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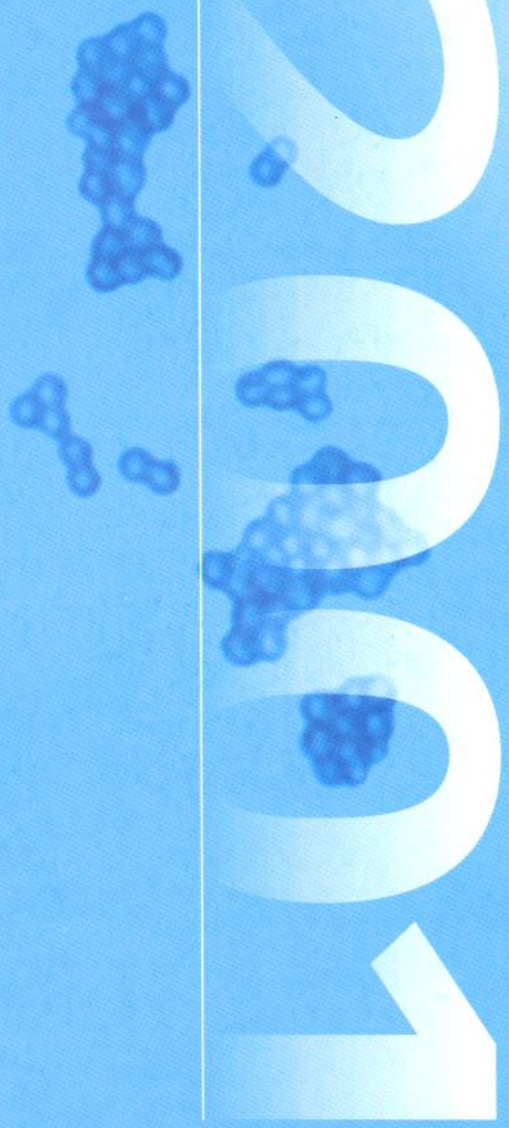
Interventions against antimicrobial resistance

A review of the literature and exploration of modelling cost-effectiveness



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Anti-Microbial Resistance
Cost-Effectiveness Analysis

INTERVENTIONS AGAINST ANTIMICROBIAL RESISTANCE: A REVIEW OF THE LITERATURE AND EXPLORATION OF MODELLING COST-EFFECTIVENESS

A report prepared for the Global Forum for Health Research

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EXECUTIVE SUMMARY

1. Introduction

Antimicrobial resistance (AMR) is one of the biggest challenges to face global public health at the beginning of the third millennium. However, there is little accurate information concerning many aspects of AMR, in particular, the cost and/or effectiveness of various strategies that may prevent the emergence of AMR and/or limit the transmission of resistant organisms, or resistance determinants. The Global Forum for Health Research therefore provided funding to:

1. Review current knowledge concerning the cost and/or effectiveness of (medical) interventions aimed at reducing the emergence and transmission of AMR in humans; and
2. Explore the feasibility of, and issues involved in, the development of an economic model to assess the cost-effectiveness of interventions to address AMR in humans.

2. Literature review – Methodology

A systematic literature review was undertaken to describe and critically appraise studies reporting on: (i) the costs and/or effectiveness of strategies to prevent, and control the spread of, AMR; and (ii) the cost of resistance. Literature was identified through contact with key international figures and institutions in the field of AMR, and through searching major electronic bibliographic databases. Approximately 155 studies were reviewed, following clearly defined inclusion and exclusion, and quality assessment strategies. Meta-analysis was inappropriate, and thus a qualitative overview provided.

3. Literature review – Results

From this review it would appear that most studies:

1. Are from the developed world (principally the United States);
2. Are mostly hospital/other institution-based, with few community level interventions;
3. Are concerned with control of transmission as opposed to prevention of emergence;
4. Cover "micro" interventions, such as hand washing, but not more "macro" policy interventions, such as legislation, global control of drug availability, tax/subsidy; and
5. Do not measure the cost impact of AMR to the health service, patients or society.

There were few studies examining strategies to reduce AMR in developing countries, although several focusing upon prescribing were reviewed. This may be a reflection of pharmaceuticals being widely available at a community level (with few restrictions governing their availability) and, as a consequence, much inappropriate prescribing. Given the focus on prescribing, it is not surprising that analysis tended to be concentrated at the community level.

Overall, there appears to be no definitive evidence (cost and/or effectiveness), which suggests that one specific control measure (or combination) is particularly more successful than another in containing the spread of AMR. In addition, many interventions that impinge on levels of antimicrobial usage, and thus ultimately levels of resistance, are also not currently subject to such formal evaluation.

4. Modelling cost-effectiveness ─ techniques and methods

Modelling is an extrapolation of the main parameters that influence the phenomenon of interest, and then a construction of relationships between these parameters. There are six main forms of modelling in common use that might be applied to AMR:

1. Decision-analytic models;
2. Markov-chain models;
3. Monte-Carlo simulation;
4. Mathematical models;
5. Statistical models;
6. Macro-economic models.

These forms of modelling differ in their theoretical and methodological basis, the purpose for which they are designed, the manner of presentation and the level of data required. The theoretical and methodological features of each of these forms of model are summarized in chapter 4.

5. Modelling cost-effectiveness ─ factors in model development

In considering the range of possible approaches to modelling for AMR there are several specific factors that are important in determining which is most suitable:

1. Contextual factors, such as socio-economic environment, type of health care system and demographic characteristics of the population;
2. Policy goal of the intervention, such as a focus upon resistance or infection, micro or macro intervention and the prevention of emergence or transmission of AMR;
3. Outcome of interest, referring to focusing more widely upon resistance or health;
4. Temporal factors and the role of changes over time;
5. Extent of endogeneity of parameters within the model (i.e. those explained by the model);
6. Discounting of future costs and benefits; and
7. Handling uncertainty, in both the development of new antimicrobials and the development of resistance.

These will determine the relevant parameters to be collected, and how the relationships between them will be constructed. These factors are outlined in chapter 5.

6. Modelling cost-effectiveness – "minimum" data set

As well as the broader structural issues, outlined in chapter 5, there is a requirement for specification of variables of importance and the collection of data related to them. Although these will vary according to the final model structure, there will likely be a "minimum data set" of variables that would be required whatever the specific model developed. Chapter 6 considers the variables that would most likely comprise such a "minimum data set" within categories of:

1. Epidemiological or clinical factors relating to resistance;
2. Cost factors relating to resistance;
3. Pattern of antimicrobial usage;
4. Impact on AMR in humans from non-human consumption of antimicrobials; and
5. Information concerning the costs and effectiveness of the policy evaluated.

7. Discussion and research agenda

In terms of the current literature, there is a narrow focus upon the closed hospital system and concentrating upon the effects of policies aimed at reducing *transmission* rather than *emergence* of resistance. However, although it will be easier to identify the outcome of strategies aimed at reducing transmission in a closed environment, these are not likely to produce an optimal long-term outcome (i.e. a stable balance of the costs and benefits of antimicrobial use). This is because of the possible irreversibility of AMR and the potentially severe harm that could be imposed as a result. Yet, given the increasing importance of evidence-based medicine, strategies that have been evaluated using experimental methods and well-conducted economic evaluations, may be prioritized above these policies, which are much more difficult to evaluate. This is a danger that should be avoided both by awareness among policy-makers of the relative challenges associated with evaluating different types of policy, and by awareness among the research community of the importance of evaluating policies that may potentially be more important, even if the rigour with which they can be evaluated is smaller than for the potentially less important policies.

Overall, there appears to be no definitive evidence (cost and/or effectiveness) that suggests that one specific control measure (nor indeed a combination of measures) is particularly successful in containing the spread of AMR. Although it would seem that suveillance is a basic pre-requisite to tackling AMR, in the absence of evidence it is difficult to go further in making recommendations, or in suggesting priorities for research among those interventions assessed here. Readers are referred to the WHO Global Strategy for the Containment of Antimicrobial Resistance as presenting the most current and complete "best advice" on interventions to tackle AMR, how these should be implemented, and research priorities.

In terms of developing a model to assess the cost-effectiveness of strategies to tackle AMR, the appropriate and desirable model will need to satisfy four broad criteria of feasibility, sensitivity, relevance and flexibility. Considering these criteria, and this review of modelling as applied to AMR, two broad options are outlined:

1. A "macro-model" approach that attempts to integrate factors within a broad-based model aiming to assess strategies on a more "global" level; and

2. A “suite” of micro sub-models, each “embedded” within a given set of primary parameters, such as country, disease and level of intervention (e.g. hospital or community), which determine which of the “suite” of sub-models is most appropriate for that context.

A definitive recommendation concerning which form of modelling to pursue is not possible at present, as it depends upon both feasibility and relevance to the question and context concerned. However, it is clear that there needs to be further research into the modelling of AMR. Although such a model will require substantial investment of time and resources, the potential benefits of such a model, if accurately specified and incorporating quality data, could be vast in terms of the potential health benefit to current and future generations.

CONTENTS

LIST OF FIGURES AND TABLES

ABBREVIATIONS AND ACRONYMS

a.d.	acute diarrhoea
AIDS	acquired immune-deficiency syndrome
AMPs	antimicrobial management programmes
AMR	antimicrobial resistance
AMX	amoxicillia
AMX-C	AMX-clavulante
ARI	acute respiratory infection
BMT	bismuth, metronidazole, tetracycline
BPI	bacteriologically proven infection
CCS	case control study
CCT	controlled clinical trial
CDC	communicable disease centre
CE	cost-effectiveness
CFE	cefuroxime
CFR	cefuroxime
CGE	Computable General Equilibrium
CHG	greenhouse gases
CON	conventional (self-administered treatment)
CRD	Centre for Reviews and Dissemination
CT	current therapy
DALY	Disability-Adjusted Life Year
DARE	Database of Abstracts of Reviews of Effectiveness
DOTS	directly observed treatment shortcourse
DSS	decision support system
EDL	essential drugs list
GBP	pounds sterling
GBS	group-B streptococcus
GNSS	gram negative neonatal sepsis
GPs	general practitioners
HCWs	health care workers
HIV	human immunodeficiency virus
ICU	intensive care unit
IMSS	Mexican Social Security Institute
INH	isoniazid
INRUD	International Network for the Rational Use of Drugs
ISI	Institute of Scientific Information
LRTI	lower respiratory tract infection
MAC	*Myobacterium avium*
MDR	multi-drug resistant
MDR-TB	multi-drug resistant tuberculosis
MeSH	medical sub-headings
MIC	minimum antimicrobial concentration
MoH	Ministry of Health
MRSA	*Staphyloccus aureus*
NHS	National Health Service

OAC	Omerazole, amoxycillia and clarithromycin
OAM	Omerazole, amoxycillia and metronidazole
ORS	oral rehydration salts
PPI	proton pump inhibitor
PSNP	Penicillin-non-susceptible pneumococci
PSP	Penicillin-susceptible pneumococci
QALY	Quality-Adjusted Life Year
RCTs	randomized controlled trials
RIF	rifampin
SDD	Selective Decontamination of the Digestive tract
SDDTTCG	Selective Decontamination of the Digestive Tract Trialists' Collaborative Group
SMAC	Standing Medical Advisory Committee
SMC	marginal social cost
ST	suggested therapy
STB	susceptible tuberculosis
TB	tuberculosis
URTIs	upper respiratory tract infections
USD	United States dollars
UTIs	urinary tract infection
VRE	vancomycin-resistant *enterococci*
WHO	World Health Organization

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- Participants at the Health Economists Study Group, Nottingham, July 2000, for comments on some of the issues presented in this report.

The usual caveat applies.

Chapter 1: INTRODUCTION

Antimicrobial resistance (AMR) is one of the biggest challenges to face public health at the beginning of the third millennium, with the emergence of a "post-antibiotic" era threatening current and future medical advances (Neu 1992, Tomasz 1994, Murray 1994, Fox 1996, ACSP 1996, Liss & Batchelor 1987). As well as increased mortality and morbidity (Astagneau *et al* 1999, Haley *et al* 1985), AMR also influences costs to the health service, patients and society. For example, health care costs associated with treatment of resistant infections in the United States have been estimated at USD4 billion to USD7 billion annually (approximately 0.5% to 0.9% of total US health care costs) (American Society for Microbiology 1995, John & Fishman 1997). In the United Kingdom in 1989 a five-week outbreak of *Staphyloccus aureus* (MRSA) cost GBP 12,935 (Mehtar *et al* 1989), and in 1995 the cost of containing an MRSA outbreak in a district general hospital was estimated to be more than GBP 400,000 (Cox *et al* 1995).

The emergence and transmission of AMR is the product of a complex mix of inter-related factors concerning the micro-organism, the individual and the environment (for further detail concerning the epidemiology and clinical background to AMR see annex 1). AMR bacteria causing global concern include multi-drug resistant *Mycobacterium tuberculosis*, penicillin-resistant *Streptococcus pneumoniae,* and methicillin-resistant *Staphylococcus aureus* (Neu 1992, Kunin 1993, Tomasz 1994, Cox *et al* 1995). However, despite increasing awareness, across both the medical (Williams 1986, Levy 1992, Kunin 1993, Murray 1994, Tomasz 1994, Pringle 1995, Reeves and Lewis 1995, Hollis-Triantafillou 1996) and lay communities (Cannon 1995, Garrett 1995, Hunt 1996) of the rising prevalence of resistance to antimicrobial drugs and the contribution that taking antimicrobials makes to the development of such resistance, there is little evidence that the use of such drugs is decreasing. (One rational policy response, of course, would be to decrease use of antimicrobials, particularly where usage results in no or very little benefit.) Indeed, in the UK, a recent report has shown the reverse to be true (Davey *et al* 1996).

Although AMR has a significant impact on current health care expenditure and health of the population (Smith *et al* 1996), it is the potential long-term impact that resistance, and specifically failure to tackle resistance, will have that is arguably of greatest concern. Although there is a growing body of epidemiological research and mathematical modelling in AMR (e.g. Austin *et al* 1999b, Bonhoffer *et al* 1997), there remains little accurate information on the magnitude of the problem in different pathogens and in various locations, the speed of development and abatement of AMR, the relative magnitude and importance of various causative factors in the emergence and spread of AMR, and, in particular, the cost and effectiveness of various strategies that may prevent the emergence of AMR and/or limit the transmission of resistant organisms, or resistance determinants[1].

[1] Note also that although there has been some work by economists on the conceptualisation of AMR (as a form of externality, outlined in annex 2) (Evans 1984, Phelps 1989, Coast et al 1998), and on possible

Given the disparate nature of evidence concerning strategies to combat AMR, the Global Forum for Health Research provided funding to:

1. Review current knowledge concerning the cost and/or effectiveness of (medical) interventions aimed at reducing the emergence and transmission of AMR in humans; and

2. Explore the feasibility of, and issues involved in, the development of an economic model to assess the cost-effectiveness of interventions to address AMR in humans.

This report describes the methodology and results relating to each of these aims. Following this introduction, the literature review methodology is outlined in chapter 2 with results detailed in chapter 3. Chapter 4 considers the main modelling techniques that may be applied to AMR, with chapter 5 considering the factors of importance in constructing a model of AMR, and chapter 6 proposing a possible "minimum data set" that might be collected by countries on an ongoing basis. Chapter 7 concludes with a discussion and suggested directions for future research.

economic responses to it (Coast et al, 1996, 1998, Smith & Coast 1998), there as been little empirical research. Estimates of the cost impact of AMR are therefore few and, inevitably, relatively crude.

Chapter 2: LITERATURE REVIEW – METHODOLOGY

As outlined in chapter 1, the aim of the literature review was to describe and critically appraise studies reporting on: (i) the costs and/or effectiveness of (medical) interventions proposed to prevent and control the spread of AMR in humans; and (ii) the cost consequence of resistance. The present chapter details the search methodology undertaken to identify relevant literature and the methodology followed to review the literature collected.

2.1 Search process

2.1.1 Initial consultation with experts

As an initial part of the search strategy several key international figures and institutions, in the field of antimicrobial resistance were approached concerning work in progress or which might be unpublished or in draft form. The full list of those from whom this information was initially requested is given in annex 3, and the initial letter sent to them is reproduced in annex 4. Following this initial correspondence, several of those contacted suggested further individuals or institutions who were subsequently contacted (see annex 5).

Overall, this correspondence revealed that there are few individuals or institutions who are currently conducting research concerning the cost-effectiveness of *interventions* (particularly for developing countries), or knew of such work being conducted elsewhere (for details concerning responses from these contacts, see annex 6). Although this may be seen as a rather "negative" result, in that there is little additional evidence to use in this review, it does highlight the paucity of research and information available on the economics of resistance, and confirms the results of the main literature review.

A further initial source of information was from attendance, by one of the authors (RS), at an international workshop on antibiotic resistance, hosted by the Centre for International Development at Harvard University[2]. Several papers at this workshop considered economic issues concerning resistance, and alternative policies for addressing resistance. The papers of relevance from this workshop are reviewed in the results section (Laxminarayan *et al* 2000a and b).

2.1.2 Electronic bibliographic database search

Based on a review of literature search terms completed for previous analyses, a comprehensive matrix of key terms (see annex 7) was developed by the researchers for use in searching the major electronic bibliographic databases: Medline, the Institute of Scientific Information (ISI), EMBASE, Greyliterature, the York Databases, OPAC 1997

[2] *Antibiotic Resistance: Global Policies and Options*. Center for International Development at Harvard University, Harvard University, MA, USA, Monday 28 February 2000.

and the Cochrane Library Online (further details, including dates covered by these databases, are provided in annex 8). The search was conducted in four phases.

Phase 1 literature search

The search matrix was applied to the Medline database for an initial search to assess the need for subsequent modifications depending upon results obtained. Medline was chosen as an appropriate database to test the search strategy as it is widely recognized as the premier source for bibliographic and biomedical literature.

This first phase of the literature search using Medline, resulted in over 7,000 references being identified. Analysis of the results suggested the majority of abstracts obtained were in the searches that used "antimicrobial" and "antibiotic" as keywords. Abstracts for the "antiviral", "antimalarial" and "antiprotozoal" searches revealed few additional relevant articles. As a consequence it was decided to drop these keywords from future searches.

Initial review of the abstracts obtained from the "antimicrobial" and "antibiotic" searches, revealed that many of the articles were duplicated across the different search strategies with the majority of articles (2,000) cited in at least one of the "cost", "intervention", "control" and "prevention" categories (see annex 7). These 2,000 articles were downloaded for review with a revision of the keyword matrix completed (see below).

Phase 2 literature search

A series of combination terms were introduced to ensure that any additional studies not captured in Phase 1 were included. For instance, "patient-isolation" and "antibiotic-restriction" were added. In addition, combination terms were introduced to reduce the potential for duplication across search categories.

This search improved upon the Phase 1 search by adding the word "comparator/comparative/comparison" to "cost", "intervention", "control" and "prevention" categories, as MeSH terms in Medline, in an attempt to reduce the results of the Medline[3] search to a more manageable number by making the search more precise. This search was completed again for the Medline database with approximately 375 studies downloaded for review.

Phase 3 literature search

Based on the review of approximately 2,375 studies downloaded from the Phases 1 and 2 searches, the following key word matrix was applied for each of the other databases searched for the literature review:

[3] Note that "comparator" etc were not used in the searches for the remaining databases, as the number of articles obtained from initial searches were not as extensive as those obtained from Medline.

Search 1	Resistan*+microbe/biotic/viral + (cost + economic or polic*)
Search 2	Resistan*+microbe/biotic/viral + (cost + infection control or infection prevention)
Search 3	Resistan*+microbe/biotic/viral + (cost + intervention or rotation or cohorting)
Search 4	Resistan*+microbe/biotic/viral + (cost + patient isolation or hand washing or education or disinfection)
Search 5	Resistan*+microbe/biotic/viral + (cost + restriction polic* or strateg*)

In all, approximately 3,000 abstracts (including the Medline searches from Phases 1 and 2) were downloaded for review.

Phase 4 literature search

Following completion of a draft of this report, it was clear that few papers identified referred to developing countries. Thus, in consultation with the Global Forum for Health Research and the World Health Organization (WHO), a further literature review was completed specifically focusing upon developing countries. Medline was then searched specifically for developing countries, with search terms including: "prescribing", "antibiotic/antimicrobial/antiviral" "developing countr*/world", "Latin/South America" "Asia" and "Africa". The search did not include "resistan*", following the suggestion made by the Global Forum and WHO that many developing countries are primarily concerned with measuring the extent of inappropriate prescribing, as a precursor to understanding the extent of AMR. In addition, the International Network for the Rational Use of Drugs (INRUD) provided a list of relevant developing country references, and WHO provided the literature they had reviewed for the WHO Workshop on the Development of a Global Strategy for the Containment of Antimicrobial Resistance (WHO 1999). From this search strategy 35 studies were selected for inclusion in the review.

2.1.3 Reviews of references sourced from additional papers

An additional 20 articles were ordered from references contained in the bibliographies of those articles selected for the initial review from the above search methodology.

2.2 Review methodology

2.2.1 Identification of papers for ordering

An initial review of abstracts from the literature search, and articles obtained from correspondence with relevant experts, was completed by (another of the authors) PW, who categorized all articles according to the following criteria: (i) conceptual studies about preventing the spread of AMR; (ii) economic evaluations; (iii) effectiveness studies; (iv) cost studies; (v) epidemiology studies; or (vi) not relevant. Approximately one third of all articles reviewed were not relevant.

Of the studies that were classified according to the first five categories, approximately 60% were either conceptual studies or epidemiological studies. Given the large number of abstracts, it was decided to focus on the economic evaluations, effectiveness and cost studies with the following characteristics: (i) containing a comparative assessment of an intervention; (ii) considering cost and/or effectiveness; and (iii) with the primary function of the intervention being to address AMR.

On this basis, approximately 200 abstracts were selected for further review. The abstracts of these studies were then circulated to authors RS, JC and MM, who recommended whether they should be included in the study. On this basis, approximately 120 studies were ordered for inclusion in this review. A further 35 studies focusing specifically on developing countries were ordered following consultation with the Global Forum and WHO.

2.2.2 Review process

The criteria for selecting studies were their potential to provide information relevant to the research questions and the methodological rigour of the study design. There were essentially four phases of the review process. These are discussed below:

1. Matching the appropriate study design to the theme of the project;
2. Study inclusion and exclusion criteria;
3. Data extraction issues; and
4. Data presentation issues.

Matching the appropriate study design to the theme of the project

The type of study design selected is dependent on the question under evaluation[4]. Randomized controlled trials (RCTs) are considered to be the best method for exploring questions relating to the efficacy or effectiveness of interventions because of their ability to control for confounding variables (known or unknown) between comparison groups. Whilst non-randomized controlled clinical trials control for known confounders, their conclusions may be biased due to unknown confounders that tend to over-estimate the effectiveness of health care interventions. Other study designs, such as case-controlled or cohort studies, are appropriate for addressing questions relating to the epidemiological and clinical evidence concerning emergence and spread of resistance. Table 1 summarizes the types of study designs preferentially selected for each of the themes.

[4] Ideally strategies would, of course, be evaluated in an experimental study comparing outcomes and costs between groups of patients randomized between routine strategy and a new strategy. However, from the practical, and potentially ethical, point of view this is often impossible to implement (Nystrom 1994). Observational studies may be used, but their results can be less reliable than those of experimental studies and practical considerations often mean they are unfeasible. However, we have adopted an approach in this review in which both forms of study are considered as offering potentially valuable information.

Table 2.1: Summary of the key themes of the review and the study designs considered appropriate for inclusion in this project

Theme to be explored	Type of studies selected
1. Cost impact of resistance	Observational studies. Preference given to prospective cohort studies.
2. The costs and/or effectiveness of interventions proposed to prevent and control AMR	Experimental studies and economic evaluations. Preference given to RCTs.

Table 2 summarizes the hierarchy of evidence identified by the National Health Service (NHS) Centre for Reviews and Dissemination (1996) for the evaluation of treatment efficacy. Studies have been divided into experimental studies suitable for examining effectiveness of interventions, and observational studies suitable for examining the emergence and spread of resistance.

Study inclusion and exclusion criteria

Studies with good methodological designs (I or II) were selected in preference to those with methodologically weaker designs (III) for each of the review themes. It should be noted, however, that the decision to include or exclude studies on the basis of methodological quality was dependent on the availability of literature. Studies were selected if they addressed at least one of the two key themes, used the appropriate study designs described in table 1 for each of these themes and were published in English (resource constraints preventing translation services). Studies not meeting these criteria were excluded from the review and the reasons noted on a selection form. All studies were graded according to the criteria outlined in table 4, with a summary of the assessment of each study contained in annex 9.

Data extraction

Method of data extraction

Criteria used to assess the quality of quantitative and economic studies were varied, and different standardized data extraction forms were therefore used for each type of study (see annex 10). Checklists were developed for the purpose of profiling each paper and highlighting methodological strengths and weaknesses. Data extraction forms were piloted on a small number of studies before a final form was decided upon (following good practice, such as suggested by Mulrow & Oxman (1996)). It should be noted, however, that the data extraction forms were not used to derive a quantitative scale (numerical score) as the interpretations of such scores can be problematic. In particular, there is a tendency to assume that a high score on such data extraction is indicative of internal validity, when in fact such scores tend to represent good quality of reporting.

Table 2.2: Summary of the hierarchy of evidence on the effectiveness of health care interventions based on criteria developed by the CRD

Hierarchy of evidence	
Experimental studies—suitable for use when determining the effectiveness of interventions	
I. Randomized controlled trial (RCT)	Participants (or other units) were assigned prospectively to two (or more) alternative forms of health care by a random allocation process.
II. Controlled clinical trial (CCT)	
II-1a. Quasi-randomized CCT	Participants (or other units) were assigned prospectively to two (or more) alternative forms of health care by a quasi-random allocation method.
II-1b. Non-randomized CCT	Intervention and control groups allocated at baseline using non-random methods and followed prospectively.
Observational studies—unsuitable for examining the effectiveness of interventions, but acceptable when describing the emergence and spread of resistance.	
I. Cohort study with data obtained prospectively	An intervention and control group defined by exposure (or not) to an intervention between baseline and follow-up rather than allocation to an intervention group. Outcome measures are administered at baseline and after a prospective follow-up. Studies utilizing concurrent controls (same location and time-frame) are methodologically superior to those using groups selected from the geographically different (but comparable) areas or historical controls.
II. Cohort study with data obtained retrospectively	An intervention and control group defined by exposure (or not) to an intervention between baseline and follow-up rather than allocation to an intervention group. Longitudinal data on study outcomes are obtained retrospectively between two time points. Studies utilizing concurrent controls (same location and time-frame) are methodologically superior to those using groups selected from the geographically different (but comparable) areas.
III. Case-control study (CCS)	Allocation into the two groups is on the basis of an observed outcome (for example the presence or absences of a disease) rather than on the basis of the intervention received between two time points.

Reliability of data extraction

Whilst the use of standardized data extraction sheets should improve reliability, this process was monitored. The first 10 studies identified were assessed by three reviewers (PW, RS, JC) independently of one another. Agreement on each of the domains covered in the extraction sheets was compared qualitatively to identify any inconsistencies between assessors. A random sample of 10 further papers was then selected throughout the duration of the remainder of the project and coded by all the reviewers involved in the

project to ensure that the data extraction remained reliable. This inter-rater reliability check indicated that PW and JC were 100% consistent in ratings applied. RS and PW rated 10% of studies differently. However, the main reviewer (PW) had included studies (rating them as moderate risk) with RS applying a high-risk status, and therefore suggesting that these studies should not be included. This difference of opinion was therefore not viewed as a significant problem, indicating that it was likely that *more* studies would have been included by PW than RS. This suggests that we can be confident that no relevant studies would have been excluded from the review by PW.

Quantitative studies

For quantitative studies, a hierarchy of evidence was used based on the CRD guidelines discussed above. In particular, good quality experimental studies (RCTs) were given greater weight, observational studies given less weight and non-comparative studies given the least weight. A data extraction checklist was developed for the purposes of this review (see form 1, annex 10) using a basic structure derived from quantitative checklists already in existence (Oxman 1994, Downs & Black 1998).

Economic evaluations

Economic evaluations identified during literature searching were summarized using a checklist developed to include standard criteria developed by Drummond *et al* (1997) (see form 2, annex 10). The parentheses within the checklist refer to specific sections of Drummond *et al* criteria. The checklist was used to determine whether the study would be retained in subsequent analyses on the basis of methodological quality.

Critical appraisal of studies

The critical appraisal of studies, using the information derived from data extraction sheets, was conducted in order to limit bias arising from the reviewing process. There are two main sources of bias: (i) those arising from methodological problems associated with the studies included in the review; and (ii) those arising through the interpretation of studies by a reviewer (minimized in part due to the use of data extraction sheets).

Study validity (for systematic reviews) can be defined as the degree to which its design and conduct are likely to prevent systematic errors of bias (Moher *et al* 1995). There are four sources of systematic errors that might arise in experimental trials examining the effectiveness of interventions against antimicrobial resistance, which have been summarized in table 3.

Table 2.3: Types of bias that affect the validity of experimental studies included in systematic reviews

Type of bias	Definition and indicators of the presence of bias
Selection	Systematic differences between intervention and control groups. Those determining the eligibility of participants should have no fore-knowledge of the treatment assignment. Allocation into treatment groups should be performed by a randomization process conducted independently of the recruitment team, and with controls (such as permutated block design) to ensure that the randomization process cannot be decoded. Selection processes that are liable to selection bias include: (i) any non-random method for the allocation of individuals into treatment or control groups (ii) quasi-randomized designs allocating individuals on the basis of alternation, case record numbers, days of week (iii) randomly generated allocation lists that have not been adequately concealed from the recruitment team.
Performance	Systematic differences in care provided apart from the intervention being evaluated. The blinding of those providing and receiving care can protect against performance bias. Whilst blinding is desirable, it should be noted that not all interventions can be provided in this way (for example, it is obvious to the patient whether they have been interviewed by a care coordinator or not).
Attrition	Systematic differences in withdrawals from the trial across follow-up. This form of bias may threaten the validity of the study if one group deviates from the designated treatment, or individuals withdraw from one of the treatment groups.
Detection	Systematic differences in outcome assessment. The blinding of the treatment allocation from those assessing the study outcomes (as well as the participants themselves) can limit detection bias, although this is not always possible if participants are aware of their treatment allocation. Bias may also arise through the selective reporting of study results. Authors should specify their primary analyses *a priori,* and report the findings of all such results (regardless of whether they support or refute the study hypotheses).

The critical appraisal of observational studies also involved the evaluation of potential bias, but is less clear-cut than that of experimental studies, primarily because such studies are more prone to serious selection bias due to their inability to control for unknown confounders. Thus, the reviewer judged whether all the important confounders had been identified and adequately controlled for through stratification or matching techniques. Issues relating to attrition and detection bias in trials are of equal applicability to cohort and case control studies. Finally, performance bias can also be problematic, as one must establish that individuals were exposed *only* to the intervention of interest, with no other competing exposures present that might influence study outcomes.

A simplistic approach towards the assessment of the validity of studies included in the review was made, using criteria suggested in the Cochrane Handbook (Mulrow & Oxman

1996). Each paper was assessed and rated according to criteria of low, moderate or high risk of bias, as summarized in table 4. Information on the degree to which studies are free from bias is reported (see annex 9). Any study that was classified as high risk was not reported in the summary of findings from the literature review, as the conclusions were significantly weakened by the methodology applied in the particular studies.

Table 2.4: Criteria for assessing the validity of studies included in a systematic review

Risk of bias	Relationship to individual criteria	Definition
Low risk	Plausible bias unlikely to seriously alter the results	All of the criteria met
Moderate risk	Plausible bias that raises some doubt about the results	One or more criteria partly met
High risk	Plausible bias that seriously weakens confidence in results	One or more criteria not met

It should be noted that the final methodological cut-off point for inclusion of all types of studies in this review inevitably depended on the overall quality of the literature retrieved and, as a consequence, a flexible approach was adopted.

Data presentation

It was decided that any form of meta-analysis for this project would be inappropriate, as studies are too heterogeneous to be combined using formal statistical methods. A qualitative overview of the studies is therefore provided (NHS Centre for Reviews and Dissemination 1996). Judgements about the importance to be attached to particular pieces of evidence are made explicit. Descriptions are given for each theme, concentrating upon the particular settings, individuals included in the studies, interventions with associated outcomes and the robustness of the studies. Information about the characteristics and results of particular studies is displayed as appropriate.

Chapter 3: LITERATURE REVIEW – RESULTS

Strategies and interventions to control AMR may be dichotomized as follows (further details on each intervention strategy outlined can be found in annex 11):

1. **Antimicrobial reduction measures** that aim to decrease the *emergence* of resistance by decreasing selection pressure through policies restricting or guiding the more effective use of antimicrobials. Such policies are based on the premise that there is a link between the use of antimicrobials and the level of resistance in the community (De Mann *et al* 2000). Examples of these types of policies include: (i) combination therapies and vaccinations to combat resistance; (ii) antimicrobial restriction policies; and (iii) prescriber education, feedback and use of guidelines to reduce inappropriate prescribing; and

2. **Alternative approaches** which aim to reduce the *transmission* of resistant organisms and/or determinants of resistance, often through ensuring that the environment in which the patient is treated is disinfected to minimize the potential for the spreading of resistance. Such measures include: (i) surveillance policies; (ii) decontamination attempts; (iii) hand washing; and (iv) epidemic-control policies.

It should be noted that there might be some overlap between these two approaches. For instance, efforts are increasingly dedicated towards limiting, rather than completely eliminating, resistance. This is often achieved by use of either one of the two above approaches, or through a combination approach (e.g. an antimicrobial restriction policy with associated epidemic control policies) (Rice 1999).

The methods described in chapter 2 resulted from the review of 177 AMR-related studies. Of these, 50 studies were found to be of a background/conceptual nature, 68 were effectiveness studies, 10 were economic evaluations, 2 were cost studies, 12 were studies of a modelling nature and 35 were studies specifically relating to AMR in developing countries. The key characteristics of the economic evaluation, effectiveness and cost studies are summarized in annex 9, with an assessment of their overall methodological validity (i.e. high, moderate or low risk of bias) also included[5]. The key findings from the review of the literature on the cost-effectiveness and effectiveness of antimicrobial reduction measures and alternative approaches are reviewed below. Key findings relating *specifically* to developing countries are reviewed in section 3.3.

3.1 Antimicrobial reduction measures that affect emergence of AMR

There have been a number of review articles that have examined the overall effectiveness of measures to reduce or contain the emergence of resistance through antimicrobial reduction measures. For instance, John and Fishman (1997) assess the role of hospital

[5] Note that only studies judged as being of moderate or low risk of bias are discussed in the text.

infectious disease physicians in terms of their capacity to reduce the costs associated with AMR. A number of antimicrobial-related strategies are reviewed which include education, formulary restrictions, pharmacy justification, formulary substitution, computer surveillance of prescribing, laboratory item costing, purchase plans, as well as a number of multidisciplinary approaches. It is claimed that effective implementation of such approaches can result in savings of up to USD 500,000 annually, although there is an implicit acknowledgement that these savings may be restricted to the immediate periods following introduction of such interventions. The main conclusion, however, is that there is no *single* AMR strategy that is likely to be completely effective. Rather, it is suggested that multidisciplinary antimicrobial programmes (that include a combination of the above interventions) may be the most effective approach to countering AMR. Jarvis (1996) agrees, but states that multidisciplinary approaches need to be combined with well-targeted clinician education programmes to maximize effectiveness. Notwithstanding this, literature relating to specific strategies is reviewed below.

3.1.1 Combination therapies

Overview

Often, where there is an outbreak of infection or, more particularly, when an AMR strain of bacteria is identified, broad-spectrum drugs are used for treatment. However, such drugs are often costly and may actually worsen resistance through "selection pressure" which encourages the emergence of multiple-drug-resistant organisms (Joshi and Milfred 1995). Alternatively, combination courses of antimicrobials (often based on use of conventional agents) may be more cost-effective in combating the virulence of resistant strains (Milatovic 1987, Hilf *et al* 1989). For instance, Strausbaugh *et al* (1992) and Walsh *et al* (1993) both examine the effectiveness of rifampin, in combination with other antimicrobials, to fight MRSA in hospital settings, Raad *et al* (1997) examine the use of minocycline and rifampicin impregnated catheters for the prevention of catheter-related bloodstream infections and Scharfstein *et al* (1999) examine five combination therapies to combat *Mycobacterium avium* complex in AIDS.

In a slightly different approach, De Mann *et al* (2000) test different combinations of antimicrobials to identify whether the emergence of resistant strains in the treatment of septicaemia can be halted through different drug regimes. Vakil *et al* (1996) follows a similar approach in a cost-effectiveness analysis of regimes for the eradication of *Helicobacter pylori* in duodenal ulcer, while Spanik *et al* (1998) compare the aetiology of infection, costs and outcomes for neutropenic patients who have, and have not, received antimicrobials.

Specific studies

For combination antimicrobial therapies as a means of combating AMR, 12 studies were assessed. Of these, 10 were classed as being methodologically of moderate risk, with the remainder classified as high risk. The key features of all studies are summarized in annex 9, while the findings of the 10 more methodologically robust studies are reported below.

In the Walsh *et al* (1993) study of the eradication of MRSA, a combination therapy involving rifampin was assessed, to ascertain whether resistance to rifampin could be overcome if used with another antimicrobial. In a randomized double-blind multi-centre comparative trial, the effectiveness of intervention 1 (treatment with novobiocin plus rifampin) was compared with intervention 2 (treatment with trimethoprime-sulfamethoxazole (T/S) plus rifampin). In a study involving 90 people, it was found that the emergence of resistance to rifampin was more pronounced in subjects receiving treatment with intervention 2 (14%) than in patients receiving treatment according to intervention 1. Successful clearance of the MRSA strain was also higher in the cohort that received care according to intervention 1. However, this study also found that the response to either combination depended on host factors, particularly the age of the patient and the site of the MRSA colonization.

In contrast, a study by Raad *et al* (1997) examined the effect of coating central venous catheters with minocycline and rifampin to prevent the emergence of catheter-related colonization and bloodstream infections. In a multicentre, randomized clinical trial involving 281 hospitalized patients, 147 catheters were pre-treated with trido-declymethyl-ammonium chloride and coated with minocycline and rifampin, 151 untreated, uncoated catheters were then used as controls. The results of this trial suggested that colonization occurred in 26% of uncoated catheters and 8% of coated catheters. Catheter-related bloodstream infection developed in 5% of patients with uncoated catheters and in no patients, with coated catheters. The study concluded that, contrary to the findings of Walsh *et al* (1993), no adverse effects related to antimicrobial resistance were seen. It was suggested that the use of coated catheters could result in cost savings.

In a cost analysis using decision-tree modelling, Laxminarayan *et al* (2000) used antibiotic resistance surveillance data to ascertain the optimal treatment option for acute otitis media. Three interventions were assessed: (i) current therapy (CT), which involved treatment using the following: amoxicillin (AMX), cefaclor/cefixime/ceftibutin; trimethorprim/sulfamethoxazole; macrolides; AMX-clavulante (AMX-C); and cefuroxime/cefprozil; ceftriaxome; (ii) suggested therapy 1 (ST1), which used AMX for initial therapy; and high-dose AMX-C or cefuroxime (CFE) for treatment failure; and (iii) Suggested Therapy 2 (ST2) which used high dose AMX; high dose AMX-C; and CFR. As AMR has become an increasing problem in the treatment of acute otitis media, resistance estimates were included in the model. The study found that more expensive antimicrobials do not necessarily imply better health outcomes, and that a shift towards less expensive first line therapy can reduce acute otitis media without compromising overall levels of health. The model also suggested that, as levels of AMR rise, it is of greater benefit to use ST2 in place of ST1. This was marginally more expensive than ST1, but still more cost-effective than the CT.

In a cost-effectiveness analysis by Scharfstein *et al* (1999) of AIDS related infections, a Monte Carlo analysis was completed for five different clinical treatment (combination drug) therapies aiming to combat *Mycobacterium avium* complex (MAC). This study is important as the costs and outcomes were found to differ according to the combination

therapy adopted, in addition, combination therapy appeared to reduce the risk of resistance from use of clarithromycin alone (Benson *et al* 1996). (Note the therapies assessed all involved use of different antimicrobials in combination with clarithromycin─ see annex 9 for more detail.) The model included measures of drug adherence and resistance, whereby it was assumed that if resistance developed, the efficacy of the relevant prophylactics would reduce and that both treatment cost and mortality for a breakthrough infection would rise. In one scenario it was assumed that resistant organisms developed in 11% and 29% of patients who developed MAC, while on azithromycin or clarithromycin, respectively, for six months or more, and that for such patients the mortality and cost associated with a breakthrough MAC infection doubled. Results suggested that the combination therapy, beginning with azithromycin and changing to clarithromycin, and then rifabutin (if needed after major toxicity), was the most cost-effective of the five options.

De Mann *et al* (2000) demonstrated that policies chosen with respect to the empiric use of antibiotics do matter in terms of controlling antimicrobial resistance. This study was set against a backdrop that fear of infection in neonatal intensive care units often leads to inappropriate (early) use of broad spectrum antimicrobials that tend to select for resistant bacteria. In particular, it was found that an antimicrobial regimen that avoids using amoxicillin and cefotaxime in the early treatment of septicaemia reduces the relative risk for colonization with bacilli resistant to this therapy. Substituting these antimicrobials for penicillin G and tobramycin for early onset septicaemia, and flucloxacillin and tobramycin for late onset septicaemia, lowers the risk of resistance by 18 times than if amoxicillin and cefotaxime are used.

Similarly, a study by Vakil *et al* (1996) examined the cost-effectiveness of different treatment regimens for the eradication of *Helicobacter pylori* in duodenal ulcer. This study is important for demonstrating that antimicrobial treatment regimens should differ according to *levels* of drug resistance. The antimicrobial regimens assessed were: (i) two-week triple drug therapy (metronidazole, bismuth, tetracycline with H2 receptor antagonist); (ii) two-week treatment involving omeprazole and amoxicillin; and (iii) a two-week regimen of omeprazole and clarithromycin. Traditional H2 receptor antagonist therapy was used as a control. A decision tree analysis was used to allow for the following uncertainties: (i) non-compliance with treatment protocols whereby non-compliant patients would have decreased eradication rates (two thirds of those in compliant patients); and (ii) levels of resistance, estimated to be at 24% for metronidazole. This study indicated that intervention (iii) is effective where metronidazole resistance is high or where it is anticipated that there will be poor compliance with the more complicated triple drug regimens of (i) and (ii). In comparison, it was found that intervention (i) is optimal where metronidazole resistance rates are <36%.

Likewise, in a case-control study by Spanik *et al* (1998), the aetiology, costs and outcomes of neutropenic patients who developed bacteremia during antimicrobial prophylaxis were compared to neutropenic patients, who had not yet received antimicrobials. Interestingly, this study indicated that antimicrobials did not increase the

proportion of multi-drug resistant isolates causing bacteraemias for those patients receiving them. However, streptococcal, enterococcal and *S. maltophilia* bacteraemias were more common in cases receiving prophylaxis. As a result, the costs of care were found to be higher in those patients that received antimicrobials─with the only benefit (that was statistically significant) being an improvement on the quality of life, due to prolonged afebrile neutropenic days.

While these "combination" antimicrobial studies are useful in demonstrating that choice or combination of antibiotic regime does have an effect on overall levels of AMR, (e.g. Walsh *et al* 1993, Vakil *et al* 1996, De Mann *et al* 2000), some studies are restricted as they do not take account of the cost of the intervention (e.g. Walsh *et al* 1993, De Mann *et al* 2000). However, those studies that did measure the cost-effectiveness of combination therapies (and more specifically the cost of resistance) indicated that:

1. Combination treatments that prevent the emergence of AMR can save costs (e.g. Raad *et al* 1997);
2. Mortality and costs associated with treatment more than doubled in cases where resistance emerged (Scharfstein *et al* (1999); and
3. The use of more expensive antimicrobials does not necessarily imply better health outcomes (or greater reductions in AMR) (Laxminarayan *et al* 2000).

Note that there was also little acknowledgement in any of the reviewed studies that choice of antimicrobial therapy may only be effective for a short period of time, until bacterial resistance develops to the particular combination therapy.

3.1.2 Vaccinations

Overview

Another way to combat the emergence of resistance is through the use of preventive measures, such as vaccination. Sohn (1998) suggests that preventing infections with safe and effective vaccinations will not only reduce the development of AMR, but may also lead to more cost-effective ways to control resulting disease. For the case of amoxicillin-resistant pneumococci, Thompson (1999) agrees, believing that potential savings related to the reduction of recurrent acute otitis media episodes, should be included in the evaluation of pneumococcal conjugate vaccines. The case of pneumonia vaccination as a preventive measure is reviewed below, with studies examined by Fine *et al* (1994), Farr *et al* (1995) and Jimenez *et al* (1996).

Specific studies

Three studies of the effectiveness of vaccination for pneumonia were examined, with all being classified as methodologically at moderate risk of bias. Fine *et al* (1994) and Farr *et al* (1995) examined the effectiveness of vaccinations to prevent pneumococcal pneumonia. In well-defined studies, both authors were able to demonstrate the protective effectiveness of pneumococcal vaccination for preventing pneumococcal bacteremia, although Fine *et al* (1994), through a comprehensive meta-analysis, suggested that vaccination is effective in lowering risk of pneumonia in low-risk, but not necessarily

high-risk, adults. In a Spanish study, Jimenez *et al* (1996) conducted a cost-effectiveness analysis of whether the introduction of a universal vaccination programme for those over 60 years of age was effective over a range of incidence rates of pneumococcal pneumonia. Assuming a 66% vaccination efficacy rate, it was demonstrated that the introduction of a universal vaccination programme would result in a financial benefit-cost ratio of 2.3:1 and a benefit per case prevented of USD 2,656 (hence inferring cost-effectiveness).

However, given the small sample of studies assessed, further analysis is required in terms of the cost-effectiveness of the use of vaccinations to halt the spread of AMR, both for pneumonia and other diseases, before more definitive conclusions can be drawn about the overall value of this approach in terms of preventing AMR.

3.1.3 Antimicrobial restriction

Overview

Antimicrobial drug costs comprise a significant part of overall hospital budgets in developed countries, with some studies reporting that they account for approximately 20% to 30% (Kunin 1985). In an era of greater accountability for funds expended, and against a background of widespread inappropriate prescribing and use of antimicrobials (Kunin 1989, Dunagan & Medloff 1993), combined with a significant increase in the spread of AMR (Toltzis *et al* 1998, Climo *et al* 1998), hospitals are increasingly implementing control measures to encourage more efficient prescribing. In terms of reducing the incidence of AMR, this is an area of significant interest, as there is a suggested causal link between levels of antimicrobial use and the incidence of antimicrobial resistance (De Mann *et al* 2000).[6] Some studies have suggested that there is a causal link between the prevalence of MRSA and the overall amount of antibiotic regulation or control existing across countries (Janknegt 1996).

However, there is no widely agreed consensus that antimicrobial restriction policies will necessarily reduce the prevalence of AMR. For instance, Lenski (1997) suggests that it is increasingly difficult to eliminate resistant genotypes through suspending use of antimicrobials. This is because the effectiveness of controlling the spread of AMR is critically dependent on the relative "fitness" of resistant and other sensitive genotypes. In addition, given the externality producing characteristics of AMR, transmission often occurs via other vectors (e.g. cross-infection) that negate the effectiveness of antimicrobial restriction policies (Gould 1999). Further, McGowan (1994) suggests that many restriction policies are centred at site-specific (hospital) locations, and, given the nature of AMR, restriction policies may be more effective if implemented at a macro (multi-centre) level.

