during the period 1997-2001.

Table 7.2. AMR in *E. coli* *

Ampicillin	20-40% - Canada, Sweden, Italy, Japan 40-60% - USA, Argentina, Brazil, Chile, Venezuela, Northern Europe, Greece, Australia, Singapore >60% - Columbia, Mexico, Poland, Turkey, Spain, South Africa, Hong Kong, Philippines, Taiwan
Cotrimoxazole	0-20% - Italy, Australia, Japan 20-40% - Canada, USA, Argentina, Chile, Europe 40-60% - Brazil, Columbia, Mexico, Venezuela, Turkey, South Africa, Hong Kong, Philippines, Taiwan, Singapore
Ciprofloxacin	< 10% - South Africa > 10% - Hong Kong, Singapore, Philippines, Taiwan
Ceftazidime	generally less than 5%

* Sources: SENTRY and MYSTIC[33]

The AMR rates observed in the South African pilot site were similar to those reported to both SENTRY and MYSTIC. The data on cotrimoxazole and ciprofloxacin resistance from the Indian pilot sites were roughly similar to those observed in South Asian countries. However, the exact methodology used is important. For example, the SENTRY and MYSTIC data showed higher AMR rates in isolates from older age groups and in those from men[33].

A survey on *E. coli* isolated from the stools of healthy children from communities in various countries found geographical differences. Significantly higher AMR rates and levels of multi-drug resistances were observed in China as compared to Venezuela, and in Venezuela as compared to the USA[34]. A more recent study reported higher AMR rates in faecal *E. coli* isolated from Asia and South America and the rates varied substantially between centres[35]. Differences in AMR rates between urban and rural settings were not seen at the Vellore site but have been demonstrated elsewhere[36]. One reason for the higher AMR rates observed in pathogens isolated in two of the Indian sites could be prior therapy with an ABM. Lower AMR rates in commensals as compared to pathogens have also been noted by other researchers[37]. Very high AMR rates among faecal *E. coli*, as seen in the Mumbai site, have also been reported elsewhere[38]. In the Durban site, very high AMR rates were observed to cotrimoxazole among *S. pneumoniae* and *H. influenzae* and to ampicillin among *H. influenzae.*

7.2 ABM use

ABM use was measured at all sites by examining prescriptions, either retrospectively or prospectively during exit interviews. Data were collected to calculate the percentage of prescriptions containing a specific ABM and the DDD prescribed per 100 patients visiting the facility. Although data were to be collected from several facilities belonging to different types, levels to which this was achieved at different sites varied. Collection of data on purchase/sales/dispensing (bulk use) directly from dispensing facilities was attempted at two sites.

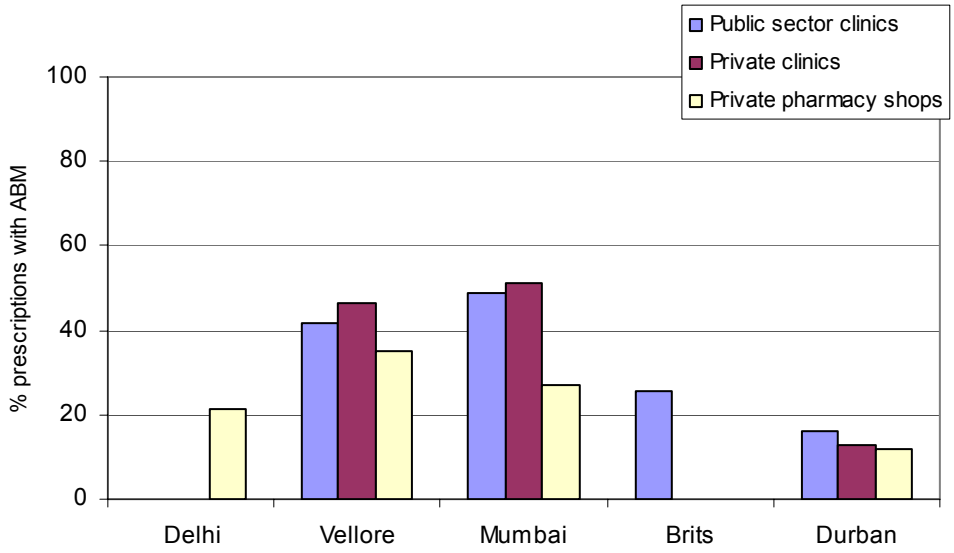
Although ABM use appeared to vary between the sites, any differences should be interpreted with caution. The legal systems and their application vary significantly between these sites. The types of facilities, although depicted here as three broad types, also varied.

The percentages of prescriptions containing ABMs at different sites are shown in Table 7.3 and Figure 7.2.

Table 7.3. Percentage of prescriptions containing antibiotics

Site	Public health facilities	Private general practices	Pharmacies
Delhi, India	--	--	21.5
Vellore, India	41.9	46.5	34.9
Mumbai, India	48.6	51.2	26.8
Brits, South Africa	25.5	--	--
Durban, South Africa	16.1	13.0	11.8