Restriction policies may also take a number of different forms. For instance, use of certain drugs can be prohibited (with treatment by substitutes recommended) and formulary restrictions can also be enforced. Here, hospital pharmacists can override the

[6] Note, however, that Steinke and Davey (2000) report that the association between antibiotic prescribing and resistance may be subject to bias or confounding.

decisions of prescribing practitioners when inappropriate antimicrobial use is recommended. In contrast, there are also studies that assess the effectiveness of "loosening" antimicrobial restrictions (through increasing the availability of antimicrobials). For instance, Rubin *et al* (1996) assess the consequences of approving over-the-counter sales of oral antibiotics in the treatment of urinary tract infections (UTIs). This is despite evidence suggesting considerable bacterial resistance to antimicrobials (up to 25% for trimethoprim) used in the treatment of UTIs (Nicolle 1994, Davey *et al* 2000).

Specific studies

Fourteen studies that evaluated the effect of antimicrobial restrictions were assessed for this study (see annex 9). Of these, only five (Evans *et al* 1990, Himmelberg *et al* 1991, Toltzsis *et al* 1998, Climo *et al* 1998 and Rubin *et al* 1996) were classified as being at moderate risk of bias, with the remainder classed as high risk. In terms of the methodologically robust studies, Evans *et al* (1990) were broadly concerned with assessing whether a restriction policy had any effect on changing general prescribing behaviour. In contrast, three studies focused on the restriction of **specific** antimicrobials. Climo *et al* (1998) examined the restriction of clindamycin, while Himmelberg *et al* (1991) and Toltzsis *et al* (1998) both assessed restrictions for ceftazidime (and also imipenem-cilastatin for Himmelberg *et al* (1991)). Rubin *et al* (1996) took a different approach by evaluating the effectiveness of **increasing** the availability of antimicrobials.

In the Evans *et al* (1990) study, the duration of prophylactics prescribed for surgical patients was observed for six months at one hospital. Over this observation period it was found that many antimicrobials were being prescribed for longer than was deemed clinically necessary. As a consequence, a restriction policy was introduced where stop-orders were placed by computer on those antimicrobials for which inappropriate use had been identified. The restriction policy was viewed as effective in reducing the incidence of inappropriate prescribing. A crude cost analysis suggested that this resulted in savings to the hospital of approximately USD 45,000 during the six months that the restriction policy operated in this particular hospital.

Climo *et al* (1998) concentrated upon clindamycin, due to an outbreak of C. *difficle*-associated diarrhoea in 1993 that was associated with increased use of clindamycin. As a consequence, in 1994 hospital formulary controls were introduced for this drug that led to an overall reduction in its use, as well as a sustained reduction in the mean number of cases of C. *difficle*-associated diarrhoea. While a parallel increase was noted in the use of other antibiotics (which were close substitutes to clindamycin), an elementary cost analysis suggested that the formulary restriction policy led to a realization of overall cost-savings. This was attributed to the result of the decreased incidence of C. *difficle*-associated diarrhoea.

Toltzsis *et al* (1998) and Himmelberg *et al* (1991) examined restriction policies for the same drug (ceftazidime). Himmelberg *et al* (1991) also examined the impact of the restriction policy on imipenem-cilastatin. This study found that, upon removal of the policy, use of the restricted antimicrobials increased by 158%. It was concluded that

inappropriate use of these antimicrobials occurred significantly more often after the restrictions were removed, but it was also noted that the incidence of nosocomial infections did not differ substantially between the two periods. The Toltzsis *et al* (1998) study reached a similar conclusion, that the restriction policy was effective in terms of reducing ceftazidime use; importantly, however, the incidence density of ceftazidime-resistant organisms increased while the restriction policy was in place.

Rubin *et al* (1996), examined the consequence of reducing restrictions on antimicrobials for the treatment of urinary tract infections (UTIs). This study examined the effect of increasing the availability of related antimicrobials through approving over-the-counter sales. However, the study found that the costs of placing UTI treatments over-the-counter outweighed the benefits, unless there was extensive patient education to allow for correct diagnosis. The expected costs associated with the increasing prevalence of AMR were a significant factor leading to this conclusion.

The data obtained by Toltzsis *et al* (1998) and Himmelberg *et al* (1991) advocate a cautionary approach to the introduction of restriction policies to combat the spread of AMR. This is because such policies, while being successful in reducing antimicrobial use, may not have a similar impact on curtailing the emergence of AMR. However, the findings of Rubin *et al* (1996) suggest that care should be taken in increasing the availability of some antimicrobials, due to the likely increased incidence of AMR stemming from likely incorrect diagnosis (and hence antimicrobial treatment).

3.1.4 Prescriber education, feedback and the use of guidelines

Overview

The extensive use of antibiotics has contributed to the emergence and spread of antibiotic resistant bacteria in the community (Gonzales *et al* 1999). Much of this has been associated with inappropriate prescribing practice in the community, due to lack of knowledge (Kunin 1993, Bruneton *et al* 1997), inadequate diagnosis (Bosu 1997, Mamun 1991, Hogerzeil 1993), incorrect drug selection (Hui 1997, Hossain 1982) and incorrect drug regimen (Chalker 1997, Gumodoka *et al* 1996). The rate of development of resistance appears to have accelerated in recent years (Goern *et al* 1998) and now some strains, such as vancomycin-resistant *enterococci* (VRE), methicillin-oxacillin-resistant *Staphylococcus aureus* (MRSA) and antibiotic resistant *Streptococcus pneumoniae*, are widespread (Gonzales 1999, Smith 1999). The use of education interventions (whether physician, patient or a combination), prescriber feedback and specific guidelines for recommended treatment protocols have been suggested as a possible means of reducing the inappropriate use of antimicrobials (Ameyaw 1997, Kristinsson 1995, Sia 1997). Through better information, more rational prescribing choices become possible and potentially help to reduce the risk of increasing the incidence of AMR.

Specific studies

Education studies
Two effectiveness studies (Gonzales *et al* 1999 and Smith 1999) were reviewed for their analysis of education strategies, although it should be noted that the Smith (1999) study was viewed as methodologically at high risk of bias.

The Gonzales *et al* (1999) study was a prospective, non-randomized control trial set in four primary care practices in the United States. It tested the effect of educational material about the correct treatment for uncomplicated acute bronchitis in adults on the overall number of antibiotic prescriptions. In the intervention group, patients received household and office-based patient educational materials, while clinicians received education about appropriate prescribing, practice profiling (antibiotic prescription rates for acute bronchitis calculated from the previous winter) and academic detailing. Academic detailing was applied in the education sessions and took the form of: (i) emphasizing effective techniques of patient-clinician communication; (ii) understanding and targeting patient and clinician motivations; and (iii) encouraging two-way communication. In contrast, a limited intervention group received only office-based promotional material, while in the control group usual care was provided (with no additional education information provided).

It was found that there was a substantial decline in prescribing in the full intervention group (from 74% to 48%), but none at the control and limited intervention sites. In addition, health outcomes did not appear to differ across the intervention groups, as repeat practice visits did not change significantly between sites or over time. Although no costs were measured, this study is nevertheless potentially useful in demonstrating the effectiveness of educational materials, particularly for clinicians, in terms of reducing inappropriate prescribing trends.

The Smith (1999) study is in agreement with Gonzales *et al* (1999), in that inappropriate antibiotic use declined following a clinician education campaign, although these findings should be treated with caution given the poor methodological quality of this study. These studies are both limited, however, in that an overall assessment as to how levels of AMR changed in response to these policies was not measured.

Prescriber feedback
Three effectiveness studies (Zwar *et al* 1999, Mainous *et al* 2000 and Skaer *et al* 1993) were examined with one, Skaer *et al* (1993), classified as being at high risk of bias. Zwar *et al* 1999 and Mainous *et al* 2000 both examined the influence of prescriber feedback policies on prescribing for upper respiratory tract infections (URTIs). Both were methodologically at moderate risk of bias.

The Zwar *et al* (1999) study was set against a backdrop of inappropriate URTI prescribing in Australia. The effectiveness of prescriber feedback and management guidelines were assessed for their impact in reducing prescribing by trainee General Practitioners (GPs) in New South Wales hospitals. The intervention group received

education on appropriate treatments for URTI and feedback on their prescribing patterns for three different periods. An educational outreach visit was also made to high prescribers during periods 2 and 3. The control group was given education material on an unrelated topic. This study indicated that antibiotic prescribing for URTI by the intervention group declined significantly over the three periods. As a consequence, it was concluded that prescriber feedback and management guidelines were useful in changing prescribing trends, and that this study provided a model for targeting educational input to those prescribers who most needed to change their behaviour. However, the intervention was viewed as relatively cost-intensive with the most expensive part of the intervention being the face-to-face visits, at a cost of $A 110 per doctor. Despite this, a crude costing analysis indicated that, if extrapolated to 10,000 GPs, more rational prescribing would lead to savings of $A 3.19 million over 2 years. This compared with an annual cost for the programme of $A 2.05 million.

Mainous *et al* (2000) examined the impact of three interventions for URTI prescribing across four primary care practices in the USA. In Intervention Group 1, performance feedback was given to practitioners, in Intervention Group 2, patients received education materials, while in Group 3, patients received education and practitioners received feedback. The results of this study are interesting in that they differ from the findings of Zwar *et al* (1999), indicating little, if any, difference between the three interventions. In particular, it was concluded that prescriber feedback without reward/penalty is not effective in influencing prescribing practices for URTI. However, given the lack of a "no-intervention" control, this study does not provide adequate information on whether *any* of these interventions is more effective than not intervening.

These studies suggest that further analysis is required into the overall effectiveness (and cost) of prescriber feedback interventions that attempt to encourage more rational prescribing and hence reduce the incidence of AMR. The design of feedback mechanisms and their links to sanctions/rewards also requires further research.

Prescriber guidelines

Six effectiveness studies (Sirnavin (1998), Pestotnik *et al* (1996), Kristensen *et al* (1999), Levine *et al* 1999, Brooks *et al* 1999 and McConachy *et al* 1999) were reviewed concerning the impact of guidelines on overall hospital prescribing. The Kristensen *et al* 1999 study was the only methodologically robust study. This study used a modelling approach (using a decision support system (DSS) for the guidance of empirical antibiotic therapy) that suggested that DSS (for correct bacterial diagnosis) could be effective in guiding antimicrobial therapy. However, further work is required in this area, both from an effectiveness and cost-effectiveness perspective. Indeed, some commentators (e.g. McGowan 1995) have suggested that "guidelines for practice", in terms of encouraging infection control, are not always based on scientific validation and, hence, their appropriateness as effective tools can be questioned in reducing the incidence of AMR.

3.2 Alternative approaches that affect transmission of AMR

There are a number of alternative measures available to reduce the transmission of AMR. For example, in a review article by Wenzel *et al* (1991), three widely-used methods to control for MRSA are discussed; isolation procedures, strict hand washing, and effective treatment of the carrier state to minimize further infection. While the article supports the effectiveness of such interventions, few of the studies reviewed are of a methodologically suitable quality and there is thus a need for further analysis. In addition, it has been suggested (e.g. Mehtar 1995) that it may be more cost-effective to **prevent** the initial development of AMR, than introduce measures to further halt the spread of AMR (Mehtar 1995).

3.2.1 Surveillance

Overview

Over time, with the increase in nosocomial infection rates, a greater emphasis has been placed on the surveillance of such infection. Initially, in the early 1960s, such surveillance techniques were carried out by a physician or "hospital epidemiologist", but over time surveillance activities have become increasingly carried out by nurses (Eikhoff *et al* 1969). The prime aim of these early surveillance programmes was to obtain epidemiological evidence that could be used for the basis of informed measures to control for the further outbreak of nosocomial infections (Langmuir 1963, Haley *et al* 1985).

Despite the widespread use of surveillance techniques (particularly in the USA where in the late 1970s over one half of the country's hospitals had infection control surveillance activities (Haley *et al* 1980)), there is little available analysis on the overall effectiveness of surveillance approaches. Although there are several early studies suggesting that surveillance programmes had led to reduced infection risks (Moore 1974, Shoji *et al* 1974, Cruise & Foord 1980, Starling *et al* 1997), these studies are lacking in methodological rigour.

More recent surveillance programmes, although still having a strong epidemiological emphasis, are now increasingly focused on encouraging physicians to modify patient management techniques, based on the results of screening for resistance (Waterer *et al* 1999, Breurer *et al* 1999). Indeed, as nosocomial pathogens become more widespread, there is a greater reliance on the use of susceptibility testing (Pfaller & Herwaldt 1997), to ensure that appropriate treatment is prescribed.

Specific studies

Broad surveillance of nosocomial infections

Five effectiveness studies were reviewed (Haley *et al* 1985, Bloom *et al* 1996, Starling *et al* 1997, Hacek *et al* 1999, and Drobniewski *et al* 2000) that assessed the impact of surveillance programmes on levels of nosocomial infections. Haley *et al* (1985) and Bloom *et al* (1996) were classified as being at moderate risk of bias and are discussed below. The other studies were viewed as being at high risk of bias.

Haley *et al* (1985) undertook to determine whether infection surveillance and control programmes that had been established in a random sample of US hospitals had a significant influence on the hospitals' nosocomial infection rates over a 5-year period. The study examined a random sample of 338 hospitals through use of surveys and questioning of those hospital personnel most likely to have important duties related to infection surveillance and control. To estimate the nosocomial infection rates in 1970 (before any of the sample hospitals had established their infection surveillance and control programmes), approximately 500 adult patients admitted in 1970 were randomly selected for each hospital (169,518 in total). This number was compared with 169,526 in 1975/1976, after the surveillance programmes were installed.

In particular, this study examined surveillance programmes for nosocomial UTI, surgical wound infection, pneumonia and bacteria after controlling for other characteristics of the hospitals and their patients. Essential components of effective programmes were found to include: (i) conducting organized surveillance and control activities; (ii) having a trained infection control physician and an infection control nurse per 250 beds; and (iii) a well-developed system for reporting infection rates to surgeons. The study concluded that hospitals possessing these three components reduced their hospital infection rates by 32%, while those hospitals that did not have these effective components saw overall infection rates in hospitals increase by 18% between 1970 and 1976.

In contrast, Bloom *et al* (1996) assessed the cost-effectiveness of three management strategies for S. *aureus* nasal carriage, and the prevention of subsequent infection, in chronic ambulatory haemodialysis patients. Intervention 1 involved screening for S. *auerus* nasal carriage and, for positive results, treatment with mupirocin calcium. Intervention 2 required no screening, and treatment occurred with muprirocin calcium irrespective of S. *aureus* nasal carriage status. Control treatment involved no prevention strategy, with infection treatment only. Using a decision analysis approach, modelling indicated that, if 75% of S. *aureus* infections are attributable to nasal carriage in haemodialysis patients, treatment with muprocin calcium (with or without screening) decreases the amount of infections by approximately 45% to 55%. Both Interventions 1 and 2 were found to be more cost-effective than the control, however, although while periodic screening is more expensive than Intervention 2 it has a greater potential to reduce overall levels of AMR.

Surveillance and modification of behaviour

Two studies were assessed. The first study, an economic evaluation by Breurer *et al* (1999), examined whether susceptibility testing leading to modifications in patient management was cost-effective. The second study, by Waterer *et al* (1999), examined surveillance techniques (the use of blood culturing) for the treatment associated with community-acquired pneumonia, although it was judged as methodologically being at high risk of bias.

The Breuer *et al* (1999) study occurs against a backdrop in the USA where most physicians treating *Helicobacter pylori* (H. *pylori*) infections do so without relying on the

use of antimicrobial susceptibility testing to choose the best regimen of antimicrobials. This is despite the increased prevalence of resistant H. *pylori* strains. Using a decision analysis model to compare two outcomes from different treatment regimens (one based on susceptibility testing and altered antimicrobial management) this analysis was able to demonstrate that pre-treatment susceptibility testing is cost-effective in certain situations. However, cost-effectiveness was dependent on the difference in drug costs between the two regimens—if alternative drug costs were high and the cure rate in resistant strains low then susceptibility testing would not be cost-effective. The authors also acknowledged that this model was useful for indicative purposes only (as not all relevant costs were measured).

3.2.2 Decontamination

Overview

Decontamination of patients and the surrounding treatment environment is often advocated to control the spread of AMR. In the first instance, colonization and infection with gram-negative bacilli are common in intensive care units where patients often require prolonged intubation and mechanical ventilation (Verwaest *et al* 1997). Following Stoutenbeek *et al* (1984), who pioneered the technique, selective "decontamination" of such patients is routinely undertaken to prevent nosocomial infections. This occurs through the use of an antimicrobial-decontaminating regimen, which aims to eradicate aerobic gram-negative bacilli while maintaining the flora of the gastrointestinal tract (Quinio *et al* 1996).

In contrast, decontamination of the surrounding treatment environment can take a variety of forms. This may include: (i) the refurbishment of wards to cleanse resistant organisms (Barakate *et al* 1999); (ii) the use of disinfectants (e.g. hydrogen peroxide on fabrics) (Neely and Maley 1999) and/or ethanol on syringes (Preus *et al* 1993) to prevent the incidence of bacterial transmission.

Specific studies

Six decontamination studies were reviewed, of which three concerned selective-decontamination antimicrobial approaches (Verwaest *et al* 1997, Quinio *et al* 1996 and Cockerill *et al* 1992). All three selective decontamination studies were classed as being at moderate risk of bias. Of the other studies, the use of ethanol on syringes as a decontamination strategy (Preus *et al* 1993) was the only study not at high risk of bias. While none of the studies were economic evaluations, some costs were included in the selective decontamination studies.

Selective decontamination studies

Verwaest *et al* (1997) evaluated the effectiveness of two regimens for selective decontamination of the digestive tract in mechanically ventilated patients. A total of 660 patients requiring mechanical ventilation for at least 48 hours were randomized into one of three treatment groups: (i) Group A, which received conventional antibiotic treatment; (ii) Group B, which received a combination of oral and enteral ofloxacin-amphotercin; and (iii) Group C, which received enteral polymyxin E-tobramycin-amphotericin B. The

study concluded that, while the intensive care unit (ICU) mortality rate between the groups was virtually the same, *increased* AMR was recorded in both the intervention groups (B and C) compared with the control.

As a consequence, Verwaest *et al* (1997) concluded that the preventive benefit of selective decontamination processes was highly debatable. This is because no beneficial effect on survival was noted and because the decontamination strategy actively *encouraged* the emergence of multiple antibiotic-resistant organisms. The study also indicated that selective decontamination adds significantly to the costs of ICU care given that patients in Group C stayed significantly longer in the ICU than the control (Group A). This was a limited cost analysis, however, in that only antimicrobial costs were measured.

In contrast, Quinio *et al* (1996) undertook a selective decontamination programme on 72 admissions to ICU. These patients were treated with amphotericin B, colistin sulfate (polymixin E) and gentamicin while patients in the control received a placebo. This study found the opposite of Verwaest *et al* (1997)─that reduced incidences of pneumonia were reported, particularly reducing contamination of the nares and oropharynx (but not of the bronchi). The authors report that after selective decontamination was stopped recolonization happened quickly. In particular, the nosocomial infection rate was significantly reduced in the treated group. Limited analysis of antimicrobial expenditure indicated savings of 42% in the intervention group.

Similar conclusions were noted by Cockerill *et al* (1992). In a randomized controlled trial, the effectiveness of selective decontamination was determined for surgical and trauma ICU patients in a tertiary referral hospital. Selective decontamination of the digestive tract was achieved through use of oral and non-absorbable antimicrobial agents and parenteral cefotaxime. This study found that selective decontamination of the digestive tract decreases subsequent infection rates, especially by gram negative bacilli, in patients during long-term stays in ICUs.

A definitive assessment as to whether selective decontamination studies are effective cannot be made on the basis of these studies. Verwaest *et al* (1997) comment on the difficulties associated with comparing different selective decontamination trials, as different definitions and criteria for diagnosis of infection are often used. However, while selective decontamination procedures may have led to significant advances in terms of infection control for critically ill patients, the emergence of multiple antibiotic-resistant micro-organisms associated with this treatment (e.g. Verwaest *et al* 1997) suggest caution in adopting this approach to contain the spread of AMR.

Other decontamination studies

Although the study by Barakate *et al* (1999), on the decontamination of a hospital ward to eliminate MRSA through refurbishment, is methodologically at high risk of bias, it is interesting as it demonstrates the difficulty of containing the spread of MRSA. Here, complete refurbishment of the infected ward failed to produce a lasting reduction in

MRSA detection because a significant part of the contamination process occurred through health professional-to-patient contact.

The Neely *et al* (1999) study into the use of disinfectants for the treatment of hospital fabrics to limit the spread of antibiotic-resistant bacteria is also methodologically at high risk of bias. While this study indicated that some disinfectants are useful for eradicating bacteria on fabrics (e.g. curtains and sheets), such policies should not be introduced in isolation, given the patient-hospital worker transmission nexus.

The Preus *et al* (1993) study is more case-specific in examining how to prevent the transmission of resistant bacteria between periodontal sites during subgingival application of antibiotics. In a well-specified study, it was demonstrated that after dispensing minocycline periodontal formula via injection, syringe tips that were not washed with ethanol remained culture positive. Through more effectively cleaning dental implements associated with treatment before re-use, the potential for bacterial transmission is reduced.

3.2.3 Hand washing

Overview

Hand washing has been associated with reducing the risk of transmission of infectious diseases, and there is some evidence to suggest that this technique is particularly effective for the fecaloral and respiratory routes (Gwaltney *et al* 1978, Larson 1988, Larson *et al* 1992). In addition, for antibiotic resistant strains of *S. epidermidis*, cross-infection with such strains is common and it is believed that one possible route for cross-infection is through patient and staff skin contact (Hedin *et al* 1993). As a consequence, hand washing with disinfectants is often advocated as a means of eliminating skin bacteria and preventing the transmission of infection.

However, it is difficult to evaluate the effectiveness of hand washing procedures as evidence of effectiveness relies on information gained from randomized-controlled trials. For interventions such as hand washing, it is unlikely that such an approach is possible as it would require an ethics committee to advocate not washing hands for a control group. Nevertheless, Nystrom (1994) believes that priority should be given to increasing compliance with hand washing: his review article suggests that physicians are often ranked lowest out of all medical staff in terms of washing their hands.

Specific studies

Four hand-washing studies were identified for review. Larson *et al* (1992) examined hand-washing practices, resistance and density of hand flora in Peru, while in a Swedish study, Hedin & Hambraeus (1993) examined the effect of using a daily hand scrub on antibiotic resistant *Staphylococcus epidermidis*. Wade *et al* (1991) examined the effect of different disinfectants on the survival rates of different bacteria. Webster *et al* (1993), in an Australian study, examined the impact of hand washing in reducing the incidence of MRSA. These studies were all methodologically at high risk of bias and as a consequence not reviewed in detail.

3.2.4 Response to epidemics (multiple control policies)

Overview

Policies are often introduced in hospitals in reaction to epidemics, many of which are associated with the spread of methicillin-resistant *Staphylococcus aureus*. The spread of MRSA across countries and in many hospitals has caused significant morbidity and mortality (Boyce 1991). It is spread most frequently among patients by contact with colonized hands of health care workers who acquire the organism after direct patient contact or after the handling of contaminated material (Peacock 1980). MRSA infections occur frequently in patients with respiratory failure and cutaneous wounds and decubiti, and also where patients have been on cephelosporins or broad spectrum antibiotics (Murray-Leisure 1990). Once established in a hospital institution MRSA is difficult to control and, as a consequence, multifactor control measures are often advocated.

While control programmes across hospitals differ in degree, they nevertheless have some common elements that include: (i) the isolation of infected patients from those who are not infected; and (ii) the introduction of stricter hygiene measures (e.g. hand washing by hospital personnel and use of protective clothing). Other programmes may be more extensive and may include education policies (e.g. providing information to hospital staff about how to further minimize cross-infection) as well as the introduction of antimicrobial restrictions (Dunkle *et al* 1981, Rao *et al* 1988).

While there are few reliable studies to allow a rigorous assessment of epidemic-control attempts, some have argued that they are costly as they achieve little at great expense (Barrett *et al* 1998).

Specific studies

Ten effectiveness studies (Dunkle *et al* 1981, Rao *et al* 1988, Guiget *et al* 1990, Murray-Leisure *et al* 1990, Jewell 1994, Valls *et al* 1994, Jernigan *et al* 1995, Maloney *et al* 1995, Fazal *et al* 1996 and Chaix *et al* 1999) were examined which involved the implementation of epidemic-control policies following an outbreak of MRSA in hospital settings. All studies were based in the USA except: (i) the Guiget *et al* (1990) and the Chaix *et al* (1999) studies, which are French; and (ii) a Spanish study by Valls *et al* 1994. Most studies reported that the rate of MRSA prevalence fell after epidemic-control policies were introduced, with the exception of the Fazel *et al* (1996) study. This found no evidence to suggest that epidemic-control policies were successful in controlling for the prevalence of MRSA. However, all these findings should be viewed with caution as all studies (excepting the Chaix *et al* 1999 analysis) are judged to be methodologically at high risk of bias.

In their cost-effectiveness study, Chaix *et al* (1999) attempted to compare the costs and benefits of an MRSA control programme in an epidemic setting. A total of 27 randomly selected patients who had ICU-acquired MRSA infection (with a 4% carriage rate) were compared to matched controls who were not infected with MRSA to obtain an estimate of the additional costs associated with MRSA treatment. The costs of the epidemic-control

programme (screening, isolation, hand washing and barrier procedures) were compared with the care provided to non-infected patients. The cost analysis indicated that the total costs of the epidemic-control programme ranged from USD 340 to USD 1,480 per patient and that it cost approximately USD 9,275 more to treat MRSA patients than those who were not infected. It was considered of overall benefit if a 14% reduction in the MRSA infection rate occurred as a result of the control programme.

These estimates have to be weighed against those produced by Barrett *et al* (1998) who question the costs associated with attempting to control endemic MRSA. They estimate that it costs a minimum of GBP60,000 to adapt a normal ward for one cohort isolation, and further studies have also suggested that comprehensive efforts to control MRSA in a district hospital, including the opening of an isolation ward, are extremely costly ─ more than GBP400,000 as estimated by Cox *et al* (1995).

While no definitive recommendations can be provided, given the quality of these studies, Guiget *et al* (1990) highlight some of the risk factors affecting the spread of MRSA, which are useful in terms of further understanding how an effective epidemic-control policy should be designed. Two of these are: (i) the prior duration of patient hospitalization (particularly in intensive care); and (ii) the number and type of invasive procedures carried out on patients. Dunkle *et al* (1981) comment that the maintenance and transfer of antimicrobial resistant plasmids among organisms seems to require the continued presence of antimicrobials.

3.3 Interventions to reduce AMR in developing countries

Overview

Although the effects of AMR are documented in developed countries, there is arguably greater potential for harm in the developing world, where many of the second and third line therapies for drug-resistant infections are unavailable, and many of the narrow spectrum antimicrobials available in the developed world are not affordable (Fasehun 1999, Smith 1999). However, the review presented above in sections 3.1 and 3.2 shows a paucity of evidence from developing countries concerning interventions to tackle AMR. It is not clear, though, how applicable the evidence relating to developed countries would be in the developing country context, where there are many factors that would be likely to change the cost and effectiveness of these interventions (many of these factors are outlined in annex 12). The present section therefore reports on a supplementary literature search, focusing specifically on developing countries, with a relaxed search criteria to consider interventions that, although not specifically focused on tackling AMR, would be likely to influence it.

In many parts of developing countries, problems associated with AMR are often more severe than those experienced in developed countries. This is often attributed to the inappropriate, and prophylactic use of antimicrobials (Guyon *et al* 1994, Bojalil & Calva 1994, Nizami *et al* 1996, Paredes *et al* 1996, Hui *et al* 1997, Reyes *et al* 1997, Rodolfo *et al* 1997), with the main outcome being the occurrence of nosocomial infections, due to strains that are far more drug resistant that those encountered in developing countries

(Wolff 1993). The problem of inappropriate prescribing in developing countries is exacerbated by: (i) the somewhat "liberal" availability of antimicrobials (with many products being non-essential or "wasteful" (Melrose 1982)); and (ii) the frequent sale of such products by "untrained peddlers, general merchants and other drug sellers" (Kafle *et al* 1992).

In 1977, in order to counteract this problem, WHO developed the concept of "primary health care", where an important element is the availability of an Essential Drugs Programme to ensure a supply of necessary drugs (Hartog 1993). Since then, much work has been completed by WHO, in tandem with INRUD, to ensure that not only the availability of appropriate drugs is encouraged, but that correct prescribing and quality of care also occurs (Hogerzeil *et al* 1993, Hogerzeil 1995). As a consequence, many interventions to reduce the prevalence of resistance in the developing world are increasingly being focused on appropriate education of prescribers (e.g. Mabadeje *et al* 1991, Bexell *et al* 1996). Lack of patient compliance with treatment protocols is also a significant problem, but efforts to encourage the "correct" use of antimicrobials are compounded by low literacy rates (Nizami *et al* 1996).

However, most studies reviewed for the analysis presented in this report did not focus on specific interventions to combat the emergence and transmission of *resistance*. Instead, the majority were concerned with assessing the extent of *inappropriate prescribing* in general. However, such studies allow a better understanding of the extent of drug usage, and contributing factors, and as a consequence enable appropriate interventions to be developed.

Specific studies

Some 35 developing country studies were reviewed. Of these, approximately 19 were cost-effectiveness or effectiveness studies with eight focusing on the Asian region, seven from Latin America and four being of African origin. Of these, only 10 were classified as being methodologically at moderate risk of bias. All studies are summarized in the "Developing country" section of annex 9. Many of these studies assessed prescribing patterns for antimicrobials, and although not specifically focusing on the link between prescribing and AMR, there is a working assumption that inappropriate prescribing will contribute to increased AMR. A significant number of the remaining studies examined the impact of educational interventions to combat the spread of AMR. Key findings are summarized below.

Prescribing

A total of eight studies examined prescribing trends in the developing world, with two from China (Peng *et al* 2000 and Hui *et al* 1997), three from Mexico (Reyes *et al* 1997, Calva 1996, and Bojalil *et al* 1994), two from Pakistan (Nizami *et al* 1996 and Qazi 1999) and one from Bangladesh (Guyon *et al* 1994). The Qazi 1999 study is at high risk of bias and, as a consequence, is excluded from the review below.

The Peng *et al* (2000) study was set in Heifei City, China, and aimed to identify the determinants of self-medication and antibiotics abuse for children and juveniles. In a

case-control study, 1,596 students were assessed to see whether their parents were "self-prescribing" (i.e. without medical consultation) their children with antimicrobials. This study indicated that the rate of parental self-medication was approximately 60%, with the rate of antibiotic abuse (inappropriate use) estimated at 35.7%. Among other factors, it was noted that there is a relationship between antibiotic self-prescribing and left-over (from previous treatments) household antimicrobials.

In a similar study, Hui *et al* (1997) assessed the diagnosis and treatment of acute respiratory infection (ARI) according to WHO criteria for the diagnosis and treatment of this illness. A total of 750 cases of ARI were examined in rural China, with the study indicating that antimicrobial misuse is common. For instance, 47% of children in country hospitals, 25% in townships and 18% in villages received antimicrobials without prescription. Severe abuse of antimicrobials was also widespread (whereby two incompatible antimicrobials were used for treatment). The study concluded that antimicrobial misuse is a significant problem in China, which is contributing significantly to the spread of AMR.

A study in Mexico (Reyes *et al* 1997) also examined the impact of inappropriate antimicrobial use for ARI (and also acute diarrhoea (AD)). This study took place in four primary health care clinics with the prescribing patterns observed for a total of 377 patients. This study reported high levels of inappropriate prescribing, with prescriptions for antimicrobials justified in only 13.5% of cases. Non-compliance with treatment protocols was 60% for patients suffering from ARI and 56% for those with AD.

Further misuse of antimicrobials in Mexico is highlighted by Calva (1996) and Bojalil *et al* (1994). In studies that used the same sample population (1,659 households in a periurban community in Mexico City), it was noted that: (i) use of antimicrobials for the treatment of diarrhoea was inappropriate, with 37% of patients receiving courses of antimicrobials when such treatment was warranted in only 5% of cases (Bojalil *et al* 1994); and (ii) antimicrobials were frequently misused with 72% of purchases made for insufficient quantities of drugs, with two thirds of all people not using them for the correct period (Calva 1996).

In Asia, Guyon *et al* (1994) and Nizami *et al* (1996) noted similar problems concerning prescribing trends. For instance, Guyon *et al* (1994) assessed drug-use patterns and quality of care in 80 public sector facilities in rural Bangladesh. In an analysis of 2,880 prescriptions, consultations and drug-dispensing decisions, it was found that 41% of drug prescriptions given were inadequate, with 17% of patients treated with metronidazole (irrespective of the diagnosis). Evidence was also presented to suggest that only 55% of patients understood the correct dosage requirements. Similarly, Nizami *et al* (1996) reported that, for Pakistan, there is a need to improve prescribing techniques and, similar to Bojalil *et al* (1994), concluded that unnecessary prescribing of antimicrobials in the treatment of diarrhoea, was a significant problem.

Education programmes to combat the spread of AMR

Two studies were reviewed that assessed the impact of education policies in the developing world. In a randomized controlled study in Zambia, Bexell *et al* (1996) examined the impact of three continuing education seminars (within four months) on quality of patient management and rational drug use. An analysis of 5,685 patient cards indicated that for health centres receiving patient education the average number of drugs per patient decreased from 2.3 to 1.9. In addition, the proportion of patients managed with non-pharmacological treatments increased from 1% to 13.2%. It was also noted that recorded history taking, examination and diagnosis improved more in the intervention group than in the control.

In contrast, in the Santoso (1996) study in Indonesia, a controlled study assessed the impact of two different methods of education intervention for treatment of patients with acute diarrhoea. These education interventions took the form of: (i) a small group face-to-face intervention involving 8 to 12 people; and (ii) a seminar type intervention involving 60 to 80 people. Three districts were randomly selected in Indonesia with 15 health centres selected from each district, with one remaining as a control (i.e. no education intervention). This study found that both interventions were equally effective in improving overall levels of knowledge of prescribing and appropriate management of acute diarrhoea. However, although significant reductions were noted for both interventions (as opposed to the control), a greater reduction was evident for the seminar education intervention.

Although these studies indicate the effectiveness of education campaigns, there is no evidence to suggest that such interventions are cost-effective. While further research is warranted, there is a need for more careful analysis in terms of designing programmes that work best for the specific contexts in the developing countries.

Alternative interventions

Goodman *et al* (1999) completed a cost-effectiveness analysis of malaria control in sub-Saharan Africa. While this study is not centrally concerned with evaluating malarial control interventions that minimize resistance, it nevertheless, takes into account resistance in evaluating chemoprophylaxis interventions. The results indicated that cost-effectiveness varied according to levels of resistance as follows: (i) for antenatal chloroquine chemoprophylaxis with 50% RII/RIII chloroquine parasitological resistance, the cost-effectiveness range was USD14 to USD93; and (ii) for sulfadoxine-pyrimethamine intermittent treatment with 10% RII/RIII resistance, the cost-effectiveness range was USD4 to USD29. However, the chloroquine regimen was less cost-effective than the sulfadoxine-pyrimethamine regimen, even when the resistance was the same for both drugs, because the sulfadoxine-pyrimethamine regimen was cheaper. Goodman *et al* (1999) further suggest that because of the rapid growth in drug resistance, modelling must take into account such changing levels, as this will affect the ultimate cost-effectiveness of interventions. In conclusion, this study reports that there are ranges of cost-effective malarial treatments available─however, these are not always affordable from the perspective of very-low income countries.

3.4 Summary

From this review it would appear that most studies:

- Are from the developed countries (principally the USA)
- Are mostly hospital/other institution based, with few community level interventions
- Are concerned with control of transmission as opposed to prevention of emergence
- Cover "micro" interventions, such as hand washing, and not more "macro" policy interventions, such as legislation, global control of drug availability, tax/subsidy
- Do not measure the cost impact of AMR to the health service, patients or society.

For antimicrobial control measures, a number of studies were examined that involved the use of combination or specific choice antimicrobial regimens to combat the incidence of AMR. These studies (Walsh *et al* 1993, Vakil *et al* 1996 and De Mann *et al* 2000) were able to demonstrate that such interventions have the potential to lower drug-specific resistance (at least in the short-term). Further studies that incorporated measures of the cost of resistance indicated that: (i) combination treatments that prevent the emergence of AMR can save costs (Raad *et al* 1997); (ii) the costs associated with treatment more than doubled when resistance emerged (Scharfstein *et al* 1999); and (iii) the use of more expensive antimicrobials do not imply better health outcomes or necessarily, a lowering of resistance (Laxminarayan *et al* 2000). However, for treatment with combination therapies, the longevity of effectiveness requires further analysis as it could be suggested, that, over time, resistance would develop to specific drug combinations, which, at present, are effective in combating AMR.

In addition, while there is some evidence to suggest that vaccination is a useful measure to prevent the spread of AMR, further research is required. This is because the studies that were assessed for this review concentrated on pneumonia (Fine *et al* 1994, Farr *et al* 1995, Jimenez *et al* 1999), where it was suggested that the effectiveness of vaccinating might be restricted to some circumstances. However, there is a whole ambit of diseases for which the preventive effect of vaccination may be a valid approach, but at present the available literature is not comprehensive enough to allow a rigorous assessment of effectiveness and cost-effectiveness.

The literature assessing the effectiveness of antimicrobial restriction policies (Evans *et al* 1990, Climo *et al* 1998, Toltzsis *et al* 1998, Himmelberg *et al* 1991) is not able to provide definitive answers. While there is some clear evidence that restriction policies affect the overall levels of practitioner prescribing (Evans *et al* 1990), there is no evidence suggesting a commensurate relationship with overall incidence of AMR (Toltzsis 1998, Himmelberg *et al* 1991). There are a number of possibilities as to why this might be the case: (i) there may be a lagged effect between restricting the use of an antimicrobial regimen and the actual incidence of AMR (suggesting that studies which take a longer time horizon might be appropriate); (ii) inappropriate drug use may be so widespread in both the wider community and hospital setting, that a restriction policy at a local level (e.g. one hospital) will have little impact (thus suggesting that a regional (or macro) policy may be more appropriate); or (iii) the substitution effects of other drug use

(recommended as alternatives to the restricted therapy) may also interact and affect the overall level of AMR. However, a study by Rubin *et al* (1996), cautioned against increasing the availability of some antimicrobials (specifically those related to UTIs), as this may lead to increases in the prevalence of mis-diagnosis, and hence ineffective antibiotic use. This has the potential to increase levels of AMR.

Education policies (including prescriber feedback and the use of guidelines) were also assessed as to their overall impact on AMR (Gonzales *et al* 1999, Zwar *et al* 1999, Mainous *et al* 2000). While there is some evidence concerning the use of education policies (which were deemed more effective when aimed at practitioners as opposed to patients) (Gonzales *et al* 1999), the evidence is mixed concerning the use of prescriber feedback. Zwar *et al* (1999) demonstrated the effectiveness of such measures, although the feedback provided was deemed as quite costly. It is clear that further cost-effectiveness analysis of such techniques is required as: (i) McGowan (1995) suggests that some "guidelines" are not based on scientific validation and, as a consequence, may be an inappropriate tool for reducing the incidence of AMR; and (ii) the effect of reward/sanction prescriber-related feedback is not well understood (Mainous *et al* 2000). Likewise, the overall impact that such measures are likely to have on AMR also requires additional assessment.

For alternative control measures, there is some evidence to suggest that surveillance of nosocomial infections has had some effect on reducing the consequences of hospital infections (Haley *et al* 1985, Bloom *et al* 1996), with more recent studies examining whether physicians will modify behaviour based on susceptibility testing (Breuer *et al* 1999). While this study indicated that the cost-effectiveness of susceptibility testing depends on the cure rate of resistant strains, there is also some tentative evidence to suggest that physicians do not always modify practice based on susceptibility testing (Waterer *et al* 1999). This suggests that further research is required before a more definite assessment can be made as to its overall impact on reducing the incidence of AMR.

The results of the review of selective patient decontamination procedures suggest that there should be great caution in advocating this approach as a means of halting the spread of AMR. In particular, Verwaest *et al* (1997) found that selective decontamination has no beneficial effect on survival and that this process actually encouraged the emergence of AMR. While the literature reviewed suggests that the jury is still "out" on the overall effectiveness of selective decontamination (Ferrer *et al* 1994), it is nevertheless recommended here that selective decontamination should not currently be advocated.

The majority of studies examining the influence of site decontamination (e.g. the cleaning of wards) are not well specified, and Barakate *et al* (1999) suggest that such policies should not be introduced in isolation, given the patient-hospital staff transmission nexus. Likewise, the studies that examined the effectiveness of hand washing were methodologically poor, and as a consequence further analysis is required before more definitive conclusions can be reached as to whether such controls help reduce the spread of AMR. However, Nystrom (1994) recommends that increased attention be focused on

encouraging compliance with hand-washing protocols, as there is some evidence to suggest that physicians often do not wash their hands between treatments.

Finally, a number of epidemic-control policies have been introduced to combat the incidence of AMR. In particular, Chaix *et al* (1999) suggested that it cost USD9,275 more to treat MRSA patients than those who were not infected, although this estimate differs considerably from those that suggest epidemic-control cost estimates of more than GBP400,000 per hospital (Cox *et al* 1995). This suggests the careful analysis of hospital specific epidemic-control policies, given that the incidence of AMR spreads well beyond each individual hospital. Indeed, it may be the case that epidemic-control policies at a hospital specific level are not cost-effective, as opposed to broader economy-wide approaches.

Chapter 4: MODELLING COST-EFFECTIVNESS – TECHNIQUES AND METHODS

Modelling is used in many different disciplines, and simply refers to the systematic structuring of relationships between variables in order to create a simplified replica of the particular phenomenon of interest (Ward 1989). It is the extrapolation of the main parameters that (it is assumed) influence a phenomenon of interest, and then the construction of relationships between these parameters. These models are then typically used to structure and/or analyse data.

Economics, as a behavioural (social) science, uses such models frequently to try to replicate, in a manageable manner, the complex interactions between people and institutions. Typically, such models are mathematical representations of quantitative relationships among variables such as employment, wages, inflation, tax, and exchange rates. Although all quantitative models are (to a greater or lesser degree) mathematical by nature, they differ in aim[7], theoretical basis and mathematical or statistical basis. For example, they may be concerned with a particular sector of the "world", such as the hospital or the community setting, they may be aimed at explaining what is, rather than predicting what might be, they may include a temporal dimension, or they may be based, for example, on Bayesian analysis. The aim with all economic models, however, is to determine the position of equilibrium—the point of stability in the system.

Although this "tradition" of modelling has carried over from other areas of economics to health economics, the necessity to model at more "micro" levels has led to the influence of other health-related disciplines upon economic modelling; principally epidemiology, statistics, operations research and decision-science (Buxton *et al* 1997). There are thus a considerable range of modelling "techniques", which might be pursued when considering evaluation of interventions within health and health care (Sheldon 1996, Buxton *et al* 1997).

Section 4.1 provides an example of a basic model construct, whilst the main forms of modelling are outlined in section 4.2.

4.1 Basic model construct: an example of the transmission of AMR

When considering strategies designed to reduce the transmission of AMR, such as hand washing, it is necessary to have a model of how such transmission occurs. One possible construct of transmission in hospitalized patients is given in table 1.

[7] Important here is whether the analysis is to be conducted in terms of the interaction between different economic agents (e.g. sectors of the economy), by the behaviour of different markets within the economy (e.g. goods, labour, financial), or by the interaction of supply and demand (i.e. production and consumption). One could feasibly construct a model to consider AMR within each of these categories. For example, according to the interaction of medical and agricultural sectors, the relationship between medical labour (e.g. physician reimbursement) and product (e.g. antimicrobial) markets, or the relationship between the demand for, and supply of, antimicrobials.

Table 4.1: Hypothetical model for the transmission of resistant bacteria

Transmission = (Baseline Resistance) x (Antibiotic Exposure) x (Patient-to-Patient Contact) / (Colonising Dose)

	Baseline Resistance	Antibiotic Exposure	Patient-to-Patient Contact (Direct or Indirect)	Colonisability of Recipient
	X	X (x 1,000)	Y	Z
Mechanisms	Present a priori	Suppression of normal flora?	Physical contact (direct or via intermediaries)	
Issues	How to quantify resistant colonies conveniently? How to quantify the resistant species or the resistance genes?	What are key variables? Mode of administration? Effect on normal flora?	Any surrogate measures?	Is colonizability reduced by nasal/gastric tubes? By antibiotics? Are resistant organisms less virulent?
Possible preventive measures	Screen all patients for resistant organisms before entry to ICU	Minimize total antibiotic exposure (resistance may be fostered by "unrelated" agents)	Standard infection control measures. Isolate *all* patients?	Reduce risk factors

The model assumes that resistance acquisition is exogenous (rather than arising from spontaneous mutations to resistance in the patient's endogenous flora)[8]. The model thus delineates a sequence of four events that might occur when there is transmission of a resistant strain of micro-organism from one patient to another.

The first is the baseline level of resistance in the index patient. The model might not have to assume that the patient is infected by the resistant strain, but just that the patient is colonized by the resistant strain which is not causing at present any ill-effects. It is likely that there are more colonized than symptomatic patients with resistance and the colonization of a symptomatic patient probably contributes heavily to the difficulties in controlling the spread of resistant organisms within hospitals.

The second event in the chain of transmission is postulated to be expansion of the clones of resistant organisms by the administration of antibiotics, i.e. antibiotic exposure. Although resistance is clearly fostered by the administration of antibiotics, the quantitative relationship between drug use and resistance is an area that is distinctly unclear at present. We might, for example, postulate that it is due to suppression of normal flora.

[8] Note that one of the main issues for discussion in development of a model, and subsequent empirical testing, is the degree to which resistance develop endogenously within the system and that which is transmitted exogenously.

The third component of the model is patient-to-patient transfer of resistance. This might be direct patient-to-patient contact, or indirect via hospital staff, families and other means, such as casings of electronic thermometers. It is also possible that airborne spread plays a role. It might be difficult to model the traffic between colonized or infected patients and other patients, and the extent to which movement of personalized objects create such problems. In this area an intervention might be established such as hand-washing protocols.

The fourth component of the transmission equation is the "colonizability" (ease with which colonization of the patient by a resistant bug may occur) of the recipient, which will be effected by use of things such as gastric tubes and treatments which reduce gastric acidity (where administration of antibiotics may increase the likelihood of infection by drug resistant bacteria as the ability of the normal flora to protect against colonization by exogenous organisms is reduced, which has been termed colonization resistance).

The result of this model is that a simple equation could be developed to express the likelihood of transmission as proportional to the extent of baseline resistance, antibiotic exposure, extent of contact amongst patients, including through intermediaries, and inversely proportional to the colonization dose. Such a model allows consideration of different interventions to reduce the prevalence of resistant organisms, e.g. hand washing, patient isolation, patient screening.

4.2 Main modelling methods

More generally, there are six main forms of modelling which might be applied in the assessment of interventions designed to prevent or control resistance:

1. Decision-analytic models;
2. Markov-chain models;
3. Monte-Carlo simulation;
4. Mathematical models;
5. Statistical models;
6. Macro-economic models.

These forms of modelling differ in their theoretical and methodological basis, the purpose for which they were designed, the manner of presentation and the level of data required. The theoretical and methodological features of each of these forms of model are summarized below. A brief review of studies that have applied these models to assessing interventions to address AMR is presented in annex 13, and an illustrative Monte Carlo simulation model for multi-drug resistant tuberculosis is shown in annex 14.