Table 7.2: Percentage of prescriptions containing any ABM

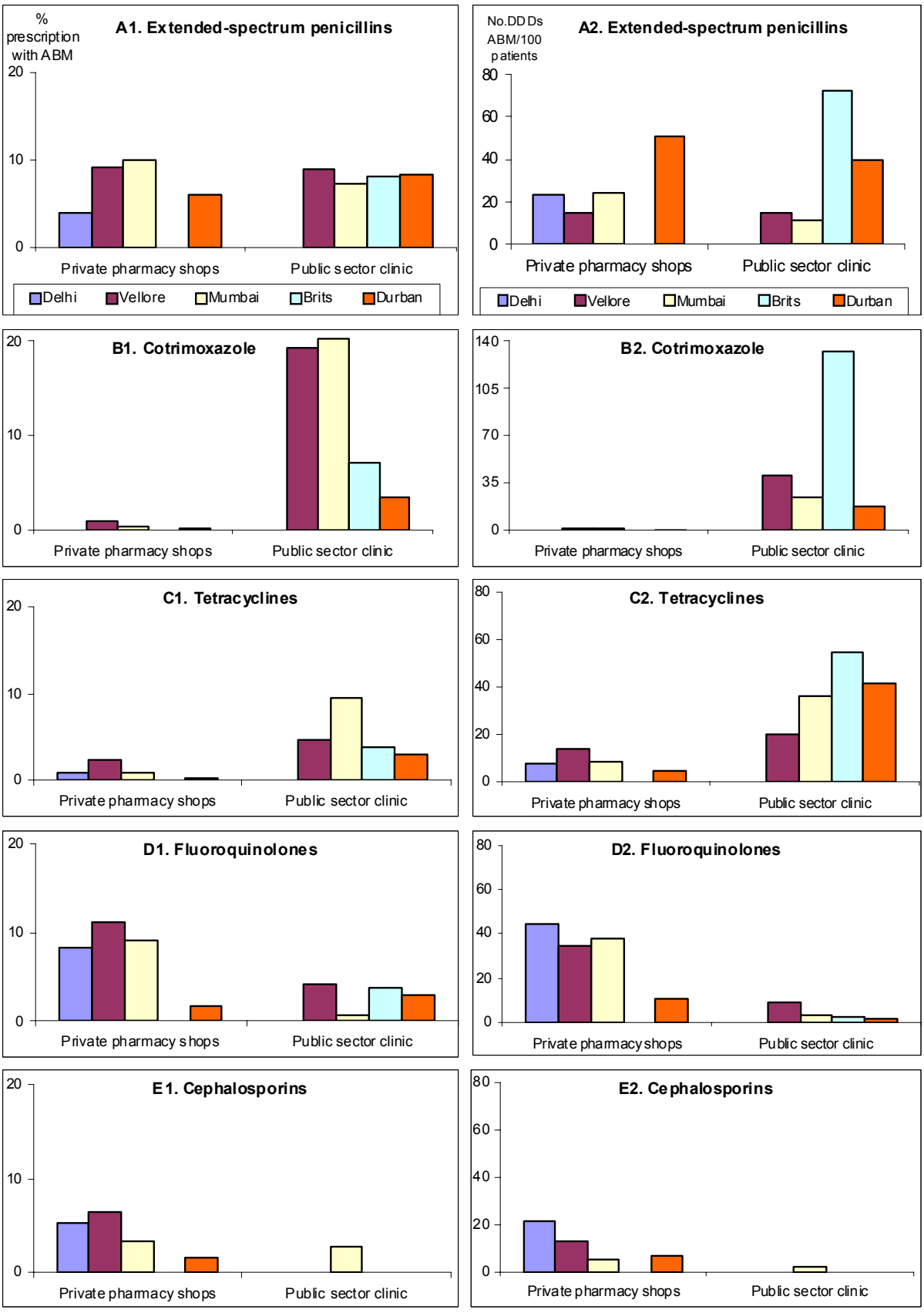


The Indian sites appeared to have much higher ABM use compared to the South African sites in all types of facility: public sector, private general practice and pharmacies. However, such a comparison should be made with caution as there were substantial differences in data collection methods and comparison between sites was not an objective.

Annual use of specific ABM measured as percentage of prescriptions and as DDD prescribed per 100 patients per year in public sector facilities and in private pharmacies for all five sites is shown in Figure 7.3. In general, inexpensive ABM, such as cotrimoxazole and tetracycline, historically in longer use, were used more widely in public sector settings, whereas the newer more expensive ABMs, such as fluoroquinolones and cephalosporins, were more widely used in the private sector.

Table 7.3 (A-E): Annual use of specific ABM at different sites measured from prescription data

Percentage of prescriptions with specific ABM | **No.DDDs of specific ABM per 100 patients**



Data collected only from pharmacies in Delhi and only from clinics in Brits

Extended-spectrum penicillins appeared to be used almost equally by private and public facilities at all sites. However, the number of DDDs prescribed for these ABMs appears to be much higher in South Africa than in India.

The utility of expressing ABM use in DDD terms was shown, particularly with reference to the fluoroquinolones and cephalosporins. These ABMs seemed to be used more in the private sector at all sites. However, in both India and South Africa, the difference was shown even more starkly when use was expressed as DDD prescribed per 100 patients.

The private-public difference was reflected in the rural versus urban use at the one site (Vellore) where this was looked for. In the rural areas where government-run facilities are responsible for a major part of health care, inexpensive ABMs like cotrimoxazole and extended-spectrum penicillins supplied by the government were mostly used. In the urban areas where private practitioners provide a good proportion of health care, newer groups of ABM such as fluoroquinolones were used more frequently. As noted for AMR, overall there was no significant trend in ABM use over time.

Different methods were used to assess bulk use in the Vellore and Delhi sites, which did allow for some comparison of *trends in use* with methods involving exiting patient interviews. However, due to differences in numerators and denominators, no comparison of absolute use could be made using these two methods. Indeed, as will be explored in more depth in Chapter 8, determination of an appropriate denominator was always a challenge in measuring ABMs, especially when attempting to depict exposure per unit population.

Only a limited number of studies have reported on ABM use. The results of 35 country studies from 1988 to 2002, which followed the standard WHO/INRUD methodology, are summarized in Table 7.4[39]. In general, it would appear that surveys performed in African countries showed lower ABM use than did those performed in parts of Asia. A similar trend was seen between the three Indian and two South African sites.

Table 7.4: Percentage of patients receiving ABMs

Percentage of patients receiving ABMs	Countries
20-40%	Malawi, Bangladesh, Zimbabwe, Tanzania, Ecuador, Guatemala, Cameron, Macedonia
40-60%	Yemen, Uganda, Indonesia, India (Karnataka), Niger, Uzbekistan, Namibia, Mozambique, Ghana, Eritrea, Oman
>60%	Indonesia, Sudan, Pakistan, Niger, India (West Bengal)

There is also a paucity of data on specific ABM use in developing countries. Data from developed countries show that the non-hospital sales of ABMs vary considerably between countries[40]. An analyses of surveys on ABM use in children published during 2000-2005, identified studies only from developed countries. There were significant qualitative and quantitative differences in prescription practices between countries[41].

7.3 ABM use and AMR

AMR rates to ABMs historically in use for longer periods were highest in all areas. Resistance to fluoroquinolones was much higher in sites in India, where the use was also higher. However, the time periods over which data were collected in all five pilot sites were too short to uncover fully any temporal associations between use and resistance.

AMR rates observed in one area could be unrelated to local ABM use. For example, high AMR rates were seen in a remote rural community unlikely to be under selection pressure from ABM use[42]. Another issue is the linkages between resistance mechanisms to unrelated groups of ABMs[43]. Although reversion to susceptibility may occur with individual ABMs, once established, AMR is most often retained by a variety of mechanisms. For example, several resistance determinants are located together in mobile, transmissible gene cassettes or integrons in *E. coli*. Use of any one ABM in this group can lead to maintenance of all determinants. There are also other mechanisms of resistance, such as the effect of efflux pumps seen with Gram-negative bacilli. Such resistance may also be acquired and can result in resistance to entirely different classes of ABMs. A model developed using population genetic methods and epidemiological observations indicated that the time scale for emergence of resistance under a constant selective pressure is typically much shorter than the decay time after cessation or decline in the volume of ABM use. It also showed that significant reductions in resistance require equally significant reductions in ABM consumption[44].

All these factors make it difficult to measure the associations between specific ABM use and changes in AMR at a community level, especially in the short term. However, in a study involving 20 countries, penicillin non-susceptibility and macrolide resistance among *S. pneumoniae* were found to be significantly higher in countries with higher use of these ABMs[45]. Hospital-based data also show associations between use of specific ABMs and isolation of resistant bacteria[46].