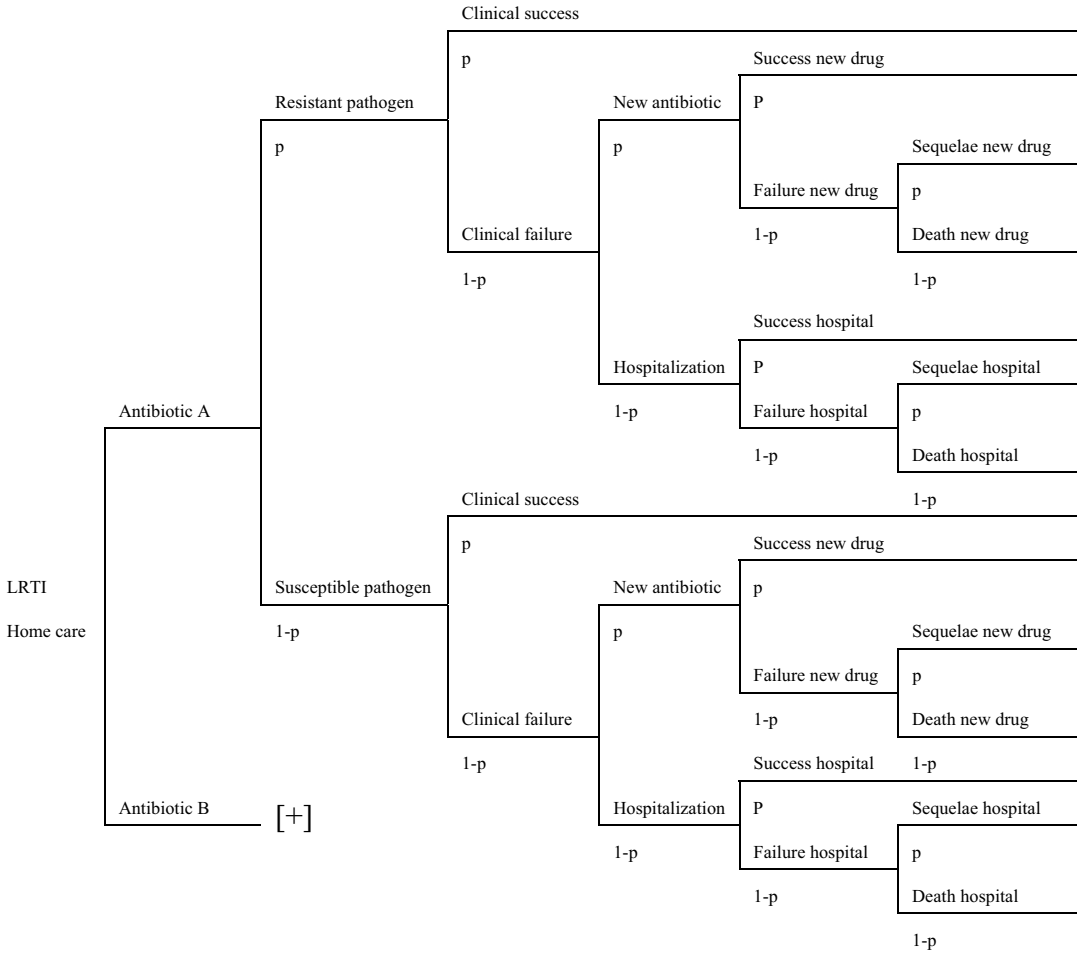
4.2.1 Decision-analytic models

The techniques of decision analysis are in common usage by practitioners of economic evaluation in health care. A seminal contribution by Weinstein and Fineberg (1980)

showed how principles of decision analysis could be applied in health care. The main focus of their research initiative was as a quantitative clinical epidemiology tool for physicians who wish to quantify expected risks, benefits, utilities and, sometimes costs associated with alternative treatment options for *individual* patients. This method was later adopted for structuring and analysing *collective* decisions in health care including within economic appraisal (Detsky *et al* 1997a).

Decision analysis for economic evaluation proceeds by structuring of the problem using a decision tree, which is a graphical representation tracing probable pathways and consequences (for example, health outcomes and costs) that can arise as a result of a decision between, for example, intervention A or intervention B. An example of a decision tree is produced in figure 4.1.

Figure 4.1: Example of a decision tree



Any individual suffering from LRTI follows a path from left to right. The first split is at a *choice,* or *decision, node*, where the path is determined by choice of treatment A or B. Later splits occur as the result of *chance nodes.* The probabilities on each branch indicate

how many individuals follow that branch as a proportion of the number reaching the chance node. The total probability for all branches leaving a chance node must therefore be 1 (or 100%). Although more than one branch may result from a decision or chance node, it is recommended that only two be used where possible, as if one probability is changed there is only one way of changing the probability on the other branch (Detsky *et al* 1997b).

Analysis is carried out by what is know as "averaging out the tree", whereby the costs, weighed by the probability of their occurrence for each intervention strategy, are summed to determine the expected (average) cost. Outcomes of interest are dealt with in a similar way. These expected average costs and outcomes are then compared with intervention strategies using standard economic evaluation methodology (Detsky *et al* 1997d).

Decision analytic models tend to be relatively easy to construct and use, with specific computer packages designed around an explicit decision analysis tree (e.g. SMLTree) (Detsky *et al* 1997a,b). The advantages of depicting the problem in this way are that the researcher can quickly identify the data components required (for example, probabilities, costs and effectiveness measures) to conduct the analysis, and structuring the problem in this way helps to separate issues of *fact* from issues of *value* (Detsky *et al* 1997c). For example, the probability of an event happening might be a factual issue to be informed by epidemiological or clinical data, whereas the value to a patient of avoiding a particular outcome is a subjective value judgement requiring the input of preference data. This technique also identifies where data are missing or incomplete, and must therefore be complemented with assumptions or expert opinion. The effect of such weaker data can then be tested very easily in sensitivity analysis, particularly if the tree has been constructed in a computer package. Finally, this approach allows the inclusion of data from numerous sources rather than having to rely upon one particular observed evaluation, such as a rare, but significant side effect that may not be observed in any specific evaluation.

There are three main disadvantages of this modelling structure. First, various pieces of information from different studies and populations can be put together in the same model. This has led to the approach being termed "Frankenstein's monster" (O'Brien 1996), referring to the analyst bringing disparate parts together to form a model in the hope that they will behave in a predictable way. Second, these models can quickly become unwieldy in both a conceptual and a practical sense, as well as be open to deliberate bias on the part of the researcher (Khan & Miller 1999). Third, they are, by their nature, generally used in micro circumstances.

In modelling the impact of interventions for AMR there is the potential for such an approach to yield a model that would quickly become highly unwieldy. For assessing interventions on a more micro level, however, within a closed system, using good quality data and/or a very focused intervention, this form of analysis is the most straightforward. For example, it might be appropriate for assessing the value of hand washing within a hospital setting. There is, however, the potential for developing various "sub-models" and

then combining them to provide a more system-wide model, although the practicalities of this option would require further exploration.

The major drawback for decision analytic modelling in AMR is that it is only really appropriate where there is a specific decision to be made (e.g. choose drug A or drug B to treat disease X) within a closed system. It is not clear how well the model would work when used to predict the consequences of uncertain and exogenous shocks, which are not the result of a "decision" (e.g. resistance rises through international travel, change in income of the population or changes to the structure of the health care system). These decision-analytic models also tend to be used in comparative static analysis, whereas resistance is an essentially dynamic process requiring a degree of continuous dynamic evaluation. However, there is a version of the decision-analytic model that explicitly models changes over time; this is considered next.

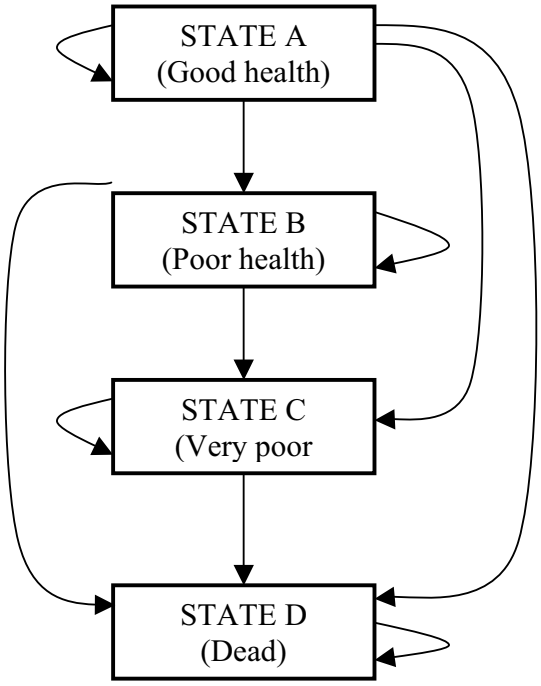
4.2.2 Markov "chain" models

Some diseases and treatments/interventions are characterized by a "profile" of recurrence of disease states, or by treatment "algorithms". In using the decision-tree approach as outlined above, the difficulty is that the researcher is trying to portray in a rather static way the dynamic process of the continuous movement through stages of disease or treatment over time (Detsky *et al* 1997e). An alternative approach in these circumstances is to use a Markov "chain" model, which allows the inclusion of probabilistic changes between a finite number of health states over time, and is therefore a way of rolling the decision tree approach forward over a long time period and introducing "feedback" loops (entry and exit to a state on multiple occasions) (Detsky *et al* 1997e, Briggs & Sculpher 1998, Sonnenberg & Beck 1993).

Markov models construct relationships between possible states of the world over a specific time period within what is termed the Markov "cycle" (the period during which one cycle through the model occurs). This cycle is determined by the length of time at which, for example, the presence or absence of some key indicator is examined (e.g. cost, mortality or quality of life). Typically the cycle is monthly (within a one-year period) or annually (within a multi-year period). The model requires specification of possible states, probability of entry to (and exit from) these states, and the time period(s) involved for a hypothetical cohort of persons being treated or at risk of disease. In principle the Markov model extends decision tree analysis to account for a flow of persons through a specified number of states according to a set of transitional probabilities between different (health) states for each particular "cycle" of the model.

For a detailed treatment of the Markov model in decision-making analysis, readers are referred to Sonnenberg & Beck (1993), although the logic of a Markov model is illustrated in figure 2, which provides a hypothetical Markov structure for a disease involving four possible states over some time period X.

Figure 4.2 State transition diagram for Markov model



The Markov model would, perhaps, be more suitable for the analysis of interventions involving AMR than simple decision-tree analysis as, in theory, it allows for a "lifetime" model to be constructed. It allows for the incorporation, for example, of the probability of resistance to different drug/bug combinations, the differential risk involved at times of hospital admission or other activities, probabilities of new technologies and therapies developing over time and variance in effectiveness rates of antimicrobials over time according to development of resistance to them.

Markov models do, however, require strict assumptions concerning zero memory. That is, the transition probabilities depend only upon the health state patients are in and not on how long they have been in that health state, or how they got there. Whether this Markov assumption is met in practice for any given problem is often difficult to determine. There might also be problems in extrapolation of data to fit the time-frame required by the model, for example, in having information only at six and twelve monthly periods, where a model which requires monthly data has been designed. This moves us into issues of whether we can extrapolate using linear or non-linear means over the period of interest, and whether point estimates are available or applicable.

4.2.3 Monte Carlo (stochastic) simulation

The modelling techniques discussed thus far are essentially deterministic, in the sense of requiring input of specific "average" data (e.g. "average" rates of resistance or "average" cost of care). Often, however, this is either impossible, as these data are not available, or

inadequate in covering the variation between individuals, such as individual probability of health impact from infection with a resistant organism or differences in resistance rates between drugs for the same disease. In this case some form *of stochastic simulation model* is required, in which probabilities may be input from a specified or (pseudo-) random distribution. Thus, probabilities may be generated for movement between states, with costs and outcomes attached to each state. By running the model an average cost/outcome is estimated as a sample from a population. By running the model repeatedly the output may be taken as representative of the population as a whole.

Monte Carlo simulation analysis is a technique that deals with this range of "uncertainty", by allowing a model to be constructed, and then "run" several (hundred or thousand) times to produce an average expected effect. It has been used previously in the study of the spread of infectious diseases, such as HIV (Le Pont 1996) and influenza (Peterson *et al* 1993, Ackerman 1990). An illustrative Monte Carlo simulation model for multi-drug resistant tuberculosis is presented in annex 14.

In running such a simulation to determine the impact of hand washing within a hospital, for example, initial populations of patients and staff would be created using particular parameter values, then the simulation would be run during which patient admissions and discharge from hospital would occur, members of staff would leave and new members of staff would be employed, patient and staff would interact (in terms of transmission of bacteria and resistance), and hand washing would or would not be complied with. The model would then be run over a specified period in order to establish the likely impact of the new hand-washing policy, for example after it has been implemented for one month, six months, one year and 10 years.

The advantage of Monte Carlo modelling is that uncertainty and randomness (for example, rate of development or transmission of resistance, links between antimicrobial consumption and resistance and possible development of new antimicrobials) can be introduced, by using probability distributions rather than point estimates of variables. The production of predicted values with confidence intervals, using a number of simulation iterations, allows a more robust prediction of the likely outcome.

Although Monte Carlo techniques tend to be most useful at the individual or small group level, and within a relatively closed and definable system, such as the hospital, this is usually because mathematical, or other deterministic approaches, are used at "population" levels where population means may be derived. However, there is no reason in principle why this model could not be used more broadly in community and societal estimation of the consequences of resistance and policies to change resistance. This just adds to the complexity of the particular simulation.

4.2.4 Mathematical models

Mathematical modelling, in a sense, is at the core of modelling of any description─a relational description of variables. However, mathematical modelling per se tends to construct a series of, for example, differential equations in which those relationships are

described. These equations are then programmed into a computer package, where they are "solved" for a given set of data. Such models may be of a micro nature, but more often in economics and epidemiology are at a "macro" or system level. The advantage of this type of model is its great degree of flexibility and the ability to handle complex interrelationships. However, the models can be costly, in time and resources, to construct and amend, and a "user-interface" is generally required.

Mathematical models have been developed for analysis of viral infections such as HIV (Ho *et al* 1995, Bonhoffer *et al* 1996, Austin *et al* 1999). Although in the case of bacterial infections, where within host dynamics are not so easily measurable, there have been fewer advances. The field of pharmacokinetics, which considers mathematical models of drug absorption and elimination, has formed the basis for development of a dynamic model of resistance (Lolland & Towser 1995, Austin *et al* 1999).

It is possible that the mathematical approach may be adapted or built upon in developing a cost model for the economic outcome of resistance in terms of emergence and spread within populations. An alternative is for mathematical models of the epidemiology of emergence and spread of resistance be used to generate data to input into one of the other forms of model which may be applied to the economics of resistance. There is a desire, particularly in widespread dissemination and use of a model, for the model to be relatively simple to use and adapt. Although comprehensive in nature, mathematical models have the disadvantage of a general complexity in construction, leading to difficulties in adaptation and amendment and making them relatively inflexible compared with the other forms of model discussed.

4.2.5 Statistical models

Statistical models present a means of structuring data around a particular form of analysis, often driven by underlying statistical theory or methodology felt to be appropriate (e.g. Bayesian). Typically in economics, and health economics, statistical techniques are restricted to forms of regression analysis that attempts to define the relationship (linear or otherwise) between a series of independent variables upon a dependent variable. Regression analyses are popular in microeconomics because, by log transformation, elasticities can be derived for independent variables. For example, regressing quantity demanded by price levels, when logged, provides the elasticity or sensitivity of demand to changes in price. Thus, in modelling resistance one could use such a method of analysis to derive the sensitivity of the level of resistance to, for example, dose or duration of treatment. More advanced methods, such as two-stage least squares regression, enable the production of a value for a dependent variable that may not be readily observable.

More recently, multilevel modelling has been pursued within microeconomics, as it has been within the social sciences more generally (Goldstein 1995). This is a statistical method applied to the analysis of hierarchical, or "nested" data. For example, GPs within a general practice, within a health authority, within a region within a country. This has growing applications within the social sciences, and may be of interest in modelling

resistance within hospitals within particular communities, for example. However, this sort of modelling is useful only at an explanatory level, using observational data, rather than for the purposes of evaluating new interventions or policies where assumptions will be needed.

Overall, these statistical techniques are methods for analysing collected data, rather than for use in deriving conceptual models of the inter-relationships between the variables of interest. Although such techniques might be useful in the analysis of data, they could not drive the development of a model of resistance.

4.2.6 Macro-economic models (e.g. Computable General Equilibrium)

Thus far the paper has considered "micro" modelling techniques, which are the most commonly used in health economics. However, within "mainstream" economics it is macro economics where modelling is most advanced and most frequently utilized. Typically this is to specify quantitative relationships between economy wide variables, such as wage rates, inflation and exchange rates. There are a variety of such models, that differ according to the level of analysis, methodology and theoretical basis (e.g. monetarist or Keynesian). However, they may be useful avenues to explore in the modelling of AMR, as AMR potentially has a large "macro" effect in terms of the wealth and health of a country, as well as the potential for policies to be "macro" in nature, such as legislation, tax/subsidy, or permits.

One particularly interesting feature of macro-models is the use of a "multiplier" effect. For example, Keynsian models in particular emphasize that the generation of employment and income in one sector will stimulate growth within others─the basis for public works schemes and subsidy to encourage foreign investment within "deprived" areas. Within the modelling of AMR it might be fruitful to consider the "multiplier effect" of resistance within one area encouraging resistance in another area, or in the reduction in use of one antimicrobial causing an increase in (over)use of others. It may also be possible to encompass a multiplier effect in the benefits and/or cost of a particular policy overall, rather than just accounting for the direct causal impact observed (e.g. a "hospital policy" multiplier effect on health and social cost within the community).

One model of specific interest here is the Computable General Equilibrium (CGE) model, which differs from many other macro models in being based on microeconomic theory (that is, based on individual rather than aggregate data) (Arrow & Debreu 1954). It is therefore often used in the analysis of taxation policy (Shoven & Whally 1984). Although initially used for comparative static analysis of policy resulting in change between equilibria, recent developments have incorporated dynamic adjustment (see McKibben & Sachs, for example).

CGE, and macro-models more generally, have had little application in health and health care. However, it may provide an interesting and useful avenue for assessing the economic impact of AMR upon countries, as it is a good tool when: (i) there are many inter-industry interactions (through the input-output table: industry A uses a lot of the

output of industry B which collapses as a result of policy change, or import competition for example); (ii) there are economy-wide constraints that mean many industries may be affected (a global or partial increase in wages); and/or (iii) there are other kinds of interdependencies (greenhouse gases affect all countries in the world, independently of who emits them; this gives rise to a new set of national and international markets in permits).

The first two would obviously be studied with a single country model, and the third would use a world-trade model. It is the suitability for use in circumstances outlined in (iii) above that might prove useful in assessing AMR, as it will affect industries and countries differently (for example, depending on their ability to respond to AMR, or because of their different production/trade structures that may affect or influence AMR in reducing the labour force and increasing health expenditures)[9].

Overall, consideration of a macro-economic model as applied in the area of AMR may be fruitful if: (i) the evaluation of the influence of policies upon wider, economy wide, variables is desirable (particularly applicable, perhaps, in developing countries); and/or (ii) a generalized, less detailed analysis is required to compare the consequences of a variety of nationally applicable interventions (taking into account the issue of allocative efficiency).

[9] The Australian Bureau of Agricultural and Resource Economics (ABARE), for example, has conducted extensive work in applying the CGE model in permit trading for greenhouse gases (GHG), and there may be an obvious analogy between GHG and AMR in that both are conceptualised as externalities.

Chapter 5: MODELLING COST-EFFECTIVENESS – FACTORS IN MODEL DEVELOPMENT

In considering the range of possible approaches to modelling for AMR, as outlined in chapter 4, there are several specific factors that require consideration in determining which is most suitable, the most important of which are:

1. Contextual factors, such as socio-economic environment, type of health care system and demographic characteristics of the population;
2. Policy goal of the intervention, such as a focus upon resistance or infection, micro or macro intervention or prevention of the emergence or transmission of AMR;
3. Outcome of interest, referring to a focus upon resistance or health more widely;
4. Temporal factors and the role of changes over time;
5. Extent of endogeneity of parameters within the model (i.e. those explained by the model);
6. Discounting of future costs and benefits; and
7. Handling uncertainty, in both the development of new antimicrobials and the development of resistance.

These will determine the relevant parameters to be collected, and how the relationships between them will be constructed. These factors are outlined in this chapter. A review of the possible variables that would ideally be required to model the cost-effectiveness of interventions, and which might form the basis for prospective studies concerning AMR, or of interventions to tackle AMR, are considered in chapter 6.

5.1 Contextual factors

Contextual factors establish the background against which the intervention will be assessed, and will (in part) determine the feasibility and cost-effectiveness of an intervention. Three specific aspects of context are particularly important.

First, socio-economic and cultural background in the country of interest will be an important contextual influence. This will include factors such as national income, urban/rural mix, industrial or agricultural economy, education and, especially, literacy levels, age and demographic profile. For example, in an urban setting, where people live in close proximity to one another, an isolation policy may have much greater impact than in a rural setting where people are already relatively isolated. National income, and the proportion devoted to health care, are also important as there may be a lack of resources for some policies. For example, Nigeria spends approximately USD3 per person on public health per year, so any policies aimed at tackling AMR would have to be feasible within such a restricted budget.

Second, the type of health care system influences the context in which an intervention is provided. Here, factors for consideration might include the extent of private versus public finance and provision, the comprehensiveness of the coverage of the population by health

care insurance (public and/or private), whether there is a "gatekeeper" of some sort, such as a primary care physician, the availability of over-the-counter pharmaceuticals, particularly antimicrobials and the overall level of health care expenditure. For example, whether the health care system operates on a competitive or non-competitive basis would be expected to influence the extent to which it would be likely to support a coordinated response. There is evidence that variations in the proportion of insurance coverage of out-of-pocket expenditures, for example, influence overall levels of antibiotic prescribing, and the types of antibiotic (i.e. newer or older) prescribed (Dong *et al* 1999). Also, in some developing countries there are issues of availability of funding to enable consumption of prescribed courses of antimicrobials, and the possibility of the "selling on" of such drugs compromising possible interventions to reduce resistance levels.

Third, the level of public health, including provision of clean water, standards of housing, importance of tropical disease and level of immunocompromise (HIV/AIDS). For example, in areas with poor sanitation, the reduction in use of antimicrobials is likely to be ineffective given the rapid growth and transmission of infection in such conditions, which might warrant attention to these aspects as a strategy for reducing resistance rather then those aimed at reduction in use of antimicrobials per se. The presence of HIV and AIDS provides a confounding factor to AMR by increasing the susceptibility of people to infection, particularly by resistant organisms, and thus promoting the emergence and transmission of such organisms.

The impact of these factors upon the feasibility and cost-effectiveness of strategies is perhaps most easily envisaged by considering the differences between strategies for the developed versus developing world. Because tropical conditions encourage the survival of bacteria, more pathogens and commensals are found in tropical environments than in temperate climates (Rosas *et al* 1997). The warm and humid tropical climate and the low levels of health care, hygiene, and sanitation contribute to a relatively high prevalence of infectious disease in developing countries. The high prevalence of infectious disease in turn means that there is both a high need for and a high usage of antimicrobials. However, combined with a variety of socio-economic and behavioural factors, this leads to the relatively quick emergence and dissemination of resistant strains, and has an effect on the feasibility and cost-effectiveness of strategies to combat resistance (Sack *et al* 1997, Hoge *et al* 1998, Bennish *et al* 1992, Lima *et al* 1995, Bogaerts *et al* 1997, Dalsgaard *et al* 1996, Mukhopadhyay *et al* 1996, Githui *et al* 1993, el Baghdadi *et al* 1997)[10]. Such factors thus ideally need integration within the model. Although establishing a technical and quantitative relationship may be difficult, assessment of their potential influences nevertheless requires consideration.

[10] Further elements of importance in the development of AMR in developing countries are outlined in annex 12.

5.2 Policy goal

It is important to establish what the policy being assessed aims to achieve. This is important in three respects.

First, it is important to establish the balance between interventions designed to prevent the emergence, and/or control transmission, of *resistance* and those designed to prevent *infection* itself. Within developing countries in particular, as well as within specific regions or for specific diseases (such as TB in New York), it may well be that policies to reduce levels of infection will be more cost-effective *in reducing resistance* than those designed specifically to prevent/control resistance. The externality nature of resistance means, of course, that if the infection itself is reduced, ceteris paribus, resistance must also be reduced. If this is the case then the model, or the application of the model, should recognize the need to make comparisons between interventions designed to address resistance and those designed to address infection itself. In many instances these may be public health interventions, such as vaccine for TB, safe sex for gonorrhoea or good food hygiene to prevent salmonella.

Second, it is important to establish whether the level of analysis is to be concerned with "micro" or "macro" strategies. The most obvious distinction here is between policies aimed at an *institution* versus those aimed at the *community*. For example, whether the strategy is one of implementing hand washing within a hospital, or whether it is one of a change in payment systems for general practitioners (family doctors) to reduce prescribing within the community.

Third, whether the policy is focused upon preventing *emergence* of resistance, at which many current policies aimed at reduction in consumption of antimicrobials are targeted, or reducing *transmission* of resistance, which is the main focus of most other interventions, such as hand washing, cohorting and isolation. The appropriate level of intervention will be determined to a large extent by the position on the sigmoid distribution curve (i.e. emergence can only be tackled during the lag phase). It is important to note, however, that factors of importance in assessing costs and effects of interventions will vary according to whether it is *control* or *prevention* that is required.

5.3 Outcome of interest

Any policy will only be deemed to be effective or cost-effective relative to some specified outcome of interest. It is therefore important to specify what that outcome will be. With respect to resistance, the important issue here is whether the outcome of interest is resistance per se or the wider influence on health.

Although this is key for the technical analysis of cost-effectiveness as it determines the basis for evaluation, it is of more fundamental importance in determining the value of interventions. If the focus is upon reducing levels of resistance, for example, then this may be achieved whilst being consistent with overall levels of health being *reduced*,

since the emergence and spread of resistance will, ceteris paribus, be reduced as the consumption of antimicrobials is reduced ─ at the extreme, to zero.

Of course, too great a reduction in antimicrobial usage would result in a sub-optimal level of use of antimicrobials entailing a reduction in current health benefits, possibly in non-trivial areas. For example, reducing antimicrobial use in treatment of sore throats may yield negligible deterioration in health benefits, but reducing antimicrobial use for treating more serious infection (e.g. TB) in hospital, or in the community, may lead to increased ill-health and possibly increased costs (to the health care sector in terms of later, more intensive treatment, and to the individual or society in terms of lost production through days off work ─ this latter cost may be significant, particularly in developing countries). Clearly this would be deemed inappropriate, but this illustrates that it is not maximizing the *reduction* of resistance that is important, but attaining an *optimal* level of resistance given the costs and benefits associated with antimicrobial use. This issue is explored in more detail in Coast *et al* (1998).

A concern with the optimal use of antimicrobials requires an attempt to balance the positive and negative impact of using antimicrobials. In turn, this means that any model for assessing the value of alternative interventions must be able to incorporate both these positive and negative aspects of antimicrobial usage.

5.4 Temporal factors

An important issue is whether the model will be used for comparative static analysis (i.e. where adjustment and effect is immediate and complete within the time period of the model), or will be a dynamic model (i.e. where endogenous variables adjust to changes in exogenous variables over several time periods). Given the variance over time of resistance rates[11], as well as other parameters, the cost-effectiveness of interventions would be expected to change, relative to each other, over time also. In constructing a model aimed at addressing "allocative efficiency" this issue is particularly pertinent. Dynamic models are, however, likely to be more complex and costly to maintain, as data require continual updating and there needs to be some "damping" feature such that short-term fluctuations do not necessarily lead to continuous changes to recommended policy.

5.5 Extent of endogeneity of the model

Another factor is the degree of "endogeneity" desired. That is, variables explained *by* the model rather than supplied *to* the model (and hence not explained by it). For example, is the change in resistance to be integrated and therefore explained by the model, or to be provided as an exogenous variable to the model? More broadly, the methods for handling a variety of exogenous variables must be considered. For example, the effect of the "exogenous" factors of antimicrobial use in animals (agricultural and veterinary use), the natural development of mutations that are resistant, and the impact of international travel. This latter issue is one of the model being based on a "closed" or "open" system.

[11] And, importantly, the differential in time scale between emergence of resistance and its decline.

An open system would allow for the importation of resistance, such that resistance generated in any one particular country can result in resistance in other countries. Although countries (or even smaller localities) may both provide the source of, and be the victims of, increased resistance, transfers of the problem may be unequal in quantity (see Halkos (1993, 1995) for discussion of this problem in relation to acid rain). Once resistant micro-organisms have developed, their spread, like that of all infectious diseases, will be dependent on a large number of epidemiological factors. This could greatly influence the level of resistance within a community, potentially even to such a large extent that policies aimed at reducing antimicrobial usage within a particular region would be ineffectual given a much larger effect on resistance through other modes of spread.

5.6 Discounting future costs and benefits

A particularly important factor relates to the discounting of future costs and benefits, and reflects also the inter-generational nature of AMR. Much of the effect of both antimicrobial resistance, and interventions to prevent/control it, are likely to be incurred by future, as well as current generations. These future generations have no voice in the policy decisions taken in the present, and problems therefore exist of weighting decisions between generations. Policies that may be developed to address increasing antimicrobial resistance will therefore have to weigh the current costs of reducing the consumption of antimicrobials, against the future costs of not reducing current consumption.

Economic evaluation usually takes account of this balance of current and future costs and benefits by explicitly discounting costs and benefits to give an equivalent present value. For example, at the current UK Treasury recommended rate of 6%, discounting would result in costs and benefits occurring in 64 years time being valued in the present day at only 2% of their non-discounted value. Even relatively large absolute costs, which occur far in the future might, therefore, be insignificant after taking into account time preference. Discounting in relation to antimicrobial resistance is explored in further detail in Coast *et al* (1996).

However, individual time preference is not universally accepted as a basis for discounting, and there may be moral reasons for not using a positive discount rate (Krahn & Gafni 1993). There is much controversy over the role of discounting in health care at the current time (Krahn & Gafni 1993, Sheldon 1992, Broome 1994), particularly as it affects questions of intergenerational equity. Many intellectual and philosophical thinkers have viewed the positive time preference of individuals as “an unfortunate failing of human reason, an intellectual or moral weakness, potentially harmful to social welfare…” (Krahn & Gafni 1993, p.409). The idea that the rate at which social programmes should be discounted can be equated to an average of the time preferences of individuals is relatively new, and is based on the assumption that the preferences of the living generation should be the only ones that count (Krahn & Gafni 1993). It may be that social discount rates should reflect collective value judgements and moral issues, rather than just the preference that individuals have for their own consumption over time (Broome

1994). This may particularly be the case where the effects of a programme are irreversible and deleterious. Whilst in the long run micro-organisms may lose some resistance to antimicrobials, it is certainly not an effect that can be reversed immediately and at will. There is an issue therefore as to whether the rate at which the costs of resistance should be discounted is zero or positive, and if positive what that rate should be.

The issue of discounting will become particularly relevant in comparison of the cost-effectiveness of interventions designed to prevent *emergence* of resistance, and those designed to control *transmission*, as illustrated in Figure 5.1.

Figure 5.1: The development of antimicrobial resistance over time

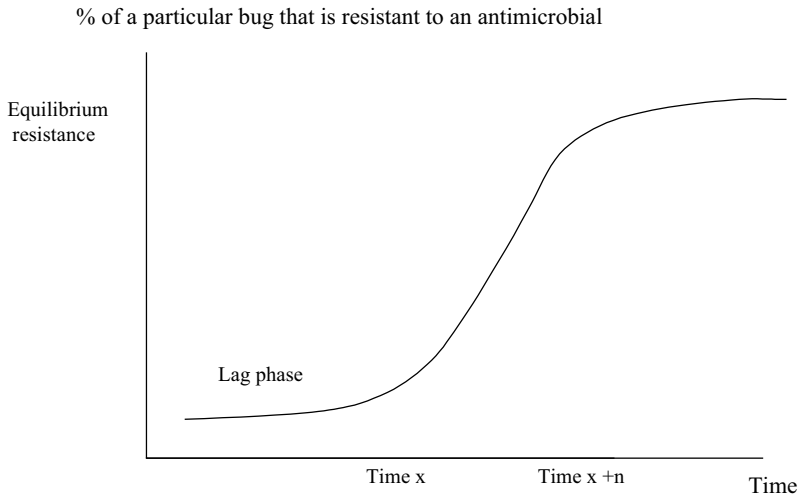


Figure 5.1 indicates the lag phase before resistance begins to appear, followed by a rapid increase in the proportion of organisms found to be resistant, followed by a third phase in which the proportion of resistant strains reaches an equilibrium─although this equilibrium varies considerably between different organisms, and is determined by a number of factors including the relative fitness of resistant and sensitive strains of an organism and the selection pressure.

Taking the case of resistance to penicillin in the hospital setting as one of the first examples of resistance that was noted, the lag phase would have occurred during the 1940s, with time x, the time at which the rise in resistance began to occur, taking place around 1947 (Ashley & Brindle 1960). Time x+*n*, at which the equilibrium point had been reached would have been after about 1960. Once time x+*n* has been reached, only policies that reduce transmission of the organism will (generally) be valuable as a means

of reducing the consequence of resistance on health. Prior to this point, and particularly when in the lag period, it is possible to affect both the rise towards resistance and the final level of equilibrium by altering the selection pressure, that is, by reducing usage of antimicrobials.

It is important to note the influence that discounting may have on the choice between policies that affect transmission and those that affect the selection pressure for the development of resistance. Where there are limited resources available to deal with the problems of antimicrobial resistance and where discounting at a positive rate is undertaken, policies that reduce transmission of already resistant organism for which the benefits can be seen today ─ may seem to be more efficient than policies which affect the selection pressure for the development of resistance ─ the effects of that may not be seen until the distant future (particularly when the issue of multiple resistant organisms is taken into account). Yet in terms of the health impact on future generations the benefit of reducing the pressure towards greater selection of resistance is likely, in absolute terms, to be much greater. This is obvious when considering figure 1: policies to reduce transmission will never avoid all the ill health associated with a resistant organism (and this may be particularly true in community environments), whereas policies that avoid the emergence of resistance could avoid all the additional ill health associated with the resistant organism. Thus, the conclusion may always be to implement interventions to control *transmission* of current resistance, rather then interventions to prevent *emergence* of future resistance, which leads to a counter-intuitive policy recommendation.

Discounting at a positive rate may, therefore, lead to major harm being imposed on future generations. In the case of penicillin, as the future generation (compared with 1940) we might well reflect on whether we wish that early use of antimicrobials had been more cautious ─ and that the future had not, apparently, been discounted so heavily.

5.7 Handling uncertainty

Numerous variables related to the evaluation of policies for dealing with antimicrobial resistance are shrouded in uncertainty. However, of particular importance is the level of uncertainty associated with: (i) the future development of new antimicrobials; and (ii) the nature of the sigmoid curve for any specific antimicrobial in any particular context.

5.7.1 Uncertainty in development of new antimicrobials

The uncertainty related to the development of new antimicrobials has been previously considered by the authors (Coast *et al* 1996), where it was noted that no new classes of antimicrobials have been developed since the 1960s.

The implication of uncertainty about the development of new antimicrobials is that we may incur costs now (in terms of morbidity and mortality) for future benefits (in terms of reduced morbidity and mortality), which may in fact not be needed if the development of new antimicrobials keeps pace with the emergence of resistance. This type of uncertainty could, theoretically, be dealt with by the inclusion of a risk premium (Sugden & Williams

1978) (added to the discount rate whether zero or positive) as, essentially, the probability of finding a new antimicrobial agent each year. Evidence about recent development of antimicrobials would suggest that such a risk premium would probably be quite small.

5.7.2 Uncertainty in the development of resistance

The sigmoid distribution for any antimicrobial in any particular context is also extremely uncertain: as indicated earlier, the epidemic curve will be the same, but the duration of the lag phase and the proportion of isolates resistant at the stabilization phase will vary with the particular condition.

The uncertainties concerning the likely impact of emerging resistance are difficult to deal with. One option would be to model many different options to obtain an idea of the expected benefits of policies under different scenarios. Another option is to be more cautious about use of antimicrobials (and therefore pressure for selection), given uncertainty, than one would be under a situation of certainty. This is because it is possible to learn from experience and increase antimicrobial usage later, but too much usage now may have irreversible effects (see Arrow and Fisher (1974) for detailed analysis in relation to non-renewable resources). As Arrow and Fisher state "… the point is that the expected benefits of an irreversible decision should be adjusted to reflect the loss of options it entails." (Arrow and Fisher (1974), p. 319) At its most extreme, this would imply viewing policies to reduce the emergence of resistance as a form of insurance (see Broome (1994) in relation to global warming).

These types of policies would reduce the risks of a scenario in which antimicrobials were useless in the fight against serious infectious diseases, which could in turn lead to extensive morbidity and mortality. Hence there could be benefit, in terms of risk reduction, in acting to avoid the emergence of resistance, even if the uncertainty associated with both the sigmoid distribution (and the possible development of new antimicrobials) meant that the expected net benefit of such policies compared with those aiming to reduce transmission, would be large or small, positive or negative. An alternative way of conceptualizing this issue is to think in terms of the natural regenerative capacity of susceptible antimicrobials ─ as Pearce and Turner suggest "… if we wish to sustain renewable resources we must be careful to harvest them at a rate no greater than their natural regenerative capacity" (Pearce & Turner (1990), p. 39).

Overall, of particular relevance in modelling either of these uncertainties is that they may be of much greater importance for one type of policy than the other. The impact of policies that aim to inhibit *emergence* of antimicrobials is likely to be much more subject to the influence of these uncertainties than policies to reduce *transmission*, the benefits of which are likely to be much more immediate and for which there is information about the sigmoid distribution, if not about the development of antimicrobials. As with discounting, this may bias the analysis against interventions that focus upon emergence, and more effort may be devoted to interventions aimed at reducing transmission as their cost-effectiveness can be estimated with a greater degree of certainty.

Chapter 6: MODELLING COST-EFFECTIVENESS – "MINIMUM" DATA SET

As well as the broader structural issues, outlined in chapter 5, which must be accounted for in the construction of a model, there will be the requirement for specification of variables of importance and the collection of data related to them. Although these will be expected to vary according to the final model structure, and thus with factors such as whether the model is concerned with transmission or emergence, there is a "minimum data set" of variables that would be required whatever the specific model developed.

For example, in order to develop the fundamental link between resistance levels and the use of antimicrobials, any model would require parameters concerning the epidemiolgical process involved in the emergence and spread of resistance, the pattern of drug use and the evolutionary "cost" of resistance (i.e. the relative transmission potential of sensitive and resistant organisms). The difficulties with getting this kind of information on a community level cannot be underestimated, and perhaps the highest priority is therefore for point surveillance studies determining resistance levels and usage of antimicrobials.

This chapter considers, as a result of the review of available literature (reported in the companion volume to this report) and the discussion of modelling the cost-effectiveness of AMR strategies, the variables that comprise such a "minimum data set". Some of these are intervention specific, but many are concerned with the assessment of basic epidemiological, contextual and economic factors, which it would be desirable to collect on an on-going basis as soon as possible. The variables are classified into the following groups:

1. Epidemiological or clinical factors relating to resistance;
2. Cost factors relating to resistance;
3. Patterns of antimicrobial usage;
4. Impact on AMR in humans from non-human consumption of antimicrobials; and
5. Information concerning the costs and effectiveness of the policy evaluated.

Data collection that is excessively burdensome is unlikely to be successful, particularly in developing countries where resources are more limited, and as such the recommendations for data collection have taken into account the need for data to be relatively easy to collect on a routine basis.

6.1 Epidemiological or clinical factors relating to resistance

Modelling the cost-effectiveness of interventions for addressing AMR is clearly dependent upon the interaction of both effectiveness and cost, involving information on the epidemiology of disease and the clinical outcome of an intervention, both in terms of the impact of interventions upon resistance, and then the relationship between resistance and health impact (in terms of mortality, morbidity etc.), and the effect of resistance and the intervention upon cost to the health care sector, to industry, to individuals, and to

society as a whole. Whatever model is constructed, and whatever modelling technique is used, the interaction between these two areas will be of primary concern, and the data requirements will be practically identical.

Information will be required for each specific bug/drug combination, as these will vary in importance across country ─ e.g. malaria, HIV, TB ─ and factors relevant to each specific bug/drug combination will affect the assessment of the most appropriate intervention.

In terms of more specific clinical data required, there are three important areas:

1. The pattern of AMR;
2. The transmissibility and persistence of AMR; and
3. The influence of AMR on health.

6.1.1 What is the pattern of AMR?

First, and of fundamental importance for modelling the cost-effectiveness of interventions, is the pattern of AMR itself, including current rates of resistance to specific bug/drug combinations and the changes in resistance over time, to enable the position on the various sigmoid distribution curves to be determined.

This is important, as during the "lag phase", interventions that prevent the emergence of resistance may be more cost-effective than those that aim to reduce transmission, and vice versa as resistance increases over time. If resistance can be shown to be on an upward trajectory of the exponential section of the curve for one antimicrobial, then it may be that there is little that may be done to halt the increase in resistance, implying that resources would be better allocated to interventions aimed at reducing transmission during the lag phase or "steady state" sections of the curve, or to reducing usage of other specific antimicrobials that remain in the lag phase. For example, levels of MRSA differ across countries (even among regions and between hospitals and community), which dictates where the level is on the curve and therefore whether it is more cost-effective to have a policy of reduced consumption (prevention of emergence) or not (control of transmission).

Such baseline information may well be scarce, and thus surveillance and case-finding are a prerequisite to intervention ─ it will be impossible to assess the appropriateness of an intervention without being aware of the scale and type of the problem. However, it would appear that there are no agreed methods for sensitivity testing in many countries, no facilities (or very limited facilities) in others, and no agreed definitions of what resistance actually is in a technical sense. Thus, some urgent work on establishing a precise, and commonly adopted, definition of resistance is required, as well as ensuring that at least some minimal facilities are in place to enable testing and data to be collected. Once these are established, routine data would be desirable on:

- Systematic sampling studies to map the prevalence of bacterial pathogens and AMR in the general population
- Current rates of resistance to specific bug/drug combinations
- Changes in resistance over time, across specific drug/bug combinations and geographically
- Selective pressures (e.g. dose and serum level of antimicrobials) that lead to the development of resistance.

These will allow estimation of the distribution curve for each drug/bug combination and allow surveillance of emerging antibiotic resistance, which is essential for clinical practice and for rational policies against antibiotic resistance.

6.1.2 What is the transmissibility and persistence of AMR?

Of particular importance is monitoring the transmission and persistence of antibiotic resistant and sensitive bacteria within hosts. Assessment of data on these factors will also facilitate the testing of existing models of the epidemiology of AMR. For assessment of transmissibility and persistence, data would be desirable concerning:

- Sources from which antimicrobials can be obtained and the proportion obtained from each source
- The effect of resistance to first-line therapies on the growth of resistance to second- and third-line therapies
- The link between use of one antimicrobial and the emergence of resistance in another
- The origin and fate of resistant (and sensitive) organisms, such as the entry and dissemination within hospitals, and the relationship of these to hospital practice, the fate of organisms once patients are discharged and transmission via hospital staff.

6.1.3 What impact does AMR have on health?

As discussed in chapter 5, to compare interventions for resistance with each other, and with wider alternative uses of the resources, cost-effectiveness must be expressed in terms of a comparable final "health" outcome, such as the cost per death, per QALY (Quality-Adjusted Life Year) or per DALY (Disability-Adjusted Life Year) averted. For this it will be necessary to establish links between different resistances (e.g. mutation rate and the transmission rate) and "health", and to model the impact over a relatively long time period, such as 10 or 20 years. Information is clearly required about the concentration of resistant microbes that is needed before there is a meaningful effect on "health". This will included data concerning:

- Relationship between laboratory observed resistance, level of infection with resistance organisms and clinical effect and
- Difference in effectiveness of interventions in reducing resistance versus clinical parameters (especially death and morbidity).

6.2 Cost factors relating to resistance

Any model will need to include information about the costs associated with resistance. This suggests a number of issues, standard in the conduct of economic evaluation, but which must also be tackled in the context of modelling. First, what will be the perspective of the model: the cost of resistance to which is important as it will determine the range of costs to be incorporated. For a comprehensive model a wide range of costs will need to be assessed, including not just those of implementation and potential treatment cost-savings, but "indirect costs" to households related to productive activities, and costs to society more generally from the consequences on taxation, tourism and pharmaceutical investment. It is therefore important to gain information relating to:

- Resource effect, in terms of increased hospital admission and/or length of stay for those with resistant versus sensitive infections, and the influence of AMR on GP visits, pharmaceutical expenditure and other treatment and
- The distribution of these costs across different sources (e.g. hospital, patient, government) to obtain an estimation of where the burden of cost falls.

6.3 Pattern of antimicrobial usage

Particularly for interventions concerned with preventing the *emergence* of resistance, data will be required on the relationship between antimicrobial consumption and the development and retention of resistance. Although hospitals are viewed as "hot-zones", where selection of multiple resistance strains is most commonly identified, the bulk of antimicrobial consumption occurs in the community. As a primary selection pressure driving changes in the frequency of resistance is the volume of drug use, establishing a precise quantitative relationship between antimicrobial consumption and the frequency of resistance in community settings is vital. Estimating this relationship has been difficult to date, however, due to the lack of longitudinal studies that record both resistance *and* consumption patterns (Nissinen *et al* 1995). In addition, there has been some debate on the transfer of resistance from the hospital to the community and vice versa[12].

Furthermore, there is a need for a clear and agreed definition of what constitutes the "pattern" of antimicrobial usage, as it is not clear from the literature whether tonnage used or number of prescriptions is the best correlate with resistance. It is also important to note that crude summary statistics may not be helpful in this respect. For example, data on how many tablets are consumed in a given area over a given period will mask the consequences of whether this reflects a large number of people taking small (possibly sub-therapeutic) doses versus the same number of tablets being taken as larger therapeutic doses by a smaller number of people. It is the detailed patterns of drug use

[12] There are three main ways in which resistance can occur in hospitals: (i) colonization of hospital staff by resistant strains, which are transmitted to patients (Rhainehart *et al* 1990, Reboli *et al* 1990, Pearson *et al* 1992); (ii) widespread and often inappropriate use of broad-spectrum antibiotics (Pechere 1994, Emmerson 1994, Emmi *et al* 1994); and (iii) introduction of a resistant organism by the admission of infected or colonized patients who serve as reservoirs for resistance (Mulligan *et al* 1993). The debate is on the relative impact of these three forms of generation of resistance.

and supply which need to be built into predictive models rather than just overall statistics (although models based on the latter are useful for obtaining general "rules of thumb" for guiding drug policy).

With this in mind, it is desirable to collect data, for specific areas and over specific time periods, concerning:

- Mechanism of resistance development, maintenance and transmission, including the effect of antimicrobial use on gut flora, development of a "reservoir" of resistance within host, transference of resistance between micro-organisms
- Tonnage of antimicrobials used
- Number of prescriptions written
- Type of drug prescribed/used and regimen (e.g. dose, oral or injected administration)
- Conditions under which these drugs were prescribed
- Source of drugs (private/public, pharmacy/GP/hospital etc.)
- Compliance with recommended regimens
- Long-term effect of antimicrobial usage on AMR by surveillance in infected patients and normal hosts
- Incentives (intended and unintended) that might affect prescribing and
- Drug pricing levels.

6.4 Effect on AMR in humans from non-human consumption of antimicrobials

There is little current information concerning the effect on resistance in humans from the use of antimicrobials in animals. There is therefore a need for basic information concerning the prevalence of antimicrobial use in animals, in agriculture and veterinary practice, and the associated levels of resistance in the animal population.

6.5 Information concerning the costs and effectiveness of the policy evaluated

Finally, for any model to provide information about particular interventions, information about the expected consequences and costs of those interventions will inevitably be needed. Although this chapter is considering parameters that might act as "background" or baseline information from which to assess the consequences of interventions or polices to tackle AMR, it is important to note that information concerning epidemiological and clinical information, and cost estimation, applies here also.

For interventions where antimicrobial usage is reduced, it will be important to assess the impact on cost and health of choosing *not* to use antimicrobials in the current situation. For some interventions, that have been the subject of randomized controlled trials, some of this information will be available, but frequently such trials merely compare the use of one antimicrobial with another. In this latter situation there is little information available about the effects of giving no antimicrobial treatment at all.