Data from the different sites do, however, suggest an urgent need for interventions to contain the already high AMR rates. Containment could result in a reversal, or more realistically, a reduced rate of increase in AMR. As envisaged in the WHO Global Strategy for Containment of Antimicrobial Resistance, reducing ABM use is the primary means of achieving this containment of AMR[47]. The data show the need for interventions to promote rational ABM use in these areas. Only with data can the urgent need for action be demonstrated to policy makers. Reducing overall use of ABMs, as well as use of specific ABMs like fluoroquinolones and cephalosporins, could be targets for such interventions. Continued monitoring of future trends in AMR and ABM use is also required. Furthermore, the data collected can act as one of the baseline estimates to evaluate impact of interventions aimed at rational ABM use.

8. Lessons learnt and recommendations

8.1 Background

As part of the global effort to contain the rising trends in AMR rates, a pilot project was initiated with the long-term aim of collecting data on the pattern and the quantity of ABM use and its association with changes in susceptibility patterns of bacteria prevalent in resource-poor communities. The data collected could help in developing targeted interventions and could be used later in evaluating the impact of interventions designed to contain AMR. Multidisciplinary capacity building was another intended outcome.

Since AMR changes require several years to be measurable and data collected at several time points are needed to understand the association, it was necessary to establish sustainable surveillance systems in various parts of developing countries and in areas assumed to have different patterns of ABM use and AMR rates. The areas chosen had differing modes of health-care delivery, and the health systems were all weaker compared to systems in industrialized countries. The health-seeking behaviour of the populations also differed. Therefore, it was necessary to develop protocols best suited to each of these areas to collect data on ABM use and AMR. These differing experiences were intended to help in making recommendations on methodologies suitable for community surveillance of ABM use and AMR in resource-constrained settings. Comparison between the data collected in the different sites was not part of the objectives.

8.2 Achievements

The following achievements of the pilot projects were noted.

1. Pilot projects were carried out at sites in South Africa and India to ascertain the feasibility of undertaking long-term surveillance of AMR and ABM use in communities in these areas.
2. Data on ABM use and AMR were collected from all sites for a minimum period of 12 months. From some sites data were available over a two-year period.
3. The information gathered will be useful to start locally relevant interventions. The cooperation established with the sites will help in pilot testing such interventions.
4. Useful information on methods to study ABM use and AMR in communities was generated.
5. Several issues related to logistics of long-term surveillance were identified and practical solutions suggested.
6. Recommendations for expanding such systems in the future could be made.
7. The mere fact of involving several health-care facilities at the community level in data collection itself increases awareness regarding the issue of increasing resistance to antibacterial therapy and its relation to ABM use.

8.3 Lessons learnt concerning methodology

Community-based surveillance projects on this scale have rarely been conducted in resource-constrained settings, especially in Africa and Asia. The methodological challenges faced in each site, which impacted on data quality, are important as they provide useful lessons.

8.3.1 AMR

The projects were initiated to develop and pilot-test methods to understand time trends in given areas, and in consequence different methods of data collection were used at different sites. If the same methodology is followed throughout in an area, the data could be used for comparing time trends in that area and also for evaluating the impact of interventions carried out in that area. However, in order to compare data from different sites (which was not an objective of this project), better standardization of different aspects of data collection would be required.

8.3.1.1 Collection of indicator bacteria

- *E. coli* was used to document AMR at four sites while *S. pneumoniae* and *H. influenzae* were used at one site. Sites using *E. coli* were able to generate higher numbers of isolates to document AMR. For surveillance of AMR on a large scale and among populations in the community, *E. coli* has been used successfully in other studies and is probably the most popular indicator bacterium for this purpose[48, 49]. *S. pneumoniae* and *H. influenzae* have been used to document AMR by other workers[50]. Like *E. coli*, these can be a part of normal flora but have the potential to cause disease. There are other bacteria in the respiratory tract that can be reservoirs of resistance and practical for documenting AMR.
- Using commensal bacteria with a potential to cause infections is a good method to generate surveillance data on AMR. Non-fastidious organisms like *E. coli* are probably more suitable for this purpose than 'difficult to handle' organisms like *S. pneumoniae* and *H. influenzae,* especially in areas where the performance of bacteriological procedures is still in the developmental stage. It may be worth considering using more than one type of indicator organism to understand more clearly the AMR issues in a given area.
- Various methods were pilot-tested for collecting isolates for surveillance of AMR. *E. coli* isolated from urine samples of individuals with suspected or proven UTI had a different susceptibility pattern from those from individuals with no evidence of infection. Therefore, it is necessary to define and standardize the sources if comparison between sites is an objective. It may also be necessary to include commensals in a planned manner in order to obtain sufficient numbers of isolates for time trend analyses.
- Using urine as source of *E. coli* had several advantages. Compliance for this type of sample collection was good. In two sites, both pathogens and commensals were obtained separately for testing by applying a few additional simple steps to differentiate uninfected individuals from infected ones. This was done by asking for symptoms and testing by dipsticks for leucocytes and nitrate reductase. This method had the additional advantage of providing treatment for those participating subjects who were infected. However, training and supervision is required for all staff collecting samples. The numbers of isolates obtained by this approach were smaller than those obtained using faecal samples for *E. coli*. With faecal *E. coli*, only commensal flora could be tested, and the patients had to make a return visit to the clinics to submit the samples. This has the

potential to bias the selection towards those who return to the clinic for further treatment and towards those who are already on treatment. Both methods of collecting isolates are suitable for surveillance and the decision between them could be based on logistics, cost and acceptability by the community and investigators. If only commensals are used, the data generated may not be useful for making treatment guidelines. Mechanisms have to be built in to avoid biases in selection.

- Using pregnant women as the source of *E. coli* has the advantage that they represent the 'healthy' community population. Data generated may be expected to be homogenous across sites and to allow comparability. However, men are excluded by this selection method, and the sample collection centre has to be restricted to antenatal clinics. There is a possibility that men carry more resistant bacteria, since urinary tract infection is much rarer in men than in women.
- Patients and relatives coming to the clinic were used for collecting faecal samples. A large proportion of subjects thus included were receiving ABM treatment. Hence it is worth considering collecting such samples directly from the community, as has been done in other studies, in order to minimize biases in sampling and to exclude those being treated with ABMs[49]. However, such approaches are more labour intensive.
- Adding a service component (providing treatment for those infected or using the data to decide on ABM therapy) and explaining clearly to patients the benefit of participating in the study helps to increase compliance of patients in providing clinical specimens. This was done in a number of sites but, where it was not done, patients were reluctant to provide specimens.
- The sites in Delhi and Vellore used methods to increase the yield of commensal *E. coli*. One site used perineal wipes while the other used a method of inoculation into broth and then subculture. Both methods helped in increasing the yield of commensal *E. coli*. The degree of cooperation required from the patients is less in the case of the latter method.
- Those receiving ABM treatment were excluded at some sites by asking for a history of ABM use. There were no significant differences between isolates obtained from those being treated and those not being treated with ABMs at the site where samples were collected from both groups. However, a simple history of ABM use may not be very reliable. A better method might be to use simple tests, such as urine bioassays, to assess prior ABM use[51].
- Only one isolate per person was used. Although this can lead to under-estimation of the actual prevalence of resistance, this is a practical method in resource-poor settings and may not be a limitation for a surveillance method. It also prevents testing of duplicates of the same isolate from the same patient, a common occurrence when routine hospital data are used for surveillance.
- Other methods of identifying AMR in faecal flora have been described[52]. A recently described direct plating method reduces cost significantly while retaining sensitivity and specificity.
- Considerable difficulties were experienced by the single site that chose to collect respiratory isolates (Durban). The number of isolates obtained by this method was inadequate. A decision to use commensal flora could perhaps help in increasing yield, but these would have to be obtained from specimens other than sputa. Although some of

the respiratory isolates obtained were likely to be commensal bacteria, it was not possible to distinguish commensal from pathogen in this study site.

8.3.1.2 Methodology for susceptibility testing

- Susceptibility was tested by disc diffusion at four sites and by the MIC method at the fifth. The former is more cost effective and therefore allows more isolates to be tested. This method is well standardized and is in routine use in many laboratories. Adopting this method as the method of choice can facilitate in extending data collection to other sites. Testing for MIC can be technically more exacting and therefore more prone to error in laboratories not conversant with this method. Although, several isolates can be MIC tested on one set of media, sufficient numbers of isolates need to be available for testing at each sitting, in order to make this cost effective. If numbers isolated are too small, as happened at the site performing this method, there will be a need for additional facilities for safe and effective storing of the isolates till testing.
- Inference drawn for trends in AMR will depend entirely on the quality of the test results. Therefore close attention has to be paid to technical issues related to AMR testing. The use of standard operating procedures for identification and susceptibility testing is but one way of strengthening quality assurance in this regard. Although all sites followed NCCLS (CLSI) criteria and practised routine quality control procedures, data from some sites suggested the possibility of technical errors and lack of adherence to CLSI guidelines. Therefore, it is important to have a co-ordinated and structured quality assurance programme for any surveillance programme. This should include proficiency testing and mechanisms for feedback and education.
- Even with good quality assurance schemes, there can be inter-laboratory variation in disc diffusion results. A possible additional method of control would be to record and submit all zone sizes for analysis by the coordinating body.

8.3.1.3 Sample size and data

- Sample size was calculated statistically to allow estimation of time trends and for future evaluation of the impact of interventions. The preliminary data generated can be used to verify and modify, if necessary, these calculations.
- The anticipated numbers of isolates could not be obtained in most sites, particularly where the site sought to obtain pathogens. Careful and realistic planning and monitoring is required to avoid this. The deliberate collection of commensals in some sites helped to ensure that the required sample size was obtained.
- Although monthly time series analysis was planned, most sites experienced problems in obtaining sufficient numbers of isolates every month. Data from these sites thus had to be pooled and analysed per quarter (three months). In longer-term surveillance programmes, it may be enough to have quarterly data analyses, since significant monthly variations are not expected and were not found. However, collecting smaller numbers every month may be more sustainable than collecting the total required numbers at intervals with periods of inactivity in between.

8.3.1.4 Data management

- In any surveillance programme, the data entry format has to be designed in consultation with a statistician, in order to facilitate collection of all required data from all sites. The data entry formats used in the pilot sites differed in the features incorporated and this affected the ease of analysis.
- Various types of errors were seen, including data entry errors and errors in interpretation. Procedures need to be built in to minimize data entry errors.

8.3.2 ABM use – Prescription data

ABM use prescription data were collected by exit interviews at three sites in India and from records maintained at the facilities at two sites in Africa. Feasibility, logistics and cost were the prime considerations when developing these pilot projects. The objective was to evaluate the feasibility of community-based surveillance in resource-poor settings. Although a complex multistage cluster design was followed in each site, the model developed appears to be feasible. However, several issues for improvement were identified.

8.3.2.1 Sampling

Sampling involves the selection of a number of study 'units' from the study population. At all sites ABMs could be obtained by the population through the private and public sectors. The main agencies prescribing or dispensing/selling ABMs for out-patients were the public sector primary health clinics, private general practices, the out-patient clinics of the public sector and private hospitals, and private pharmacies.

- A multistage sampling was performed. In the first stage, clusters (facility types prescribing or dispensing ABMs) were identified in the private and public sectors at each site. In the next step, the facilities to be included in each cluster were decided upon. At the third stage, the number of prescriptions containing ABM to be examined per month per facility was determined. The decisions taken therefore, at each site, included the types of facilities to be sampled, the number of facilities per type and the number of prescriptions to be examined per facility per month. There were no existing specific recommendations on how this could be done, although the sites were referred to the standard WHO/INRUD guidelines for assessing drug use in health facilities[53]. The facility types were decided by the investigators based on local knowledge. The number of facilities to be included was decided on the basis of available lists of such facilities obtained from local bodies (such as the pharmacy association or medical association). The facilities were then selected either by random sampling or based on convenience. The latter method was more commonly applied. For determining the numbers of prescriptions to be examined, a modification of the recommendations in the 1993 WHO guidelines was used[53]. The aim was to obtain 30 ABM-containing prescriptions from each facility each month and to include at least 20 facilities. The plan was to include 10 facilities from each facility type, but this was only achieved in some sites.
- This approach of multistage sampling is practical, it appears to be satisfactory and is included in the current recommendations on assessing medicine use in communities[54]. Three of the five sites measured ABM use in various facility types in both the public and private sectors in order to better reflect the health-care seeking behaviour of the local communities. However, the numbers and selection of facilities need to be reviewed and

refined. The clusters and the numbers per cluster need to reflect the health-seeking behaviour of the population in the area. For example, if 80% of the population seeks health care in the public sector, 80% of the facilities need also to be in the public sector. However, establishing who uses what kind of facility in which sector is very complex and may be impossible to do in many resource-poor settings. For example, while it may be true that more than 80% of the South African population is uninsured, they may also resort to out-of-pocket purchase of health services and medicines, while being nominally "public sector dependent". In India, the majority of people access health care in the private sector, despite the presence of public sector facilities.

- Including multiple private and public sector facility types can improve the validity of any inferences that may be drawn. Selecting appropriate facilities in developing countries can be difficult for several reasons, including the non-availability of accurate listings of facilities, lack of information and variability in the catchment population of facilities, overlap in the areas of service by facilities, and a lack of cooperation from randomly selected facilities.
- The number of prescriptions to be examined per month was decided upon based on the variations expected. The minimum number of 30 antibiotic-containing prescriptions per facility per unit of time should be acceptable for cross-sectional surveys, but a more precise sample number could be derived for time series analyses using the data generated in this study.