Chapter 7: DISCUSSION AND RESEARCH AGENDA

7.1 Literature review

Although there are a range of complex interactions that are little understood between microbes, humans, antimicrobial agents and the environment, it is clearly accepted that the emergence of resistance is, at least in part, a natural biological response of micro-organisms to the selection pressures exerted by the use of antimicrobial agents. Thus, although the complete eradication of AMR may be a theoretically feasible goal, it is not an optimal one as it would require significant, if not total, reduction in the use of antimicrobial agents. The challenge is therefore to create a strategy that will optimize the balance between the effectiveness of the antimicrobial agents and the emergence and spread of resistance to them. Such a strategy will need to recognize the complex interactions mentioned, and any strategy will therefore likely comprise a balanced mix of a variety of policy options and interventions. It is the determination of this balance that is critical, and will depend upon relative costs as well as morbidity and mortality, and raises the additional question of how best to determine the cost-effectiveness of combinations of these interventions. Given the diversity of many variables between developed and developing cpuntries, it is also likely that optimal strategies would vary considerably between them, but all strategies should share the same goals of the determination of this optimal balance of use of antimicrobial agents.

This report has presented the results of a comprehensive review of literature that provides evidence of the cost and/or effectiveness of a range of possible policies and interventions to combat the emergence and transmission of AMR[13]. From this review it would appear that most studies:

- Are from the developed world (principally the USA)
- Are mostly hospital/other institution based, with few community level interventions
- Are concerned with control of transmission as opposed to prevention of emergence
- Cover “micro” interventions, such as hand washing, and not more “macro” policy interventions, such as legislation, global control of drug availability, tax/subsidy and
- Do not measure the cost impact of AMR to the health service, patients or society.

Overall, there appears to be no definitive evidence (cost and/or effectiveness) that suggests that one specific control measure (nor indeed a combination of measures) is particularly successful in containing the spread of AMR. Although it would seem that suveillance is a basic prerequisite to tackling AMR, in the absense of evidence it is

[13] It should be noted that the review focussed on interventions undertaken with the *primary* aim of preventing the development or transmission of AMR. Thus, many interventions which may effect AMR, but are not implemented with the express purpose of doing so, were not reviewed but could be of relevance (e.g. there are three papers reviewed which focus on selective decontamination *specifically applied to AMR*, although there are over 20 papers which consider selective decontamination of the digestive tract in general (SDDTTCG, 1993).

difficult to go further in making recommendations, or in suggesting priorities for research among those interventions assessed here.

However, running in parallel to this review has been the development of the WHO Global Strategy for the Containment of Antimicrobial Resistance (WHO, 2000). This strategy, building upon reviews such as the one presented here, as well as a series of wide-ranging consultations with leading international experts (including one of the present authors, RS), presents a range of recommended inteventions, future research strategies and an implementation plan. It is not appropriate, nor feasible, to summarize these here, but interested readers are referred to the strategy document as representing the most current and complete "best advice" on interventions to tackle AMR, how these should be implemented, and research priorities.

In terms of the review presented in this report, it is also worth bearing in mind that, unfortunately, many interventions that impinge on levels of antimicrobial usage, and thus ultimately levels of resistance, are not currently being subjected to such formal evaluation. For example, prescribing schemes, whose main purpose is to result in more cost-effective prescribing, are beginning to be set up by Primary Care Groups in the UK. Many of these schemes incorporate financial incentives to reduce prescribing of antimicrobials, but they are not being subjected to any formal evaluation. Such formal evaluation of these schemes must be encouraged if information about their relative cost-effectiveness is to be set against the information that this review has found for other types of intervention.

Of particular concern is the somewhat narrow focus of the literature, with much that currently exists being strongly focused on the closed hospital system and concentrating upon the effects of policies aimed at reducing transmission rather than emergence of resistance. However, this is unsurprising, as it will be easier to identify the impact of policies aimed at reducing *transmission* (at least in the initial case) than those aimed at stopping the *emergence* of resistance. This is because, for example, those to whom the organism is transmitted are more easily identifiable, the issue of discounting is less challenging, the uncertainty associated with levels of resistance is much less, and the problem of measuring option value does not have to be confronted (conversely of course, policies aimed at avoiding the emergence of resistance are subject to the very real difficulties of identifying the consequences on resistance, of dealing in an acceptable way with issues of time preference and intergenerational equity, and of dealing with the considerable uncertainty about the extent to which resistance will develop in the presence and absence of intervention). Similarly, it will be easier to identify the effect of policies in a closed environment such as a hospital or day-care centre for young children, than in the open environment of the community.

Unfortunately, the policies that are likely to be easiest to evaluate are not likely to produce an optimal long-term outcome (i.e. stable balance of costs and benefits of antimicrobial usage) given the importance of remaining at lower points on the sigmoid distribution curve because of the apparent irreversibility of much resistance and the potentially severe harm that could be imposed as a result. Yet, given the increasing

importance of "evidence-based medicine", policies that have been evaluated using experimental methods, such as randomized controlled trials and well-conducted economic evaluations, may be prioritized above those policies that are much more difficult to evaluate. This is a danger that should be avoided both by awareness among policy-makers of the relative challenges associated with evaluating different types of policy, and by awareness among the research community of the importance of evaluating policies that may potentially be more important, even if the rigour with which they can be evaluated is less than for the potentially less important policies.

These conclusions also support the importance of tackling the "10/90 disequilibrium"─ that most of the research is curently undertaken in, and for, developed countries, whereas those who are the least capable of handling AMR, and therefore more likely to suffer from its impact, are in developing countries, where a minority of research efforts are placed. However, this is also of relevance to developed countries. Emergence of AMR anywhere in the world constitutes a global risk because of the potential of transmission. In this sense it highlights too the notion of "Global Public Goods for Health", and that much of the potential problem of AMR for the developed world may only be tackled through solutions targetted at the developing world (Smith and Coast, 2001).

7.2 Modelling cost-effectiveness

Arguably, the single biggest problem faced in the assessment of the impact of AMR, and the cost and effectiveness of interventions to reduce emergence and transmission of AMR, is the lack of a coherent and comprehensive model of AMR. There are a range of factors affecting AMR, and interventions that might retard it, but to assess the impact that any one, or a combination, of these policies and interventions might have requires a means of specifying the relationships and interactions between the major relevant factors.

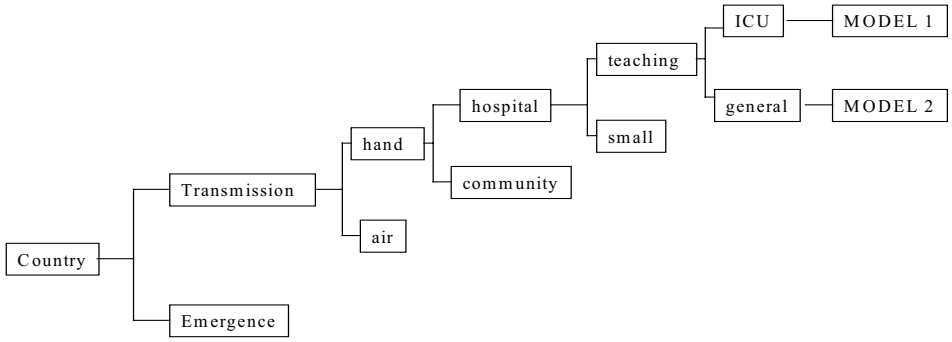
This report has also, therefore, outlined the significant issues that arise when trying to conceptualize and construct such a model of AMR. In considering this variety of complex, and at times possibly conflicting, issues, the appropriate and desirable model will need to satisfy, as far as possible, four broad criteria. First, it should be *feasible*, in terms of, for example, the quality/quantity of data, cost and timeliness. Second, it should be *sensitive*, able to detect and respond to changes in resistance, health outcomes and cost due to changes in policy/intervention, background resistance and other exogenous shocks. Third, it should be *relevant*, taking into account, for example, the specific context of the country, health system and culture. Fourth, it should be *flexible*, enabling easy modification to parameter values or model structure according to, for example, country, disease and pathogen. Considering these four criteria, and based on this review of modelling as applied to AMR, the authors feel that there are two broad options for modelling.

First, to attempt a very broad, "macro-model" that attempts to integrate these factors (including socio-economic ones) within a model aiming to assess strategies on a more global level. One might picture this as a form of equation, with parameters for a host of variables, including health care system, current rates of resistance and so forth. This

would have two advantages: it would be "holistic" in encompassing the major variables of interest from a national perspective; and at this broad level data, initial data at least, could be expected to be available. Thus, it would be *relevant* and *flexible*. There is inevitably some question about its *feasibility* at the present time, mainly because such a model has not been attempted before. A feasibility study would solve this initial concern. The main disadvantage would be that the model might be *insensitive* to small changes in parameters.

Second, one could specify a "suite" of micro models, each "embedded" within a given set of primary parameters, such as country, disease and level of intervention (e.g. hospital or community), which determine which of the "suite" of sub-models is most appropriate for that context. One might picture the process of identifying the appropriate "model" for specific contexts as stylized in figure 7.1 in the form of a "decision tree".

Fig 4. Stylised 'decision' process to determine model to use to assess cost-effectiveness



Here one might, for example, determine the country for analysis, whether the intervention is for transmission or emergence control, whether this transmission is by hand or by air, whether it is in the hospital or community, the size of the hospital, whether it is an ICU or some other ward, and thus use "model 1" for assessing which intervention would be most cost effective.

The advantage of this approach would be that the model(s) would likely be very *sensitive* to changes in parameter values. The approach should, if constructed appropriately, encompass the *relevant* parameters, although the major disadvantage of this approach is that each of the sub-models would have to be developed, and the effect of each of the contextual factors would have to be specified in order to determine which model would be most appropriate. This is likely to be a complex and time-consuming task, and one that may result in a model that is *inflexible* and unwieldy. It may, however, be possible to reduce this problem by "bundling" together different interventions that may be used (with

some indication of synergies and interactions), and thus analysing these discrete "bundles". The choice of interventions to include in these "bundles" could be made on the grounds of expert opinion concerning what might rationally be used in combination, or on grounds of affordability. Of course, it may be that pursuing such "bundling" creates an additional layer of difficulty, and by assessing combinations there is a potential for the complexity of the process to be increased. Finally, there is also some question mark over the *feasibility* of generating such a model(s), particularly given the level of data that might be required, compared to what may be available (this is not to be underestimated, as the review suggests there is little good information available at present).

From the issues presented in this report, it is quite clear that there needs to be further research in the modelling of AMR. The most expedient way to make progress might be to select one disease and context to develop a model of AMR, exploring the feasibiltiy and desirability of the macro and micro approaches as discussed, and integrating issues such as hospital impact, travel and migration, and animal use of antimicrobials as outlined in this report. This could then be adapted according to what within the model needs to be made specific to the disease, country and so forth, and what might remain as "generic", to facilitate "copying" to other diseases and settings.

The time and resources that would be required to develop a model for determining optimal policy responses to antimicrobial resistance should not be underestimated. These will include the intellectual resources required for the development of the model and the specification of the relationship between parameters, the financial resources required for obtaining data for use in models and the commitment of those undertaking both tasks. Yet the potential benefits of such a model, if accurately specified and incorporating quality data, could be vast in terms of the potential health benefit to current and future generations.

REFERENCES

Abraham EP, Chain E (1940). An enzyme from bacteria able to hydrolyze penicillin (letter), *Nature*; 146: 837.

Ackerman E, Longini IM, Seaholm S *et al* (1990). Simulation of mechanisms of viral interference in influenza. *Int J Epidemiol;* 19: 444-454.

Adjepon-Yamaoah K (1980). Drugs for the tropics: their uses and abuses. *Africa Health*; 14: 6.

Agom JK, Akanni AO, Dawodu TO (1990). Quality of ampicillin/cloxacillin preparations on the Nigerian market. *Nigerian Journal of Pharmacology*; 21: 36-8.

Ali HM, Homeida MM, Abdeen MA (1988). Drug dumping in donations to Sudan. *Lancet*; 333: 538-9.

Alubo SO (1994). Death for sale: a study of drug poisoning and deaths in Nigeria. *Soc Sci Med*; 38: 97-103.

American Society for Microbiology (1995). Report of the ASM task force on antibiotic resistance, *Antimicrobial Agents and Chemotherapy*; Supplement: 1-23.

Ameyaw M, Ofori-Adjei D (1997). The impact of three forms of educational interventions on dispensing practices. Presented at ICIUM Chang Mai. http://www.who.int/dap-icium/posters /2b1_txt1.html

Amyes SGB (2000). The rise in bacterial resistance. *British Medical Journal*; 320: 199-200.

Anderson RM (1999). The pandemic of antibiotic resistance [news]. *Nat Med*; 5(2): 147-9.

Anglim AM, Klym B, Byers KE *et al* (1997). Effect of a vancomycin restriction policy on ordering practices during an outbreak of vancomycin-resistant Enterococcus faecium, *Archives of Internal Medicine*; 157: 1132-1136.

Anon (1993). Tuberculosis: a global emergency. *World Health Forum*; 14: 438.

Anon (1995). Guidelines on the control of methicillin-resistant Staphylococcus aureus in the community. Report of a combined Working Party of the British Society for Antimicrobial Chemotherapy and the Hospital Infection Society. *J Hosp Infect*; 31(1): 1-12

Anon (1998). Revised guidelines for the control of methicillin-resistant Staphylococcus aureus infection in hospitals. British Society for Antimicrobial Chemotherapy, Hospital Infection Society and the Infection Control Nurses Association. *J Hosp Infect*; 39(4): 253-90.

Arason VA, Kristinsson KG, Sigurdsson JA *et al* (1996). Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ;* 313: 387-91.

Arif K, Ali SA, Amanullah S, *et al* (1998). Physician complinace with national tuberculosis treatment guidelines: a university hospital study. *Int. J Tuberc Lung Dis*; 2: 225-230.

Arrow KJ, Fisher AC (1974). Environmental preservation, uncertainty and irreversibility. *Quarterly Journal of Economics*; 88: 312-319.

ASCP Susceptibility Testing Group (1996). United States geographic bacteria susceptibility patterns 1995. *Am J Clin Pathol*; 106: 275-281

Ashley DJB, Brindle MJ (1960). Penicillin resistance in staphylococci isolated in a casualty department. *Journal of Clinical Pathology*; 13: 336-338.

Astagneau P, Fleury L, Leroy S *et al* (1999). Cost of antimicrobial treatment for nosocomial infections based on a French prevalence survey. *Journal of Hospital Infection;* 42: 303-312.

Attef OA, Ali AA, Ali HM (1997). Effect of Khat chewing on the bioavailability of ampicillin and amoxycillin. *J Antimicrob Chemother*; 39: 523-5.

Austin DJ, Anderson RM (1999a). Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. *Philos Trans R Soc Lond B Biol Sci;* 354: 721-38.

Austin DJ, Anderson RM (1999b). Transmission dynamics of epidemic methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci in England and Wales. *J Infect Dis;* 179(4): 883-91.

Austin DJ, Kristinsson KG, Anderson RM (1999c). The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci USA;* 96: 1152-6.

Avorn J, Harvey K, Soumerai SB *et al* (1987). Information and education as determinants of antibiotic use: report of Task Force 5. *Rev Infect Dis*; 9 Suppl 3: S286-96.

Avorn J, Monane M, Gurwitz JH *et al* (1994). Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA*; 271(10): 751-4.

Ayliffe AG (1975). Antibiotic policies. *J Antimicrob Chemother;* 1(3): 255-7.

Ayliffe GA, Babb JR, Taylor L *et al* (1979). A unit for source and protective isolation in a general hospital. *BMJ*; 2: 461-5.

Ballereau F, Prazuck T, Schrive I *et al* (1997). Stability of essential drugs in the field: results of a study conducted over a two-year period in Burkina Faso. *Am J Trop Med Hyg*; 57: 31-6.

Bamberger DM, Dahl S (1992). Impact of voluntary vs. forced compliance if third-generation Cephalosporin use in a teaching hospital*, Arch. Intern. Med;* 152: 554-557.

Barakate MS, Harris JP, West RH *et al* (1999). A prospective survey of current methicillin-resistant *staphylococcus aureus* control measures, *Australian and New Zealand Journal of Surgery;* 69: 712-716.

Barrett SP, Mummery RV, Chattopadhyay (1998). Trying to control MRSA causes more problems than it solves, *Journal of Hospital Infection;* 39: 85-93.

Bastian I, Rigouts L, Van Deun A *et al* (2000). Directly observed treatment, short-course strategy and multi-drug resistant tuberculosis: any modifications required? *Bulletin of the World Health Organization;* 78: 238-251.

Bauchner H, Wise P (2000). Antibiotics without prescription: bacterial or medical resistance? *The Lancet;* 355: 1480.

Beck MA, Levander OA (1998). Dietary oxidative stress and the potentiation of viral infection. *Annu Rev Nutr*; 18: 93-116.

Bennish ML, Salam MA, Hossain MA *et al* (1992). Antimicrobial resistance of Shigella isolates in Bangladesh, 1983-1990: increasing frequency of strains multiply resistant to ampicillin, trimethoprim-sulfamethoxazole, and nalidixic acid. *Clin Infect Dis*; 14: 1055-60.

Benson CA, Cohn DL, Williams P *et al* (1996). A phase III prospective, randomised double-blind study of the safety and efficacy of clarithromycin versus rifabutin versus clarithromycin plus rifabutin for the prevention of Mycobacterium avium complex infection in HIV+ patients with

CD4 counts less than or equal to 100 cells/mm$^{3.}$ *Third Conference on Retroviruses and Opportunistic Infections*, Washington, DC, 28 Jan-2 Feb.

Bergmans P, Dawans V, Schmets G *et al* (1997). Inappropriate drug-donation practices in Bosnia and Herzegovina, 1992 to 1996. *N Engl J Med*; 337: 1842-5.

Bexell A, Lwando E, von Hofsten B *et al* (1996). Improving drug use through continuing education: a randomized controlled trial in Zambia. *Journal of Clinical Epidemiology;* 49: 355-357.

Bisognano C, Vaudaux PE, Lew DP *et al* (1997). Increased expression of fibronectin-binding proteins by fluoroquinolone-resistant Staphylococcus aureus exposed to subinhibitory levels of ciprofloxacin. *Antimicrob Agents Chemother*; 41(5): 906-13.

Block A, Cauthen G, Onorato I (1994). Nationwide survey of drug resistant tuberculosis in the United States. *Journal of the American Medical Association*; 271: 665-671.

Bloom BS, Fendrick M, Chernew ME (1996). Clinical and economic effects of Mupirocin Calcium on preventing *Staphylococcus aureus* infection in Hemodialysis patients: a decision analysis. *American Journal of Kidney Diseases;* 27: 687-694.

Bogaerts J, Verhaegen J, Munyabikali JP *et al* (1997). Antimicrobial resistance and serotypes of Shigella isolates in Kigali, Rwanda (1983 to 1993): increasing frequency of multiple resistance. *Diagn Microbiol Infect Dis*; 28: 165-71.

Bojalil R, Calva JJ (1994). Antibiotic misuse in diarrhea: a household survey in a Mexican community. *Journal of Clinical Epidemiology;* 47: 147-156.

Bonhoeffer S, Lipsitch M, Levin BR (1997). Evaluating treatment protocols to prevent antibiotic resistance. *Proc Natl Acad Sci USA;* 94(22): 12106-11.

Bosu W, Ofori-Adjei D (1997). Survey of antibiotic prescribing patterns in government health facilities of the Wassa district of Ghana. *East African Medical Journal*; 74: 138-142.

Bower CK (1999). Resistance responses of microorganisms in food environments. *Int J Food Microbiol;* 50: 33-44.

Boyce JM (1991). Should we vigorously try to contain and control methicillin-resistant *Staphyloccus aureus*? *Infection Control Hospital Epidemiology;* 12: 46-54.

Breathnach AS, de Ruiter A, Holdsworth GM *et al* (1998). An outbreak of multi-drug-resistant tuberculosis in a London teaching hospital. *J Hosp Infect*; 39(2): 111-7.

Breuer T, Graham DY (1999). Costs of diagnosis and treatment of Helicobacter pylori infection: when does choosing the treatment regimen based on susceptibility testing become cost-effective? *The American Journal of Gastroenterology;*. 94: 725-729.

Brewer TF, Heymann SJ, Harris JB (1997). Tuberculosis control in Asia and the Western pacific: a role for computer modelling. *Ann. Acad. Med. Singapore;* 26: 642-6.

Briggs A, Sculpher M (1998). An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics;* 13: 397-409.

Brooks A, Ekleberry A, McMahon J *et al* (1999). Evaluation on clinical practice guidelines on outcomes of infection in medical Intensive Care Unit patients. *Infectious Diseases in Clinical Practice;* 8: 97-106.

Broome J (1994). *Counting the cost of global warming.* White Horse Press, Cambridge.

Brunetone C, Maritoux J, Fontaine D (1997). Asessment in 7 African countries of the advice given in private drugstores through local researchers role playing customers. Presented at ICIUM Chang Mai. http://www.who.int/dap-icium/posters/1b2_fin.html

Burgess DS (1999). Pharmacodynamic principles of antimicrobial therapy in the prevention of resistance. *Chest;* 115(3 Suppl): 19S-23S.

Burke JP, Pestotnik SL (1999). Antibiotic use and microbial resistance in intensive care units: impact of computer-assisted decision support. *J Chemother*; 11(6): 530-5.

Buxton M, Drummond M, Van Hout B *et al* (1997). Modelling in economic evaluatio: an unavoidable fact of life. *Health Economics;* 6: 217-228.

Calder PC (1999). Yaqoob P. Glutamine and the immune system. *Amino Acids*; 17(3): 227-41.

Calva J (1996). Antibiotic use in a periurban community in Mexico: a household and drugstore survey. *Social Science and Medicine;* 42: 1121-1128.

Cannon G (1995). Superbug. Nature's revenge Virgin Publishing, London.

Cantwell MF, Binkin NJ (1996). Tuberculosis in sub-Saharan Africa: a regional assessment of the impact of the human immunodeficiency virus and national tuberculois control program quality. *Tuber Lung Dis*; 77: 220-226.

Cargill K (1997). *Modelling the direct costs and future rates of antimicrobial resistance of haemophilus influenzae in lower respiratory tract infection.* MSc Thesis, London, City University.

Carbon C (1999). Costs of treating infections caused by methicillin-resistant staphylococci and vancomycin-resistant enterococci. *J. Antimicrob Chemotherapy;* 44: 31-36.

Carling PC, Fung T, Coldiron JS (1999). Parenteral antibiotic use in acute-care hospitals: a standardised analysis of fourteen institutions. *Clinical Infectious Diseases;* 29: 1189-96.

Carmeli Y, Troillet N, Karchmer AW *et al* (1999). Health and economic outcomes of antibiotic resistance in Pseudomonas aeruginosa. *Archives of Internal Medicine;* 159: 1127-1132.

Cash R (1996). Inappropriate treatment for dysentery. *BMJ*; 313: 181-2.

Cefai C, Richards J, Gould FK *et al* (1990). An outbreak of Acinetobacter respiratory tract infection resulting from incomplete disinfection of ventilatory equipment. *J Hosp Infect*; 15(2): 177-82.

Chaix C, Durand-Zaleski I, Alberti C *et al* (1999). Control of endemic methicillin-resistant Staphylococcus aureus. A cost-benefit analysis in an intensive care unit. *JAMA;* 282: 1745-1751.

Chalker J, Phuong N (1997). Combating the growth of resistance to antibiotics. Presented at ICIUM Chang Mai. http://www.who.int/dap-icium/posters/2E1_txtf.html

Chan JC (1999). Combining bacterial resistance in skin and skin-structure infection: importance of beta-lactamase inhibition. *American Journal of Therapeutics;* 6: 13-18.

Chaulk CP, Kazandjian VA (1998). Directly observed therapy for treatment completion of pulmonary tuberculosis. Consensus statement of the public health tuberculosis guidelines panel. *JAMA;* 279: 943-948.

Chaulk C, More-Rice K, Rizzo R *et al* (1995). Eleven years of community-based directly observed therapy for tuberculosis. *Journal of the American Medical Association*; 274: 945-951.

Cheng AF, Frebch GL (1988). Methicillin-resistant *Staphylococcus aureus* bacteraemia in Hong Kong. *Journal of Hospital Infection;* 12: 91-101.

Chin DP, Crane CM, Ya Diul M (2000). Spread of Mycobacterium tuberculosis in a community implementing recommended elements of tuberculosis control. *JAMA;* 283: 2968-2974.

Climo MW, Israel DS, Wong ES *et al* (1998). Hospital-wide restriction of clindamycin: effect on the incidence of *Clostridium difficile*--associated diarrhea and cost. *Annals of Internal Medicine;* 128: 989-995.

Clode FE, Kaufmann ME, Malnick H *et al* (2000). Distribution of genes encoding putative transmissibility factors among epidemic and nonepidemic strains of Burkholderia cepacia from cystic fibrosis patients in the United Kingdom. *J Clin Microbiol;* 38(5): 1763-6.

Coast J, Smith R, Millar MR (1996). Superbugs: should antimicrobial resistance be included as a cost in economic evaluation? *Health Economics;* 5: 217-226.

Coast J, Smith RD, Millar MR (1998). An economic perspective on policy antimicrobial resistance. *Social Science and Medicine*; 46(1): 29-38.

Cockerill FR, Muller SR, Anhalt JP *et al* (1992). Prevention of infection in critically ill patients by selective decontamination of the digestive tract. *Annals of Internal Medicine;* 117: 545-553.

Cohn DL, Bustreo F, Raviglione MC (1997). Drug-resistant Tuberculosis: review of the worldwide situation and the WHO/IUATLD Global Surveillance Report. *Clinical Infectious Diseases;* 24: S121-30.

Corcoran GD, Kirkwood EM, (1999). Revised guidelines for the control of methicillin-resistant Staphylococcus aureus infection in hospitals. *J Hosp Infect;* 41: 72-74.

Cookson B (1995). Aspects of the epidemiology of MRSA in Europe. *J Chemother*; 7 Suppl 3: 93-8.

Couper MR (1997). Strategies for the rational use of antimicrobials. *Clin Infect Dis*; 24 Suppl 1: S154-6.

Cox RA, Conquest C, Malaghan C *et al* (1995). A major outbreak of methicillin-resistant Staphylococcus aureus caused by new phage-type (EMRSA-16). *Journal of Hospital Infection;* 29: 87-106.

Crawford J, Foote M, Morstyn G (1999). Hematopoietic growth factors in cancer chemotherapy. *Cancer Chemother Biol Response Modif;* 18: 250-67.

Cruse PJE, Foord R (1980). The epidemiology of wound infection: a 10 year prospective study of 62,939 wounds. *Surg. Clin. North America;* 60: 27-40.

Dalsgaard A, Mortensen HF, Molbak K *et al* (1996). Molecular characterization of Vibrio cholerae O1 strains isolated during cholera outbreaks in Guinea-Bissau. *J Clin Microbiol*; 34: 1189-92.

Dancer SJ (1999). Mopping up hospital infection. *J Hosp Infect*; 43(2): 85-100.

Davey PG, Bax RP, Newey J *et al* (1996). Growth in the use of antibiotics in the community in England and Scotland in 198-93. *BMJ*; 312: 613.

Davey P, Steinke D, MacDonald T *et al* (2000). Not so simple cystitis: how should prescribers be supported to make informed decisions about the increasing prevalence of infections caused by drug-resistant bacteria? *British Journal of General Practice;* 50: 143-146.

Davies GR, Pillay M, Sturm AW *et al* (1999). Emergence of multidrug-resistant tuberculosis in a community-based directly obesrved treatment programme in rural South Africa. *Int. J. Tuberc. Lung Dis;* 3: 799-804.

De Man P, Verhoeven BAN, Verbrugh HA *et al* (2000). An antibiotic policy to prevent emergence of resistant bacilli. *The Lancet;* 355: 973-978.

Detsky A, Naglie G, Krahn M *et al* (1997a). Primer on medical decision analysis. Part 1 – getting started. *Medical Decision Making;* 17: 123-125.

Detsky A, Naglie G, Krahn M *et al* (1997b). Primer on medical decision analysis. Part 2 – building a tree. *Medical Decision Making;* 17: 126-135.

Detsky A, Naglie G, Krahn M *et al* (1997c). Primer on medical decision analysis. Part 3 – estimating probabilities and utilities. *Medical Decision Making;* 17: 136-141.

Detsky A, Naglie G, Krahn M *et al* (1997d). Primer on medical decision analysis. Part 4 – analysing the model and interpreting the results. *Medical Decision Making;* 17: 142-151.

Detsky A, Naglie G, Krahn M *et al* (1997e). Primer on medical decision analysis. Part 5 – working with Markov processes. *Medical Decision Making;* 17: 152-159.

Dodge CP (1990). Health implications of war in Uganda and Sudan. *Soc Sci Med*; 31 :691-8.

Douglas JG, McLeod MJ (1999). Pharmacokinetic factors in the modern drug treatment of Tuberculosis. *Clin. Pharmacokinetics;* 37: 127-146.

Dowell S, Butler JC, Giebnik MD *et al* (1999). Acute otitis media: management and surveillance in an era of pneumococcal resistance. *The Nurse Practitioner;* 24: 1-16.

Downs SH, Black N (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epid & Comm Health;* 52: 377-384.

Drobniewski FA, Watterson SA, Wilson SM *et al* (2000). A clinical, microbiological and economic analysis of a national service for the rapid molecular diagnosis of tuberculosis and rifampicin resistance in *Mycobacterium tuberculosis. J. Med. Microbiol;* 49: 271-278.

Drummond MF, O'Brien B, Stoddart GL *et al* (1997). *Methods for the economic evaluation of health care programmes.* Oxford, Oxford University Press.

Dua V, Kunin CM, White LV (1994). The use of antimicrobial drugs in Nagpur, India. A window on medical care in a developing country. *Soc Sci Med*; 38: 717-24.

Dunagan WC, Medoff G (1993). Formulary control of antimicrobial usage. What price freedom? *Diagn. Microbiol. Infect. Dis;* 16: 265-274.

Dunkle LM, Naqvi SH, McCallum R *et al* (1981). Eradication of epidemic methicillin-Gentamicin-Resistant *Staphylococcus aureus* in an intensive care nursery. *The American Journal of Medicine*; 70: 455-458.

Eandi M, Zara GP (1998). Economic impact of resistance in the community. *International Journal of Clinical Practice (supplement);* 95: 27-38.

Eikhoff TC, Brachman PS, Bennett JV *et al* (1969). Surveillance of nosocomial infections in community hospitals. I. Surveillance methods, effectiveness and initial results. *Journal of Infectious Diseases;* 120: 305-317.

Einarsson S, Kristansson M, Kristinsson KG *et al* (1998). Pneumonia caused by penicillin-non-susceptible and penicillin-susceptible pneumococci in adults: a case control study. *Scandanavian Journal of Infectious Diseases*; 30: 253-6.

El Baghdadi J, Lazraq R, Ibrahimy S *et al* (1997). Survey of primary drug resistance of Mycobacterium tuberculosis in Casablanca, Morocco. *International Journal of Tuberculosis and Lung Disease*; 1: 309-13.

Elting LS, Rubenstein EB, Rolston KV *et al* (1997). Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin. Infect. Dis;* 25: 247-259.

Esezobo E, Offiong E (1986). In vitro studies on some brands of oxytetracycline capsules available in Nigeria. *Nigerian Journal of Pharmacology*; 17: 24-8.

Espinal MA, Kim SJ, Suarez SJ (2000). Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA;* 17: 2537-2545.

Evans RG (1984). *Strained mercy: the economics of Canadian health care.* Butterworths, Toronto.

Evans RS, Pestotnik SL, Burke JP *et al* (1990). Reducing the duration of prophylatic antibiotic use through computer monitoring of surgical patients. *The Annals of Pharmacotherapy;* 24: 351-354.

Ewig S, Ruiz M, Torres A *et al* (1999). Pneumonia acquired in the community through drug-resistant Streptococcus pneumoniae. *Am J Respir Crit Care Med*; 159(6): 1835-42.

Fagbule D, Kalu A (1995). Case management by community health workers of children with acute respiratory infections: implications for national ARI control programme. *J Trop Med Hyg*; 98: 241-6.

Farmer *et al* (1999). The global impact of drug resistant tuberculosis. Harvard Medical School and Open Society Institute: 168.

Farr BM, Johnstonm L, Cobb DK *et al* (1995). Preventing pneumococcal bacteremia in patients at risk. *Archives of Internal Medicine;* 155: 2336-2340.

Fatkenheuer G, Taelman H, Lepage P (1999). The return of tuberculosis. *Diagn. Microbiol. Infect. Dis;* 34: 139-146.

Fasehun F (1999). The antibacterial paradox: essential drugs, effectiveness and cost. *Bulletin of the World Health Organization;* 77(3): 211-216.

Fazal BA, Telzak EE, Blum S *et al* (1996). Trends in the prevalence of Methicillin-resistant Staphylococcus aureus associated with discontinuation of an isolation policy. *Infection Control and Hospital Epidemiology;* 17: 372-374.

Feather A, Stone SP, Wessier A *et al* (2000). Now please wash your hands: the handwashing behaviour of final MBBS candidates. *J Hosp Infect;* 45: 62-4.

Felmingham D, Gruneberg RN (2000). The Alexander Project 1996-1997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. *J Antimicrob Chemother*; 45(2): 191-203.

Ferrer M, Torres A, Gonzales J *et al* (1994). Utility of selective digestive decontamination in mechanically ventilated patients. *Annals of Internal Medicine;* 120: 389-395.

Fey D, Safranek TJ, Rupp M *et al* (2000). Ceftriaxone-resistant salmonella infection acquired by a child from cattle. *The New England Journal of Medicine;* 342: 1242-1249.

Field HJ, Coen DM (1986). Pathogenicity of herpes simplex virus mutants containing drug resistance mutations in the viral DNA polymerase gene. *J Virol*; 60(1): 286-9.

Filho-Lima JV, Vieira EC, Nicoli JR (2000). Antagonistic effect of Lactobacillus acidophilus, Saccharomyces boulardii and Escherichia coli combinations against experimental infections with Shigella flexneri and Salmonella enteritidis subsp. typhimurium in gnotobiotic mice. *J Appl Microbiol*; 88(3): 365-70.

Fine MJ, Smith MA, Carson CA (1994). Efficacy of pneumococcal vaccination in adults: a meta-analysis of randomized controlled trials. *Archives of Internal Medicine;* 154: 2666-2667.

Fleischer W, Reimer K (1997). Povidone-iodine in antisepsis--state of the art. *Dermatology*; 195 Suppl 2: 3-9.

Floyd K, Wilkinson D, Gilks C (1997). Comparison of cost-effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa. *BMJ;* 315: 1407-1411.

Fox R (1996). The post-antibiotic era beckons. *J R Soc Med;* 89(11): 602-3.

Frieden T, Fujiwara P, Washko R *et al* (1995). Tuberculosis in New York City: turning the tide. *New England Journal of Medicien*; 333: 299-303.

Frieden T, Sterling T, Pablos-Mendez A *et al* (1993). The emergence of drug-resistant tuberculosis in New York. *New England Journal of Medicine*; 328: 521-526.

Friis H, Mortensen N, Pinholt H *et al* (1989). Regional variation in the use of antibiotics in four Danish Hospitals. *Infection;* 17: 139-141.

Fujiwara PI, Cook SV, Rutherford CM *et al* (1997). A continuing survey of drug-resistant tuberculosis, New York City, April 1994. *Archives of Internal Medicine;* 157: 531-536.

Fujiwara PI, Larkin C, Frieden TR (1997). Directly observed therapy in New York City. *Clinics in Chest Medicine;* 18: 135-147.

Garau J, Xercavins M, Rodriguez-Carballeira M *et al* (1999). Emergence and dissemination of quinolone-resistant Escherichia coli in the community. *Antimicrob Agents Chemother;* 43(11): 2736-41.

Garcia-Garcia ML, Ponce de Leon A, Jimenez-Corona ME *et al* (2000). Clinical consequences and transmissibility of drug-resistant tuberculosis in southern Mexico. *Arch Intern Med;* 160(5): 630-6.

Garrett L (1995). Mutating microbes. *Independent on Sunday*; 17: 64-65.

Gastinne H, Wolff M, Delatour F *et al* (1992). A controlled trial in intensive care units of selective decontamination of the digestive tract with non-absorbable antibiotics. *New England Journal of Medicine;* 326: 594-599.

Gerding DN (2000). Antimicrobial cycling: lessons learned from the aminoglycoside experience. *Infect Control Hosp Epidemiol*; 21(1 Suppl): S12-17.

Gin AS, Lipinski LA, Honcharik N (1994). Impact of a target drug monitoring program on the usage of Clindamycin. *The Canadian Journal of Hospital Pharmacy;* 47: 53-58.

Githui WA, Kwamanga D, Chakaya JM *et al* (1993). Anti-tuberculous initial drug resistance of *mycobacterum tuberculosis* in Kenya: a ten-year review. *East African Medical Journal;* 70: 609-612.

Glass RI *et al* (1992). Epidemic cholera in the Americas. *Science;* 256: 1524-1525.

Goel P, Ross-Degnan D, Berman P *et al* (1996). Retail pharmacies in developing countries: a behavior and intervention framework. *Soc Sci Med*; 42: 1155-61.

Goern GV, Pfaller MA, Kugler K *et al* (1998). Prevalence of antimicrobial resistance among respiratory tract isolates if streptococcus pneumoniae in North America: 1997 results from the SENTRY antimicrobial surveillance program. *Clinical Infectious Diseases;* 27: 64-70.

Goh KL, Cutler A, Chua ABS (1999). Optimal treatment for duodenal ulcer disease: a cost-decision analysis in Malaysian patients. *Journal of Gastroenterology and Hepatology;* 14: 32-38.

Goldmann DA, Weinstein RA, Wenzel RP *et al* (1996). Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *Journal of the American Medical Association;* 275: 234-240.

Goldstein H (1991). Nonlinear multilevel models, with an application to discrete response data. *Biometrika*; 78: 45-51.

Goma Epidemiology Group (1995). Public health impact of Rwandan refugee crisis: what happened in Goma, Zaire, in July 1994? *Lancet*; 345: 339-44.

Goodman CA, Coleman PG, Mills AJ (1999). Cost-effectiveness of malaria control in sub-Saharan Africa. *The Lancet;* 354: 378-85.

Gonzales R, Sande M (1995). What will it take to stop physicians from prescribing antibiotics in acute bronchitis? *Lancet;* 345: 665.

Gonzales R, Steiner JF, Lum A *et al* (1999). Decreasing antibiotic use in ambulatory practice. Impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in Adults. *JAMA;* 281: 1512-1519.

Gorbach SL (2000). Probiotics and gastrointestinal health. *Am J Gastroenterol*; 95(1 Suppl): S2-4.

Gorman LJ, Sanai L, Notman AW *et al* (1993). Cross infection in an intensive care unit by Klebsiella pneumoniae from ventilator condensate. *J Hosp Infect*; 23(1): 27-34.

Gould IM (1999a). Stewardship of antibiotic use and resistance surveillance: the international scene. *J Hosp Infect*; 43 Suppl: S253-60.

Gould IM (1999b). A review of the role of antibiotic policies in the control of antibiotic resistance. *The British Society for Antimicrobial Chemotherapy;* 43: 459-465.

Greene JN, Poblete SJ, Krieff D (1999). New direction in antimicrobial therapy. *Chest Surgey Clinics of North America;* 9: 1052-3359.

Guiget M, Redacewicz MD, Leclercq MD *et al* (1990). Effectiveness of simple measures to control an outbreak of nosocomial Methicillin-Resistant Staphylococcus aureus infections in an intensive care unit. *Infection Control Hospital Epidemiology;* 11: 23-26.

Gumodoka B, Vos J, Berge Z *et al* (1996). Injection practices in Mwanza region, Tanzania: prescriptions, patient demand and sterility. *Tropical Medicine and International Health*; 1: 874-880.

Gustafsson LL, Wide K (1981). Marketing of obsolete antibiotics in Central America. *Lancet*; 1: 31-3.

Guyon AB, Barman A, Ahmed JU *et al* (1994). A baseline survey on use of drugs at the primary health care level in Bangladesh. *Bulletin of the World Health Organization;* 2: 265-271.

Gwaltney JM, Moskalski PB, Hendlye JO (1978). Hand-to-hand transmission of rhinovirus colds. *Annals of Internal Medicine;* 88: 463-7.

Gyssens IC, Kullberg BI (1995). Improving the quality of antimicrobial drug use can result in cost-containment. *Pharm. World Science;* 17: 163-167.

Haak H (1988). Pharmaceuticals in two Brazilian villages: lay practices and perceptions. *Soc Sci Med*; 27: 1415-27.

Haas DW, Bonczar T (1996). Effect of replacing cefotaxime with ceftizoxime in a hospital where penicillin-resistant pneumococcal disease is prevalent. *Journal of Antimicrobial Chemotherapy;* 38: 293-299.

Haas DW, Milton S, Kreiswirth BN *et al* (1998). Nosocomial transmission of a drug-sensitive W-variant Mycobacterium tuberculosis strain among patients with acquired immunodeficiency syndrome in Tennessee. *Infect Control Hosp Epidemiol*; 19(9): 635-9.

Hacek DM, Suriano T, Noskin GA *et al* (1999). Medical and economic benefit of a comprehensive infection control program that includes routine determination of microbial clonality. *Microbiology and Infectious Disease;* 111: 647-654.

Hadiarto M, Tjandra Y, Huduyo A (1996). Treatment of multidrug resistant tuberculosis in Indonesia. *Chemotherapy*; 42 (suppl. 3): 24-29.

Haley RW, Culver DH, White JW *et al* (1985). The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. *American Journal of Epidemiology;* 121: 182-205.

Haley RW, Morgan WM, Culver DH *et al* (1985). Update from the SENIC project. Hopsital infection control: recent progress and opportunities under prospective payment. *American Journal of Infection Control;* 13: 97-108.

Halkos GE (1993). Sulphur abatement policy. Implications of cost differentials. *Energy Policy;* Oct: 1035-1043.

Halkos GE (1995). Economic incentives for optimal sulfur abatement in Europe. *Energy Sources;* 17: 517-534.

Hannan MM, Azadian BS, Gazzard BG *et al* (2000). Hospital infection control in an era of HIV infection and multi-drug resistant tuberculosis. *J Hosp Infect*; 44(1): 5-11.

Hartog R (1993). Essential and non-essential drugs marketed by the 20 largest European pharmaceutical companies in developing countries. *Social Science and Medicine;* 37: 897-904.

Hateley PM, Jurnaa PA (1999). Hand washing is more common among healthcare workers than the public. *BMJ*; 319: 519.

Hedin G, Hambraeus A (1993). Daily scrub with chlorhexidine reduces skin colonization by antibiotic-resistant Staphylococcus epidermidis. *Journal of Hospital Infection;* 24: 47-61.

Hensher M (1999). Budget planning assistance for North-West Province: TB and HIV/AIDS/STD Programmes. Final Report, 23 September.

Heymann SJ, Sell R, Brewer TF (1998). The influence of program acceptability on the effectiveness of public health policy: a study of directly observed therapy for Tuberculosis. *American Journal of Public Health;* 88: 442-445.

Hilf M, Yu V, Sharp J *et al* (1989). Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. *American Journal of Medicine*; 87: 540-546.

Himmelberg CJ, Pleasants RA, Weber DJ *et al* (1991). Use of antimicrobial drugs in adults before and after removal of a restriction policy. *American Journal of Hospital Pharmacists;* 48: 1220-1227.

Hoge CW, Gambel JM, Srijan A *et al* (1998). Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. *Clin Infect Dis*; 26: 341-5.

Hogerzeil HW, Bimo Ross-Degnan D, Laing RO (1993). Field tests for rational drug use in twelve developing countries. *The Lancet;* 342: 1408-1410.

Hogerzeil H (1995). Promoting rational prescribing: an international perspective. *British Journal of Clinical Pharmacology;* 39: 1-6.

Hogerzeil HV, Bimo, Ross-Degnan D *et al* (1993). Field tests for rational drug use in twelve developing countries. *Lancet*; 342: 1408-10.

Hollis-Triantafillou J (1996). Over the counter antibiotics. *BMJ*; 312: 644.

Holmberg SD, Solomon SL, Blake (1987). Health and economic impacts of antimicrobial resistance. *Rev Infect Dis*; 9(6): 1065-78.

Hossain M, Glass R, Khan M (1982). Antibiotic use in a rural community in Bangladesh. *International Journal of Epidemiology*; 11: 402-405.

House of Lords Select Committee on Science and Technology (1998) 7th Report. London: HMSO.

Hui L, Li X-S, Zeng XJ *et al* (1997). Patterns and determinants of use of antibiotics for acute respiratory tract infection in children in China. *The Pediatric Infectious Disease Journal;* 16: 560-564.

Hunt L (1996). Perfect culture for a 'superbug'. *The Independent*; 27: part 2:7.

Hyatt JM, Schentag (2000a). Potential role of pharmacokinetics, pharmacodynamics, and computerized databases in controlling bacterial resistance. *Infect Control Hosp Epidemiol;* 21(1 Suppl): S18-21.

Hyatt JM, Schentag (2000b). Pharmacodynamic modeling of risk factors for ciprofloxacin resistance in Pseudomonas aeruginosa. *Infect Control Hosp Epidemiol*; 21(1 Suppl): S9-11.

Isenberg SJ, Leonard A, Wood M (1995). A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. *The New England Journal of Medicine;* 332: 5622-566.

Janknegt R (1996). The treatment of staphylococcal infections with special reference to pharmacokinetic, pharmodynamic and pharmacoeconomic considerations. *Pharm. World. Sci;* 19: 133-141.

Jarvis W (1996). Preventing the emergence of multi-drug resistant microorganisms through antimicrobial use controls: the complexity of the problem. *Infection Control and Hospital Epidemiology;* 17: 490-495.

Jepson RG, Mihaljevic L, Craig J (2000). Cranberries for treating urinary tract infections. *Cochrane Database Syst Rev;* (2): CD001322

Jepson RG, Mihaljevic L, Craig J (2000). Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev;* (2):CD001321.

Jernigan JA, Titus MG, Dieter HM *et al* (1995). Effectiveness of contact isolation during a hospital outbreak of Methicillin-resistant *Staphylococcus aureus. American Journal of Epidemiology;* 143: 496-503.

Jewell M (1994). Cost containment using an outcome-based best practice model for the management of MRSA. *J. Chemother;* 6: 35-39.

Jimenez FJ, Guallar P, Rubio C (1996). Cost-effectiveness analysis of pneumococcal vaccination in the elderly Spanish population. *British Journal of Medical Economics;* 10: 193-202.

John J, Fishman NO (1997). Pragmmatic role of the infectious diseases physician in controlling antimicrobial costs in the hospital. *Clinical Infectious Diseases;* 24: 471-85.

Johri RK, Zutshi U (1992). An Ayurvedic formulation 'Trikatu' and its constituents. *J Ethnopharmacol*; 37: 85-91.

Jones L (1999). Science, medicine, and the future. Genetically modified foods. *BMJ*; 318: 581-4.

Joshi N, Milfred MS (1995). The use and misuse of new antibiotics. *Archives of Internal Medicine;* 155: 569-577.

Kafle KK, Gartoulla RP, Pradhan YMS *et al* (1992). Drug retailer training experiences from Nepal. *Social Science and Medicine;* 35: 1015-1025.

Karstaedt AS, Jones N, Khoosal M (1998). The bacteriology of pulmonary tuberculosis in a population with high human immunodeficiency virus seroprevalence. *Int. J. Tuberc Lung Dis;* 2: 312-316.

Kaye ET, Kaye KM (1995). Topical antibacterial agents. *Infect Dis Clin North Am*; 9(3): 547-59.

Kennedy P, Hamilton LR (1997). Psychological impact of the management of methicillin-resistant Staphylococcus aureus (MRSA) in patients with spinal cord injury. *Spinal Cord*; 35(9): 617-9.

Khan Z, Miller D (1999). Modeling economic evaluations of pharmaceuticals: manipulation or valuable tool? *Clinical Therapeutics;* 21: 896-908.

Kibbler CC, Quick A, O'Neill AM (1998). The effect of increased bed numbers on MRSA transmission in acute medical wards. *J Hosp Infect;* 39: 213-219.

Kigotho AW (1997). Ugandan doctors request antibiotic moratorium. *Lancet*; 350: 1014.

Kistinsson K (1995). Epidemiology of penicillin resistant pneumococci in Iceland. *Microbial Drug Resistance*; 1: 121-125.

Kollef MH (1994). The role of selective digestive tract decontamination on mortality and respiratory tract infections. A meta-analysis. *Chest*; 105(4): 1101-8.

Krahn M, Gafni A (1993). Discounting in the economics evaluation of health care interventions. *Medical Care*; 31: 403-418.

Kroodsma KL, Kozal MJ, Hamed KA *et al* (1994). Detection of drug resistance mutations in the human immunodeficiency virus type 1 (HIV-1) pol gene: differences in semen and blood HIV-1 RNA and proviral DNA. *J Infect Dis*; 170(5): 1292-5.

Kristensen B, Andreassen S, Leibovici L *et al* (1999). Empirical treatment if bacteraemic urinary tract infection: Evaluation of a decision support system. *Danish Medical Bulletin;* 46: 349-53.

Kunin CM (1985). The responsibility if the infectious disease community for the optimal use of antimicrobial agents. *Journal of Infectious Diseases;* 151: 388-398.

Kunin CM (1989). Problems in antibiotic usage. In Mandell GL, Douglas RG, Bennett JE (eds), "*Principles and practice of infectious diseases*", 3rd edition, New York, John Wiley and Sons, pp. 427-434.

Kunin CM (1993). Resistance to antimicrobial drugs─a worldwide calamity. *Annals of Internal Medicine;* 118: 557-561.

Kuyvenhoven MM, Verheij TJM *et al* (2000). Antimicrobial agents in lower respiratory tract infections in Dutch General Practice. *Br. Journal of Gen. Practice;* 50: 133-134.

Land T (1992). Combating counterfeit drugs. *Nature*; 355: 192.

Landgren FT, Harvey KJ, Mashford ML *et al* (1988). Changing antibiotic prescribing by educational marketing. *Med J Aust*; 149: 595-9.

Langendijk PS, Schut F, Jansen GJ *et al* (1995). Quantitative fluorescence in situ hybridization of Bifidobacterium spp. with genus-specific 16S rRNA-targeted probes and its application in fecal samples. *Appl Environ Microbiol*; 61(8): 3069-75.

Langmuir AD (1963). The surveillance of communicable diseases of national importance. *New England Journal of Medicine;* 268: 182-192.

Lansang MA, Lucas-Aquino R, Tupasi TE *et al* (1990). Purchase of antibiotics without prescription in Manila, the Philippines. Inappropriate choices and doses. *J Clin Epidemiol*; 43: 61-7.

Larson EL (1988). A causal link between handwashing and risk of infection? Examination of the evidence. *Infection Control;* 9: 28-36.

Larson E, Kretzer EK (1995). Compliance with handwashing and barrier precautions. *J Hosp Infect;* 30: 88-106.

Larson EL, McGinley KJ, Foglia A *et al* (1992). Handwashing practices and resistance and density of bacterial hand flora on two pediatric units in Lima, Peru. *American Journal of Infection Control;* 20: 65-72.

Laxinarayan R, Jernigan DB, Dagman MD *et al* (2000a). *"Using antibiotic resistance surveillance data in the optimal treatment of acute otitis media: a decision analysis model"*. Unpublished paper.

Laxinarayan R, Brown B (2000b). *Bacterial resistance and the optimal use of antibiotics.* University of Washington Economics Discussion Paper.

Ledingham IM, Alcock SR, Eastaway AT *et al* (1998). Triple regimen of selective decontamination of the digestive tract, systemic cefotaxime, and microbiological surveillance for prevention of acquired infection in intensive care. *Lancet*; 1: 785-90.

Lee PR, Lurie P, Silverman MM *et al* (1991). Drug promotion and labeling in developing countries: an update. *J Clin Epidemiol*; 44 Suppl 2: 49S-55S.

Lenski RE (1997). The cost of antibiotic resistance─from the perspective of a bacterium. *CIBA Foundation Symposium;* 207: 131-140, 141-151.

Levander OA (1997). Nutrition and newly emerging viral diseases: an overview. *J Nutr;* 127(5 Suppl): 948S-950S.

Levine EM, Ghai V, Barton JJ *et al* (1999). Intrapartum antibiotic prophylaxis increases the incidence of gram-negative neonatal sepsis. *Infectious Diseases in Obstetrics and Gynecology;* 7: 210-213.

Levy SB (1992). *The antibiotic paradox. How miracle drugs are destroying the miracle.* Plenum Press, New York.

Le Mire M, Wing L, Gordon DL (1996). An audit of third generation cephalosporing prescribing in a teriary care hospital. *Aust NZ Journal of Medicine;* 26: 386-90.

Lima AA, Lima NL, Pinho MC *et al* (1995). High frequency of strains multiply resistant to ampicillin, trimethoprim-sulfamethoxazole, streptomycin, chloramphenicol, and tetracycline isolated from patients with shigellosis in northeastern Brazil during the period 1988 to 1993. *Antimicrob Agents Chemother*; 39: 256-9.

Liss RH, Batchelor FR (1987). Economic evaluations of antibiotic use and resistance — a perspective: Report of Task Force 6. *Reviews of Infectious Diseases;* 9: S297-S313.

Lockwood WR (1974). Antibiotics anonymous. *N Engl J Med*; 290(8): 465-6.

Mabadeje AFB, Akintonwa AA, Ashorobi RB (1991). The value and effects of implementing an essential drugs list in the lagos University Teaching Hospital. *Clinical Pharmacology and Therapeutics;* 50: 121-124.

Macintyre CR, Plant AJ, Hendrie D (2000). The cost-effectiveness of evidence-based guidelines and practice for screening and prevention of tuberculosis. *Health Economics;* 9: 411-421.

Magee JT, Pritchard EL, Fitzgerald KA *et al* (1999). Antibiotic prescribing and antibiotic resistance in community practice: retrospective study, 1996-8. *BMJ;* 319: 1239-40.

Mainous AG, Hueston WJ, Love MJ *et al* (2000). An evaluation of statewide strategies to reduce antibiotic overuse. *Family Medicine;* 32: 22-29.

Mainous AG, Heuston WJ (1998). The cost of antibiotics in treating upper respiratory tract infections in a Medicaid population. *Archives of Family Medicine;* 7: 45-49.

Maloney SA, Pearson ML, Gordon MT *et al* (1995). Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Annals of Internal Medicine;* 122: 90-95.

Mamun K (1991). Prevalence and genetics of resistance to commonly used antimicrobial agents in faecal enterbacteriaceae from children in Bangladesh. PhD Thesis, University of Liverpool.

Maranetra K (1996). Treatment of multidrug resistant tuberculosis in Thailand. *Chemotherapy*; 42 (suppl. 3): 10-15.

Martin MA (1994). Methicillin-resistant Staphylococcus aureus: the persistent resistant nosocomial pathogen. *Curr Clin Top Infect Dis*; 14: 170-91.

McCaig LF, Hughes JM (1995). Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA*; 273(3): 214-9.

McConachy KA, Cuell S, Kent PJ *et al* (1999). Surgical antibiotic prophylaxis in a private hospital: compliance with guidelines. *The Australian Journal of Hospital Pharmacy;* 29: 5-9.

McCray E, Weinbaum CM, Braden CR *et al* (1997). The epidemiology of tuberculosis in the United States. *Clinics in Chest Medicine;* 18: 99-113.

McGowan JE (1995). Success, failures and costs of implementing standards in the USA – lessons for infection control. *Journal of Hospital Infection;* 30: 76-87.

McGregor A (1997). Counterfeit drugs flood developing world. *Lancet*; 350: 1690.

McGuckin M, Waterman R, Porten L *et al* (1999). Patient education model for increasing handwashing compliance. *Am J Infect Control*; 27: 309-314.

McNulty C, Logan M, Donald I *et al* (1997). Successful control of Clostridium difficile infection in an elderly care unit through use of a restrictive antibiotic policy. *Journal of Antimicrobial Chemotherapy;* 40: 707-711.

Meers PD (1988). Infection control in developing countries. *J Hosp Infect*; 11: 406-10.

Mehtar S, Drabu YJ, Mayet F (1989). Expenses incurred during a 5-week epidemic methicillin-resistant Staphylococcus aureus outbreak. *J Hosp Infect*; 13(2): 199-200.

Mehtar S (1995). Infection control programs─are they cost effective? *Journal of Hospital Infection;* 30: 26-34.

Milatovic D, Braveny I (1987). Development of resistance during antibiotic therapy. *European Journal of Clinical Microbiology*; 6: 234-244.

Miller JM, Yu VL (1991). Methicillin-resistant staphylococcal colonization and infection in a long-term care facility. *Ann Intern Med*; 114(2): 107-12.

Millar MR, Brown NM, Tobin GW *et al* (1994). Outbreak of infection with penicillin-resistant Streptococcus pneumoniae in a hospital for the elderly. *J Hosp Infect*; 27(2): 99-104.

Mitchison D (1979). Basic mechanisms of chemotherapy. *Chest*; 76: 771S-781S.

Moher D, Jadad A, Nichol G *et al* (1995). Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Controlled Clinical Trials;* 16: 62-73.

Moore WL Jr (1974). Nosocomial infections: an overview. *American Journal of Hospital Pharmacy;* 351: 832-88.

Moore RD, Chaulk CP, Griffiths R *et al* (1996). Cost-effectiveness of directly observed versus self-administered therapy for Tuberculosis. *American Journal Respir Crit Care Med;* 154: 1013-1019.

Morgan AS, Brennan PJ, Fishman NO (1997). Impact of a vancomycin restriction policy on use and cost of vancomycin-resistant enterococcus. *The Annals of Pharmacotherapy;* 31: 970-973.

Muder RR, Brennen C, Wagener MM *et al* (1996). Temporal shifts in traits of Vibrio cholerae strains isolated from hospitalized patients in Calcutta: a 3-year (1993 to 1995) analysis. *J Clin Microbiol*; 34: 2537-43.

Mulrow CD, Oxman A. Cochrane Collaboration Handbook (1996, updated 1 March 1997). In The Cochrane Collaboration (ed), *The Cochrane Library (database on disk and CDROM),* Oxford: Update Software.

Munishi GK (1991). The development of the Essential Drugs Program and implications for self-reliance in Tanzania. *J Clin Epidemiol*; 44 Suppl 2: 7S-14S.

Murray BE (1994). Can antibiotic resistance be controlled? *N Engl J Med;* 330: 1229-30.

Murray-Leisure KA, Geib S, Graceley D *et al* (1990). Control of epidemic methicillin-resistant Staphylococcus aureus. *Infection Control Hospital Epidemiology;* 11: 343-350.

Nathwani D, Malek M (1999). Cost considerations in the evaluation of new therapies for Gram-positive bacteria. *International Journal of Antimicrobial Agents;* 13: 71-78.

Neely AN, Maley MP (1999). 3% Hydrogen Peroxide for the Gram-Positive disinfection of fabrics. *Journal of Burn Care Rehabilitation;* 20: 471-7.

Neu HC (1992). The crisis in antibiotic resistance. *Science;* 257: 1064-1073.

Neu HC (1994). Antimicrobial chemotherapy, 1934-1994. *Antimicrobial Infectious Diseases Newsletter*; 13: 1-8.

New York City Department of Health (1999). Tuberculosis: information summary 1999. New York: New York City Department of Health.

NHS Centre for Reviews and Dissemination (1996). *Undertaking systematic reviews of research on effectiveness (CRD report 4),* York: University of York.

Nicolle LE (1994). Prevention and treatment of urinary catheter-related infections in older patients. *Drugs and Aging;* 4: 379-391.

Nissinen A, Leinonen M, Huovinen P *et al* (1995). Antimicrobial resistance of Streptococcus pneumoniae in Finland, 1987-1990. *Clin Infect Dis*; 20(5): 1275-80.

Nizami SQ, Khan IA, Bhutta ZA (1996). Drug prescribing practices of General Practitioners and Pediatricians for childhood diarrhoea in Karachi, Pakistan. *Social Science and Medicine;* 42: 1133-1139.

Nystrom B (1994). Impact of handwashing on mortality in intensive care: examination of the evidence. *Infection Control and Hospital Epidemiology;* 15: 435-436.

O'Brien B (1996). Economic evaluation of pharmaceuticals: Frankenstein's monster or Vampire of trials? *Medical Care;* 34: DS99-DS108.

Obaseiki-Ebor EE, Akerele JO, Ebea PO (1987). A survey of antibiotic outpatient prescribing and antibiotic self- medication. *J Antimicrob Chemother*; 20: 759-63.

Ogunbona FA, Oluwatudimu OO (1985). Effect of a non-European (Nigerian) diet on the bioavailability of nitrofurantoin in man. *Int J Pharmaecutics*; 29: 191-3.

Okeke I, Lamikanra A (1995). Quality and bioavailability of tetracycline capsules in a Nigerian semi-urban community. *International Journal of Antimicrobial Agents*; 5: 245-50.

Okeke I, Lamikanra A, Edelman R (1999). Socioeconomic and behavioural factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerging infectious diseases*; 5 (1). Serial online, available from: http://www.cdc.gov/ncidod/eid/vol5no1/okeke.htm

Orr KE, Gould FK, Perry JD *et al* (1994). Therapeutic beds: the Trojan horses of the 1990s? *Lancet*; 344: 65-6.

Orrhage K, Nord CE (2000). Bifidobacteria and lactobacilli in human health. *Drugs Exp Clin Res*; 26(3): 95-111.

Oxman AD (1994). Checklists for review articles. *BMJ;* 309: 648-651.

Papia G, Louie M, Tralla A *et al* (1999). Screening high-risk patients for methicillin-resistant Staphylococcus aureus on admission to the hospital: is it cost effective? *Infect Control Hosp Epidemiol*; 20(7): 473-7.

Park MM, Davis AL, Schluger NW *et al* (1996). Outcome of MDR-TB patients, 1983-1993. Prolonged survival with appropriate therapy. *Am. J. Respir. Crit. Care. Med;* 153: 317-324.

Paredes P, de la Pena M, Flores-Guerra E *et al* (1996). Factors influencing physicians' prescribing behavior in the treatment of childhood diarrhoea: knowledge may not be the clue. *Soc Sci Med*; 42: 1141-53.

Paterson DL, Mulazimoglu L, Casellas JM *et al* (2000). Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in Klebsiella pneumoniae isolates causing bacteremia. *Clin Infect Dis*; 30(3): 473-8.

Patrick L (2000). Nutrients and HIV: part two--vitamins A and E, zinc, B-vitamins, and magnesium. *Altern Med Rev*; 5(1): 39-51.

Peacock JE Jr, Marsik FJ, Wenzel RP (1980). Methicillin-resistant *Staphylococcus aureus*: introduction and spread within a hospital. *Annals of Internal Medicine;* 93: 526-532.

Pearce DW, Turner RK (1990). *Economics of natural resources and the environment.* Harvester Wheatsheaf, London.

Pearson CA (1995). The role of district hospitals and the action in international medicine network. *Infect Dis Clin North Am*; 9: 391-405.

Peng B, Tong S, Parton KA (2000). Family self-medication and antibiotics abuse for children and juveniles in a Chinese city. *Social Science and Medicine;* 50: 1445-1450.

Pestotnik SL, Classen DC, Evans RS *et al* (1996). Implementing antibiotic practice guidelines through computer-assisted decision support: clinical and financial outcomes. *Annals of Internal Medicine;* 124: 884-890.

Pfaller MA, Herwaldt LA (1997). The clinical microbiology, laboratory and infection control: emerging pathogens, antimicrobial resistance and new technology. *Clinical Infectious Diseases;* 25: 858-70.

Phelps CE (1989). Bug-drug resistance. *Med Care;* 27: 194-203.

Pittet D, Mourouga P, Perneger TV (1999). Compliance with handwashing in a teaching hospital. Infection Control Program. *Ann Intern Med;* 130: 126-130.

Plowman R, Graves N, Griffin M *et al* (1999). *The socio-economic burden of hospital acquired infection.* The Public Health Laboratory Service, Part 1, 2 and Appendices.

Ponticelli C, Tarantino A, Vegeto A (1999). Renal transplantation, past, present and future. *J Nephrol*; 12 Suppl 2: S105-10.

Preus HR, Lassesn J, Aass AM *et al* (1993). Prevention of transmission of resistant bacteria between periodontal sites during subgingival application of antibiotics. *Journal of Clinical Peridontol;* 20: 299-303.

Price DJ, Sleigh JD (1970). Control of infection due to Klebsiella aerogenes in a neurosurgical unit by withdrawal of all antibiotics. *Lancet*; 2: 1213-5.

Qazi SA (1999). Antibiotic strategies for developing countries: experience with acute rspiratory tract infections in Pakistan. *Clinical Infectious Diseases;* 28: 214-8.

Quinio B, Albanese J, Bues-Charbit M *et al* (1996). Selective decontamination of the digestive tract in multiple trauma patients: a prospective double-blind, randomized, placebo-controlled study. *Chest;* 109: 765-772.

Raad I, Darouiche R, Dupuis J *et al* (1997). Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. *Annals of Internal Medicine;* 127: 267-274.

Raad I, Hanna H (1999). Intravascular catheters impregnated with antimicrobial agents: a milestone in the prevention of bloodstream infections. *Support Care Cancer;* 7: 386-390.

Rahal K, Wang F, Schindler J *et al* (1997). Reports on surveillance of antimicrobial resistance in individual countries. *Clin Infect Dis*; 24 Suppl 1: S169-75.

Rahman F, Andersson R, Svanstrom L (1998). Medical help seeking behaviour of injury patients in a community in Bangladesh. *Public Health*; 112: 31-5.

Rao N, Jacobs S, Joyce L (1988). Cost-effective eradication of an outbreak of Methicillin-resistant Staphylococcus aureus in a community teaching hospital. *Infection Control Hospital Epidemiology;* 9: 255-260.

Raviglione M, Snider D, Kochi A (1995). Global epidemiology of tunerculosis: mortality and morbidity of a worldwide epidemic. *JAMA*; 273: 220-226.

Reeves DS, Lewis DA (1995). Over the counter anti-infectives – of benefit to whom? *Journal of Antimicrobial Chemotherapy;* 36: 579-83.

Reeves DS, Finch RG, Bax RP *et al* (1999). Self-medication of antibacterials without prescription (also called 'over-the-counter' use). A report of a Working Party of the British Society for Antimicrobial Chemotherapy. *Antimicrob Chemother*; 44(2): 163-77.

Reichman LB (1996). Multidrug resistance in the world: the present situation. *Chemotherapy;* 42: 2-9.

Reyes H, Guiscafre H, Munoz O (1997). Antibiotic noncompliance and waste in upper respiratory infections and acute diarrhea. *Journal of Clinical Epidemiology;* 50: 1297-1304.

Rice LB (1999). Successful interventions for Gram-negative resistance to extended-spectrum B-Lactam antibiotics. *Pharmacotherapy;* 19: 102S-128S.

Rieder H, Cauthen G, Comstock G *et al* (1989). Epidemiology of tuberculosis in the United States. *Epidemiology Review*; 11: 79-98.

Rodolfo J, Lozano J, Ruiz J *et al* (1997). Drug prescription patterns of recently graduated physicians in Colombia [abstract]. *J Clin Epidemiology*; 50 Suppl 1: 26S.

Ronsmans C, Islam T, Bennish ML (1996). Medical practitioners" knowledge of dysentery treatment in Bangladesh. *BMJ*; 313: 205-6.

Rosas I, Salinas E, Yela A *et al* (1997). Escherichia coli in settled-dust and air samples collected in residential environments in Mexico City. *Applied and Environmental Microbiology;* 63: 4093-4095.

Rubin N, Foxman B (1996). The cost-effectiveness of placing urinary tract infection treatment over the counter. *Journal of Clinical Epidemiology;* 49: 1315-1321.

Saavedra J (2000). Probiotics and infectious diarrhea. *Am J Gastroenterol*; 95(1 Suppl): S16-8.

Sack RB, Rahman M, Yunus M *et al* (1997). Antimicrobial resistance in organisms causing diarrheal disease. *Clin Infect Dis*; 24 Suppl 1: S102-5.

Salako LA (1991). Drug supply in Nigeria. *J Clin Epidemiol*; 44 Suppl 2: 15S-9S.

Sbarbaro JA (1997). Directly observed therapy: who is responsible? *Clinics in Chest Medicine;* 18: 131-133.

Scharfstein JA, Paltiel AD, Weinstein M (1999). The cost-effectiveness of prophylaxis for *mycobacterium avium* complex in Aids. *International Journal of Technology Assessment in Health Care;* 15: 531-547.

Schentag JJ (1999). Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance. *J Chemother*; 11(6): 426-39.

Scrimshaw NS, SanGiovanni JP (1997). Synergism of nutrition, infection, and immunity: an overview. *Am J Clin Nutr*; 66(2): 464S-477S.

SDDTTCG (Selective Decontamination of the Digestive Tract Trialists' Collaborative Group) (1993). Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. *BMJ*; 307: 525-32.

Sebille V, Chevret S, Valleron AJ (1997a). Modelling the spread of resistant nosocomial pathogens in an intensive care unit. *Infect. Control Hosp. Epidemiology;* 18: 84-92.

Sebille V, Valleron AJ (1997b). A computer simulation model for the spread of nosocomial infections caused by multidrug resistant pathogens. *Comput. Biomed. Res;* 30: 307-22.

Seppala H, Klaukka T, Vuopio-Varkila J *et al* (1997). The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med*; 337(7): 441-6.

Settle CD, Wilcox MH (1996). Review article: antibiotic-induced Clostridium difficile infection. *Aliment Pharmacol Ther;* 10: 835-841.

Shafer RW, Edlin BR (1996). Tuberculosis in patients infected with human immunodeficiency virus: perspective on the past decade. *Clinical Infectious Diseases;* 22: 683-704.

Shakoor O, Taylor RB, Behrens RH (1997). Assessment of the incidence of substandard drugs in developing countries. *Trop Med Int Health*; 2: 839-45.

Shahid NS, Rahaman MM, Haider K *et al* (1985). Changing pattern of resistant Shiga bacillus (Shigella dysenteriae type 1) and Shigella flexneri in Bangladesh. *J Infect Dis*; 152: 1114-9.

Sheretz RJ, Reagan DR, Hampton KD *et al* (1996). A cloud adult: the Staphylococcus aureus-virus interaction revisited. *Ann Intern Med;* 124: 5395-47.

Shimada M, Kamakura T, Ita Saka H *et al* (1993). The significance of methicillin-resistant Staphylococcus infection in general surgery: a multivariate analysis of risk factors and preventive approaches. *Surg. Today;* 23: 880-884.

Shlaes DM, Gerding DN, John JF Jr *et al* (1997). Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Clin Infect Dis*; 25(3): 584-99.

Shoji KT, Axnick K, Rytel MW (1974). Infections and antibiotic use in a large municipal hospital 1970-1972: a prospective analysis of the effectiveness of a continuous surveillance program. *Health Lab. Science;* 11: 283-92.

Sieradzki K, Roberts RB, Serur D *et al* (1999). Heterogeneously vancomycin-resistant Staphylococcus epidermidis strain causing recurrent peritonitis in a dialysis patient during vancomycin therapy. *J Clin Microbiol*; 37(1): 39-44.

Silvestri L, Mannucci F, van Saene HK (2000). Selective decontamination of the digestive tract: a life saver. *J Hosp Infect*; 45(3): 185-90.

Simmons B, Bryant J, Neiman K *et al* (1990). The role of handwashing in prevention of endemic intensive care unit infections. *Infect Control Hosp Epidemiol;* 11: 589-594.

Singh J, Raje N (1996). The rise of Western medicine in India. *Lancet*; 348: 1598.

Sirinavin S, Suvanakoot P, Sathapatayavongs B *et al* (1998). Effect of antibiotic order form guiding rational use of expensive drugs on cost containment. *Southeast Asian Journal of Tropical Medicine and Public Health;* 29: 636-642.

Shanson DC, Johnstone D, Midgley J (1985). Control of a hospital outbreak of methicillin-resistant Staphylococcus aureus infections: value of an isolation unit. *J Hosp Infect*; 6(3): 285-92.

Sia I, Valerio J (1997). The effects of an intervention on the selling behaviour of sarisari (variety) store keepeers in some villages in the Philippines. Presented at ICIUM Chang Mai. http://www.who.int/dap-icium/posters/3C4_txtf.html

Skaer TL, Sclar DA, Won JK (1993). Effect of academic detailing on the utilisation of intravenous antimicrobial therapy. *Current Therapeutic Research;* 53: 349-355.

Skull S, Shelby-James T, Morris P *et al* (1999). Streptococcus pneumoniae antibiotic resistance in Northern Territory children in day care. *J Paediatr Child Health*; 35(5): 466-71.

Smith DW (1999). Decreased antimicrobial resistance after changes in antibiotic use. *Pharmacotherapy;* 19: 129S-132S.

Smith RD (1999). Antimicrobial resistance: the importance of developing long term policy. *Bulletin of the World Health Organization*; 77(10): 862.

Smith RD, Coast J (2001). Antimicrobial resistance and Global Public Goods for Health. *Global Public Goods for Health.*Beaglehole R, Woodward D, Drager N *et al* (ed), World Health Organization (forthcoming).

Smith RD, Coast J (1998). Controlling antimicrobial resistance: a proposed transferable permit market. *Health Policy*; 43(3): 219-32.

Smith RD, Coast J, Millar MR (1996). Over-the-counter antimicrobials: the hidden costs of resistance. *Journal of Antimicrobial Chemotherapy;* 37: 1031-1032.

Spratt BG (1996). Antibiotic resistance: counting the cost. *Curr Biol*; 6(10): 1219-21.

Spika JS, Waterman SH, Hoo GW *et al* (1987). Chloramphenicol-resistant Salmonella newport traced through hamburger to dairy farms. A major persisting source of human salmonellosis in California. *N Engl J Med*; 316(10): 565-70.

Sohn YM, (1998). Use of vaccine in the era of antimicrobial resistance: need of effective pneumococcal vaccines. *Yonsei Medical Journal;* 39: 611-618.

Sonnenberg F, Beck J (1993). Markov models in medical decision making: a practical guide. *Medical Decision Making;* 13: 322-338.

Spanik S, Krupova I, Drgona L *et al* (1998). Etiology, cost of antimicrobial therapy and outcome in neutropenic patients who developed bacteremia during antimicrobial prophylaxis: a case-controlled study. *Antiinfective Drugs and Chemotherapy;* 16: 223-226.

Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance (1998). The Path of Least Resistance. The Publications Unit, PHLS Headquarters Office, 61 Colindale Avenue. London NW9 5DF. Also available @ http://www.doh.gov.uk/smac/html

Starling CEF *et al* (1997). Applying the Centers for Disease Control and Prevention and National Nosocomial Surveillance system methods in Brazilian hospitals. *American Journal of Infections Control;* 25: 303-311.

Steinke D, Davey P (2000). The association between antibiotic resistance and community prescribing: a critical review of bias and confounding in published studies. *Clinical Infectious Disease* (in-press).

Strang JK (1996). Tracing patients in rural Africa. *Lancet*; 348: 1083-4.

Strausbaugh LJ, Jacobsen C, Sewell DL *et al* (1992). Antimicrobial therapy for methicillin-resistant Staphylococcus aureus colonization in residents and staff of a veterans affairs nursing home care unit. *Infection Control and Hospital Epidemiology;* 13: 151-159.

Sugden R, Williams A (1978). *The principles of practical cost-benefit analysis*. Oxford: Oxford University Press.

Summerfield D (1993). Health in the developing world. Health loses out to the arms trade. *BMJ*; 307: 387.

Suo J, Yu M, Lee C *et al* (1996). Treatment of multidrug resistant tuberculosis in Taiwan. *Chemotherapy*; 42 (suppl. 3): 20-23.

Swann Committee (1969). Report of Joint Committee on the Use of antibiotics in Animal Husbandry and Veterinary medicine. HMSO, London, September 1969.

Taylor RB, Shakoor O, Behrens RH (1995). Drug quality, a contributor to drug resistance? *Lancet*; 346: 122.

Teare EL (1999). UK handwashing initiative. *J Hosp Infect*; 43(1): 1-3.

Temte JL, Shult PA, Kirk CJ (1999), Amspaugh J. Effects of viral respiratory disease education and surveillance on antibiotic prescribing. *Fam Med;* 31(2): 101-6.

Thamlikitkul V (1988). Antibiotic dispensing by drug store personnel in Bangkok, Thailand. *J Antimicrob Chemother*; 21: 125-31.

Thompson D (1999). The costs of antimicrobial treatment failure in Acute Otitis Media. *The American Journal of Managed Care;* 5: S1000-S1003.

Thwaites RT, Frost JA (1999). Drug resistance in Campylobacter jejuni, C coli, and C lari isolated from humans in north west England and Wales, 1997. *J Clin Pathol*; 52(11): 812-4.

Toltzis P, Yamashita T, Vilt L *et al* (1998). Antibiotic restriction does not alter endemic colonisation with resistant Gram-negative rods in a pediatric intensive care unit. *Critical Care Medicine;* 26: 1893-1899.

Tomasz A (1994). Multiple-antibiotic resistant pathogenic bacteria. A report on the Rockefeller University workshop. *New England Journal of Medicine;* 330: 1247-1251.

U.S. Congress, Office of Technology Assessment (1995). *Impacts of antibiotic-resistant bacteria.* OTA-H-629 U.S. Government Printing Office, Washington DC.

Vakil N, Fennerty MB (1996). Cost-effectiveness of treatment regimens for the eradication of *Helicobacter pylori* in duodenal ulcer. *The American Journal of Gastroenterology;* 91: 239-245.

Valls V, Gomez-Herruz P, Palacios-Gonzalez R *et al* (1994). Long-term efficacy of a program to control methicillin-resistant Staphylococcus aureus. *European Journal of Clinical Microbiol. and Infectious Dis;* 13: 90-95.

Valway SE, Sanchez MP, Shinnick TF *et al* (1998). An outbreak involving extensive transmission of a virulent strain of Mycobacterium tuberculosis. *N Engl J Med*; 338(10): 633-9.

Vanchieri C (1996). Contaminated stethoscopes are common in era of antibiotic resistance. *Ann Intern Med*; 125(2): I54.

van den Bogaard AE, Stobberingh EE (1999). Antibiotic usage in animals: impact on bacterial resistance and public health. *Drugs;* 58(4): 589-607.

van den Bogaard AE, Stobberingh EE (2000). Epidemiology of resistance to antibiotics. Links between animals and humans. *Int J Antimicrob Agents*; 14(4): 327-35.

van der Geest S (1991). Marketplace conversations in Cameroon: how and why popular medical knowledge comes into being. *Cult Med Psychiatry*; 15: 69-90.

van Houten MA, Luinge K *et al* (1998). Antibiotic utilisation for hospitalised paediatric patients. *International Journal of Antimicrobial Agents;* 10: 161-4.

van Oirschot JT (1994). Vaccination in food animal populations. *Vaccine*; 12(5): 415-8.

Vazquez L, Encinas MP, Morin LS *et al* (1999). Randomised prospective study comparing cost-effectiveness of teicoplanin and vancomycin as second-line empiric therapy for infection in neutropenic patients. *Haematologica;* 84: 231-236.

Verwaest C, Verhaegen J, Ferdinande P *et al* (1997). Randomised, controlled trial of selective digestive decontamination in 600 mechnically ventilated patients in a multidisciplinary intensive care unit. *Critical Care Medicine;* 25: 63-71.

Vila J, Vargas M, Ruiz J *et al* (2000). Quinolone resistance in enterotoxigenic escherichia coli causing diarrhea in travelers to india in comparison with other geographical areas. *Antimicrob Agents Chemother*; 44(6): 1731-3.

Wade JJ, Casewell MW (1991). The evaluation of residual antimicrobial activity on hands and its clinical relevance. *Journal of Hospital Infection;* 18: 23-28.

Walsh TJ, Standiford HC, Reboli AC *et al* (1993). Randomised double-blinded trial of Rifampin with Either Novobiocin or Trimethoprim-Sulfamethoxazole against Methicillin-Resistant *Staphylococcus aureus* Colonization: Prevention of Antimicrobial resistance and Effect of Host Factors on Outcome. *Antimicrobial Agents and Chemotherapy;* 37: 1334-1342.

Ward S (1989). Arguments for constructively simple models. *Journal of the Operational Research Society;* 40: 141-153.

Ware G, Ford DJ (1993). Cost benefit of pharmacy audit and nonrestrictive antibiotic policy. *New Zealand Medical Journal;* 106: 120.

Waterer GW, Jennings G, Wunderink RG (1999). The impact of blood cultures on antibiotic therapy in pneumococcal pneumonia. *Chest*; 116: 1278-1281.

Webster J, Faoagali JL, Cartwright D (1993). Elimination of methicillin-resistant Staphylococcus aureus from a neonatal intensive care unit after handwashing with triclosan. *J. Paediatr. Child Health;* 30: 59-64.

Weis SE (1997). Universal directly observed therapy: a treatment strategy for tuberculosis. *Clinics in Chest Medicine;* 18: 155-163.

Wenzel RP, Nettleman MD, Jones RN *et al* (1991). Methicillin-resistant Staphylococcis aureus: implications for the 1990s and effective control measures. *The American Journal of Medicine;* 91: 3B-221S-227S.

White AC, Atmar RL, Wilson J *et al* (1997). Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities and clinical outcomes. *Clinical Infectious Diseases;* 25: 230-239.

WHO (1993). WHO declares tuberculosis a global emergency (press release). Geneva: WHO/31, 23 April.

WHO (1999). World Health Report 1999: making a difference. Geneva: WHO.

WHO (1999). Global tuberculosis control. WHO Report 1999. Geneva: WHO, WHO/TB/99.259.

WHO (1999). Containing Antimicrobial Resistance. Review of the literature and report of a WHO workshop on the development of a global strategy for the containment of antimicrobial resistance, Geneva, Switzerland, 4-5 February 1999. World Health Organization, Geneva, WHO/CDS/CSR/DRS/99.2.

WHO (2000). Global Strategy for the Containment of Antimicrobial Resistance. Geneva. (Draft 1: WHO/CDS/CSR/DRS/2000.1. Draft 2: WHO/CDS/CSR/DRS/2001.2). Due for final release September 2001.

WHO (2000). *Global Tuberculosis Control 2000.* World Health Organization; http://www.who.int/gtb/publications/globrep00/summary.hmtl

WHO Report on the Tuberculosis Epidemic (1995). Geneva, Switzerland: World Health Organization; 1995:1-28. WHO/TB/95.183.

WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994-1997 (1998). http://who.int/gtb/publications/dritw/index/html.

Wilcox MH, Cunniffe JG, Trundle C *et al* (1996). Financial burden of hospital acquired *Clostridium difficile* infection. *Journal of Hospital Infection;* 34: 23-30.

Williams J (1986). Antibiotic Policy. *Scandanavian Journal of Infectious Disease;* 49: 175-81.

Wilson KH, Blitchington RB (1996). Human colonic biota studied by ribosomal DNA sequence analysis. *Appl Environ Microbiol*; 62(7): 2273-8.

Winebrake J J, Farrell AE, Bernstein MA (1995). The Clean Air Act's sulfur dioxide emissions market: estimating the costs of regulatory and legislative intervention. *Resource and Energy Economics;* 17: 239-260.

Wolff MJ (1993). Use and misuse of antibiotics in Latin America. *Clinical Infectious Diseases;* 17: S346-351.

Woodward RS, Medoff G, Smith MD *et al* (1987). Antibiotic cost savings from--formularly restrictions and physician monitoring in a medical-school-affiliated hospital. *The American Journal of Medicine;* 83: 817-823.

World Bank (1993). World Bank Development Report: 1993. Washington: The World Bank.

Yang YH, Fu SG, Peng H *et al* (1993). Abuse of antibiotics in China and its potential interference in determining the etiology of pediatric bacterial diseases. *Pediatr Infect Dis J*; 12: 986-8.

Yew WW (1999). Directly observed therapy, short-course: the best way to prevent multidrug-resistant tuberculosis. *Chemotherapy*; 45: 26-33.

Yoshida J, Kondo H *et al* (1998). Computerised antibiogram for methicillin-resistant staphylococcus aureus in chest surgery. *Japanese Journal of Thoracic and Cardiovascular Surgery;* 47: 368-76.

Zafriri D, Ofek I, Adar R *et al* (1989). Inhibitory activity of cranberry juice on adherence of type 1 and type fimbriated Escherichia coli to eucaryotic cells. *Antimicrob Agents Chemother*; 33(1): 92-8.

Zhang L (1996). Treatment of multidrug resistant tuberculosis in China. *Chemotherapy*; 42 (suppl. 3): 16-19.

Zhang LX, Kan GQ (1992). Tuberculosis control programme in Beijing. *Tuber Lung Dis*; 73: 162-166.

Zwar N, Wolk J, Gordon J *et al* (1999). Influencing antibiotic prescribing in general practice: a trial of prescriber feedback and management guidelines. *Family Practice;* 16: 495-500.

Annex 1: CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF AMR

This annex provides a background to the clinical aspects of AMR.

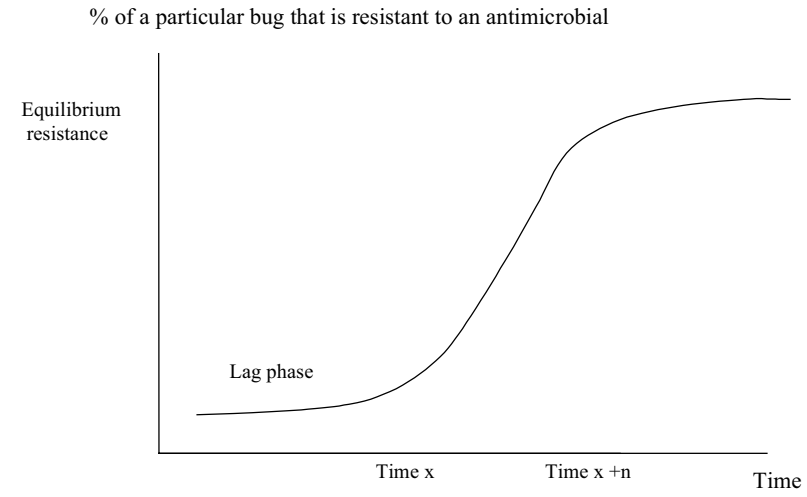
A1.1 Factors contributing to the emergence of resistance in the micro-organism

There are five main mechanisms of antimicrobial resistance: enzymatic destruction; alterations of the cell wall to prevent entry of the antimicrobial; increased efflux of the antimicrobial if entry occurs; chemical modification of the antimicrobial; and modification of the site or metabolic pathway targeted by the antimicrobial. The genetic elements encoding these mechanisms may be inherently present in all strains of an organism. Alternatively, resistance may arise in previously sensitive isolates, through random mutation, or by acquisition from the environment (transformation), other organisms (conjugation), or from bacteriophages (transduction). Such mutation or acquisition is likely to result in an immediate alteration in the sensitivity pattern of the organism.

However, antimicrobial resistance may also develop more gradually, as evidenced by a sequential rise in the MIC (minimum antimicrobial concentration) required to inhibit organism growth until a "breakpoint" is breached (Neu 1994). Once this has occurred, the organism is designated "resistant." Unlike the MIC, the "breakpoint" concentration is arbitrary and international variations in its level make comparison of resistance rates difficult. Standardization of "breakpoints" is, therefore, urgently required.

As might be predicted from Darwinian evolution, antimicrobial usage exerts a selection pressure favouring the emergence of resistance (Austin *et al* 1999c, Arason *et al* 1996, Nissinen *et al* 1995). However, for any particular antimicrobial, the correlation between consumption and resistance is complicated by many factors, including the relative "fitness" of sensitive and resistant strains, together with the existence of genetic elements simultaneously coding for resistance to several antimicrobials (Magee *et al* 1999). In this latter case, a reduction in use of all of the antimicrobials with resistance encoded on these single elements is required before any effect on the sensitivity pattern may be seen. Under constant selection pressure, the proportion of organisms resistant to a given antimicrobial over time results in a curve with a sigmoid (epidemic) distribution, as illustrated in figure A1.1 (Austin *et al* 1999c).

Figure A1.1: The development of antimicrobial resistance over time (adapted from Austin *et al* 1999c)



After a "lag phase", the proportion of resistant organisms increases until an equilibrium is reached. The duration of this "lag phase" is determined by the magnitude of the selection pressure, and the survival advantage antimicrobial resistance confers on organisms. In the presence of a constant selection pressure, a point will eventually be reached at which the rate of resistance development increases rapidly until the proportion of strains resistant to the antimicrobial reaches "equilibrium". At "equilibrium", the proportion of resistant organisms may range from 10% to 90%, and is determined by the relative fitness of resistant and sensitive strains, the genetic basis and stability of resistance, and the magnitude of the selection pressure (Anderson 1999).

Antimicrobial selection pressure may be intensified by exposing micro-organisms to concentrations that are below their MIC, i.e. concentrations that are less than that required to inhibit microbial growth (Burgess *et al* 1999).

Although the acquisition and maintenance of resistance mechanisms may exact a "genetic cost" on the organism, microbial adaptations may occur within the organism that minimize this (Spratt 1996). In some organisms, the "maintenance costs" of resistance may be negligible, or resistance may confer other advantages (e.g. beta-lactamase resistance in *S. aureus*). This may explain why some organisms retain their resistance pattern despite the removal of specific selection pressure. For some organisms, antimicrobial resistance appears to be reversible (Arason *et al* 1996, Nissinen *et al* 1995,

Seppala *et al* 1997), although the "time to decay" is likely to be longer than the "lag time" to generation (Austin *et al* 1999*a*)[14].

The "genetic cost" to the organisms may also be manifest in alterations in virulence and transmissibility. In some organisms and/or strains, resistance may be associated with a reduction in virulence (Field & Coen 1986), while in others virulence is equal (Muder *et al* 1991) or enhanced (Bisognano *et al* 1997). Transmissibility may also be similarly affected.

A1.2. Factors contributing to the emergence of resistant organisms in an individual

Resistant micro-organisms can be acquired either directly, or indirectly from food, (Bower *et al* 1999, Spika *et al* 1987), animals (van den Bogaard 2000, Fey *et al* 2000), inanimate surfaces, and from contact with other individuals. Travel to areas with higher rates of antimicrobial resistance is also an important element.

In an individual patient, any factor leading to compromised antimicrobial activity, e.g. the presence of medical devices (Sieradzki *et al* 1999), limited access to the site of infection, whether anatomical (Kroodsma *et al* 1994) or otherwise (e.g. abscesses), predisposes to the emergence of resistant micro-organisms. Prolonged or recurrent treatments and co-existing medical conditions, especially immunosuppression, are also critical factors.

Antimicrobial exposure inevitably exerts a selection pressure on the pathogen being actively treated, as well as commensal organisms, 80% to 90% of which are currently non-culturable (Wilson & Blitchington, 1996; Langendijk *et al* 1995). Therefore, its potential to act as a reservoir for antimicrobial resistance genes may be immense. As the "normal" commensal flora acts to inhibit the attachment and multiplication of pathogenic micro-organisms by various mechanisms, its disturbance may also facilitate colonization with exogenously acquired pathogens. Consequently, the aim of antimicrobial therapy must be to destroy the pathogen rapidly and efficiently, while producing the least amount of "collateral" damage. This can be achieved by giving careful consideration to the agent employed, its spectrum of activity, method of administration, penetration to the site of infection, magnitude of dose, frequency of administration, duration of therapy, and the use of agents in combination, such as in TB and HIV therapy.

The importance of optimizing antimicrobial therapy on an individual basis is increasingly being recognized. This is especially important for agents with low therapeutic indices (e.g. aminoglycosides), or for the management of serious infections requiring prolonged therapy (e.g. endocarditis or osteomyelitis) (Schentag 1999).

[14] There are three main reasons why removal of selection pressure may not be associated with a decrease in the prevalence of resistance. First, some resistances are linked (Paterson *et al* 2000), requiring a reduction in the use of all associated antimicrobials to produce any impact. Second, the resistance mechanism or gene encoding may provide an unrelated selective advantage to the organism. Third, the "genetic cost" to the organism of maintaining resistance in the absence of selection pressure may be minimal.

Just as the presence of resistance determinants has implications for the genetic "fitness" of the micro-organism, infection with resistant organisms has important consequences for the individual. Antimicrobial resistance may delay the onset of effective therapy and increases the risk of hospitalization, morbidity, and mortality (McCaig & Hughes 1995), as well as the costs associated with patient management (Cox *et al* 1995). The emotional burden to patients and relatives is difficult to determine but may be substantial (Kennedy & Hamilton 1997). In addition, the presence of resistant organisms may restrict patients' freedom and also directly limit further treatment options (e.g. as is the case for cystic fibrosis patients who acquire MRSA or *Burkholderia cepacia*). Alternative antimicrobial agents may be less effective, less convenient and/or have more adverse effects (e.g. vancomycin and teicoplanin in the treatment of MRSA).

A1.3. Factors contributing to the emergence of resistant-organisms in health care settings

Hospitals provide an ideal environment for the emergence and spread of resistant organisms (Schlaes *et al* 1997). The widespread use of antibiotics for both treatment and prophylaxis has resulted in an environment with an increasingly antimicrobial resistant endemic flora. This is exacerbated by the tendency for hospitalized patients to receive broader spectrum agents than those treated in the community. The choice of antimicrobial agent used for empirical and prophylactic therapy in a hospital is determined largely by the prevalence of resistance within that institution and the community it serves.

Increasing numbers of resistant organisms are likely to require antimicrobials with ever broader spectrums of activity, which, in turn, will lead to escalating costs, exacerbate the problem of resistance, and limit future antimicrobial treatment choices. The situation is further complicated by the presence of increasing numbers of patients who are particularly vulnerable to infection, either through an underlying disease process (e.g. AIDS, malignancy), or through medical interventions (e.g. chemotherapy, organ transplantation, catheterization). Hospital patients, in general, may also have alterations in their commensal flora induced by diet and stress, which further increases their susceptibility to acquisition or overgrowth of resistant organisms.

As well as promoting the development of resistant organisms, hospitals also provide greater opportunities for subsequent transmission between individuals and between individuals and the environment. Some species of organisms are intrinsically more transmissible than others, e.g. *Eschericia coli* O157 compared with *Campylobacter sp.* However, transmissibility also varies with different strains within the same species, e.g. *Burkholderia cepacia* (Clode *et al* 2000), *Mycobacterium tuberculosis* (Valway 1998). The presence of antimicrobial resistance is a further influencing factor, resulting in organisms with a decreased (Garcia-Garcia *et al* 2000), equivalent, or increased ability to spread (Haas *et al* 1998) when compared to sensitive organisms.

Studies on outbreaks of resistant organisms in health care settings have implicated transient carriage on the hands, rather than colonization, of health care workers as the main mode of transmission in the health care settings (Martin *et al* 1994). Enhanced

transmission of MRSA from nasally colonized staff has, however, been documented in the presence of viral upper respiratory tract infections (Sheretz *et al* 1996).

Transmission of resistant organisms may occur directly, or indirectly from equipment (e.g. stethoscopes (Vanchieri 1996), beds (Orr *et al* 1994), respiratory equipment (Gorman *et al* 1993, Cefai *et al* 1990), other surfaces (Dancer 1998)), between patients and between patients and health care workers. Spread is further facilitated by the cohorting of particularly vulnerable patients, as evidenced by two recent outbreaks of multi-drug resistant (MDR) TB in HIV positive patients in two London hospitals (Breathnach *et al* 1998, Hannan *et al* 2000).

A1.4. Factors affecting emergence of resistant organisms in a community

Individuals within the community are also being exposed to ever-increasing numbers of antimicrobials. Indeed, in the UK, it has been estimated that 80% of all human antimicrobial prescribing is in the community, with a large proportion thought to be unnecessary (Standing Medical Advisory Committee report). It is therefore not surprising that recent studies have suggested that resistant organisms may be more prevalent in the community than was previously considered (Felmingham & Gruneberg 2000, Garau *et al* 1999, Ewig *et al* 1999).