8.3.2.2 Data collection

- Data were collected by qualified pharmacists or specially trained individuals at most sites. However, the data quality varied, especially in relation to the more detailed data required for calculating the number of DDDs per 100 patients. Where data on doses and durations are not consistently recorded, such calculations will not be possible. These data were more prone to error and showed much wider fluctuations than the data based on the percentage of ABM-containing prescriptions. Analysing data on additional ABM use, where patients had received more than one ABM, was difficult using the data sets provided. Attention to training and supervision of data collectors is essential.
- The required sample sizes, according to the agreed protocols, were often not obtained in most sites. There were wide variations in the numbers of prescriptions noted between months and facility types in some sites. The reasons for these variations were myriad, but such variations could be minimized by continuous monitoring.
- Monthly data did not show much variation. However, collecting data every month in a systematic manner is probably more sustainable than data collection at intervals of 3 to 6 months.
- Planning interventions is made easier if data are collected on the indications for ABM use. Such data are, however, difficult to analyse because of the number of variables. If common out-patient illnesses can be grouped (e.g., based on systems, symptoms), data useful for developing interventions can be generated. One site attempted to determine the degree of compliance with Standard Treatment Guidelines, and thus with the Essential Drugs List (EDL).

8.3.2.3 Data management

Data management is an important aspect of long-term surveillance and this aspect requires careful planning and implementation. Well-designed data entry formats and committed local supervision are mandatory. Where multiple files and formats are used, the chances are errors are multiplied.

- Information necessary for basic measurements of ABM use (percentage of patients receiving specific ABM; number of DDDs of a specific ABM per patient attendance or population/time period) and that required to understand appropriateness of ABM use (e.g., diagnosis, compliance with EDL) need to be collected and entered in a uniform manner. Additional data, if necessary, can be collected as decided by individual sites.
- The data entry format should allow entering information on those not receiving ABM as well as those receiving ABM into the same data set. This will be helpful in all calculations, including measures such as confidence intervals. Unfortunately, the denominators (total number of patients with and without ABM) were kept as separate files in most sites and had some errors.
- Analysing data on additional ABMs where patients had received more than one ABM was difficult using the data sets provided. This aspect also needs to be accommodated in the revised data collection format.
- There were several errors in the data sets from most sites and repeated dialogues were needed to rectify these. Local supervision is very important to reduce such errors.

8.3.2.4 Measurements for ABM use

Data were collected to allow measurements of ABM use as a percentage of prescriptions and as DDD prescribed per 100 patients. Both measures were useful in understanding different aspects of ABM use. Both were collected from prescriptions, and there is a possibility that individuals do not always purchase the total amount prescribed, mostly for financial reasons.

- Data to calculate the percentage of prescription with ABM is easy to collect and permits an understanding of preferences and pattern of ABM use, as well as comparisons to be made between time points and, to a certain extent, areas. However, the quantity of ABMs used in an area cannot be calculated from these data.
- ABM exposure calculated as DDD per unit population per unit time in a community can give information on the magnitude of exposure. Ideally, the total population served by the facilities should be the denominator. Since there was no defined catchment population for facilities at the sites used in the pilot projects, this number was difficult to obtain. A full representation of facilities dispensing ABM in the catchment area is required if the total population is to be used, but even this will ignore the effect of highly mobile populations. For logistics, cost and accessibility reasons, not all facility types in the area were sampled at all sites, and sampling was random at only one site. Thus, the measurements made here will not allow calculations on exposure per unit population in the area (nor was this an objective of these surveillance projects). Using the total number of patients seen in a particular time period as the basis for the denominator calculation does allow comparisons over time in given facility types. Whether the trends in the

clusters studied reflect trends in the area depends on the generalizability of data from the facilities sampled.

- As a minimum, therefore, data on the percentage of ABM-containing prescriptions must be collected. Although the trends over time in the more complex (and therefore more error-prone) DDD-based measures were similar, collecting such data is valuable for understanding ABM use in a particular area.
- It is also worthwhile considering the development of mathematical models to estimate exposure per unit population, based on data that is practical to collect in resource-poor settings.
- Collecting data on denominators requires particular attention. For prescription data, the total numbers of patients counted (with and without ABMs) to obtain the desired numbers of ABM-containing prescriptions was used as the denominator. The appropriate method for exit interviews, as done in some sites, would be for one person to count the total number of patients and identify those with ABMs and a second person to interview those with ABMs. An alternative method could be to examine the records retained in facilities (whether computerized or paper-based, prescriptions or duplicate bills) and to extract numerator (ABM prescriptions) and denominator (total prescriptions). Such records may, however, not be available in some settings. Mixed methods, whereby the numerator is collected from patient exit interviews and the denominator from facility records, risk error and may result in apparently very low ABM use. This is because the numerator is likely to be incomplete (with some ABM patients not being interviewed) while the denominator will be complete (not missing any patients with or without ABMs). Therefore special care has to be taken to standardize the method used and to train the data collectors accordingly.
- Use data were analysed also at individual and cluster level at some sites. No significant differences were observed for use within one facility type by either method. However, this result can be different if there are substantial differences between facility types in the total numbers of patients included per facility.

8.3.3 ABM use - bulk sales/purchase

These data were collected from two sites. Collecting data directly from facilities selling or dispensing ABMs, at least in theory, can be easier and more reliable. However, collection of this type of data was difficult and required full cooperation of commercial establishments. There were no widely accepted recommendations for collecting such data from public and commercial establishments. As in exit interviews, sampling is important and adequate representation of all facility types of interest is required. In neither of the two sites was it possible to collect bulk sales data from a representative sample of all facility types dispensing/selling ABMs.

The choice of denominator for such data is also more problematic. Where the number of sampled facilities is far smaller than the total in the geographical area, use of the total population (for example, in a municipal ward) may not be accurate, although it would be useful for depicting trends over time in that setting. The alternative method, in which the number of patients seen in a particular time period is extrapolated to the full operating time of the facility in a month, is highly dependent on the generalizability of the sampled time period. If this is not typical of the entire time period, it may introduce a bias.

The amount of ABM purchased by a facility need not necessarily be sold in the same month and can affect time trend analyses. This uncertainty can be overcome by using sales/dispensing data. However, such data may be unavailable, particularly in private pharmacies where sales data has tax implications. In India, private pharmacies tended to purchase little and often, there being an incentive for quick turnover, thus limiting the potential impact of unsold medicines on time trends of ABM consumption. Whichever method is used, purchase and sales data from the same facility type should not be mixed, as otherwise comparison between facilities cannot be done.

8.3.4 AMR and ABM use

AMR and use data collected for one-two years is inadequate to show significant associations. In the short term, changes in AMR rates are unlikely to occur and subtle changes are difficult to measure accurately. On the other hand changes can also be influenced by antibiotic usage not measured in the surveillance programme.