The large volume of antibiotics used in the community reflects a public and professional perception that antimicrobials are generally safe and advantageous. Factors influencing prescribing practices include patient, peer, commercial expectations and pressures, as well as fear of the consequences of non-treatment (Avorn *et al* 1987).

In communities where antimicrobial use is relatively high, resistance rates in both pathogens (Felmingham *et al* 2000, Vila *et al* 2000) and commensals (Arason *et al* 1996) exceed those for areas where stricter control is exercised. Nevertheless, regulation may decrease the rate of development rather than prevent its emergence. In the UK, the advantages of permitting over-the-counter access to a limited range of antimicrobial agents (Reeves *et al* 1999) have recently been discussed. The availability of over-the-counter antimicrobials has generated much debate (Smith *et al* 1996, Bauchner and Wise 2000, ands the House of Lords Select Committee on Science and Technology's 7th Report 1998).

The total volume of antimicrobial consumption in agriculture is much greater than the total human consumption, and as such the "environmental" impact would be expected to be greater. The use of antimicrobials at sub-inhibitory concentrations as growth promoters in livestock has generated particular concern. However, the relationship between antimicrobial use in animals and the emergence of resistant organisms in humans is still debated. Nevertheless, some studies have suggested that epidemiological links can be demonstrated (Thwaites *et al* 1999, van den Bogaard *et al* 1999). The use of antibiotic resistance as a gene uptake marker in genetically modified crops is also a potential cause for concern (Jones 1999).

In humans in developing countries, it is likely that inadequate dose, duration of treatment, or inappropriateness of the agent used is particularly important in promoting resistance development, with both short- and long-term implications for the individual and the local and global community.

Once resistance has emerged, its spread within the community is facilitated by alterations in population demographics, together with social changes and attitudes. In the developed world, different working patterns have resulted in an increased number of day-care centres for young children. Transmission of resistant organisms within these facilities has been described (Skull *et al* 1999). At the other extreme, longer life spans have effectively led to cohorting of particularly vulnerable individuals in residential and nursing homes (Millar *et al* 1994*,* Cox *et al* 1995). Changes in behaviour patterns, such as an increase in sexual promiscuity and "sex tourism" also contributes to the burden of resistance. Travel to, and immigration from, areas where resistance is more common is becoming increasingly relevant, as is increased population density in urban areas, with the establishment of "urban ghettos".

Annex 2: CONCEPTUALIZING RESISTANCE AS AN EXTERNALITY

Antimicrobial resistance is an externality associated with the production of health[15]. That is, the consumption[16] of a good (the antimicrobial) to improve "health" generates an external effect in reducing the susceptibility of disease to treatment by that (and potentially other) antimicrobial treatments. Such an externality is the result of privately optimal decisions excluding a relevant societal cost, and thus creating a discrepancy between that optimal private decision and the optimal societal decision[17].

More specifically, antimicrobial resistance is a **negative** externality because it has adverse consequences for society as a whole, whereby the cost borne by the individual is somewhat less than that borne by society. This can be illustrated graphically as follows[18].

Figure A2.1 shows the incremental value (inverse demand) curve for antimicrobials, plotting the quantity of antimicrobials consumed against the marginal value of consumption of those antimicrobials. The higher curve, V^1, occurs if patients know for certain that the bacteria involved are not resistant to antimicrobials. The lower curve, V^2, occurs if patients know for certain that bacteria are resistant. Patients are unlikely to know in advance whether their infection will resist treatment from an anti-microbial or not, and thus their inverse demand, or incremental value curve, is therefore the probability weighted average of the two curves, V^1 and V^2. This is signified by V^*.

The essence of the problem is that the probability of resistance (P) rises with aggregate use, thus V^* begins on the left axis at V^1 and eventually approaches V^2 as aggregate use rises. If private marginal cost (C) is considered to be constant for ease of analysis, then private optimal consumption is where private marginal cost (C) intersects the inverse demand curve V^* at quantity N^0. Marginal social cost from this activity occurs because each additional dose changes the probability (P) that all users confront resistant bacteria. This external cost, if added to the private cost (C), creates marginal social cost (SMC). This will be equivalent to (C) where the quantity of anti-microbials consumed is zero, but will steadily rise, thus the divergence between SMC and C will increase the more that anti-microbials are consumed. From a societal prospective, optimal consumption is, therefore, where SMC intersects V^* which will be at N^1.

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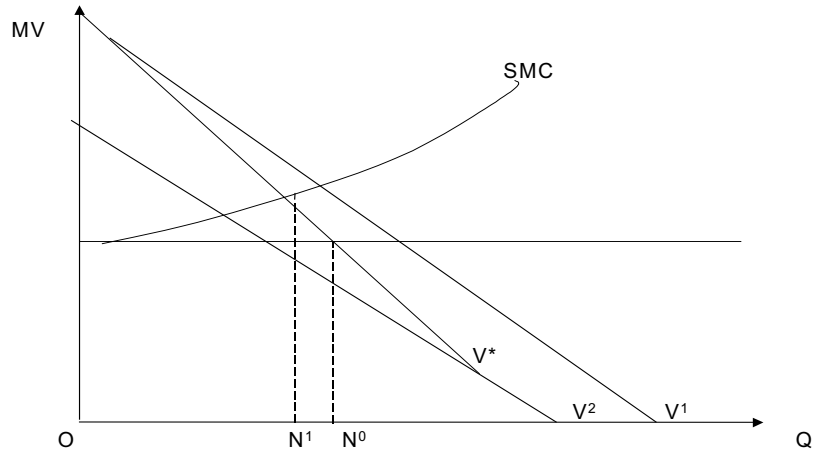
[15] And, of course, in its agricultural use, the production of food. Incorporation of this would add complexity to the model, and for the policy maker to determine the balance of human resistance with productivity levels of meat production. The view taken in this report is that the general boundaries between health and agriculture within government means that resistance, and the impact of antimicrobial use, may be separately modelled within each sector. The exogenous influence of agricultural use may be integrated without upsetting the general conceptual model presented for the health sector.

[16] Note that this externality is not associated with the production of antimicrobials *per se*, but with their consumption.

[17] The essential problem therefore being the difference being individual and population maximisation of "health" (particularly in the presence of third party funding of treatment).

[18] Based on Phelps (1989).

Figure A2.1: External cost of resistance



Where MV = marginal value
Q = quantity of antimicrobials consumed

Mathematically, this relationship may be expressed as follows[19]:

$$E^R_t = f(A_t, X^i_t) \qquad (1)$$

where E^R_t = the extent of the (negative) externality in time *t*;
A_t = the quantity of antimicrobials consumed in time *t*;
X^i_t = a vector of other factors that may determine the level of resistance.

While each single use of an antimicrobial has only a small effect on the probability of a resistant strain developing (i.e. small impact on E^R_t), these minor consequences add up across all other users within society. Within this vector will be included the natural level of resistance that exists in a population, resistance produced in previous time periods and increases in resistance that might result from factors such as population mobility and population density.

In general, antimicrobials are expected to have a positive impact upon the treated individual, as well as upon those individuals who would, in the absence of antimicrobials, have been infected by the treated individual. Thus, resistance is just one of a number of costs and benefits that can be expected to arise from the use of antimicrobials. Costs, which may occur (in addition to resistance), are the side-effects associated with antimicrobial use, drug and administration costs, and the problem that use of antimicrobials can make diagnosis of the cause of infection difficult. Benefits, conversely, may include an improved outcome for the patient, reduced transmission of pathogens that would lead to disease in others, and a reduction in morbidity associated with sub-clinical infections that would otherwise be "accidentally" treated. The latter two

[19] Based on Coast *et al* (1998).

benefits in essence comprise a **positive** externality, which results from taking antimicrobials. The format of this externality is as described below:

$$E^{P}_{t} = f(A_t, E^{R}_{t}, X^{i}_{t},) \qquad (2)$$

where E^{P}_{t} = the positive externality associated with reduced transmission and treatment of sub-clinical infections during time *t*;
A_t = the quantity of antimicrobials used in time *t*;
E^{R}_{t} = as before (the extent of resistance in time *t*);
X^{i}_{t} = a vector of exogenous factors that might influence the positive externality.

It is important to note the presence of E^{R}_{t} in this equation. This represents the fact that, as time progresses and resistance increases, the positive externality associated with reduced transmission may in itself be reduced.

The net benefit that might be expected to result from antimicrobial usage in any period would therefore be:

$$NB^{A}_{t} = f(B_t, E^{P}_{t}, C_t, S_t, D_t, E^{R}_{t}, A_t, X^{i}_{t}) \qquad (3)$$

where NB^{A}_{t} = the net benefit resulting from antimicrobial usage in time *t*;
E^{P}_{t}, E^{R}_{t}, A_t, and X^{i}_{t} are defined as previously;
B_t = the direct benefit to the patient of taking the antimicrobial;
C_t = the drug plus administration cost;
S_t = the cost associated with side-effects;
D_t = problems caused by difficulties in diagnosis.

Whether policies aimed at reducing antimicrobial usage will be beneficial to society overall will depend on the net effects of antimicrobial usage at the margin, which will in turn depend upon the relative size of each of the elements in equation (3).

Annex 3: EXPERTS/INSTITUTIONS INITIALLY CONTACTED

A3.1 Clinical experts

Professor Wise
Department of Medical Microbiology
City Hospital Trust
Birmingham
UK

Professor Hart
Department of Medical Microbiology
University of Liverpool
UK

Professor Levy
Alliance for the Prudent Use of Antibiotics
School of Medicine
Tufts University
Boston, MA
USA

Pentti Huovinen
Chief Physician
Antimicrobial Research Laboratory
National Public Health Institute
Finland

Marc Springer
Head of Infectious Diseases Epidemiology
National Institute of Public Health and the Environment
Netherlands

David Livermore
Antibiotic Reference Unit
Laboratory of Hospital Infection
Central Public Health Laboratory
London
UK

Professor Niels Hoiby
Department of Clinical Microbiology
Rigshospitalet
Copenhagen
Denmark

Professor Richet
Laboratoire de Bactériologie
Centre Hospitalier Régional et Universitaire de Nantes
Nantes
France

Francis Fagnani
CEMICA
Bourg La Reire
France

Professor Courvalin
Institut Pasteur
Paris
France

Professor Adam
Klinikum Innenstadt der LMU
Abteilung für Antimikrobielle Therapie und Infektionsimmunologie
Munich
Germany

Professor Garcia-Rodriguez
Departamento de Medicina Preventiva
Universidad de Salamanca
Salamanca
Spain

Professor Giamarellou
Professor of Internal Medicine
Athens University School of Medicine
Athens
Greece

Professor Wiedemann
Pharmazeutische Mikrobiologie
Universität Bonn
Bonn
Germany

Rosalind Plowman
Department of Health
London
United Kingdom

A3.2 Economists with experience in resistance

Professor Charles Phelps
Provost
University of Rochester
New York
USA

Professor Mo Malek
PharmacoEconomics Research Centre
University of St Andrews
St Andrews, Scotland
UK

Professor Peter Davey,
Medicines Monitoring Unit
Ninewells Hospital and Medical School
Dundee, Scotland
UK

Professor Alan Garber
Med/Primary Outcomes
Stanford University
Stanford, CA
USA

A3.3 Institutions

Health Economists Study Group
(Mailing list of health economists)

Medical Research Council
London
UK

Wellcome Institute for the Study of the Epidemiology of Infectious Diseases
The Wellcome Trust
London
UK

Public Health Laboratory Service
London
UK

WHO
Geneva
Switzerland

Pasteur Institute
Paris
France

Centers for Disease Control and Prevention
Washington, D.C.
USA

A3.4 Developing countries (provided by the Global Forum/WHO and contacted on 20 June 2000)

Dr Mahmud Khan
khan@mailhost.tcs.tulane.edu

Dr Andrew Kitua
akitua @twiga.com

Dr N K Ganguli
icmrhqds@sansad.nic.in

Dr Adolfo Martinez Palomo
amartinez@infadm.inf.cinvestav.mx

Annex 4: INITIAL LETTER SENT

Dear xxxx,

Re: Costs and/or effectiveness of interventions to prevent and/or control antimicrobial resistance

We are currently receiving funding from the World Health Organization to conduct a literature review concerning interventions to prevent and/or control antimicrobial resistance. Within this we are aiming both to review current knowledge about the cost and/or effectiveness of interventions aimed at reducing the emergence and spread of antimicrobial resistance, and subsequently to develop a model enabling assessment of interventions aiming to reduce resistance.

As a leading expert in this field, we are writing to ask if you:

- have conducted, or know of, any unpublished work in this area;
- have conducted, or know of, any work in this area that has been published only in non-peer reviewed literature, such as monographs, internal reports, PhD theses, etc.;
- have conducted, or know of, any previous reviews conducted in this specific area;
- are taking part in, or know of, any ongoing projects of relevance to this area;
- know of anyone undertaking similar work.

We will, of course, be very pleased to send you a copy of the final report from the project, and would very much appreciate any assistance you can give us.

With best wishes,

Yours sincerely,

Annex 5: SUBSEQUENT CONTACTS

Dr Val Edward-Jones
Biological Sciences
Manchester Metropolitan University
Manchester
UK

Dr Catherine Goodman
London School of Hygiene and Tropical Medicine
London
UK

Dr Ramanan Laxminarayan
Resources for the Future
Washington, DC
USA

Dr Marc Saez
Departamento d'Economia
Universidad de Gerona
Spain

Dr Jonathon Simon
The Harvard Institute for International Development
Harvard University
Harvard
USA

Dr Martin Hensher
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Directorate: Health Financing & Economics
Department of Health
Private Bag X828
Pretoria 0001
South Africa

Annex 6: DETAILED RESPONSE FROM CONTACTS

All the initial and subsequent contacts replied[20] stating they were not undertaking current research into the cost and/or effectiveness of *interventions* to address AMR, nor did they know of such work being conducted elsewhere, except for the following:

- Catherine Goodman, London School of Hygiene and Tropical Medicine, UK, informed us of work on resistance and antimalarials, which was coincidentally being funded by the Global Forum (Goodman *et al* 1998; Goodman *et al* 1999). However, as outlined in the methods section, the review was restricted to antimicrobials, *excluding* antimalarials. A brief review of the findings of this work is, however, included as it was deemed to be an important piece of work that was readily available, and in which the Global Forum had invested financial resources.
- Meredith Caelli, New South Wales Hospital Infection Epidemiology and Surveillance Unit, University of New South Wales in Sydney, Australia, is currently undertaking a cost-effectiveness study of the use of tea tree oil as a decolonization agent for adult inpatients isolating MRSA. There is no report available for this work as yet, as the study only recently began.
- Marc Saez, University of Girona, Spain, is currently in the middle of a project considering resistant infection in ICU and in the community. Again, there are no reports available at present.
- There is a supplement to the journal "Clinical Infectious Diseases", which will soon be published, focusing on the evidence linking prescribing in primary care to resistance. A paper by Steinke and Davey (2000) is reviewed in the results section.
- The Public Health Laboratory Service has recently published a report concerning the "socio-economic burden of hospital acquired infection" (Plowman *et al* 1999). This report is somewhat tangential, as it does not consider resistance directly.

[20] It should be noted that contacts for developing countries were not made until 20 June 2000, and as of 31 August 2000 (when data gathering for this report was completed) there had been no response from them.

Annex 7: MATRIX OF SEARCH TERMS

	Resistan$				
	Antimicrobial	**Antibiotic**	**Antiviral**	**Antimalarial**	**Antiprotozoal**
Cost	(200)	(207)	(10)	(6)	(0)
Intervention	(194)	(84)	(34)	(1)	(0)
Control	(10)	(949)	(181)	(4)	(19)
Prevention	(195)	(237)	(43)	(0)	(2)
Rotation	(2)	(3)	(2)	(0)	(1)
Restriction	(136)	(482)	(38)	(0)	(5)
Combination	(611)	(916)	(273)	(1)	(14)
Strateg$	(180)	(248)	(132)	(2)	(3)
Cohorting	(4)	(10)	(0)	(0)	(0)
Isolation	(218)	(485)	(63)	(0)	(5)
Hand washing	(8)	(11)	(0)	(0)	(0)
Education	(34)	(44)	(0)	(0)	(0)
Disinfection	(22)	(237)	(0)	(0)	(0)
Model$	(241)	(605)	(239)	(1)	(14)
Economic	(35)	(36)	(2)	(0)	(2)
Policy	(39)	(85)	(2)	(0)	(0)
Surveillance	(334)	(295)	(7)	(0)	(1)
Consumption	(53)	(78)	(3)	(0)	(2)
Prescription	(21)	(44)	(2)	(0)	(0)
Vaccination	(34)	(70)	(18)	(0)	(5)

Annex 8: BIBLIOGRAPHIC DATABASES SEARCHED

- **Medline** (1966 to 2000). This database is provided by the US National Library of Medicine and is widely recognized as the premier source for bibliographic and biomedical literature. It contains more than 9.5 million records from more than 3,900 journals.
- **ISI** (the Institute of Scientific Information) **citations database** (1981-2000), which comprises the Science Citation Index Expanded and Social Sciences Citation Index.
- **EMBASE** consists of three separate databases (1980 to 2000): (i) EMBASE: excerpta medical database; (ii) EMBASE drugs and pharmacology; and (iii) EMBASE psychiatry. This database covers articles from over 3,500 international journals.
- **Greyliterature** consists of literature produced by all levels of government, academic, business and industry in print and electronic formats (which are not controlled by commercial publications). Quarterly reports are available from 1999 onwards.
- **The York Database** (established 1994) consists of the NHS Evaluation Database and the Database of Abstracts of Reviews of Effectiveness (DARE).
- **OPAC 1997** is the major document and reference supply centre for the British Library. It contains all modern books and periodicals from the United Kingdom and overseas. Two reference databases were accessed: (i) the Science, Technology and Business Collection (1975 to 2000); and (ii) the Humanities and Social Sciences Collection (1975 to 2000).
- **The Cochrane Library Online** (1990 to 2000) provides reference material from the Cochrane Collaboration which is an international organization that helps people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions. The following databases were accessed: (i) the Cochrane Database of Systematic Reviews; (ii) the Database of Abstracts and Reviews of Effectiveness; (iii) the NHS Economic Evaluation Database; (iv) the Health Technology Assessment Database; (v) the Cochrane Controlled Trials Register; and (vi) the Cochrane Methodology Register.

Annex 9: SUMMARY OF ALL PAPERS REVIEWED

Table A9.1: Combination therapies and vaccinations

Authors	Country (setting)	Intervention and design	Sample	Main outcome measures	Major finding	Quality
Combination therapies						
Scharfstein *et al* 1999	USA	CEA – using Monte Carlo simulation. Analysis of 5 different treatment regimens were compared: **Intervention 1**: rifabutin – azithromycin – clarithromycin **Intervention 2**: azithromycin – clarithromycin – rifabutin **Intervention 3**: clarithromycin – azithromycin – rifabutin **Intervention 4**: azithromycin/rifabutin combination therapy – clarithromycin **Intervention 5**: clariritromycin/rifabutin combination therapy – azithromycin	Modelled history of HIV and Aids using MC simulation – in which one hypothetical patient at a time is followed from a CD4 (helper) lymphocyte count between 201 and 300/mm^3 to death.	QALYs	The model predicts that the average HIV infected patient with a beginning CD4 count (between 201 and 300/mm^3) has total lifetime costs of approximately USD43,150 and a QALY expectancy of 42-35 months. Azithromycin prophylaxis begun after the CD4 count has declined to 50/mm^3 is the most cost-effective M.avium complex prophylaxis strategy.	Moderate risk
Spanik *et al* 1998	Slovak Republic Hospital	Case Control Study **Intervention**: assessment of neutropenic patients who developed bacteremia during antimicrobial prophylaxis **Control**: neutropenic patients with bacteremia hospitalized in the same centre before prophylaxis introduced.	N=64 cases of bacteraemias during antimicrobial prophylaxis (treatment with oral quinolone plus azole) in meutropenic cancer patients were compared with 128 cases of bacteremia in a cohort of controls.	Etiology Health outcomes Costs of care	Antimicrobial prophylaxis did not increase the proportion of multiresistant isolates causing bacteraemias in patients receiving prophylaxis. However, streptococcal, enterococcal and S. maltophilia bacteraemias were more common in cases receiving prophylaxis. The only benefit that was statistically significant for intervention group was improvement of quality of life due to prolonged afebrile neutropenic days. Costs of care higher in intervention group.	Moderate risk
Walsh *et al* 1993	UK Hospital	Randomized double-blind multicentre comparative trial **Intervention 1**: novobiocin plus rifampin **Intervention 2**: trimethoprime-sulfamethoxazole (T/S) plus rifampin	Patients/personnel infected with MRSA (90 individuals of which 84 were patients).	Successful clearance of MRSA Emergence of resistance to rifampin	Emergence of resistance to rifampin developed more when treated in combination with T/S than with novobiocin.	Moderate risk
De Mann *et al* 2000	Netherlands Hospital	Prospective cross-over study **Intervention A**: penicillin G and tobramycin used for early	Two neonatal intensive care units, 436 neonates included. Intervention A used in one unit	Risk of colonization with resistant gram negative bacilli.	The relative risk for colonization with resistant strains was 18 times higher for amoxicillin-cefotaxime than penicillin-tobramycin.	Moderate risk

		septicemia with tobramycin used for late onset septicemia; **Intervention B**: intravenous amoxicillin and cefotaxime used.	and intervention B used in the other, before swapping antibiotic regimes.			
Vakil *et al* 1996	USA Hospital	Cost-effectiveness analysis A decision analysis designed to test 3 different regimens for the eradication of H.pylori: **Intervention 1**: 2 week triple drug therapy (metronidazole, bismuth, tetracycline with H2 receptor antagonist); **Intervention 2**: 2 week omeprazole and amoxicillin ***Intervention 3****: 2 week omeprazole and clarithromycin* **Control**: traditional H2 receptor antagonist therapy	The precise regimen for the eradication of Helicobacter pylori for duodenal ulcer is uncertain	Cost-effectiveness of alternative interventions.	Intervention 1 (Triple drug therapy) is the optimal regimen in areas where metronidazole resistance rates are <36% and compliance is >53%. Intervention 2 (Omeprazole and amoxicillin) is not cost-effective unless eradication rates are greater than 74%. Intervention 3 (dual drug therapy with omeprazole and clarithromycin) is effective in regions where metronidazole resistance is high or where it is anticipated that there will be poor compliance with the more complicated triple drug therapy regimen.	Moderate risk
Raad *et al* 1997	USA Hospital	Randomized control trial **Intervention**: catheters pretreated with trido-decylmethyl-ammonium chloride and coated with minocycline and rifampin. **Control**: untreated, uncoated catheters.	Set at 5 university based medical centres, n=281 with patients >18 years who required a triple lumen polyurethane central venous catheter.	Quantitative catheter cultures Blood cultures Molecular typing of organisms to determine catheter-related colonization and blood stream infections Cost of infection	Multivariate logistic regression showed that coating catheters with minocycline and rifampin has an independent protective factor against catheter-related colonization. Note: there were no adverse effects related to the coated catheters or antimicrobial resistance levels.	Moderate risk
Laxminarayan *et al* 2000	USA Hospital	Cost analysis - decision tree to model evaluating the costs of three interventions: **Current Therapy**: amoxicillin (AMX), cefaclor/cefixime/ ceftibutin; trimethorprim/ sulfamethoxazole; macrolides; AMX-clavulante (AMX-C); cefuroxime/cefprozil; ceftriaxome. **Suggested Therapy 1**: AMX for initial therapy; and high-dose AMX-C or cefuroxime (CFE) for treatment failure; **Suggested Therapy 2**: High dose AMX; high dose AMX-C; and CFR.	Statistics for modelling derived from 112,534 paediatric patient records from Fee-For-Service providers.	Treatment costs compared between current therapy, suggested therapy 1 and 2, to determine which therapy had the greatest cost reduction.	The two suggested antimicrobial regimens were chosen to minimize treatment failures. However, these therapies also minimized costs when compared to therapy currently prescribed in the USA. High-dose amoxicillin in Treatment Strategy 2, minimized failure the most, while usual dose, amoxicillin in Suggested Therapy 1, minimized the cost most. The model suggested, that as AMR rises, it is of greater benefit to treat using Treatment Strategy 2 in place of Treatment Strategy 1.	Moderate risk
Vazquez *et al* 1999	Spain Hospital	*Randomized Prospective Case Study*	76 febrile episodes from 66 patients with hamatologic	Clinical efficacy was evaluated according to whether or not	The primary success of the 2nd-line therapy was obtained in 35 cases (46%) with no significant	High risk

		Intervention: the use of vancomycin and teicoplanin therapy in patients with neutropenia, after the failure of empirical treatment with a combination of piperacillin/ tazobactam and amikacin.	malignancies under treatment, neutropenia and fever resistant to combination piperacillin/tazobactam and amikacin – based in Spanish hospital	apyrexia was obtained after: (a) 48 hours; (b) 7 days; or at conclusion of (c) aplasia. Costs	difference between vancomycin (17/38) and teicoplanin (18/38). The costs derived from administering vancomycin and monitoring its serum levels; led to teicoplannin treatment having a similar or even lower cost.	
Strausbaugh *et al* 1992	USA Hospital (*Response to control epidemic)	Prospective case study Patients divided into group according to site of colonization and absence of foreign body as believed this affects decolonization therapy. Three treatments: **Group 1**: nasal carriers – active drug for 5 days; **Group 2**: other colonized sites – 2 active drugs for 5 days; **Group 3**: 2 active drugs for 10 days. No controls.	**Group 1**: nasal MRSA colonization, no positive skin wounds, no foreign bodies (n=17) **Group 2**: nasal MRSA or positive MRSA cultures from non-nasal site, no foreign bodies (n=6) **Group 3**: MRSA colonization at nasal or other site and presence of a foreign body (eg catheter, tracheotomy tube) (n= 11).	Rates of colonization Recolonization rates Level or resistance to rifampin	Concluded decolonization programme of rifampin, trimethoprim-sulfamethoxazole and clindamycin was ineffective as colonization of MRSA persisted.	High risk
Vaccinations						
Fine *et al* 1994	Canada Review	Meta-analysis Reviewed 9 randomized trials with 12 vaccine and control study groups evaluating clinical outcomes in adults. Focus on pnuemococcal pneumonia.	Initial review focused on 594 studies.	To estimate a summary size effect for all outcomes, Mantel-Haenszel odds ratios (Ors) and Dersimonian and Laird rate differences (RDs) and associated Confidence Intervals.	Pneumococcal vaccination is efficacious in lowering risk of pneumonia in low-risk adults but not necessarily high-risk.	Moderate risk
Jimenez *et al* 1996	Spain	Cost-effectiveness analysis **Intervention**: examining whether the introduction of a universal vaccination programme for those > 60 years is cost effective over a range of incidence rates of Pneumococcal pneumonia	Target population: 7,454,277 Spaniards aged > 60 years.	Cost-effectiveness of vaccination, number of people who would be prevented from catching pneumonia.	Introduction of a vaccination programme would cost USD97,593,663. Over the subsequent 5 years, with a basal rate of 3 Pneumococcal pneumonias per 1,000 person years, and a 66% vaccine efficacy, the programme results in a net benefit of USD127,142,481 or a benefit-cost ratio of 2.3 and a benefit per case prevented of USD2,656. Thus, the introduction of a vaccination programme for >60 years is cost-effective.	Moderate risk
Farr *et al* 1995	USA Review	Matched Case Control Study to see whether vaccination prevents pneumonia **Intervention**: vaccination **Control**: no vaccination	Patients with Pneumococcal bacteremia who were at least 2 years old or at least 65 years old.	Protective efficacy of Pneumococcal vaccine for the prevention of Pneumococcal bacteremia.	Demonstrates significant protective efficacy of Pneumococcal vaccine for preventing Pneumococcal bacteremia.	Moderate risk

Notes: **Low risk:** plausible bias unlikely to seriously alter results. **Moderate risk:** plausible bias raising some doubt about the results. **High risk :** plausible bias seriously weakening confidence in results.

Table A9.2: Antimicrobial approaches to prevent the emergence of AMR

Authors	Country (setting)	Intervention and design	Sample	Main outcome measures	Major finding	Quality
Antimicrobial restrictions						
Evans *et al* 1990	USA Hospital	Retrospective cohort study **Control:** For 6 months in one year, computer monitored patients receiving pharmaceuticals longer than necessary **Intervention**: Stop-orders on antibiotics	Hospital inpatients. 1985--3665 1986--3991	Number of patients receiving drugs longer than necessary Drug savings from reduced prescribing.	The introduction of a restriction policy reduced the incidence of prescribing for longer than necessary.	Moderate risk
Himmelberg *et al* 1991	USA Hospital	Retrospective cohort study **Intervention**: Removal of antibiotic restriction policy **Control**: Antibiotic restriction policy in place	In depth, retrospective, chart-based drug reviews were conducted for two restricted agents: ceftazidime and imipenem-cilastatin. 42 patients selected for each drug during two time periods.	Quantity and quality of antimicrobial use.	Upon removal of the restriction policy, use of restricted antimicrobials increased by 158%. Restriction policy did not affect mortality and did not appear to affect clinical need for a drug.	Moderate risk
Toltzis *et al* 1998	USA Hospital	Prospective cohort study **Intervention**: Ceftazidime restriction policy **Control**: Baseline prescribing	Consecutive children admitted to ICU pediatric care over a 19-month period.	Change in ceftazidime use. Incidence density of ceftazidime-resistant organisms.	Data fails to indicate that antibiotic restriction policies have little impact on drug resistant organisms.	Moderate risk
Climo *et al* 1998	USA Hospital	Prospective cohort study **Intervention**: Hospital formulary restriction of clindamycin **Control**: no control of clindamycin.	138 patients hospitalized with symptomatic diarrhoea.	Number of c.*difficile* cases Cost impact Effect on other antibiotic drug use	Hospital formulary restriction is an effective way to reduce incidence of resistance. Overall cost savings were realized despite increase in use of alternative antimicrobials.	Moderate risk
Rubin *et al* 1996	USA Community	Cost-effectiveness analysis of the effect of approving over-the-counter sale of oral antibiotics for the treatment of urinary tract infections (UTIs) **Intervention 1:** treatment packaged with a diagnostic dipstick **Intervention 2**: treatment sold alone after a positive test result **Control**: current UTI treatment.	Population size estimated to be about 3.3 million in a given year	The cost per UTI avoided	The economic costs of placing UTI treatment over the counter outweigh the benefits, unless there is extensive patient education to allow for correct diagnosis. Only if visits to the doctor are reduced to 64.6% of the current levels, would the benefits of the UTI treatment be realized.	Moderate risk
Woodward *et al* 1987	USA Hospital	Retrospective case study **Intervention:** antibiotic restrictions – introduced over three phases: (i) November	Before and after comparison at the Barnes Hospital, a 1,208 bed teaching hospital affiliated with the Washington University	Cost savings attributable to restrictions Estimates of higher costs due to substituted drugs	The restriction policy resulted in savings of USD2.61 per day or USD34,597 per month. Even after cost increases associated with substitution effects, the programme saved	High risk.

		1984, vancomycin use controlled; (ii) July 1985 – wide range of drugs (aminoglycosides and cephalosporins)restricted / controlled; (iii) April 1986 – more drugs restricted or controlled. No control	School of Medicine. Note: controlled drugs are subject to a stop-order at 72 hours with restricted drugs removed from the formulary (only available with permission).	Estimates of long-term trends in antibiotic costs. Incidence of bacteremia.	USD24,620 per month for all antimicrobials. In the months following the restrictions, no significant detrimental changes occurred in hospital length of stay or mortality. A retrospective analysis of 322 patients with bacteremia treated before and after restrictions, revealed that antimicrobials were used more effectively after restrictions.	
Rivkin-Berman 1992	USA Hospital	Retrospective case study **Intervention**: the introduction of an antimicrobial monitoring service, with drugs not meeting prescription criteria, substituted for others. No control	Operated for 1 year from July 1989 to June 1990. 3,546 orders for antimicrobials reviewed.	Appropriateness of prescribing physician compliance with the monitoring programme.	86% of antimicrobials met the required criteria. 9% did not meet the criteria (but were still approved), 2% were replaced by alternative therapies, and 2% represented drugs that were inappropriately prescribed. Pharmacist and physician compliance with the monitoring policy has been high.	High risk
Gin *et al* 1994	Canada Hospital	Case study **Intervention**: a drug monitoring programme for clindamycin was introduced. Before and after comparison.	Set in a 985-bed tertiary care hospital. 55 patients in the baseline period with 339 patients in the intervention period.	Number of inappropriate prescriptions. Cost avoidance (if inappropriate therapy had not been delivered)	Before programme 36.4% inappropriate (at an annual cost of USD27,8380) and after intervention, 22% inappropriate (at an annual cost of USD15,798).	High risk
Ware *et al* 1993	NZ Hospital	Prospective evaluation study of antibiotic use and costs. Examines drug audit and effects of information feedback and whether it influences prescribing.	Three periods examined for prescribing in hospital: Period A: retrospective 3 month survey to mid July 1991 Period B: protocol introduced re intravenous antibiotics (July to Sept 1991) Period C: assess the temporal effect of project up to July 1992.	Drug use - rates and choice Some costs	There was a 25% drop in intravenous antibiotic use over the time period concerned with a significant change in choice of antibiotic noted. Costs declined by 56% over the study period.	High risk
Anglim *et al* 1997	USA Hospital (*Response to epidemic)	Retrospective cohort study **Intervention**: vanomycin restriction policy implemented at hospital MRSA outbreak (October 1994). **Compared** with follow-up period: Jan-Feb 1995.	Doctors prescribing vanomycin-hydrochloride during hospitalization.	Number of grammes of vancomycin hydrochloride ordered.	Institution of control resulted in a significant decrease of VRE.	High risk
White *et al* 1997	USA Hospital	Case study: before and after comparison **Intervention**: Restriction policy (pre-approval) for intravenous amikacin, ceftazidime, ciprofloxacin, fluconazole, ofloxacin and ticarcillin/clavulanate	Records of patients with bacteremia due to gram-negative organisms reviewed for the 6-month period immediately before the initiation of antibiotic restrictions (July-Dec 1993) for same months following year.	Antimicrobial expenditures Antimicrobial susceptibility patterns Outcomes for patients with bacteremia due to gram-negative organisms	Requiring pre-approval for selected parenteral agents can decrease antimicrobial expenditures (in this study by 32%) and improve susceptibilities to antibiotics without affecting patient outcomes or length of hospital stay.	High risk

Gould *et al* 1996	UK Hospital	Prospective cohort study **Intervention**: introduction of an education "policy" booklet re appropriate prescribing. Introduction of restricted drugs.	Trends monitored for hospitals in the Grampians region (UK) which serves a population of 500,000.	Number of antimicrobials available for routine and restricted uses, annual expenditure and defined daily doses (DDD) of high expenditure antimicrobial agents.	During period of study, 30 new antibiotics considered for inclusion at hospital formulary but only 7 added and restricted. Despite this, expenditure more than doubled on antimicrobials since 1986, two thirds of increase attributed to new drugs. There was an overall increase of 46% in DDDs – highlight difficulties in controlling prescribing budgets and spread of AMR.	High risk
Morgan *et al* 1997	USA Hospital	Prospective chart review **Intervention**: implementation of a limited restriction policy requiring approval to continue vancomycin therapy beyond 72 hours of care.	A total of 333 courses of vancomycin were reviewed during 1997 for all patients at a university affiliated teaching hospital.	Appropriateness of use based on the Centres for Disease Control (CDC) and Prevention recommendations for prudent vancomycin use.	Vancomycin use not appropriate in 66% of cases. The restriction policy was effective in reducing the total grammes of vancomycin used and the total number of patients exposed to vancomycin decreased by 0.5%. Expenditures decreased by USD15,788 for the 7 month time period although the incidence of VRE remained unchanged – for up to two years after the restrictions introduced.	High risk
Bamberger *et al* 1992	USA Hospital	Prospective cohort study **Intervention 1**: introduction of voluntary guidelines for use of cefotaxime, ceftriaxone and ceftazidime **Intervention 2**: enforcement policy introduced concerning use of three drugs detailed in 1.	Study at Trugman Medical centre, a 300-bed hospital. Intervention 1: n=66 Intervention 2: n=48	Results of two audits concerning interventions compared for usage patterns, compliance with guidelines, use of susceptibility testing, costs.	Only 24.6% of courses of 3rd generation cephalosporins were initiated in compliance with the institutional guidelines for intervention1. Pharmacy expenditures during this period = USD50,000. During Intervention 2, 85.4% complied with guidelines and pharmacy expenditures decreased by 80%.	High risk
Haas *et al* 1997	USA Hospital	Retrospective cohort study Intervention: examining the effect of an antimicrobial substitution (restriction policy) where cefotaxime is replaced with ceftizoxime	Compared clinical findings among 179 adults treated with ceftizoxime and 200 patients treated with cefotaxime treated during the previous year.	Days hospitalized, days of study drug given, number of other antibiotics used, patients receiving follow-up antibiotics, overall levels of mortality.	Ceftizoxime group had a shorter mean length of stay, which paralleled a hospital-wide trend towards more efficient discharge planning. No significant difference in duration of study drug, number of other intravenous antimicrobials or likelihood of receiving additional antimicrobials after study completion. Suggests that substitution policy is effective in that cefotaxime and ceftizoxime are comparable.	High risk
McNulty *et al* 1997	UK Hospital	Before and after comparison **Intervention**: Antibiotic restriction policy aimed to reduce use of cephalosporins.	Examining control policies for *clostridium difficile* infections in an elderly care hospital unit. Before implementation of policy 1,520 patients assessed with 1,612 patients after.	Antibiotic prescribing rates for restricted drugs. Number of cases of c.*difficile* toxin-positive diarrhea	Mortality rates and length of hospital stay, unchanged. Cefuroxime prescribing and total antibiotic prescribing costs £5,150 and £8,622 respectively in the 7 month period after the change with 37 cases of c.difficile diarrhoea in the period before and 16 cases in the period after.	High risk

Prescriber education, feedback and use of guidelines						
Gonzales *et al* 1999	USA Primary care practices	Prospective, non-randomized control trial **Full intervention**: patient intervention (education materials – home and office based) and clinician intervention (education, practice profiling and academic detailing) **Limited intervention**: office based education for patients **Control sites**: usual care	Adults diagnosed as having uncomplicated acute bronchitis (n=2027) Clinicians – 56 physicians, 28 physician assistants, 9 nurses	Antibiotic prescriptions for uncomplicated acute bronchitis	Education of clinicians and patients led to declining prescribing of antibiotics.	Moderate risk
Zwar *et al* 1999	Australia Hospitals	Randomized control trial **Intervention**: Prescriber feedback and management guidelines for upper respiratory tract infection. **Control**: intervention on an unrelated topic.	GP trainees in NSW hospital environment.	Total antibiotic prescriptions per 100 encounters.	Inappropriate prescribing was reduced for upper respiratory tract infections following Prescriber feedback	Moderate risk
Mainous *et al* 2000	USA Medicaid practices	Randomized control study Four groups of primary care physicians: **Intervention 1**: performance feedback only **Intervention 2**: patient education materials only **Intervention 3**: feedback and education; **Control**: no intervention	The study included 216 physicians with 124,092 episodes of care.	Rate of antibiotic prescribing.	Prescriber feedback without reward/penalty is not effective in influencing prescribing practice for viral respiratory disease.	Moderate risk
Kristensen *et al* 1999	Denmark Hospital	Case study (modelling) **Intervention**: a decision support system (DSS) for the guidance of empirical antibiotic therapy for patients with urinary tract infections.	491 bacteraemias seen during 1992-94 were used to construct the DSS (derivation set) and 426 bacteraemias during 1995-1996, were used for the evaluation (validation) set.		A decision-theoretic approach shows promise of improving the empirical antibiotic treatment and may be used as a measure to support antibiotic policy.	Moderate risk
Smith 1999	USA Hospital	Cohort: retrospective **Intervention**: programme to reduce administration of cephalosporin, imipenem and vancomycin to reduce MRSA and VRE through 3-step education programme. No control.	Prescribing clinicians – number not specified.	Use of antibiotics Level of resistance Cost impact	Inappropriate antibiotic use declined following education, as did AMR. Costs of prescribing declined.	High risk

Levine *et al* 1999	USA Hospital	Retrospective cohort study **Aim**: Compared the incidence if group-B streptococcus (GBS) and gram negative neonatal sepsis (GNNS), following the publication of the CDC guidelines — as to whether encourage increased use of intrapartum chemoprophylaxis.	The resultant cases if neonatal sepsis that occurred for deliveries between 1992 and 1997 examined.	Use of intrapartum chemoprophylaxis Incidence of neonatal sepsis Incidence of gram-negative sepsis	This study confirmed the efficacy of published guidelines into reducing vertical transmission of GBS through increased use of intrapartum chemoprophylaxis. However, this reduction in GBS cones at the cost of increasing the incidence of ampicillin-resistant gram-negative neonatal sepsis with an increased mortality.	High risk
Brooks *et al* 1999	USA Hospital	Prospective non-blinded cohort analysis **Intervention**: Guidelines introduced for prophylactic use **Baseline comparison**: treatment given before the introduction of guidelines	Practice guidelines developed for treatment of 7 infectious diseases in ICU. Intervention: n=180 patients (4 month period); baseline: n=158 patients (3 month period)	Infection rates (lower respiratory tract infection (LRTI), urinary tract infection (UTI), sepsis of undetermined etiology); mortality and morbidity; readmission rates; and costs.	Rates for nosocomial infections: baseline vs. intervention period (per 1000 patient medical ICU days): LRTI: 6.4 vs. 5.1; UTI: 4.0 vs 4.1; soft-tissue infection: 0.8 vs. 0; intravenous catheter infection: 0.8 vs. 1.0. Baseline costs of antibiotics per patient USD548 vs. USD373 for intervention. The introduction of guidelines led to decreasing costs and lowering of AMR.	High risk
Skaer *et al* 1993	USA Hospital	Prospective cohort analysis **Intervention**: Effect of pharmacy-based academic detailing on the use of imipenem-cilastatin (broad spectrum antimicrobial) No control	Study set at the Pullman Memorial Hospital, a 42 bed rural care facility.	% of imipenem-cilastatin as a % of total antimicrobial expenditure Capacity to switch to other drugs	Before the academic detailing was introduced, imipenem-cilastitan accounted for 21% of expenditure, whereas after introduction of the academic detailing, it accounted for 14% of expenditure – accounting for a 32.7% reduction in use. Through switching to the use of other drugs, cost savings of just under USD3,000 were achieved.	High risk
McConachy *et al* 1999	Australia Hospital	Prospective cohort study **Intervention:** assessment of the effect of pharmaceutical guidelines No control	Study set in a private hospital over a 6 week period, from 9 Feb to March 1998. 197 adult in-patients returning from the operating suite to surgical wards.	Prescribing trends Correct choice of antibiotic Annual cost of prophylaxis	In the 197 cases where antimicrobials were used: 92% indicated correct choice of antibiotic and 77% indicated correct dosages. The study demonstrated that modest compliance with guidelines concerning antimicrobial prophylaxis could result in savings of over USD40,000 per year.	High risk
Pestotnik *et al* 1996	USA Hospital	Retrospective cohort study – descriptive and financial **Intervention**: implementation of prescribing guidelines. No control.	7-year study assessing 162,196 discharged patients.	Measures of antibiotic use. Rate of adverse drug events, patterns of AMR, mortality, length of hospital stay. Yearly expenditure on antibiotics.	Computer assisted decision support programme can stabilize emergence of resistant pathogens with decreased costs and improved clinical outcomes.	High risk

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Moderate risk: plausible bias that raises some doubt about the results: one or more criteria partly met.
High risk: plausible bias that seriously weakens confidence in results: one or more criteria not met.