8.3.5 General

- Collecting accurate data in sufficient quantities requires the full cooperation of different types of facilities and patients, as well as multidisciplinary capacity in the investigating team.
- The required multidisciplinary expertise (ABM use, microbiology, epidemiology, data management) was difficult to obtain in most sites. This, and the lack of frequent close supervision especially of field sites, adversely affected the quality of data in some sites.
- Data collectors adequately trained in pharmacy practice and specifically trained in the surveillance aspect of the project are required. Long-term commitment from data collecting staff therefore becomes extremely important for sustainability.
- Long distances between facilities in some areas affected data collection, and logistical arrangements made at the planning stage could not be implemented, probably because they were outside of the routine health services.
- The concept of surveillance itself was relatively new for many individuals involved in the project, both directly and indirectly. The planning process should include the means of addressing this important issue, in order to ensure cooperation from all actors, from policy makers to participants.
- Changing methodology during the period of data collection, even if it is an improvement, can adversely affect the ability to assess trends over time. Therefore, dedicating the initial few months to pre-testing methods and making the required modifications can improve subsequent data quality.

8.4 Lessons learnt concerning implementation

8.4.1 International coordination, supervision and technical support

The five projects were initiated following publication of the WHO Global Strategy for AMR Containment in 2001, with the expectation that sites could manage fairly independently, provided that suitable expertise was identified. Coordination of these projects proved to be considerably more difficult, lengthy and time consuming than expected. The following aspects would need careful consideration in future projects of this nature.

8.4.1.1 Project initiation

The process of finding suitable sites was initiated by asking interested researchers in low-income countries to submit letters of intent. Since the projects were initiated from the Medicines area within WHO, the point of first contact was with pharmacologists and pharmacists, not microbiologists. However, it was made clear that sites would only be considered if there was a multidisciplinary team, including at least one pharmacologist and one microbiologist (and preferably other disciplines also, such as clinical medicine or public health).

Following receipt of the letters of intent from a number of countries, site visits were made in four countries, and, of these, two countries - India and South Africa - were chosen. In India, eight sites were visited, from which three were chosen. In South Africa, three sites were visited, from which two were chosen. A major factor that determined selection of the two countries was that WHO had specific in-country programmes at the time, with staff working in the field of essential medicines. These staff helped a great deal in suggesting sites and facilitating introductions. Following the country visits, all sites were invited to submit proposals. Only two South African sites submitted proposals, both of which were finally accepted. In India, only four sites submitted proposals, of which three were finally accepted. No proposals were submitted from the other two countries visited.

The process of developing proposals took from six months to two years and in some cases required extensive and multiple revisions, as well as specific country visits to provide technical advice. This lengthy process could not be avoided since the new methodologies being proposed required extensive consultation and there was less capacity in proposal development than had been foreseen in some of the sites. Furthermore, this AMR programme had no dedicated staff - either on the side of principal investigators or within WHO - so the process was hampered by lack of time on both sides.

In India, a technical advisory committee to support the projects was established by the Delhi Society for Rational Use of Drugs (DSPRUD), which was also implementing the WHO Essential Drug Programme in India at that time. In South Africa, there was no formal advisory committee created, although the South African Drug Action Programme (SADAP), which was supporting the WHO Essential Drug Programme at that time, was kept abreast of developments.

All of the projects required both local and WHO ethical approval, the latter process including the necessary peer review steps.

8.4.1.2 Project supervision

Regular visits to provide technical support were made to each site by staff from WHO/HQ. Each site was visited at the beginning of data collection and then, depending on progress, one or two times per year. Observation of the data collection process and inspection of the raw data and data handling was undertaken in all sites.

The initial visit to each site just after data collection was extremely useful in ensuring that data collection was proceeding in a correct manner. For example, in one site, it became apparent during observation of data collection in private pharmacies and GP practices that

the denominator was not being collected properly for patient exit interviews. The data collectors were only interviewing patients receiving ABMs and not taking note of how many patients were not receiving ABMs. Thus what was being calculated was the percentage of ABMs that were of a specific ABM class and not the percentage of patients that were receiving a specific ABM class. In another site, it was found that the process in clinics for recruiting patients to give appropriate specimens was not being handled in a sensitive way and that many patients were thus not contributing adequate specimens. Owing to the early site visits, such potentially large errors could be corrected early and appropriately.

All the sites were initially contracted to undertake surveillance for one year. In India, two sites went on to undertake a second contract for a second year's surveillance. At the time of writing, the third site is undertaking a second year of surveillance. This second year of surveillance allowed certain methodological problems to be resolved and allowed for an improvement in data quality and processing.

Unfortunately in South Africa, neither of the two sites was able to continue for a second year of surveillance, possibly because it was difficult to gain the long-term cooperation from local partners. Furthermore, during the period of the projects, the South African Drug Action Programme (SADAP) came to an end. There was a temporary deterioration in relations between WHO and the South African National Department of Health. As a result of this, even though the projects were approved by the concerned Provincial Departments of Health, as required by law, and the National Department of Health had been in previous agreement, permission could not be obtained from the South Africa National Department of Health for WHO/HQ to undertake project site visits. This had particularly serious consequences for the Brits site where data collection was being undertaken at the time. Here there was difficulty in collecting sufficient urine specimens for AMR testing and in recruiting private facilities from which to collect ABM use data. Had it been possible to provide technical advice at this time, it may be that some of these problems could have been partially resolved. For example, collection of data on ABM use could have been extended to other public facilities on finding a lack of cooperation from private facilities. The sample of *E. coli* isolates could possibly have been increased by revising the criteria for patient selection and taking mid-stream urine samples from all antenatal patients, not just from those with symptoms.

The fact that India had an on-going country support project and a team, DSPRUD, which was facilitating the operation of a specific national advisory committee for the AMR projects, undoubtedly helped ensure that the sites in India were insulated from various "political disturbances".

Every effort was undertaken to choose sites with adequate multi-disciplinary expertise in order to be able to develop a community surveillance system for which there was no standard model. Unfortunately, the actual capacity was found to be less than expected, which meant that much more supervision and technical support had to be given than was initially planned. Furthermore, only one out of the five sites managed to organize a multidisciplinary team that met regularly to plan and implement the project and to share the data on a regular basis, as is required in an ongoing surveillance programme. In only two sites were the microbiologists intimately involved in the process of collecting samples, data entry and analysis. In the other sites, much of this work was left to the pharmacologist or

pharmacist, with the result that problems concerning AMR surveillance were not dealt with quickly.

In some sites, the principal investigators (PIs) did not sufficiently supervise data collection on the ground, leaving it to the project managers. However, this was not appropriate, since one of the overall objectives was to develop new methods for undertaking community surveillance in resource-poor settings, and this required the intimate involvement of the PIs. Thus, it happened that some problems with data collection were only revealed through field visits of the WHO/HQ team. In the two sites where surveillance was undertaken for a second year, there was a change in, or absence of, PIs or senior research staff, which resulted in serious delays and problems in proposal development, project implementation and write-up.