Table A9.3: Alternative approaches to stop the transmission of AMR

Authors	Country (setting)	Intervention and design	Sample	Main outcome measures	Major finding	Quality
Surveillance						
Haley *et al* 1995	USA Hospital	Randomized Control study **Intervention**: Surveillance and control programme introduced in 1975/76 **Control**: no surveillance and control programmes introduced in 1970.	1,782,172 patients (1970) 1,603,307 patients (1975/6)	Hospital infection rates	Initial surveillance of level of resistance and further "control" programme can limit the spread of infection	Moderate risk
Bloom *et al* 1996	USA Medicare	Cost-effectiveness analysis to assess 3 likely management strategies for *S. aureus* nasal carriage; prevent subsequent infection in chronic ambulatory hemodialysis patients: **Intervention 1**: screen for *S. aureus* nasal carriage and treat those with a positive test result with mupirocin calcium; **Intervention 2**: treat all patients weekly with mupirocin calcium; and **Intervention 3**: no prevention strategy, treat infection only.	Decision analysis model constructed from perspective of Medicare.	Incremental cost-effectiveness analysis Annual savings to Medicare.	Assuming that 75% of S.aureus infections are attributable to nasal carriage in hemodialysis patients, eliminating *S.aureus* with muprocin calcium (with or without screening) decreases the number of infections (by approximately 45-55%) while simultaneously reducing overall healthcare expenditures. Both options 1 and 2 provide more cost-effective care than control and while periodic screening (option 1) is more expensive, it has a greater potential to reduce overall levels of AMR.	Moderate risk.
Breuer *et al* 1999	USA	A decision model was developed to compare direct costs and outcomes for the treatment of Helicobacter pylori infection.	Looking at whether susceptibility testing and then altering antibiotic course is cost-effective.	Health outcomes Costs of treatment	Health outcomes between the two regimens are identical. However results suggest that routine pretreatment susceptibility testing is cost-effective. The model can be transferred to any setting dependent on the realisation of certain conditions.	Moderate risk
Waterer *et al* 1999	USA Hospital	Retrospective chart review **Intervention**: Assessing whether use of blood cultures to determine resistance, changed prescriber behaviour. No control.	Assessment of all admitted community acquired pneumonia cases (n=1805) that had blood cultures.	Whether or not blood culture results altered antibiotic treatment regimens.	Blood culture results indicating penicillin resistance failed to alter management of patients	High risk
Hacek *et al* 1999	USA Hospital	Retrospective cohort study **Intervention**: an integrated infection control programme including an in-house molecular typing laboratory capability to assess microbial clonality. No control.	Set at a hospital-based, 638-bed university affiliated medical centre in Chicago.	Infections per 1,000 patient days and % of hospitalized patients in whom nosocomial infection developed.	Nosocomial infections per 1,000 patient days declined more than 10% and the number of patients with nosocomial infections decreased 23% during the post-intervention period compared with the previous 24 months. This corresponds to a lowering of health care costs by USD4.4m over 2 years of the intervention.	High risk

Drobniewski *et al* 2000	UK Hospital	Prospective cohort study? **Intervention**: analysis of the sputum of the "Fast Track Service" (introduced by the Laboratory Service Mycobacterium Reference Unit) in 1996.	Economic analysis of the effect of use of rapid molecular assays (compared with conventional assays) on bed usage at one London hospital. Reviewed bed occupancy data, billable costs and medical notes. N = 91.	Among others, concordance of molecular assays with rifampcin resistance – comparison between molecular and conventional techniques. Treatment days saved.	Concordance of molecular results from smear-positive sputum with TB diagnosis and rifampcin resistance was: (i) for conventional analysis 95% and 92% respectively; and (ii) for molecular analysis 89% and 90% respectively. Approximately 28 days were saved in time to diagnosis using molecular assay. Among other things, it is concluded that molecular rifampicin resistance assays are reliable for diagnosis in cases with smear-positive disease.	High risk.
Decontamination						
Verwaest *et al* 1997	Belgium Hospital	Prospective randomized concurrent study **Intervention A**: control. **Intervention B**: selective decontamination: oral and enteral ofloxacin-amphotericin B **Intervention C**: oral and enteral polymixin E-tobramycin-amphotericin B	ICU patients: n = 660	Colonization and primary/secondary infection rate ICU mortality rate Emergence of AMR Length of ICU stay Antimicrobial agents costs	Selective decontamination via use of antibiotics on admittance to ICU (where high resistance exists) is debatable as it encourages AMR. No beneficial effect on survival is observed. Adds significantly to costs.	Moderate risk
Quino *et al* 1996	France Hospital	Prospective, double-blind, randomized, placebo-controlled trial **Intervention**: selective decontamination programme on admission: using amphotericin B, colistin sulfate (polymixin E) and gentamicin. **Control**: placebo	ICU – 72 patients received placebo and 76 treated patients	Colonization rates in the oropharynx, nares and bronchi. Episodes of bronchopneumonia. MRSA rates. Costs of antibiotic therapy.	Selective decontamination upon admittance to ICU reduced incidence of pneumonia and total charge of antibiotics. Length of stay unchanged.	Moderate risk
Cockerill *et al* 1992	USA Hospital	Randomized control trial **Intervention**: Selective decontamination – receipt of cefotaxime and oral, non-absorbable antimicrobials (gentamicin, ploymyxin and nystatin) for entire stay in ICU; **Control**: usual care	Set in a trauma and medical ICU in a tertiary referral hospital, whereby patients were selected whose condition suggested a prolonged stay (>3 days). N=130.	Number of infections Total hospital days Deaths Number of days in ICU	Control patients experience more infections (including bacteremias and pulmonary infections). Although the total hospital days, number of days in ICU and overall death rate were all lower in the treatment group, these differences were not statistically significant. It is concluded that selective decontamination (SDD) of the digestive tract decreases subsequent infection rates, especially by gram negative bacilli, in selected patients during long-term ICU stays.	Moderate risk

Preus *et al* 1993	Norway Hospital	Case control study **Intervention 1**: 20 syringe tips cultured for minoclycine resistant bacteria. **Intervention 2**: 10 syringe tips washed with ethanol. **Control**: 10 unwashed syringe tips	na	Number of syringe tips that were culture positive after washing with ethanol.	Washing of syringe tips with ethanol between applications will reduce transmission of AMR bacteria to other periodontal sites	Moderate risk
Barakate *et al* 1999	Australia Hospital	Prospective cohort study **Intervention 1**: Surgical ward with high MRSA cleaned and renovated. **Intervention 2**: Medical records of all MRSA colonized patients flagged (for readmission). No control.	Data collected for 995 newly colonized patients – with MRSA rates determined before and after interventions.	MRSA detection rates	Complete refurbishment/decontamination of ward did not halt MRSA spread. Flagging had little effect either.	High risk
Neely *et al* 1999	USA Hospital	Case study **Intervention**: 9 disinfectants compared to see whether effective in controlling the microbial load on polyester privacy curtains. No control.	na	Level of microbial load on polyester privacy curtains after spraying.	Disinfection of patient environment through use of hydrogen peroxide spraying can slow contamination.	High risk
Hand washing						
Hedin *et al* 1993	Sweden Hospital	Case study **Intervention**: Washing one arm for three weeks with disinfectant **Control**: other unwashed hand	10 nurses	Counts of resistant specified bacterial strains.	Hibiscrub may be of some benefit in stopping the spread of AMR	High risk
Webster *et al* 1993	Australia Hospital	Case study **Intervention**: hand washing with triclosan No control.	Assessment of hand washing effects on born neonates in a Queensland hospital.	Effect of reintroducing chlorexidine on the MRSA colonization rate The outcomes of the 12-month triclosan trial.	The triclosan trial led to a general fall in rates of MRSA. Following the reintroduction of chlorhexidine, MRSA returned to pre-trial levels. In 1990, 5.5 new cases of MRSA were reported each week while during the triclosan trial, one new case was reported each week.	High risk
Wade *et al* 1991	UK Hospital	Case control study **Intervention**: washing of hands with 4 hygienic hand disinfectants **Control:** no washing of hands	3 female volunteers (controls same as subjects)	Survival rates of resistant bacteria.	Hibisol is the most effective disinfectant in stopping the spread of AMR	High risk

Response to epidemics (multiple control policies)						
Chaix *et al* 1999	USA Hospital (Response to epidemic)	Case control study (with costs tacked on). **Intervention**: Screening, isolation, hand washing and barrier controls **Control**: no screening, isolation, hand washing and barrier controls	Twenty-seven randomly selected patients who had ICU acquired MRSA infection between January 1993 and June 1997.	Intensive care costs Threshold for MRSA carriage that would make the control strategy dominant. Length of ICU stay.	The mean cost attributable to MRSA infection was USD9,275 with a 14% reduction in the MRSA infection rate resulting in the intervention being regarded as beneficial.	Moderate risk
Dunkle *et al* 1981	USA Hospital (*Response to an epidemic)	Case control study **Intervention**: Introduction of standard control measures (American Academy of Pediatrics) No control.	Infants in two intensive care wards assessed during 1979.	Number of infants colonized with methicillin getamicin resistant staphylococcus.	Standard infection control programmes can eliminate epidemics of MRSA and control of antibiotics may prevent re-emergence of resistance strains. Maintenance and transfer of antibiotic resistance required for the continued presence of antibiotics.	High risk
Rao *et al* 1988	USA Hospital (*Response to epidemic)	Retrospective cohort study **Intervention**: strict isolation and other measures. No control.	60 patients over time who were infected with MRSA.	Patient surveillance Patient decolonization Personnel surveillance Personnel decolonization Environmental surveillance	The incidence of nosocomial MRSA cases fell to zero in 5 months after implementation of strategy	High risk
Guiget *et al* 1990	France Hospital (* Response to epidemic)	Case control study **Intervention**: patients with MRSA isolated, hand washing implemented and disinfection for visitors and staff. **Control**: MRSA-free patients	ICU--12 patients who acquired MRSA during June to March 1985.	Increase in incidence of MRSA Risk factors assessing transmission of MRSA.	Implementation of controls resulted in a sharp decline of MRSA prevalence. Risk factors identified leading to MRSA spread.	High risk
Murray *et al* 1990	USA Hospital (*Response to epidemic)	**Descriptive Case study** Intervention: implementation of a strict isolation policy	Veteran's hospital with approximately 300 admissions per month.	The number of patients successfully treated through eliminating MRSA	The monthly incidence of new MRSA patients dropped from a maximum of 16 per month to 3 or less per month – within 6 months of instigating these control measures.	High risk
Jernigan *et al* 1996	USA Hospital (* Response to epidemic)	Retrospective cohort study **Intervention**: Contact isolation and other measures **Control**: No isolation and other measures	16 patients out of 331 admissions to Neonatal Intensive Care Unit became infected with MRSA.	Rate of transmission of MRSA.	Rate of transmission of MRSA isolates significantly lower for isolated patients	High risk
Maloney *et al* 1995	USA Hospital (*Response to epidemic)	Retrospective cohort study **Intervention:** Implementation of CDC control measures (isolation to education) to reduce spread of transmission of TB. Before and after comparison.	40 patients hospitalized with multi-drug resistant TB and health care workers receiving tuberculin skin testing.	Proportion of patients with nosocomially acquired TB and rate of tuberculin skin test conversion among health care workers.	Implementing guidelines decreased nosocomial transmission of multi drug-resistant strains to patients and workers.	High risk

Fazal *et al* 1996	USA Hospital (*Response to epidemic)	Retrospective cohort study **Intervention**: isolation policy and other measures **Control**: when no isolation and barrier policies existed.	Comparison of admitted patients with MRSA over 43 month period: Period 1: 28 months prior to isolation policy Period 2: 15 months after the change in isolation policy.	Mean number of patients with MRSA	Found no evidence that failure to isolate patients with MRSA resulted in increased prevalence	High risk
Jewell 1994	USA Hospital (* Response to epidemic)	Case study **Intervention**: the introduction of "best practice" guidelines for the treatment of MRSA No control	Set in a hospital, main aim of the guidelines was to control, not eliminate epidemic levels. Features of guidelines included education, determining when isolation appropriate and among others, determining appropriate antimicrobial treatment options.	Length of stay Readmission Cost savings attributed to intervention	The intervention led to a decreased average length of stay in hospital of greater than 10 days, a reduction in the readmission rate of patients from 8.7% in 1990 to 2.7% in 1992, and a cost-saving of >USD1.9m.	High risk
Valls *et al* 1994	Spain Hospital (*Response to epidemic)	Before and after comparison **Intervention**: a cohort isolation, patient care and therapy (oral cotrimoxazole and fusidic acid ointment) introduced.	Set in a 350 bed university hospital where over a three-week period, approximately 117 cases of MRSA identified.	MRSA infection rates	MRSA infection rates declined from 8.2 to 0.7 cases per 1,000 patient days and the control programme was estimated to have prevented 76% of new MRSA cases. It was estimated that 85% of expected deaths due to MRSA in the ICU were also prevented.	High risk.

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Table A9.4: Summary of additional AMR studies reviewed

Authors	Country (setting)	Intervention and design	Sample	Main outcome measures	Major finding	Quality
Economic and costs						
Astagneau *et al* 1999	France Hospital	Cost analysis of antibiotic cost of nosocomial infections	Of 6,839 study patients enrolled in the French National prevalence survey in 1996.	Overall antibiotic cost according to regimen.	Overall cost of antibiotic treatment per patient estimated. Most expensive was in intensive care for multi-drug resistant bacteria. Cost of antibiotic treatment for nosocomial infection is a significant part of hospital expenditure and could be reduced through better control.	High risk
Wilcox *et al* 1996	UK Hospital	Cost of illness study **Intervention**: to measure the costs associated with *clostridium difficile* infection. **Control**: Patients who did not have *clostridium difficile* infection.	Intervention (case) patients (n=50) were selected if they developed diarrhoea due to C. *difficile* infection at least 48 hours after admission to the care of elderly wards in a teaching hospital. Control patients (n=90).	Antiotic usage Length of stay Antibiotic treatment of C.*difficle* infection Laboratory tests Costs of care.	Cases had a longer average length of stay than controls. Significantly higher death rates were reported in cases than in controls. Antimicrobial treatment of C.*difficile* infection, cost on average, GBP 47 per case. Most costs however, were attributable to "hotel" costs and the total identifiable cost per C.difficile infection was > than GBP 4,000 per case. This expenditure can be used to justify measures to control the spread of nosocomial infections.	High risk
Chan 1999	USA	Reviews a number of studies to assess the more cost-effective way of dealing with bacterial resistance in skin and skin-structure infection.	Examines/reviews the cost-effectiveness of studies examining B-Lactam/B-Lactamase combination therapy compared with B-lactam-stable antibiotics.	na	The use of ampicillin/sulbactam has been demonstrated to be more cost-effective than treatment with B-lactamase-stable antibiotics such as cefoxitin and imipenem/cilastatin.	na
Liss *et al* 1987	USA Review	Review article discussing issues including: (i) the cost of resistance; (ii) the economics of pharmaceutical research and development; (iii) the economics of promoting and marketing new antibiotics; and (iv) economic trends affecting antibiotic use and resistance.	na	na	Among other things, it is concluded that the economic costs of bacterial resistance require further analysis.	na
John and Fishman 1997	USA Review	Review article which assesses ways to control costs of AMR through: (i) isolation; (ii) formulary restriction; (iii) pharmacy justification; (iv) formulary substitution; (v) computer surveillance; (vi) laboratory item cost listing; (vii) purchase plans; and (viii) multidisciplinary approaches.	na	na	All studies are included, irrespective of quality. Suggests that multi-disciplinary antimicrobial management programmes (AMPs) offer the best potential for sustaining savings in antimicrobial costs. Ten recommendations are outlined for the development of guidelines.	na

Carbon 1999	France	Reviews a number of studies to assess the cost impact of MRSE and VRE.	na	na	Infections dues to MRSA and VRE – associated with increased mortality, morbidity and health costs. Prevention is a useful way forward to limit further spread.	na
Lenski 1997	USA	Conceptual article discussing the cost of antibiotic resistance from the perspective of a bacterium.	na	na	Usual analysis in the sense that it claims that restriction policies (which halt use of antimicrobials) are useless as bacteria are constantly evolving.	na
Barrett *et al* 1998	UK	Mainly conceptual, discussing how strategies that are implemented to control the spread of MRSA may be counterproductive.	na	na	More efficacious to concentrate on studies that aim to prevent spread of MRSA. For example, it costs GBP 60,000 to adapt one ward to cohort isolation – there must be better ways to spend these funds.	na
Mehtar 1995	UK	Mainly conceptual – discusses cost-effectiveness of control programmes attempting to argue that it is more cost-effective to prevent MRSA than treat it.		Calculates costs of treatment per carrier and costs of treatment for hospital.	It is argued that it is more cost effective to treat carriers of MRSA than actual infected patients with costs estimated at £374 vs. £2454 respectively.	na
Prescribing patterns						
Bergmans *et al* 1997	Netherlands Hospital	Prospective cohort study Monitoring of antimicrobial trends in an ICU for a year. Antimicrobials classified as follows: (i) prophylaxis; (ii) therapy for a bacteriologically proven infection (BPI); and (iii) therapy for a non-bacteriologically proven infection (non-BPI).	Study run from January to December 1994, all adult patients > 15 years who were ventilated, non-ventilated who were admitted to ICU: n=515.	Infections Antibiotic use Type of antibiotics	36% of patients admitted to ICU over the year had at least 1 infection with 53%, having an infection that was ICU acquired. Antibiotics were prescribed for 61% of all admissions with 59% being for BPI, 28% for non-BPI and 13% for prophylaxis. Antimicrobials were prescribed most commonly for respiratory tract infections (accounting for 49%) of antibiotics used.	Moderate risk
Van Houten *et al* 1998	Netherlands Hospital	Combined retrospective and prospective study examining trends in antimicrobial prescribing.	Set at a Pediatric Children's Hospital in the northern part of the Netherlands, over an 8-week period (1 November to 22 December) in 1994, 1995 and 1996. All hospitalized patients assessed for antimicrobial use.	Antimicrobials prescribed Number of patients receiving antimicrobials with a proven bacterial infection	Antimicrobials prescribed at least once for 36% of hospitalized children although only 12.3% of the patients who received antibiotics had a proven bacterial infection. Infants less than 2 years in age received antibiotics more frequently than older children.	Moderate risk
Mainous *et al* 1998	USA Medicaid population	Case study **Intervention**: assess nonindicated antibiotic treatment regimens for non-specific upper respiratory tract infections (URTIs)	Cross section sample of Kentucky Medicaid claims for 50,000 people seeking treatment for URTIs between 1 July 1993 and 30 June 1994	Use of antibiotics in URTI Proportionate costs and costs per episode	60% of outpatient episodes and 48% of emergency department episodes resulted in a prescription. Most frequently filled antimicrobial was amovicillin, although 2nd and 3rd generation cephalosporins were frequent. In outpatient episodes, antimicrobials account for 23% of the total costs of care – with most for non-indicated and ineffective treatments for URTIs.	Moderate risk

Mainous *et al* 1995	USA Medicaid ambulatory care	Survey of prescription medications for the common cold.	Random sample of patients who had at least one claim for treatment of a cold (n= 1,439 individuals) for 2,171 cold encounters.	Number of people receiving prescriptions for the common cold.	Majority of persons (60%) receiving inappropriate prescribing in terms of receiving antibiotics for a cold.	High risk
Friis *et al* 1989	Denmark Hospital	Case study examining regional variation in prescribing of antibiotics across regions.	4 Danish hospitals chosen for comparison.	Defined daily dosages/100 bed days	Use of antibiotics was highest in the hospital without Department of Clinical Microbiology while the highest cost hospital was found for the hospital with the greatest specialization. However, compared to Danish hospitals, USA hospitals use double the amount of antibiotics.	High risk
Lemire *et al* 1996	Australia Hospital	Retrospective cohort review of third generation cephalosporins to inpatients	Six week period between May to June 1994 – 140 patients.	Appropriateness of prescribing Outcomes: patient discharge, whether more complicate care was required or death.	Prescriptions of 3rd generation cephalasporins to inpatients was inappropriate in 31% of cases	High risk
Magee *et al* 1999	Wales GPs	Retrospective survey of antibiotic prescribing in GP surgeries and resistance to antibiotics	190 Welsh GPs between March 1996 to April 1998 (patient contacts = 1,200,000)	Use and antibiotics and rates of resistance Correlation between antibiotic prescribing and antibiotic resistance	Correlation between prescribing of an antibiotic and resistance to that antibiotic was often significant	High risk
Kuyrenhoven *et al* 2000	Netherlands GPs	Retrospective case study Analysis of prescription of antimicrobial agents in lower respiratory tract infections.	161 GPs with 25,600 relevant patient contacts registered.	Number of people receiving prescriptions.	In acute bronchitis cases, about 8 out of every 10 patients receive antibiotics – with evidence of inappropriate prescribing.	High risk
Janknegt 1996	Denmark GPs	This article reviews the treatment of staphylococcal infection – with reference to pharmacokinetic, pharacodynamic and pharmacoeconomic aspects of antimicrobial agents.	na		Epidemiological – not of much relevance. Poor assessment of pharmacoeconomic aspects.	na
Outcome of AMR						
Carmelli *et al* 1999	USA Hospital	Retrospective cohort analysis. **Intervention 1**: patients treated with one of the study agents if Pseudomonas infection was confirmed; **Intervention 2**: patients who had one or more additional positive cultures at least 48 hours after the baseline culture. Also, matched cohort study completed to examine total hospital charge on emergence of resistance.	All patients admitted between August 1, 1994 and July 31, 1996 from whom P. aeruginosa was recovered and who had been hospitalized for 2 days (n=421).	Mortality rates Emergence of secondary bacteremia Length of hospital stay following detection Daily hospital charge	The overall in-hospital mortality rate was 7.6% - 7.7% in-patients with resistant isolate at baseline and 27% in-patients with whom resistance emerged. Secondary bacteremia developed in 14% of patients with resistance. Emergence of resistance, but not baseline resistance was associated with longer hospital stay. The matched cohort analysis indicated increased total charges for patients demonstrating emergence of resistance.	Moderate risk

Einarsson *et al* 1998	Iceland Hospital	Case-control study **Intervention**: patients with Penicillin-non-susceptible Pnuemococci (PNSP) **Control**: People with Penicillin-susceptible pneumococci (PSP)	Patients from 2 hospitals identified with PNSP during 1988 to 1994.	Clinical comparisons of PSNP and PSP. Length of hospital stay. Costs.	Study indicated that more patients with PNSP than PSP had previously received antibiotics. Pneumonia in adults caused by PNSP is associated with a milder clinical presentation than PSP. PNSP pneumonia resulted in longer hospital stay and increased costs.	Moderate risk
Yoshida *et al* 1998	Japan Hospital	Case study **Intervention**: Cluster analysis using a personal computer was employed to prevent the outbreak of MRSA. No control.	120 patients from one hospital undergoing operations on the lung and mediastrinum.	Number of patients susceptible to MRSA.	A computerized antibiogram does not always strictly type MRSA strains.	High risk
Cheng *et al* 1988	Hong Kong Hospital	Retrospective Case study **Case 1**: Patients with MRSA were compared with patients who had methicillin sensitive S. aureus No control.	In-patients at a Hong-Kong Hospital between 1984 and 1986.	Differences in length of stay between resistant and susceptible MRSA strains.	Patients with MRSA had higher mean lengths of stay and mortality, then those who had susceptible strains.	High risk
Shimada *et al* 1993	Japan Hospital	Case study assessing the risk factors that determine the relationship between MRSA and antibiotic use. No control.	Patients admitted to the Department of Surgery between January 1987 and August 1991.	Risk factors leading to MRSA.	MRSA infections are higher in patients who have undergone procedures on digestive organs and those with prior treatment of specific antibiotics	High risk
Rice 1999	USA Review	Study reviewing interventions for gram-negative resistance to extended-spectrum B-lactam antibiotics.	Reviews strategies for controlling resistant bacteria	Assessed infection control measures and antibiotic control strategies.	Effective strategies depend on the nature of resistant bacteria with optimal strategies guided by detailed molecular epidemiology of different resistance genotypes.	na
Elthing *et al* 1997	USA Hospital	Review – examined significance of organ and tissue infection from 10 consecutive randomized clinical trials for patients with cancer and neutropenia.	na	Response to initial antibiotic regimen Ultimate outcome of infection Duration of therapy Duration of survival	Re cancer and neutropenia, there is no difference in outcome or frequency of bacteremia between patients who received prophylaxis and those who did not.	na

Notes: **Low risk**: plausible bias unlikely to seriously alter results: all of criteria met.
Moderate risk: plausible bias that raises some doubt about the results: one or more criteria partly met.
High risk: plausible bias that seriously weakens confidence in results: one or more criteria not met.

Table A9.5: Developing countries studies

Authors	Country (setting)	Intervention and design	Sample	Main outcome measures	Major finding	Quality
Prescribing trends						
Peng Bi *et al* 2000	China Community	Case control study **Intervention**: Parental self-prescribers of antibiotics **Control**: non-self prescribers	Heifei city, China – where 1,596 students from age 2 to 18 years were assessed to see whether parents were "self-prescribing" antibiotics for their children.	Number of self-prescribing adults.	Results of study indicated that the rate of parental self-medication for their children was approximately 60%. The relationship between antibiotic use and source of medicine (i.e. left-overs from previous treatments) was indicated for family self-prescribing	Moderate risk
Hui *et al* 1997	China Analysis of community-based health care workers	Prospective cohort study **Intervention**: specially trained observers applied the WHO criteria to study the diagnosis and treatment of acute respiratory infection (ARI) given by health care workers (HCWs) in rural areas in China.	100 randomly selected HCWs were chosen with a total of 750 cases of ARI evaluated.	Classification and distribution of ARI Abuse /inappropriate use of antimicrobials by HCWs Self-prescribed antimicrobials before receipt of medical advice Factors associated with misuse of antimicrobials	Antimicrobial misuse in the treatment of ARI in China is common with 47% of children in country hospitals, 25% of those in townships and 18% of those in villages receiving antimicrobials without prescription. Severe abuse of antimicrobials was detected in 37% of cases (i.e. the prescription of two incompatible antibiotics). The abuse of antimicrobials for ARI is a serious and costly problem, contributing to widespread AMR.	Moderate risk
Reyes *et al* 1997	Mexico Primary health care clinics	Prospective cohort study Assessing the factors associated with antibiotic noncompliance and waste among patients with acute respiratory infection (ARI) and acute diarrhea (AD).	Study took place in 4 primary care health clinics – belonging to the Ministry of Health (MoH) and the Mexican Social Security Institute (IMSS). N= 222 patients with ARI and 155 with AD.	Noncompliance Factors associated with noncompliance	Noncompliance was 60% for ARI and 55.5% for AD with prescription for an antibiotic justified in only 13.5% of cases. Noncompliance factors included: (i) increased duration of illness; (ii) complexity of treatment; (iii) younger age of patient; and (iv) inadequate physician-patient relationship. Antibiotic waste was higher in IMSS – with education strategies to improve prescribing compliance.	Moderate risk
Calva 1996	Mexico Community use of antimicrobials	Prospective random case-control study Two surveys were completed: (i) a household survey; and (ii) a drug-store survey - to ascertain use of antimicrobials in the community.	In the household survey, 1,659 households were visited, while 6 local drug store were visited (with purchasers immediately questioned having made their acquisition).	Use of antimicrobials	Of 8,279 individuals, approximately 5% said that they had used at least 1 antimicrobial in the last 2 weeks and that antimicrobials were the majority of drug sales (29%) obtained from the drug stores. Approximately two thirds of people using antimicrobials had used drugs for less than 5 days with 72% of purchasers, made for insufficient quantities of drugs. Data suggest antimicrobials are frequently misused.	Moderate risk
Bojalil *et al* 1994	Mexico Community prescribing practices	Survey of antimicrobial use in a periurban community in Mexico City	1,659 households were interviewed, from May 1989 to January 1990, in San Pedro Martir (outskirts of Mexico City)	Use of antimicrobials in diarrhoea Adequacy of antimicrobial therapy Risk factors for misuse of antimicrobials	The study revealed that an antimicrobial was used in 37% of diarrhoeal episodes, although only 5% of all episodes indicated the presence of gross blood in stools. Patients seen by a physician were more than 6 times likely to be treated with antimicrobials compared with those who did not. Those who were self-medicating	Moderate risk

					faced a higher risk of inadequate dose or drug. Findings support the need for the encouragement of more rational prescribing trends.	
Guyon *et al* 1994	Bangladesh Primary Health Care Facilities	Survey using both retrospective and prospective data Drug-use pattern and quality of care assessed in 80 public sector facilities in rural Bangladesh.	Set in 40 thana health complexes and 40 union sub-centres. A total of 2,880 prescriptions, consultations and drug dispensing practices were studied.	Treatment practices and assessment of patient care.	The average consulting time was 54 seconds with only 37% of examinations adequate and the 41% of drug prescriptions according to standard treatment guidelines (41%) were unsatisfactory. 17% of patients were treated with metronidazole, irrespective of the diagnoses with 55% of patients correctly understanding the dosage.	Moderate risk
Nizami *et al* 1996	Pakistan Community prescribing practices	Prospective cohort study Examining the prescribing patterns of GPs and pediatricians	The prescribing practices of 65 GPs and 29 pediatricians were observed between April and December 19992. A total of 990 encounters were examined.	Prescribing patterns of: (i) oral rehydration salts (ORS) (ii) antibacterials (iii) antiamoebics	It was noted that ORS were prescribed in 51% of cases, antibacterials in 36%, antidiarrhoeals in 29% and antiamoebics in 22%. Mean duration of encounters was very low with results indicating inadequate prescription of ORS and excessive prescribing of antibacterials, antidiarrhoeals and antiamoebics. There is a need to improve prescribing techniques.	Moderate risk
Qazi 1999	Pakistan Community and hospital	Review study assessing the evidence that was used to lobby the Government to overturn the recommendations of the acute respiratory tract infection (ARI) guidelines. Oral co-trimoxazole was recommended despite high levels of AMR.	4 effectiveness studies were reviewed into acute respiratory illness	Resistance to co-trimoxazole, amongst other factors	Country-wide surveillance from 1991 to 1994 revealed 78.3% to 79.9% in-vitro resistance to co-trimoxazole among S.*pneumoniae* and 59.5-61.0% among H.*influenzae* isolates. Despite this, co-trimoxazole is still recommended in the Pakistan ARI control programme.	High risk
Education programmes						
Bexell *et al* 1996	Zambia General health centres (community)	Randomized controlled trial **Intervention:** three continuing education seminars (introduced within three months) on quality of patient management and rational drug use **Control**: no education	16 centres in Lusaka included in both control and intervention. 5,685 patient cards assessed, with 2,500 before the intervention, 1,154 during and 2,031 received after the intervention.	Quality of case management Rational drug use	In the intervention health centres, the average number of drugs per patient decreased from 2.3 to 1.9 with the proportion of patients, managed with non-Pharmacological treatment, increasing from 1 to 13.2%. More appropriate use of drugs was noted in the intervention health as opposed to the control centres. Use of education seminars is effective in encouraging rational drug use in primary care.	Moderate risk
Santoso 1996	Indonesia	Case control study **Intervention**: examining the outcome of two education campaigns: (i) formal seminar; and (ii) face-to-face seminars – for approving appropriate drug use in Indonesia. **Control**: no education programme	Face-to-face discussions involved participation of about 8 to 10 people, with seminars involving discussions with people involving 60-80 people.	Prescribing Appropriate use of drugs Use of non-rehydration medications	Both interventions were equally effective in improving levels of knowledge of prescribers and appropriate management of acute diarrhoea. A significant drop in antimicrobial usage was noted from both interventions, although a greater drop was evident from the intervention of the seminar group. There was an increased trend, after education towards use of oral rehydration solutions.	Moderate risk
Mabadeje *et al*	Nigeria	Prospective cohort study	Introduced at the Lagos University	Prescribing trends	There was no statistically significant difference	High risk

1991	Hospital	Aimed to assess the effect of education workshops for doctors about the introduction of an Essential Drugs List (EDL) at a hospital.	Teaching Hospital – surveyed 120 people (including 42 interns, 40 junior residents, 18 senior residents and 20 consultants)		between post-EDL and pre-EDL prescribing habits of doctors for outpatients and inpatients. Only 56% of doctors were aware that an EDL existed. This means, that despite efforts to familiarize doctors with the EDL, the majority remained ignorant about it.	
Hartog 1997	Chile	Review article An estimation was provided about the proportion of essential drugs offered for sale in 6 regions of the developed world, by the 20 largest European Pharmaceutical companies.	The 20 largest pharmaceutical companies were chosen with 6 regions of the developing world as follows: Mexico, Brazil, French-speaking Africa, English-speaking Africa, the Middle East and India.	Number of essential drugs provided from the WHO essential drug list (1988).	Only 482 or an average of 16% of a total of 3,021 drugs are provided by pharmaceutical companies in the developing world that are classified as essential drugs or equivalent to essential drugs. The proportion provided by each company ranged from a low of 5.4% to a maximum of 39%. Results suggest that pharmaceutical companies increasingly need to focus their marketing on essential drugs for the developing world.	Moderate risk
AMR interventions						
Isenberg *et al* 1995	Kenya Hospital	Masked prospective cohort study Compared the effectiveness of three alternative treatment regimes to reduce conjunctivitis. As follows: **Intervention 1**: 2.5% solution of povidone-iodine; **Intervention 2**: 1% solution of silver nitrate **Intervention 3**: 0.5% erythromycin ointment	3,117 newly born infants were selected for inclusion with the numbers actually participating in the intervention groups as follows: Intervention 1: n=1,076 Intervention 2: n=929 Intervention 3: n=112	Rate of infection	Newborns treated with silver nitrate solutions had an overall rate of infection that was 34% higher than infants treated with povidone-iodine, and infants receiving erythromycin had an overall infection rate that was 16% higher than patients treated with povidone iodine. However, with respect to S.aureus or N.gonorrhoeae, there is no difference in effectiveness across the three groups.	High risk
Goh *et al* 1999	Malaysia	Cost of illness analysis Examining the costs of reducing Heilcobacter pylori (HP) eradication and compared 5 treatment options: **Treatment 1**: H_2RA **Treatment 2**: BMT + PRI **Treatment 3**: OAC **Treatment 4**: OMC **Treatment 5**: OAM	Decision Tree Analysis incorporating eradication rates, resistance rates, compliance and estimated costs for the treatment options	Costs of the different treatment options	The results suggest that the antimicrobial regime H_2RA was the most expensive, then BMT + PRI followed by OMC and OAM. The Omerazole, amoxycillin and clarithromycin (OAC) therapy was the most cost-effective treatment in terms of reducing Helicobcater pylori infection.	High risk
Alternative interventions						
Goodman *et al* 1999	Africa Community	Cost-effectiveness of malaria control in sub-Saharan Africa. **Treatment 1**: childhood interventions: (a) insecticide treated nets; (b) residual spraying of houses	Used mathematical models (based on probabilistic sensitivity analyses) to calculate the CE ratios for the main prevention and treatment interventions in sub-Saharan Africa.	Disability adjusted life years	The following was noted. For insecticide treatment of existing nets – the CE range was USD4 to USD10 per DALY averted; for provision of nets and insecticide treatment USD19-85; for residual spraying USD32-35; for chemoprophylaxis for children USD3-12; for	Moderate risk

		Treatment 2: prevent malaria in pregnancy: (a) chloroquine chemoprophylaxis; (b) sulfadoxine-pynmetriamine intermittent treatment **Treatment 3**: improve malaria treatment: (a) improved compliance; and (b) improved availability of 2nd and 3rd line drugs with changes in 1st line drugs.			intermittent treatment of pregnant women USD4-29; and for improvement in case management USD1-8. This analysis indicates that cost-effective interventions are available, however, achieving high coverage would use a significant proportion of health care budgets in developing countries.	
Sirinavin 1998	Thailand Hospital	Retrospective cohort study **Intervention**: use of an antimicrobial order form to assess rational use of expensive antimicrobial agents. Before and after comparison.	Admissions in Thai hospital between 1988 and 1996 where the average number of admissions per year = 21,252 to 26,361.	Rate of prescribing Costs	Costs and prescribing of three restricted drugs increased sharply when guidelines removed	High risk
Starling *et al* 1997	Brazil Hospital	Cohort (prospective) **Intervention**: Use of USA national nosocomial infection surveillance guidelines in 5 Brazilian hospitals in 1991-1995. No control.	Number of admitted patients 10,531.	Incidence of infection caused by MRSA. Cost-savings.	Surveillance and control programme successful in reducing incidence of MRSA and costs associated with treatment, than if did not have a programme.	High risk
Larson *et al* 1992	South America Hospital	Case study **Intervention**: hand washing No control.	697 patient contacts observed and 30% were followed by hand washing.	Hand washing practices Bacteriology of hand flora (type and level of AMR)	There was no significant effect of hand washing on the counts of colony-forming units.	High risk
Miscellaneous						
Rosas 1997	Mexico Community	Case study The main purpose of the study was to determine the occurrence of E.coli in both airborne and settled dust, collected from indoor and outside environments.	Airborne and settled dust was sampled (both inside and outside) at 10 a.m. from 30 homes in the southern part of Mexico City.	Serotypes, antimicrobial resistance profiles and presence of extra-chromosomal DNA plasmids	14% of isolated E.coli strains indicated susceptibility to more than 2 antimicrobials – with most of them resistant to ampicillin, ticarcillin, piperacillin and tetracycline. Note that most of these, which indicated levels of antimicrobial resistance, were isolated from settled dust in indoor environments.	High risk

Notes: **Low risk**: plausible bias unlikely to seriously alter results: all of criteria met.
Moderate risk: plausible bias that raises some doubt about the results: one or more criteria partly met.
High risk: plausible bias that seriously weakens confidence in results: one or more criteria not met.

Annex 10: REVIEW FORMS

Form 1: Quantitative study—data extraction form

Reference number:						
Author(s):						
Year of publication:	*19____*					
Country of origin:						
Type of bug/drug considered:						
Content of article:	*Review*	*Empirical*	*Other (please specify):*			
Type of Study:	*RCT*	*CCT*	*Cohort (P)*	*Cohort (R)*	*CCS*	*Other*
Relevant to review theme:	*Emergence and spread*	*Intervention (control)*	*Intervention (prevention)*			
Alternatives compared:	***For each describe: setting, content, intensity and duration***					***NOT APPLICABLE***
Intervention						
Control						
Methodology:						
Selection of controls:	*Random*	*Matched*	*Geographical*	*Historical Other*		
Adequate concealment?	*Yes*	*No*	*Not specified*	*Not applicable*		
Subjects blinded	*Yes*	*No*	*Not specified*	*Not applicable*		
Power calculation?	*Yes*	*No*	*Not specified*			
Number randomized/at baseline?	*N =*					
Number included in analysis	*n =*					
Number withdrawn (reasons)	*n =*		***Reason(s):***			
Intention-to-treat analysis	*Yes*	*No*	*Not specified*			
Study Population:						
Type						
Selection criteria described	*Yes*	*Some information given*	*No*			
Inclusion criteria						
Exclusion criteria						
Summary characteristics	*Age*	*Gender*	*Health condition*			
	Other					
Outcome measures	***List measures & whether they have been standardized (S) or not (NS)***					
Assessors blind to assignment?	*Yes*	*No*	*Not specified*	*Not applicable*		
List timing of follow-up(s)	*(1)*		*(2)*	*(3)*		
Timing of follow-up appropriate?	*Yes*	*No*	*Unclear*			
MEASURES						
Summary of results						
Additional methodological comments?						
Risk of bias (Cochrane criteria)	*Low*	*Medium*	*High*			
Relevance to review	*Low*	*Medium*	*High*			
Include in review?	***Yes***	***No***	***Discuss with research group***			

Form 2: Economic evaluation—data extraction form

Reference number:						
Author(s):						
Year of publication:	*19____*					
Year of cost data:	*19____*	*Unspecified*				
Currency used:						
Type of bug/drug considered:						
Country of origin:						
Content of article:	*Empirical*	*Review*	*Other (please specify)*			
Type of Study (1.1, 1.2):	*CoI*	*CA*	*CMA*	*CEA*	*CUA*	*CBA*
Viewpoint (1.3):	*Health system*	*Hospital*	*Society*	*Patient*	*Family*	*Other*
Relevant to review theme (2.0):	*Cost Impact*		*Intervention*			

Assessment domain	**Response categories**	**Methods appropriate?**
Competing alternatives (2.0)	*Intervention 1:* *Intervention 2:* *Control:*	
Effectiveness study design (3.0)	** RCT* ** CCT* ** cohort* ** case control* ** other observational* ** "ad hoc"* ** judgement* ** modelling*	*Yes* *No* *Unclear*
Resource use identified (4.0)	** health service: hospital GP community* ** social service:* ** patient:* ** other:*	*Yes* *No* *Unclear*
Resource use measures (5.0)	***Please specify measures below for each category***	
health service:		*Yes* *No* *Unclear*
social service:		*Yes* *No* *Unclear*
patient:		*Yes* *No* *Unclear*
other:		*Yes* *No* *Unclear*
Resource use valuation (6.0)	** specific* ** national pubs* ** local costs* ** "ad hoc"* ** judgement*	*Yes* *No* *Unclear*
Type of benefits (4.0)	***Please specify:***	
Valuation of benefits (6.0)	*NONE* ** QALYs* ** WTP* ** study specific* ** published values* ** judgement* ** other:*	*Yes* *No* *Unclear* *N/A*
Discounting (7.0)	*Done: Yes No Unclear Rate: (c)____%* *Justification:* *Rate: (b)____%*	*Yes* *No* *Unclear*
Incremental Analysis (8.0)	***Please specify comparison made:***	*Yes* *No* *Unclear* *N/A*
Sensitivity Analysis (9.0)	** Univariate* ** Multivariate* **Threshold* ** Other* ***Variables compared:***	*Yes* *No* *Unclear* *Yes* *No* *Unclear*
Summary of results		
Comments on methods		
Risk of bias	*Low* *Medium* *High*	
Relevance to review theme	*Low* *Medium* *High*	
Include in review?	***Yes*** ***No*** ***Discuss with research group***	

Form 3: Conceptual study—data extraction form

Reference number: Author(s): Year of publication: Type of bug/drug considered: Country of origin: Content of article: Relevant to review theme Year of cost data (if applicable)	*19____* *Economic theory* *Emergence and spread* *19____*	*Mathematical modelling* *Cost impact* *Unspecified*	*Interventions*	*Other conceptual* *Model development*
Methods				
Problems with methods				
Results				
Quality of research	Low	Medium	High	
Relevance to review	Low	Medium	High	
Include in review?	***Yes***	***No***	***Discuss with research group***	

Annex 11: INTERVENTION STRATEGIES

As discussed in chapter 3, there are a variety of interventions identified in the literature that have been proposed and/or implemented to address the emergence or transmission of AMR. Essentially, these can be divided into those that aim to decrease selection pressure by preventing or reducing the *emergence* of antimicrobial resistance, and those aiming to limit the *transmission* of resistant organisms and/or determinants between organisms, individuals, and the environment. Tables A11.1 and A11.2 summarize these strategies and the specific interventions that relate to them for both emergence and spread of AMR. Each intervention is then briefly described below.

Table A11.1: Prevention of emergence

Objective	Strategy	Intervention
↓ Selection Pressure	↓ Antimicrobial use in humans and agriculture	• Education of professionals on appropriate clinical indications • Education of patients • Rapid diagnosis of bacterials • Control of sensitivity data released to prescribers • Antibiotic policies • Restriction of availability • Financial incentives/disincentives • Antimicrobial cycling • Regulation on the use of antibiotics in agriculture
↓ Opportunity for Resistance Emerging	Optimal use of existing agents	• Choosing the optimal agent, dose and dosage frequency for different infections • Removal of potential septic foci / prostheses • Emphasizing/ensuring compliance • Use of antibiotic combinations
↑ Range of Agents Available	Discover/develop new agents	• Modification of existing agents / Discovery of New Classes of Antimicrobial • Discovery of new drug targets through microbial gene analysis • Genetic manipulation • Computer modelling
	Consider use of alternative treatment options	• Antiseptics • Cranberry juice for UTI • Probiotics
↓ Requirement for Antimicrobials	↑ Immune competence	• Vaccination • Nutrition • Minimize time patient is immunocompromised

Table A11.2: Control of transmission of resistant organisms/determinants

Objective	Strategy	Intervention
↓ **Transmission**	Early recognition of resistant organisms	• More rapid techniques • Surveillance • Screening patients/staff
	↓ Infectivity	• Use of antimicrobials
	↓ Opportunities for transmission	• Isolation • Hand washing • General Hygiene • Patient/Staff ratios • Bed spacing
	↓ Susceptibility to infection	• ↑ Immunity • ↑ Nutrition

A11.1 Decreasing selection pressure through decreasing use─ Education

Not all infections require antimicrobial therapy, and it should only begin when clinically necessary. Although antimicrobial prescribing has been described as an addiction (Lockwood 1974), education of clinicians on the appropriate clinical indications for therapy has had some degree of success (Temte 1999, Landgren *et al*, 1988). Other strategies have included local and national guidelines.

An alteration in patient perception is also necessary. For these reasons education strategies with the aim of reducing antimicrobial consumption should be aimed at both parties. The potential for national news and media to act as an educational tool in disseminating such information is immense, enabling the message to reach both the public and health care professionals; e.g. a public education initiative (the "Don't wear me out" poster campaign) has recently been introduced in the UK (http://www.doh.gov.uk/pub/docs/doh/antibiotics.pdf). A fact sheet on antimicrobial resistance has also been produced by the National Institute of Infectious And Allergic Diseases, National Institutes of Health, and is available at their web site (http://www.niaid.nih.gov/factsheets/antimicro.html).

More rapid diagnosis of bacterial disease
New molecular and other techniques that can give results at the bedside offers medical practitioners and patients more reassurance that antimicrobial treatment is not required.

Antimicrobial policies
Antimicrobial policies can be used to reduce demand for antimicrobials by educating clinicians about the appropriate indications for treatment and can recommend optimal regimens. Computer-assisted antimicrobial decision support systems have been shown to reduce inappropriate prescribing by enhancing the amount of information available to the clinician (Evans *et al* 1998, Burke *et al* 1999). Policies can also be used to achieve a degree of control over prescribing practices, and consequently resistance patterns (Ayliffe 1975, Price & Sleigh 1970) through controlling the supply of agents. Financial incentive schemes have also been developed in an attempt to promote adherence to antibiotic guidelines, as has the idea of antimicrobial permits (Coast *et al* 1998).

Nevertheless, the presence of linked resistances on transposons and integrons means that the influence of antibiotic policies may not be as great as once predicted (Gould 1999). Variable resistance patterns and clinical requirements are likely to necessitate tailoring of policies to individual units with regular updating based on surveillance data.

Cycling of antibiotics
This involves the selective removal or close control of certain antimicrobials during a particular time period so that the selection pressure is varied. This has met with some success in controlling aminoglycoside resistance (Gerding *et al* 1991). However, the optimal duration of the cycles of restriction and use are unknown and concern about the production of multi-resistant organisms has been raised, since evidence suggests that once one drug is discontinued the frequency of resistance does not fall rapidly, so that resistance to both/all drugs will be present concurrently (Bonhoeffer *et al* 1997).

Restriction of the use of antimicrobials or antimicrobial resistance determinants in agriculture
The Swann Committee Report (1969) recommended that antimicrobials useful in human medicine should not be used as growth promoters in animals. This has been reinforced by the WHO Consultation for the Development of Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (available at http://www.who.int/emc/diseases/zoo/who_global_principles_html), and by the House of Lords Select Committee on Science and Technology (7th Report). The development of markers other than antimicrobial resistance for genetic engineering is also required (Jones 1999).

A11.2 Reducing the emergence of resistance during treatment through optimal antimicrobial use

Basic factors
When therapy is indicated, basic factors that should always be considered include: site of infection; most likely pathogens; their likely resistance pattern; mode of action of the antimicrobial (whether cidal or static); penetration to the site of infection; route of administration; magnitude of dose; frequency of dosing; and duration of therapy. The importance of pharmacokinetics/dynamics in relation to the MIC of the organism has recently been shown (Schentag 1999, Hyatt & Schentag 2000a, Hyatt & Schentag 2000b). The removal of any foreign bodies or drainage of abscesses is also important.

Use of optimal dosing regimens of narrow spectrum agents for as short a period as is effective to treat the condition will minimize the effect on the commensal flora while maximizing activity against the pathogen. The time at which therapy is introduced in relation to bacterial load is also important. If therapy is delayed, an increased bacterial load may overwhelm the immune system. In contrast, if therapy is introduced too early in the course of disease, the immune response may be dampened which may reduce clearance – with subsequent implications for transmission – illustrating yet another facet in the optimal use of antibiotics (Austin & Anderson, 1999b).

Emphasizing/ensuring compliance
Poor antimicrobial compliance is associated with the development of resistance. This is especially pertinent to the treatment of tuberculosis where directly observed treatment short-course (DOTS) may prevent the emergence of multi-drug resistance (Yew 1999, WHO/IUAID

Global Project on Anti-tuberculosis Resistance and Surveillance 1998). It is therefore important that patients understand the importance of adherence to the treatment schedule.

Antimicrobial combinations
Using antimicrobial agents in combination is well recognized as a means of decreasing the emergence of resistance, particularly in certain organisms e.g. Mycobacteria tuberculosis and HIV. However, using antimicrobials in combination may mean that a last line drug becomes unavailable, and it has been argued that sequential drug use (cycling) may be preferable (see above), although there is the potential for all drugs to be resistant concurrently in this case.

A11.3 Increasing the range available

(i) Discovery/development of new antimicrobial agents

Modification of existing agents and discovery/development of new classes
The pace of antibiotic discovery/development has slowed considerably since the mid 1960s (Coast *et al* 1996). With a few notable exceptions, e.g. carbapenems and protease inhibitors amongst others, new agents have resulted mainly from the modification of existing agents rather than the discovery/development of new classes. Similarly, there is currently a limited number of antiviral and antifungal drug classes. This has the disadvantage that cross-resistance been the "parent and its derivatives" may occur. However, the cost of discovering/developing new agents may be prohibitive to many pharmaceutical companies (Murray 1994), and financial incentives from governments may be required.

Overcoming antimicrobial resistance mechanism
Resistance to some of the beta-lactam antibiotics, e.g. penicillin, ampicillin and piperacillin is mediated through bacterial production of an enzyme, which destroys the beta-lactam ring that these antibiotics contain. Compounds inhibiting this enzyme have been developed, e.g. clavulinic acid and tazobactam. The combination of these beta-lactamase inhibitors with beta-lactam agents has enabled the activity of these antibiotics to be maintained by overcoming the resistance mechanism of the micro-organism.

Microbial gene analysis, genetic manipulation and computer modelling
These new techniques may identify new target sites. However, it is likely that only a finite number of potential target sites remain to be identified. Nevertheless, in the future, genetic manipulation may be able to influence the mutability, competitive fitness, and transmissibility of organisms or resistance determinants.

(ii) Using alternative treatment strategies

Antiseptics
Antiseptics are well recognized as topical antimicrobial agents. Indications include: regimens for the reduction or eradication of MRSA colonization; routine and pre-op skin disinfection; prophylactic administration to surgical, burns and intravascular device sites; as well as therapy of skin infections (Kaye & Kaye 1995, Fleischer & Reimer 1997).

Probiotics
The administration of supplements of intestinal micro-organisms such as *Escherichia coli, Saccharomyces boulardii,* but mainly lactobacilli and bifidobacteria species to "normalize" the microbial content of the gastro-intestinal flora and enable it to better resist colonization with

pathogenic bacteria is emerging as a potential prophylactic or therapeutic strategy (Gorbach 2000, Filho-Lima *et al* 2000, Orrhage & Nord 2000). However, further research is required before the clinical value of this approach can be determined.

Cranberry juice
Consumption of cranberries, particularly as cranberry juice, has been used for several decades for the prevention and treatment of urinary tract infections. Some studies have suggested that there may be scientific validity (Avorn *et al* 1994, Zafriri *et al* 1989). However, a Cochrane review suggested that there was insufficient evidence at this time to recommend any cranberry product for either preventing or treating urinary tract infections (Jepson *et al* 2000a, Jepson *et al* 2000a).