8.4.1.3 Project implementation

This section summarizes a number of technical problems in implementation - either non-implementation or implementation not in accordance with the protocols. Unfortunately some of these problems were only revealed much later when the raw data were being analysed in WHO/HQ. This highlights the need for much greater supervision and technical support than could be provided with the resources available.

a. Sample size for isolates not achieved

In three sites, the anticipated numbers of isolates were not obtained every month for susceptibility testing. In the Delhi site, where the microbiologist was intimately involved in the entire project, modifications were introduced to address this issue towards the end of the study with an enormous increase in the number of isolates generated. While this change in methodology during the course of the study may well have affected comparability between months during the first year of surveillance, this modification is presently being used in a second year of surveillance. Unfortunately, the two other sites were unable to modify their protocols, resulting in inadequate numbers for meaningful analyses. Principal investigators ascribed the following reasons for obtaining insufficient numbers of isolates.

- The number of urine specimens collected was not enough to obtain the required number of isolates, and it would have proved too costly to increase the number of specimens by incorporating more clinics and collecting specimens on a daily basis.
- For specimen collection it was necessary to hire data collectors who were paid for their services and transport. This could possibly be overcome if the assistance of the relevant health authorities was enlisted to instruct staff at all clinics in the area to collect specimens for AMR surveillance programmes as part of their routine activities.
- The low rate of isolation of *S. pneumoniae* and *H. influenzae* from sputa could be explained by the reluctance of patients to provide sputa for no evident benefit, poor quality sputa that did not yield organisms, transport times that allowed only a maximum of four hours to collect samples each day, and low commitment by research assistants. The reluctance of patients to provide sputa, which was consequently of poor quality, could possibly have been overcome by providing them with results. However, this was not done since all susceptibility testing was done in one batch at the end of the project. Undertaking isolate processing only at the end of the project also precluded discovering other problems concerning AMR surveillance that could have been corrected.

b. Sample size for ABM prescriptions not achieved

In four out of the five sites, the required number of ABM-containing prescriptions was not collected from each facility each month. In one site this occurred at the beginning of the project and was corrected. In another site, it occurred at the end of the project when internal supervision became more lax. In a third site, it was found that the numbers of ABM-containing prescriptions were less than 30 per week in many facilities when data were collected for one week in four, as originally planned. Thus, a second week of data collection was conducted in all facilities each month and the problem corrected. However, in this site one facility had to be dropped due to a lack of cooperation. In a fourth site, data could not be collected, as planned in the protocol, from any facility type and none at all from private general practitioners and private pharmacies who retracted their initial agreement to participate. This resulted in less than one-third the planned ABM use data being collected. Unfortunately, this site was not able to solve these problems and the data collected from the remaining few facilities not surprisingly showed too great a variation to draw any generalizable conclusions. Principal investigators ascribed the following reasons for getting insufficient numbers of ABM-containing prescriptions.

- Many logistical issues concerning personnel, finances and transport for data collectors were unfortunately not sufficiently thought out during the proposal development phase. One site mentioned that due to the location of the different sites, lack of transport and staff workload, many training sessions had to be held so increasing cost and delaying implementation.
- Existing surveillance programmes are confined to academic and tertiary health-care institutions, hence obtaining collaboration from other facilities was difficult.
- Finding community partners used to research was not easy and required extensive lengthy negotiations.
- Health management changes and sensitivity towards research (particularly in South Africa, in view of its social past) significantly delayed the programme approval and start.
- Prescription registers were not always available or were incomplete.
- There were staff shortages and a high turnover of data collectors.

c. Inadequate processing of microbiological specimens

Although all sites were able to demonstrate seemingly adequate internal and external quality assurance, there were technical problems in three out of five sites. In one site, initial resistance rates varied greatly but settled after some months, suggesting initial teething problems that could have been associated with a change of microbiology staff and also variation in specimen collection. In a second site, not all isolates were tested with all the antimicrobials listed in the protocol, and for cefuroxime there were too many isolates with intermediate susceptibility, suggesting technical issues. It is possible that the interpretive break-points were close to the zone diameters of wild type *E. coli* populations in the area, and this would need to be investigated before any further surveillance was done. In a third site, the relevant international guidelines were not followed and so, in error, *S. pneumoniae* was tested for susceptibility to ampicillin instead of penicillin and to ciprofloxacin instead of one of the NCCLS recommended fluorquinolones. The results could not therefore be used. In

several sites, the researchers complained that the susceptibility testing was costing more than they had anticipated.

d. Variable methods of ABM data collection

ABM data collection methods did not always follow the agreed protocols, and the protocols did not always include detailed description for the data collection procedures that were subsequently needed. In one site, sales data were collected instead of purchase data in some facilities. The different data collection methods used in different sites thus made it impossible to compare these data. In several sites, it was found during supervisory visits that patients were being asked about their knowledge concerning AMR (plus the need to take a full course of ABMs) in slightly different ways by different data collectors. Fortunately, this did not affect the main analysis on ABM use.

When it was found that the denominator for the method using exiting patients (i.e., those patient not receiving ABMs and therefore not interviewed) was not being collected properly in one of the first supervisory visits, particular attention was paid to this issue in subsequent supervisory visits by WHO to all sites. Nevertheless, the accuracy of counting such patients in busy facilities was difficult to verify and it is likely that it varied somewhat between data collectors. Fortunately the data collectors in each site undertaking patient exit interviews did not change much, so the degree of error each month is likely to have been the same. Nevertheless varying degrees of error by different data collectors each month could not be excluded, and none of the sites operated any kind of quantitative checking system to investigate this. In one site, there was a continual increase in the numbers of patients attending the facilities. This resulted in a constant decrease in the percentage of patients receiving ABMs, since a fixed number of ABM-receiving patients had to be interviewed, i.e., the numerator was fixed. As this was found retrospectively on data analysis, it was not further investigated during the first year of data collection but only during the second year.

The denominator used for bulk data was also problematic. In one site, it was the population of the ward. In another site it was the total number of patients visiting the facility during one month. This latter was necessarily calculated differently for different facility types (public clinics, mission hospitals and pharmacies), depending on the data available. However, these differences in methodology and the possible problems therein were only really appreciated once data collection had finished. Thus, the accuracy of the method in the pharmacies could not be investigated, and it was not possible to verify the numbers.

e. Data management

There were some data management problems in most sites. Errors, such as spelling mistakes, wrong entries and missing data, were found in the data of all the sites on examination prior to analysis, although these were minimal in four of the five sites. Few of the sites undertook data entry and cleaning in parallel to data collection. In one site data entry was only completed one year after data collection had finished. Thus, problems were often found only after data collection had finished. This was too late to rectify the situation and not really in line with the overall concept of surveillance.

For data management, three sites used MS Excel while two sites used a locally designed FoxPro data-entry programme that could be exported into Excel within which analysis was

undertaken. In several sites, drop-down menus were not used and the variable labelling used was not intuitive (i.e., easily understood by others), so making analysis difficult. Two sites collected much more data than they needed for the analysis, which was wasteful of resources and increased the likelihood of error in the data.

One site did not know how to use Excel and had created more than 135 files covering monthly ABM use for each month. Unfortunately there were also many spelling errors, typically one drug name being spelt dozens of different ways. Even variable spellings varied from file to file. Although this problem was detected early on and guidance given, the site was not able to clean or merge the data. This had to be done in WHO/HQ after project completion and took several months. Even so, several site visits and telephone conference calls had to be arranged in order to go through the data, record by record.

f. Incorporating denominators in the data set

Four out of the five sites did not incorporate the patient denominator figures into their databases. Consequently calculation of the variables of interest (the percentage of patients receiving an ABM or the number of DDDs of an ABM per 100 patients attending the facility or per 1000 population) had to be calculated manually in Excel after merging two files. This was very time consuming and subject to error. It was checked in WHO/HQ for all sites and completely recalculated for one site. This problem arose because only ABM-receiving patients were interviewed. How to deal with the denominator was not considered at the time of data-entry programme design. In the fifth site, where the denominator was incorporated into the programme, the investigators were not able to export the data into the same Excel spreadsheet for analysis, so manual calculation still had to be done.

g. Managing combination ABMs and second ABMs in the data set

There was variation in how combination ABMs, such as ampicillin/cloxacillin, were dealt with during data entry. In one site, information on dosage and DDDs was provided as if for one ABM. This could have affected estimates for overall use for some ABMs, most notably extended-spectrum penicillins and beta-lactamase-resistant penicillins. In all sites there was a difficulty in taking second and third ABMs into account, all of them requiring manual manipulation in Excel in order to calculate total ABM use in terms of DDDs.

h. Data analysis

Unfortunately, the capacity to undertake analysis was much less than expected in most sites. Although some sites undertook an initial analysis, all the data had to be cleaned and re-analysed at WHO/HQ. Several investigators stated that most research projects of this nature in their country are given the data-entry programme by an external coordinating research institution (which then undertakes all the analysis) and that they did not have the capacity for this kind of activity. Unfortunately, this was not foreseen at the time of proposal development, neither by the PIs nor by the international coordinating team. Once it was realized that there were some serious issues of data cleaning and manipulation and that sufficient analysis could not be done locally, consultants were hired to undertake the work. However, it was extremely difficult for external consultants to understand the overall analytical objectives and what various sites had done, since the consultants had not been involved from the start of the projects.

i. Logistical problems

All sites had logistical problems. Unfortunately, in the South African sites, logistical problems, such as transport difficulties, high staff turnover and low motivation, seriously hampered data collection and appeared to be of a degree much higher than that expected during proposal development.

8.4.2 Local investigator opinion

All principal investigators felt that undertaking the projects had been worthwhile and that it had increased their understanding of the problem of AMR and the need for a multi-disciplinary approach. All admitted that the latter was difficult to create.

In discussions between the principal investigators and WHO/HQ, particularly during data collection and analysis, many valuable suggestions were made for future projects and how to facilitate implementation. A summary of suggestions from investigators to improve implementation and sustainability is given below.

- SOPs should be developed and adhered to for AMR and ABM use data collection.
- A greater multi-disciplinary approach is needed.
- Human resource development in the form of training, especially for field and laboratory staff, needs to be strengthened.
- A successful surveillance programme should form part of the routine activities at the various sites, as there is resistance to any additional workload or logistic needs that do not form part of routine activities. Incorporating surveillance in routine activities would also be cheaper.
- It is necessary to have the commitment of the various health authorities and the cooperation of the private sector in order to be able to collect good quality data for surveillance.
- Some investigators felt, in retrospect although not at the development proposal stage, that they did not have the capacity for such projects and that WHO/HQ should have designed data-entry programmes and taken full responsibility for data analysis.
- All principal investigators requested much more technical assistance than could be given with the resources available to WHO/HQ.

8.4.3 Summary

Much was achieved. However, local capacity was less than expected and there was insufficient supervision both locally and internationally. Unfortunately the technical support needed could not be given by the regional or country offices nor from the WHO country support programmes that were in agreement with these projects and had facilitated their start-up. Extra technical support was sought throughout the project cycle from various international consultants in microbiology and pharmaco-epidemiology. Unfortunately, without the resources to engage a complete team of consultants of different disciplines right from the beginning with long-term contracts to cover the complete project cycle, technical support was *ad hoc* and insufficient. The multidisciplinary nature of the projects complicated matters, particularly since there appeared to be little understanding, on the part of many

project members, of surveillance of AMR and ABM use in the community setting and its public health importance.

8.5 Recommendations

Community surveillance of ABM use and AMR is possible in resource-poor settings and can generate important information for public health planning. However, systems like these are difficult to maintain even in well-resourced settings. Although it is difficult to make one standard recommendation that will be suitable for all sites, uniformity in methodology is essential to make the data collected comparable between sites.

1. Community-based surveillance of AMR and ABM use is possible in resource-constrained settings, and the doing of it enables the development of multidisciplinary expertise for future AMR containment programmes. It is recommended that future surveillance projects be better integrated into existing routine systems, with sufficient long-term technical support to ensure adherence to standard operating procedures.

2. For ABM use, prescription data (especially that for calculating the percentage of ABM-containing prescriptions) is probably the most reliable. However, since data on DDD prescribed per 100 patients help to provide insight into ABM use, efforts must be made to collect these data and to improve their quality. Bulk use data may help in assessing ABM use, but unless issues concerning quality and reliability are addressed, they are probably not worth collecting.

3. For AMR surveillance, *E. coli* is a suitable indicator bacterium. There are different options for obtaining specimens which could yield *E. coli* isolates. Disc diffusion testing is probably better than minimal inhibitory concentration (MIC) testing, at least in resource-constrained settings.

4. A multidisciplinary approach is required to set up and maintain the project and to interpret data. Each site should have a qualified pharmacist/pharmacologist, microbiologist, community health personnel and a person competent in computerized data management. Training for data collectors, those collecting samples and managing data is essential. A standardization workshop for the investigators dealing with different aspects would be beneficial.

5. Standard operating principles (SOPs) acceptable and practical at all sites are needed for all aspects of data collection, both for AMR and ABM use. Quality assurance schemes need to be robust.

6. Database entry programmes for ABM use and AMR need to be developed to allow uniformity in standards to assure quality of surveillance data. The design of such databases should be done in consultation with experts in statistics, in order to enable appropriate analyses for time trends and measurement of impact. There should also be an in-built mechanism for assuring quality of data collected and entered into the database.

7. Methods for ensuring adherence to protocols should be included in the overall programme. Frequent, more intense regular monitoring, starting in the first month of data collection and then continuing at least every 6 months by contracted long-term consultants, is necessary to identify problems early and rectify them more effectively.

8. The feasibility of integrating surveillance systems into already existing systems, as well as the means of incorporating data generated into each country's health information systems, needs to be explored.

9. For long-term sustainability, the commitment of local stakeholders is essential. Issues requiring attention in this regard include funding and human resource development. It is worth strengthening the microbiological laboratories in order to systematically collect routine AMR data on specific pathogens in the area and to use these data to guide therapy and monitor trends among pathogens. Strengthening pharmacoepidemiology expertise in pharmacology/pharmacy departments would help in sustainable monitoring of ABM use.

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