A11.4 Decreasing the requirement for antimicrobials

Vaccination
Successful vaccination represents a feasible intervention strategy for some diseases. Indeed, increasing antimicrobial resistance has resulted in recommendations for increased vaccine research in both humans (SMAC report 1998) and animals (van Oirschot 1994).

Nutrition
Nutritional deficiencies are known to influence immune function, increasing host susceptibility and decreasing the immune response to infection (Scrimshaw & SanGiovanni 1997). However, it has also been suggested that some pathogens may become more virulent in the absence of certain nutrients (Levander 1997, Beck & Levander 2000). Studies have also demonstrated that vitamin and/or other nutritional supplementation assists in the prevention of infection, aids clearance, reduce risk of relapse and decreases infectivity (Calder & Yaqoob 1999, Patrick 2000).

Minimizing degree of immunosuppression and/or decreasing time individual is immunosuppressed
New agents are being developed that aim to induce immuno-tolerance, and these will reduce the degree of immunosuppression required in organ transplantation (Ponticelli *et al* 1999). Haematological growth factors have been shown to decrease the duration of immunosuppression, by enhancing immune recovery (Crawford *et al* 1999).

A11.5 Decreasing transmission of resistant organisms/ determinants through infection control

The transmission of resistant organisms/determinants depends on the genetic characteristics of the resistant organism/ determinant, i.e. transmissibility, the magnitude of the organism load, the infectious dose, and the opportunity for transmission, e.g. the route of transmission, proximity and susceptibility of the new hosts. Together these factors determine the transmission dynamics.

Surveillance, early recognition, of resistant organisms
Any effective infection control programme relies on the early identification of resistant organisms through surveillance. Rapid molecular methods for the detection of resistance determinants such as mecA gene in MRSA, altered penicillin binding protein proteins in pneumococci, and rpoB gene in *Mycobacterium tuberculosis* are now available. The earlier resistant organisms are identified, preferably before they have become endemic, the more rapidly

appropriate infection control measures can be instigated. This allows damage limitation and enhances cost-effectiveness, (Austin & Anderson 1999b).

Routine monitoring for changes in antimicrobial zone sizes or MICs produces an "early warning system" by enabling reductions in sensitivity to be detected before the defined breakpoint is reached (Schlaes *et al* 1997). Rapid molecular methods for the detection of resistance determinants such as mecA gene in MRSA, altered penicillin binding proteins in pneumococci, and rpoB gene in *Mycobacterium tuberculosis* are now available.

Nationally, surveillance is extremely important (Langmuir 1963). In the UK, notification and confirmation of organisms with a multiple or unusual resistance pattern is done through the Central Public Health Laboratory, Colindale. Organisms with public health implications, e.g. multi-drug resistant tuberculosis are also notified to the local Consultant in Communicable Disease Control. At a local level, feedback of surveillance data may be used to implement changes in practice within the community or the hospital, while at a national or international level, such information can inform public policy.

Patient and staff screening

Patient screening, with or without staff screening, for resistant organisms may be worthwhile in outbreak situations, where the organism is known to have epidemic potential, (EMRSA 16), or where the consequences of infection are potentially serious e.g. MRSA in heart lung transplant patients. However, the overall importance of staff colonization with organisms such as MRSA in transmission is believed to be small although it has been documented (Sheretz *et al* 1996).

Decreasing infectivity through the use of antimicrobial agents

Antimicrobial agents can play an important part in an effective infection control strategy. This may be achieved by decreasing the infectivity of an individual by eradicating or reducing the numbers of organisms present, or reducing the duration of infectivity, so that transmission is less likely. The use of mupirocin and chlorhexidine in controlling MRSA is well recognized. Other examples include treatment for cases of tuberculosis, and for *Herpes simplex* virus type 2 in a community setting. Antimicrobial prophylaxis, e.g. for contacts of open cases of tuberculosis is also of relevance.

Selective Decontamination of the Digestive tract (SDD) is a controversial regimen in the ITU setting, which aims to eliminate or reduce the load of aerobic gram-negative organisms colonizing the gastro-intestinal tract (Ledingham *et al* 1988, Gastinne *et al* 1992, Kollef 1994, Silvestri *et al* 2000). As aspiration/reflux of infected oronasopharyngeal secretions and gastric contents is thought to be important in the pathogenesis of ventilator-associated pneumonia, this regimen is believed by some to reduce the incidence of this complication. The schedule usually consists of a combination of orally non-absorbable antimicrobial agents active against gram-negative aerobic organisms and yeasts, combined with a short course (4 days) of a systemic agent, usually a cepholosporin. The principle underlying this regimen is the maintenance of an anaerobic commensal flora in the gastro-intestinal tract, as this is believed to provide "colonization resistance" to resistant organisms. Therefore, broad-spectrum antibiotics with a profound effect on the anaerobic flora are avoided. Concerns have been raised regarding the emergence of resistant organisms in units using this regimen. However, SDD has also been used in the control of resistant gram-negative organisms.

A11.6 Decreasing the opportunities for transmission – Nature of organism and patient context

Infection control measures must be appropriate to the nature of the organism, its potential effect on the individual, the health care setting and the community. Although control of some organisms such as multi-drug resistant tuberculosis is essential regardless of its patient context, for others, e.g. MRSA*, Burkholderia cepacia* or *Pneumocysistis carinii,* the measures adopted must be based on a risk assessment. Moreover, the strategy adopted must also take into consideration the endemicity of the organism concerned.

The importance of these factors is illustrated in guidelines for the control of MRSA in UK hospitals (Anon 1998). This document recommends stratification of the infection control measures adopted based on the susceptibility and nature of the patients exposed, i.e. the potential consequences of infection/colonization and the endemicity of the organism. Separate guidelines for MRSA control measures in the community are also available (Anon 1995).

Isolation of infected patients

The isolation of patients infected or colonized with resistant strains of micro-organisms in single rooms, in addition to other measures, can result in a decreased incidence of cross infection. Isolation wards have proved valuable in controlling transmission (Ayliffe *et al* 1979, Shanson *et al* 1985). Where isolation in a single room is not possible, cohort nursing of individuals infected with the same strain may be effective (Murray-Leisure *et al* 1990). However, cohorting of particularly vulnerable individuals infected with one organism may result in the spread of other organisms (Breathnach *et al* 1998, Hannan *et al* 2000).

Prevention of transmission by vectors: hand washing

It is generally agreed that hand carriage is the most important vector in transmission of organisms between patients. The importance of hand washing in infection control was first recognized by Semmelweis in the 19th century. Despite this studies have repeatedly shown poor compliance (Larson *et al* 1995).

There are several reasons for failure to achieve compliance with hand-washing protocols. In medical practice the emphasis is often on the complex, difficult and expensive elements of patient care rather than simple procedures. Stressing the importance of hand washing is compounded as the consequences of non-compliance are not immediately obvious due to a temporal delay in the subsequent onset of infection. However, in the UK, the profile of hand washing as an essential component of infection control strategies has been raised through the launch of the "UK Hand-washing Initiative" (Teare *et al* 1999).

A11.7 Attention to general hygiene

There has been concern in the literature recently that control of organisms such as MRSA is being over-emphasized to the detriment of other infection control issues, including the general fabric of buildings and standards of cleanliness in hospitals (Barrett *et al* 1998, Corcoran & Kirkwood 1999). Inadequate cleaning has been associated with outbreaks of infection (Dancer 1998). However, if MRSA is used as a "marker" for cross-infection, rather than merely a target in itself, then the instigation of general hygienic measures taken against MRSA will also be useful against other organisms.

A11.8 Other considerations

Staff-patient ratios have been identified as being important (Austin & Anderson 1999a), as has bed spacing (Kibbler *et al* 1998).

Annex 12: SPECIFIC ISSUES COMPOUNDING EMERGENCE AND TRANSMISSION OF RESISTANCE IN DEVELOPING COUNTRIES

Several factors make the emergence and transmission of resistance, and therefore strategies for combating resistance, different in developing, compared to developed, countries (Okeke 1999). These include:

- Irregular drug supply and availability of drugs from unofficial sources (Munishi 1991, Hogerzeil *et al* 1993, Salako 1991)
- Access to objective health information (Cash 1996, Ronsmans *et al* 1996, Hartog 1993, Lee *et al* 1991)
- Scarcity of well-trained health personnel, leading to community health workers and others treating minor ailments with minimal training (Pearson 1995, Thamlikitkul 1988, Kigotho 1997, Dua *et al* 1994, Singh & Raje 1996, Haak 1988, Kafle *et al* 1992, Rahman *et al* 1998, Fagbule & Kalu 1995)
- Availability, on demand, of antimicrobials without prescription from hospitals, pharmacies, patent medicine stalls (drugstores), roadside stalls, and hawkers, who usually have little or no knowledge of the required dosage regimen, indications, or contraindications (Bojalil & Calva 1994, Dua *et al* 1994, Kafle *et al* 1992, Van der Geest 1991, Wolff 1993, Obaseiki-Ebor *et al* 1987, Lansang *et al* 1990, Okeke & Lamikanra 1995, Hossain *et al* 1982, Goel *et al* 1996). In particular, these alternate sources offer the option of purchasing small quantities of medicines, while hospitals require purchase of the complete regimens, which is expensive. Thus, purchase of small samples is common, leading to subinhibitory antibiotic regimens that are predisposed to selection of resistant bacterial strains (Lansang *et al* 1990, Shahid *et al* 1985, Yang *et al* 1993)
- Poor compliance, which is common because of issues such as long distances reducing the likelihood of follow-up visits (Strang 1996), the patient being unable to read medicine labels, and because of the financial incentive (above) to discontinue treatment when symptoms disappear but before the pathogen is eliminated (Lansang *et al* 1990)
- The poor quality of many antimicrobials in developing countries (Okeke & Lamikanra 1995, Esezobo & Offiong 1986, Agom *et al* 1990, Taylor *et al* 1995)
- Shelf-life of drugs can be short in tropical countries, and drugs may quickly degrade (Taylor *et al* 1995, Ballereau *et al* 1997, Shakoor *et al* 1997, Gustafsson & Wide 1981, Ali *et al* 1988, Berckmans *et al* 1997)
- Counterfeit drugs, which do not contain the concentration of active substances stated on their labels) flourish in developing countries (Adjepon-Yamaoah 1980, Land 1992, McGregor 1997, Alubo 1994, Couper 1997)
- Changes in the effectiveness of antimicrobials by unique conditions surrounding its administration. For example, a common Nigerian meal (Ogunbona & Oluwatudimu 1985), chewing of Khat, a popular Yemeni stimulant (Attef *et al* 1997), and the Ayurvedic preparation, Trikatu (Johri & Zutshi 1992) have all been found to influence the effctiveness of antimicrobials
- Low levels of health care, urban overcrowding and improper sewage disposal encourage the exchange of resistant organisms among people and the exchange of resistance genes among bacteria, thereby increasing the prevalence of resistant strains (Okeke 1999)

- Infection control practices in hospitals are often compromised by economic conditions (Meers 1988)
- Surveillance programmes are less common and less elaborate in developing countries (Rahal *et al* 1997), with inferences about resistance trends based on more "anecdotal" evidence
- Resource constraints restrict implementation of strategies against resistance, worsened by armed conflicts, which lead to breakdown in health services and sanitation and rapid dissemination of resistant pathogens (Summerfield 1993, Dodge 1990, Goma Epidemiology Group 1995). The cost of medical treatment is beyond the means of many patients, leading to many with communicable diseases infecting others.

Annex 13: REVIEW OF MODELLING METHODS USED IN AMR

The studies discussed here were identified following the comprehensive review of the literature on cost and/or effectiveness of interventions against AMR, as described in chapters 2 and 3.

A13.1 Decision-analytic models

Three decision-analytic models were identified, which focused upon prevention or control of resistance[21] (Gyssens & Kullberg 1995, Eandi & Zara 1998, Cargill 1997). Of these, the study by Eandi and Zara (1998) provides the best illustration of the use of a decision-analytic model.

The paper by Gyssens & Kullberg (1995) is primitive in its approach, developing a computerized "flow chart" decision route for the quality evaluation of antimicrobial prescription and use that "formalizes" questions of toxicity, cost, duration, dose, etc. to lead to the most appropriate prescription of each antimicrobial. This was applied prospectively at a large hospital in the Netherlands. As part of the model, the ability to perform "what if" analyses was incorporated to assess the value of switching the type of antimicrobial, dose, duration, etc. Although not explicitly brought into the model by the authors, resistance is easily incorporated in this sort of model by virtue of (almost) instant feedback from the microbiology department concerning resistance levels, and likely effectiveness of the therapy options. This example, although primitive, demonstrates the value of the decision-analytic approach at this micro level of addressing prescribing within the relatively closed and predictable hospital system. Success here will depend crucially on the speed of transmission of microbiology results.

The study by Cargill (1997) used a decision-tree approach to assess the direct (health care) costs to the UK NHS of ampicillin resistance in *H. influenzae* in LRTI. The analysis was based on published average costs, and resistance prevalence rates gathered from a within-house pharmaceutical company database covering a number of hospitals around the UK over the period 1986 to 1996, with linear regression used to extrapolate resistance to 2006. The model itself is, however, extremely simplistic, even in the broad estimation it makes.

The Eandi & Zara (1998) study provides a detailed exposition of the use of the decision-analytic approach, based on hypothetical data for Italy. The authors identify the scarcity of data on the health consequences of resistance (i.e. the relationship between *in vitro* microbiological data and morbidity and mortality) as a critical feature for the policy application of such a model. The authors provide a comprehensive illustrative example of the decision-tree approach for selecting the most cost-effective antibiotic to treat, at home, a population of patients affected by a given community-acquired infection (e.g. LRTI). Here resistance is incorporated as a factor that determines the rate of success or failure of the treatment, which depends upon the link between resistance rate (*in vitro*) and the probability of treatment failure due to this. The authors run simulations of the model under assumptions for a variety of antibiotics

Overall, these studies show the usefulness of such, relatively simplistic, modelling for discrete decisions, within a relatively contained environment for static comparative analysis.

[21] Note that there are several which are focussed upon pharmaceutical interventions targeted at infections, but in these cases resistance is not incorporated.

A13.2 Markov "Chain" models

No studies applying Markov modelling techniques were identified.

A13.3 Monte Carlo simulation

Only one paper was identified that performed Monte Carlo simulation.

Sebille & Valleron (1997a) apply Monte Carlo simulation modelling to assess the spread of two bacterial strains in an intensive care unit in one hospital among patient and staff members. Their assumption is that two antibiotics may be used and that one bacterial strain is resistant to one of the antibiotics whilst the other strain is resistant to both. Individuals in each population of patients and staff are represented in the model by a set of clinical and epidemiological characteristics, e.g. patients include length of stay and antibiotic treatment and staff members include hand-washing compliance and colonization with the bacteria. No costs were considered.

Although limited in scope, the study does indicate the potential for Monte Carlo techniques to provide estimates of the likely impact of an intervention over time, given a number of uncertain variables, or those subject to some degree of randomness.

A13.4 Mathematical modelling

Two studies were identified that used mathematical modelling.

Sebille *et al* (1997b) use mathematical modelling to assess the impact of staff hand-washing compliance, anti-microbial policy and curtailment of colonized patients on the extent of colonization by resistant organisms within an ICU. This involves simulation of the spread of nosocomial pathogens to provide a framework for listing available knowledge, predicting benefits of those control measures and supplementing epidemiological assessment of those measured. The model is based on a deterministic stochastic model describing person-to-person spread and indirect spread between patients through staff members. The conclusion was that hand-washing compliance reduced staff member colonization, but only moderately limited patient colonization unless the ICU was isolated strictly by curtailing the admission of colonized patients. The consequence of antibiotic policy was slight. The model used was deterministic in the sense that the population was divided into three compartments, non-colonized individuals, individuals colonized by a resistant strain to the topical anti-microbial used in the ICU and individuals colonized by a susceptible strain.

Austin *et al* (1999) describe in detail the development of a mathematical model and the emergence and spread of resistant bacteria within the patient and within hospitals and communities (using MRSA in England and Wales as a working example). The model brings together pharmacokinetic and pharmacodynamic principles in a framework that mirrors the interaction between bacterial population growth, drug treatment and the immunological responses targeted at the pathogen. Such a model contributes to assessment of interventions to combat resistance in identifying areas in which more precise information is needed, particularly relating to how antimicrobial use influences the development of resistance and its health consequence (pharmacodynamics).

A13.5 Statistical modelling

Carling *et al* (1999) was the only study identified that applied linear regression to the use of antimicrobials. In this study, data from 14 hospitals in North America were analysed using multiple linear regression to evaluate the relationship between active and passive antibiotic management programmes (e.g. limited formularies versus the involvement of a clinical pharmacist) and use of antibiotics and cost per patient. The result was that the use of active programmes reduced hospital pharmaceutical expenditure. The effect on resistance was not assessed, however, its impact on resistance over time could be assessed if information on resistance rates was available.

A13.6 Macro-economic models

No studies applying macroeconomic modelling techniques were identified.

Annex 14: ILLUSTRATIVE MODEL

A14.1 Introduction

This annex presents an illustrative example of the application of one modelling technique, Monte Carlo analysis, to assess the outcomwe of an intervention to reduce AMR. A relatively common, and effective, intervention for a relatively common, but important, disease was chosen: the DOTS (Directly Observed Treatment Shortcourse) programme as a strategy for reducing multi-drug resistant tuberculosis (MDR-TB).

This intervention/disease was chosen because: (i) it affects both developing and, increasingly, developed countries (Rieder *et al* 1989, Block *et al* 1994), in particular New York (Frieden *et al* 1993); (ii) there is likely to be good data available; (iii) it has a major health impact that is relatively immediate; (iv) it is an area that the WHO Global Strategy has identified for its piloting of the Strategy (WHO 2000); and (v) it is an intervention that can reduce both the emergence *and* transmission of resistance (through improved compliance with therapy).

In order to assess the applicability of this model across different countries, the analysis was performed for both South Africa and the USA. The USA was chosen as it has good data availability. South Africa was chosen as a country that would be expected to have good levels of data compared with other developing countries, has high levels of HIV for which TB is an important disease, because it is seen as a "regional leader" for Africa, and because there were some economists there who were personally known to the authors and from whom cost data were available.

Monte Carlo analysis was chosen because it is a stochastic modelling technique that allows for uncertainty and randomness to be incorporated into the analysis. Given that much is unknown about AMR, as well as the intervention and its effect on rates of MDR-TB, it was felt that this would be a suitable model, and one that was likely to be of use generally in the assessment of AMR.

A14.1.1 Background to TB and MDR-TB

In 1993, WHO declared a "global emergency" with respect to TB (WHO 1993), and in the same year the World Bank estimated that TB accounted for around 26% of all avoidable adult deaths in developing countries (World Bank 1993). In Asia, the mortality rate from TB exceeds 50 per 100,000 (WHO 1999). In developing countries, especially those in sub-Saharan Africa, the effect of HIV has led to a doubling of TB rates (Cantwell & Binkin 1996).

Although treatments for TB, such as streptomycin, isoniazid and rifampicin were discovered decades ago, it has only been with the advent of DOTS that these treatments have shown real effectiveness (WHO 1995). Effective TB control depends both upon patients promptly seeking therapy and their successful completion of it. However, the rapid improvement often means that the full course is not completed, with the disease recurring shortly after cessation[22].

[22] This is due to the two phases of treatment. The initial bactericidal phase is directed toward rapid destruction of large multiplying populations of tubercule bacilli, which is followed by a sterilisation phase which is the period of

Partly as a result, TB is becoming increasingly resistant to anti-TB drugs (Dunagan and Medloff 1993), and MDR-TB is an increasing problem throughout the world (Maranetra 1996, Zhang 1996, Suo *et al* 1996, Hadiarto *et al* 1996). It is estimated that MDR-TB accounts for around 1% to 2% of overall TB rates, where overall TB cases are approximately 1.7 billion, with 20 million ongoing cases and 8 million new cases per year worldwide (Anon 1993). Of these, approximately 1.5 million people die from TB (excluding those who die from TB as a complication of AIDS), making it the fourth largest cause of infectious death worldwide (WHO/CDS). It is also an important disease because of its ease of transmission—by particles suspended in the air.

Over 5 million people are co-infected with HIV and TB worldwide, and in countries with an HIV epidemic, the overlap of the two populations leads to a rapid acceleration of active TB and the emergence of MDR-TB (Raviglione *et al* 1995). In the USA, for example, around 3.5% of strains are MDR-TB (Reichman 1996). It has been estimated that treating one MDR-TB patient costs the same as treating 100 patients with regular TB (Farmer *et al* 1999). For poorer countries, such costs represent an enormous burden on the health care system, and the national economy.

A particular problem with treating TB, and thus reducing the potential for further transmission, is non-compliance with treatment, which lasts for a minimum of six months (Floyd *et al* 1997). It has been estimated that in many countries more than 50% of patients treated for TB are lost to follow-up, many during the intensive initial treatment period (WHO 1999, Arif *et al* 1998). Compliance can be increased through using DOTS, which leads to a cure rate of around 95% of drug-susceptible cases. In New York City, implementation of a DOTS programme has reduced TB by 60% overall (and 75% in US-born citizens) over the last six years (New York City Department of Health 1999, Frieden *et al* 1995), with similar results in other countries (Zhang & Kan 1992).

DOTS increases cure rates through increasing compliance with therapy, by direct supervision, and by adapting drug regimens to patient needs (an effective case-management system that ensures patients take the right quality drug, in the right dose, for the right length of time). It therefore contributes to limiting the development of resistance by preventing treatment failure. Such failure occurs when patients are either dosed with poor quality drugs (counterfeit or date expired), or have limited access to, or are non-compliant with, existing therapies. Insufficient treatment of this nature leads to a series of brief reprieves and relapses in TB that grow steadily more impregnable to available medications.

It has been estimated that in countries that do not use DOTS, rates of MDR-TB may be 10% to 20% (WHO/CDS/CPE), and are increasing, compared with rates of around 1% to 2%, and being maintained, in countries where DOTS is well used.

The DOTS programme is a key element in the control of MDR-TB, when used in conjunction with availability of appropriate anti-TB drugs. It has been estimated that, for example, in regions of China where DOTS has been implemented, MDR-TB is over 30% lower than in regions where DOTS has not been implemented (WHO/CDS). It has also been estimated that out of around 200 countries who would stand to benefit from DOTS, only around 100 are currently implementing it (WHO/CDS).

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maintenance chemotherapy directed at elimination of the dormant, slowly growing organisms (Mitchison 1979). Thus, there is a period of rapid symptom relief, followed by a largely asymptomatic stage.

For this model, the cost and effectiveness of DOTS in reducing MDR-TB was compared to conventional (self-administered) treatment (CON).

A14.2 Methods

A14.2.1 Treatment assumptions used in the models

While the treatment options for DOTS and CON are broadly similar across countries in terms of recommended drug use, there are slight differences in terms of some of the treatment options adopted (e.g. length of hospitalization). Thus it is not possible to model the same treatment options for DOTS and CON in both in the United States and South Africa. As a consequence, the treatment protocols developed for modelling purposes are based on those outlined in two recent South African and US studies, which assess the cost-effectiveness of DOTS and CON. For South Africa, Floyd *et al* (1997) is relied upon, while for the US, Moore *et al* (1996) is used. The following key assumptions were also made:

- Although both studies are site specific in terms of TB application (e.g. Floyd *et al* (1997) is based in the Hlabisa District in South Africa while Moore *et al* (1996) is based in Baltimore in the USA), the modelling undertaken in this analysis assumes that the treatment protocols are representative of country-wide approaches
- Approximately 10,000 patients would receive treatment according to the identified DOTS and CON treatment protocols (described below) for both countries
- Treatment is provided for a period of six months
- Costs estimated for each of the South African and US DOTS and CON treatment options are calculated from the perspective of the health care provider (i.e. no patient or wider societal costs are incorporated).

A14.2.2 South African model for treatment of TB

The treatment models outlined in Floyd *et al* (1996) for DOTS and CON are used as a basis for modelling. These key treatment components (and associated costs) are detailed below.

Directly observed treatment model

The following treatment pattern is observed in South Africa for DOTS (see table A14.1 for a breakdown of the relevant costs).

After diagnosis, the patient is admitted to hospital where drug treatment starts:

- Patients receive daily treatment with four first line drugs: isoniazid, rifampicin, pyrazinamide and ethambutol)[23]. The average length of stay in hospital is 17.5 days
- Patients are discharged and are transported to their "supervision point" at a local hospital. A supervisor and supervision point is chosen which makes access to DOTS therapy convenient for the patients

[23] A "standard" treatment is assumed to be for TB that is drug-susceptible.

- Supervisors are given the pre-packaged drugs required for the completion of the six-month drug course. These drugs are exactly the same as those given in hospital, except that they are of a higher dose and taken on an intermittent twice weekly basis
- Patients visit their supervisors twice a week to take their drugs under direct observation, visiting on average 48 times.

Conventional (self-administered) treatment

The following treatment pattern is observed in South Africa for CON (see table A14.1 for a breakdown of the relevant costs).

After diagnosis, the patient is admitted to hospital where drug treatment starts:

- Patients stay in hospital for the first two months of treatment. This lengthy stay is designed to ensure compliance during the intensive phase when they are most infectious. Patients receive treatment according to WHO guidelines:
  - 2 months: isoniazid + ethambutol + rifampin + pyrazinamide
  - 4 months: isonizid + rifampin
- At discharge, patients are given one month's supply of drugs, and drugs are subsequently collected by the patients from their nearest clinic.

Table A14.1: Cost per patient for treatment of TB (South Africa)(*in US dollars*)

	Total costs USD1,996	
Cost item	***DOTS***	***Conventional***
Hospital stay	468.5	1,668
Visits for DOTS	81.60	Na
Outpatient visits for sputum collection	Na	33.40
Health clinic visits for collection of pills	Na	19.20
Arrangements for supervision and supervision of supervisors	38.90	Na
Drugs	36.60	40.40
Sputum examinations	Na	9.00
Management and audit	5.70	5.70
Return home at hospital discharge	Na	Na
TOTAL	**USD649.30**	**USD1,775.70**

Source: Floyd *et al* 1997.

A14.2.3 American model for treatment of TB

The treatment model outlined in Moore *et al* (1996) for DOTS and CON is used as a basis for modelling. These key treatment components (and associated costs) are detailed below.

Directly observed treatment models

The following treatment pattern is assumed for DOTS in the USA (see table A14.2 for relevant treatment costs):

- Moore *et al* (1996) assumes 80% of patients are hospitalized for the diagnosis of therapy and the initiation of treatment. At admission, patients have two X-rays performed, 10 sputum stains and cultures carried out for mycobacteria and three complete blood counts and chemistry panels to monitor therapy. A hospital length of stay of nine days is assumed (note that length of stay and costs are assumed to be the same irrespective of TB treatment, which differs from South Africa)
- Following recommendations from the American Thoracic Society and the Center for Disease Control, DOTS drugs are administered as follows:
  - Rifampin + ethambutol + pyrazinamide (daily for 15 days), Rifampin + ethambutol + pyrazinamide (twice weekly for 1.5 months), and Rifampin + ethambutol (twice weekly for four months)
- For DOTS therapy, Moore *et al (*1996) assume that there is one on-site TB clinic visit initially, with 50 subsequent patient outreach visits in the community to observe drug ingestion.

Conventional (self-administered) treatment)

The following pattern is assumed for patients in the United States who receive CON for TB (see table A14.2 for relevant treatment costs):

- Moore *et al* (1996), 80% of patients are hospitalized for the diagnosis of therapy and the initiation of treatment. At admission, patients have two X-rays performed, 10 sputum stains and cultures carried out for mycobacteria and three complete blood counts and chemistry panels to monitor therapy. A hospital length of stay of nine days is assumed (note that hospital length of stay and costs are assumed the same irrespective of TB treatment, which differs from South African case)
- Following recommendations from the American Thoracic Society and the Center for Disease Control, individual conventional treatment, drugs are administered as follows:
  - Rifampin + ethambutol + pyrazinamide (daily for 15 days), Rifampin + ethambutol + pyrazinamide (daily for 1.5 months), and Rifampin daily for four months)
- For unobserved, conventional therapy, Moore *et a*l (1996) assume that six TB-clinic visits occur during the six- month course of therapy.

A14.2.4 Conceptual model

The model (adapted from Heymann et al, 1998) is represented diagrammatically in decision-tree format, in figure A14.1. This diagram provides a representation of the likelihood of additional treatment options occurring, according to: (i) whether patients are receiving TB treatment for the first time, or whether they have previously received treatment and are, hence, receiving "repeat" TB treatment; (ii) whether patients will complete or "default" from their specific course of therapy according to specified DOTS and CON treatment protocols (defined above for South Africa and the United States); (iii) whether or not patients are HIV positive or negative; and (iv) whether patients are classified as having MDR-TB or are suffering from more susceptible strains (STB).

Table A14.2: Cost per patient for treatment of TB (USA) (*in US dollars*)

	Cost of six-month treatment USD1,994	
Component	***DOTS***	***Conventional***
Hospitalization	10,720	10,720
Clinic visit, physician fee	100	300
Outreach visit	1,300	0
Chest radiograph	64	64
Sputum, stain and culture	390	390
Complete blood count	36	36
Blood chemistry	36	36
Facility administration	518	518
Drugs		
- Isoniazid	8	9
- Rifampin	66	191
- Ethambutol	157	231
- Pyrazinamide	120	177
TOTAL	**USD13,515**	**USD12,672**

Source: Moore *et al* 1996.

These various options have associated probability distributions and cost implications, which are discussed in more detail in the next section. As patients "feed" through the various "branches" of the tree, there are a number of possible outcomes, as follows:

1. **Cure**: where the patients receiving treatment according to the defined protocols, are free from symptoms and can be described as "alive and well";
2. **Dead**: where treatment has failed and the patient has died;
3. **Ongoing**: where treatment has failed to eradicate the disease, and as a consequence the patient is still suffering from (susceptible or multi-drug resistant strains) of TB.

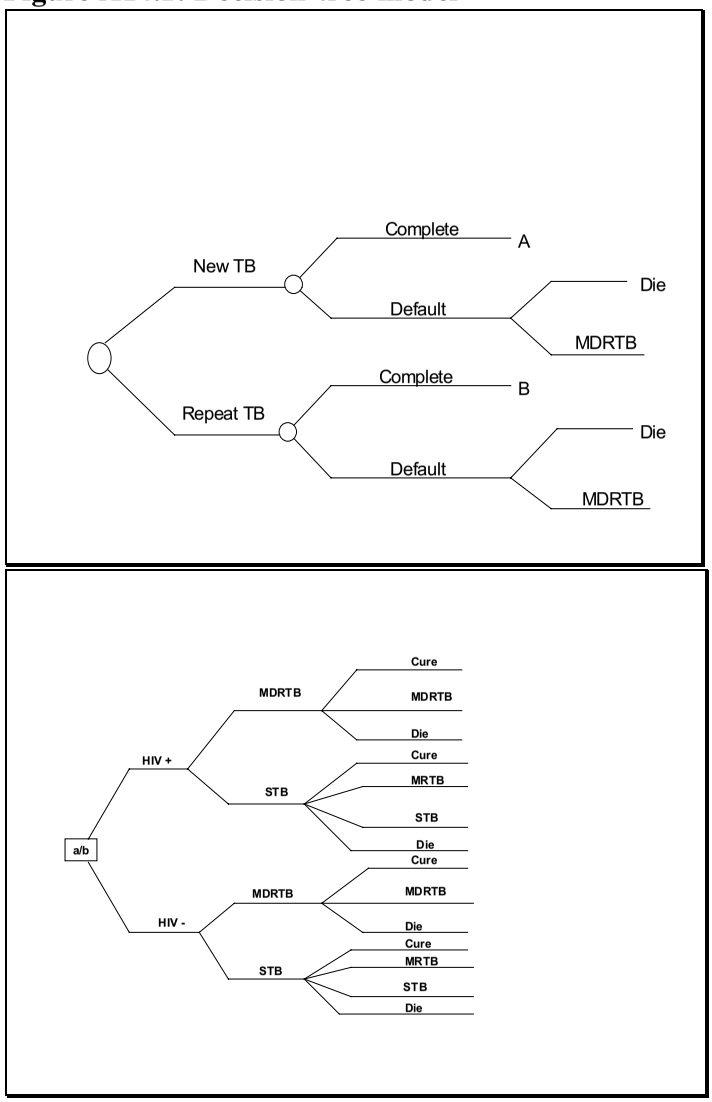
It can be expected that the treatment protocol adopted (i.e. DOTS or CON) will have its impact on the distribution of these outcomes. Specifically for the purposes here, it can be expected, a priori, that DOTS will increase the rate of treatment completion as compared to CON, and because of less defaulting there will be an increased likelihood of being cured and a reduced likelihood of either dying or contracting MDR-TB.

It is also expected that the level of mortality will be higher in South Africa than the USA, due to the higher incidence of HIV amongst TB patients in South Africa. Whether or not each country is more effective in terms of their DOTS application, is dependent on overall adherence to therapy (i.e. default rates).

In this analysis, modelling was undertaken using Monte Carlo simulation methods where the distribution of possible costs and outcomes is obtained through random selection of associated probabilities and expected costs at each node of the defined decision tree. For this exercise, each treatment option (CON and DOTS) for South Africa and the USA was generated 10,000 times, to reflect the assumption of 10,000 patients receiving treatment. The simulation package

"@RISK™" was used for this modelling exercise to obtain estimates of the overall outcome and expected cost per patient treated according to CON and DOTS in South Africa and the USA.

Figure A14.1: Decision-tree model



A14.2.5 Parameters

Detailed lists of model parameters, in terms of probability distributions, associated costs and assumptions at each node of the ecision tree, are outlined for CON and DOT treatments, for both South Africa and the USA, in tables at the end of this annex. All estimates for probabilities and costs were derived from the referenced literature, with a mean figure as used presented, with the range used in the Monte Carlo analysis in parentheses. For all variables a uniform distribution was assumed, as there was no reason to assume that any one value would be observed less than another. All cost estimates are expressed in current US dollars.

A14.3 Results

The "baseline" model was run through 10,000 iterations for each country and treatment type (i.e. DOTS or CON), to gain estimates of the number of people ending up in each outcome category (i.e. dead, cured, ongoing STB and ongoing MDR-TB). The results from these simulations are reported in table A14.3 (further details are given in the tables at the end of this annex).

Table A14.3: Outcome according to treatment protocol, South Africa and United States

	Minimum	Mean	Maximum	Standard deviation
CON (SA)				
- Die	3,307	**3,826**	4,406	171
- Cure	3,885	**4,489**	5,188	210
- MRTB	1,401	**1,610**	1,798	65
- STB	62	**75**	90	6
DOTS (SA)				
- Die	3,128	**3,645**	4,224	176
- Cure	4,164	**4,862**	5,589	227
- MRTB	1,233	**1,411**	1,584	56
- STB	66	**82**	98	7
CON (USA)				
- Die	728	**986**	1,441	111
- Cure	4,632	**5,584**	6,751	347
- MRTB	2,664	**3,304**	3,964	278
- STB	110	**126**	142	7
DOTS (USA)				
- Die	417	**875**	1,480	169
- Cure	5,195	**6,998**	8,963	753
- MRTB	514	**1,962**	3,483	707
- STB	123	**165**	209	18

These results suggest that for both the USA and South Africa, fewer people die or end up with MD-RTB, when receiving therapy according to DOTS. This is because the likelihood of defaulting treatment through DOTS is lower than CON and, as a consequence, the likelihood of being cured increases. As predicted, the mortality results for South Africa are far worse than those from the USA, this can be (in part) explained by the greater likelihood in South Africa of being HIV+ with STB or MDR-T, than in the USA.

The average cost per patient treated for each country, was also estimated according to DOTS and CON, and the results are summarized in table A14.4.

Table A14.4: Estimated average cost per patient treated according to DOTS and CON, South Africa and United States

	Expected cost per patient, US dollars			
	Minimum	**Mean**	**Maximum**	**Standard Deviation**
CON (South Africa)	$4,220	$5,987	$7,835	713
DOTS (South Africa)	$2,107	$4,395	$7,122	928
CON (USA)	$19,803	$23,944	$29,045	1,457
DOTS (USA)	$14,459	$20,522	$28,626	2,754

In both South Africa and the USA, DOTS represents a more cost-effective form of treatment than CON. In South Africa, DOTS will lead to a cost-saving of USD1,592 while in the USA DOTS will lead to a cost-saving of USD3,422.

Thus, overall the model suggests that the DOTS will ***dominate*** the CON programme in both countries. It will lead to lower expected costs and a higher rate of those cured and fewer with MDR-TB. In the case of dominance, a cost-effectiveness analysis is, therefore, not required (Drummond *et al* 1997).

A14.4 Issues arising from this illustrative modelling example

Several important lessons may be learnt from the application of the Monte Carlo modelling technique in this relatively straightforward and simple exercise.

First, a Markov model may have been more appropriate, in retrospect, in the presence of "feedback loops" from those who default or fail therapy, back into the model as a repeat case of TB. Second, the model would quickly become unwieldy. The model presented here is a simple approach to the issue of MDR-TB and there are many other parameters of relevance that could be accounted for, including, for example, international travel, co-infection or use of over-the-counter medicines. However, this would exponentially increase the number of "branches" on the tree. For example, the addition of one other chance node after the initial node would increase the number of end states from the current 24 to 48. If one considers the number of potential parameters that could be accounted for, one can imagine this model quickly gaining several hundred possible end states. Third, the model was undertaken from a narrow perspective, largely dictated by available data, and as such omits costs to patient and carer. Especially in developing countries, one might expect these to be significant in this instance.

However, the model does provide a baseline example for the consideration of the multitude of factors that would need to be addressed in the construct of a comprehensive model of AMR, and for the evaluation of interventions for MDR-TB and beyond.

A14.5 Probability and cost assumptions used in the illustrative model

Table A14.5 Probability distributions used for modelling DOTS and CONs treatment protocols, in South Africa and USA

	SA (DOTS)	SA (CON)	USA (DOTS)	USA (CON)	Source	Assumptions
INITIAL						
New TB	0.83 (0.80 to 0.85) [(A)]	0.83 (0.80 to 0.85) [(A)]	**0.45 [(M)]**	**0.45 [(M)]**	(A) Hensher 1999 and Karstaedt 1997 (M) Fujiwara *et al* 1997	
Repeat TB	0.17	0.17	**0.55**	**0.55**		
CONVENTIONAL						
Complete	Na	0.67[(L)]	Na	0.60 (0.60 to 0.70) [(W)]	(L) WHO 2000 (W) Heyman *et al* 1998, Moore *et al* 1996	(L) Note: this probability is based on a statistic that defines a completed treatment as the sum of the % of cases cured + those who completed treatment.
Default	Na	0.33	Na	0.40 (0.40 to 0.3)		
DOTS						
Complete	0.73 [(B)]	Na	0.77 (0.67 to 0.95) [(N)]	Na	(B) WHO 2000 (N) Heyman *et al* 1998, Moore *et al* 1996	(B) Note: this probability is based on a statistic that defines a completed treatment as the sum of the % of cases cured + those who completed treatment.
Default	0.27	Na	0.23 (0.33 to 0.05)	Na		
DEFAULT						
Default-Die	0.60 [(C)]	0.60 [(C)]	0.14 [(O)]	0.14 [(O)]	(C) Davies *et al* 1999 (O) Heyman ***et al*** 1998	(C) and (O) **Note: to detail assumptions as to how this was calculated**.
Default-MDR-TB	0.40	0.40	0.86	0.86		

Table A14.5 (continued)

	SA (DOTS)	SA (CON)	USA (DOTS)	USA (CON)	Source	Assumptions
HIV STATUS						
HIV +	0.49 (0.449 to 0.533) [D]	0.49 (0.449 to 0.533) [D]	0.10 (0.15 to 0.05) [P]	0.10 (0.15 to 0.05) [P]	(D) Karstaedt 1997 and Davies *et al* 1999 (P) Moore *et al* 1996	
HIV -	0.51 (0.551 to 0.467)	0.51 (0.551 to 0.467)	0.90 (0.85 to 0.95)	0.90 (0.85 to 0.95)		
HIV +						
HIV + MDR-TB	0.28 (0.177 to 0.38) [E]	0.28 (0.177 to 0.38) [E]	0.34 (0.16 to 0.52) [Q]	0.34 (0.16 to 0.52) [Q]	(E) Karstaedt 1997 and Davies *et al* 1999 (Q) Park *et al* 1996, Fujiwara *et al* 1997	(Q) Note: Park *et al* 1996 estimates 0.52 although this study focuses on a MDR-TB population, so although 52% are HIV + and MDR-TB, it does not mean the rest are HIV + and STB. In contrast, Fujiwara *et al* 1997 suggests 16% resistant to RIF and INH (hence MDR-TB) with 25% of study population, resistant to 2nd line TB therapies (hence MDR-TB). However, this population is not HIV-related.
HIV + STB	0.72	0.72	0.66 (0.84 to 0.48)	0.66 (0.84 to 0.48)		
HIV + MDR-TB						
HIV + MDR-TB DIE	0.63 [F]	0.63 [F]	0.88 (0.41 to 0.88) [R]	0.88 (0.41 to 0.88) [R]	(F) Davies *et al* 1999 (R) Heyman *et al* 1998	
HIV + MDR-TB CURE	0.25	0.25	0.05 (0.05 to 0.52)	0.05 (0.05 to 0.52)		
HIV + MDR-TB	0.13	0.13	0.07	0.07		
HIV + STB						
HIV + STB DIE	0.31 [G]	0.31 [G]	0.31 [S]	0.31 [S]	(G) Heyman *et al* 1998	(G) Note: USA probabilities are used as a proxy for South Africa as no probabilities were available for Souh African estimates.
HIV + STB CURE	0.66	0.66	0.66	0.66	(S) Heyman *et al* 1998	

Table A14.5 (continued)

	SA (DOTS)	SA (CON)	USA (DOTS)	USA (CON)	Source	Assumptions
HIV + STB MDR-TB	0.03	0.03	0.03	0.03		
HIV + STB	0.00	0.00	0.00	0.00		
HIV + STB MDR-TB	0.03	0.03	0.03	0.03		
HIV + STB	0.00	0.00	0.00	0.00		
HIV -						
HIV – MDR-TB	0.24 (0.154 to 0.33) [H]	0.24 (0.154 to 0.33) [H]	0.24 [T]	0.24 [T]	(H) Karstaedt 1997 and Davies *et al* 1999 (T) Park *et al* 1996, Fujiwara *et al* 1997	(T) Note: Park *et al* (1996) focuses on a MDR-TB population, so although 0.236 are HIV – and MDR-TB, this does not mean that the rest are STB. Fujiwara *et al* 1997 estimates that 75% to 84% of study population is STB, although this study is not HIV-related.
HIV – STB	0.76	0.76	0.76 (0.75 to 0.84)	0.76 (0.75 to 0.84)		
HIV – MDRTB						
HIV – MDR-TB DIE	0.57 [J]	0.57 [J]	0.06 (0.04 to 0.06) [U]	0.06 (0.04 to 0.06) [U]	(J) Davies *et al* 1999 (U) Heyman *et al* 1998	
HIV – MDR-TB CURE	0.29	0.29	0.59 (0.59 to 0.92)	0.59 (0.59 to 0.92)		
HIV – MDR-TB	0.14	0.14	0.35 (0.04 to 0.35)	0.35 (0.04 to 0.35)		
	SA (DOTS)	**SA (CON)**	**USA (DOTS)**	**USA (CON)**	**Source**	**Assumptions**
HIV – STB						
HIV – STB DIE	0.03 [K]	0.03 [K]	0.03 [V]	0.03 [V]	(K) Heyman *et al* 1998 (V) Heyman *et al* 1998	(K) Note: USA probabilities are used as a proxy for South Africa as no probabilities were available for South African estimates.
HIV – STB CURE	0.94	0.94	0.94	0.94		
HIV – STB MDR-TB	0.03	0.03	0.03	0.03		
HIV – STB	0.00	0.00	0.00	0.00		

Table A14.6 Cost estimates for the treatment of DOTS and CON, in South Africa and USA

Cost category	Assumptions	Cost estimate SA (CON)	Cost estimate SA (DOTS)	Cost estimate USA (CON)	Cost estimate USA (DOTS)	Source	Notes
NEW	No extra cost	$0.00	$0.00	$0.00	$0.00		
REPEAT	Additional susceptibility testing and administration	$14.70 (A)	$14.70 (A) (G)	$1,044 (H)	$1,044 (H)	(A) Derived from Floyd *et al* 1997 (H) Derived from Moore *et al* 1996	(G) Note uses sputum costs from South African CON treatment (Floyd *et al* 1997), as there are no equivalent DOTS estimates for sputum.
COMPLETE	No extra cost	$0.00	$0.00	$0.00	$0.00		
DEFAULT	- Initial cost savings as defaulting from accepted protocol (1) - Recurrence costs: future hospitalization and treatment (excl. drugs) - Future drug costs (assume MDR-TB) (2)	- ($53.85) (A) - $1,735 (A) - $1,854.35 (B)	- ($81.40) (A) - $612.70 (A) - $1,854.35 (B)	- ($976.00) (H) - $9,920.00 (H) - $1,854.35 (B)	- ($1,397) (H) - $11,020 (H) - $1,854.35 (B)	(A) Derived from Floyd *et al* 1997 (B) Bastian *et al* 2000 (H) Derived from Moore *et al* 1996	(1) Note Moore *et al* 1996 assumes that for patients who do not complete therapy, both the cost of initial hospitalization and 50% of the subsequent costs are attributed. This assumption was deemed to hold for both the USA and South Africa (2) Note that treatment costs for MDR-TB are documented in table X. It was assumed that the lowest cost 2nd line therapy would be used for the baseline analysis.
HIV – (3)	No extra cost	$0.00	$0.00	$0.00	$0.00		(3) Moore *et al* 1996 did not assess the cost-effectiveness of treatments for TB according to HIV status, as there is no evidence to suggest that TB costs will differ according to HIV status (although outcomes will). Chaulk *et al* 1998, suggest that patients with HIV + status, despite being weaker and sicker, can still expect high cure rates from TB.

Table A14.6 (continued)

Cost category	Assumptions	Cost estimate SA (CON)	Cost estimate SA (DOTS)	Cost estimate USA (CON)	Cost estimate USA (DOTS)	Source	Notes
HIV +	No extra cost	$0.00	$0.00	$0.00	$0.00		
STB	No extra cost	$0.00	$0.00	$0.00	$0.00		
MDR-TB [3]	Assume cost of 2nd line drug treatments (minus cost of initial DOTS or CON drug costs) [2]	$1,813.95 [C] [D]	$1,817.75 [C], [D]	$1,246.35 [I], [J]	$1,503.35 [I], [J]	(C) Bastian *et al* 2000 and Floyd *et al* 2000 (I) Bastian *et al* 2000 and Moore *et al* 1996	(D) Costs derived from Bastian *et al* 2000 (see table X for costs of 2nd line drug treatments for MDRTB) and Floyd *et al* 1997. (J) Costs derived from Bastian *et al* 2000 (see table X for costs of 2nd line drug treatments for MDR-TB) and Moore *et al* 1996.
CURE	No extra costs	$0.00	$0.00	$0.00	$0.00		
STB-DIE	Assume complete treatment, but require extra hospitalization until death	$1,668 [A, E]	$486.5 [A], [G]	$8,576 [H], [K]	$8,576 [H], [K]	(A) Floyd *et al* 1997 (H) Moore *et al* 1996	(E) Costs derived from Floyd *et al* 1997. Uses cost estimate for hospitalization for initial CON therapy (2 months). (G) Costs derived from Floyd et al 1997. Uses cost estimate for hospitalization for initial DOTS therapy (17.5 days). (K) Costs derived from Moore *et al* 1996. Uses cost estimate for hospitalization for initial CON/DOT therapy

Table A14.6 (concluded)

Cost category	Assumptions	Cost estimate SA (CON)	Cost estimate SA (DOTS)	Cost estimate USA (CON)	Cost estimate USA (DOTS)	Source	Notes
MDR-TB-DIE	Assume complete treatment but require extra hospitalization until death	$1,668 (A,E)	$486.5 (A), (G)	$8,576 (H), (K)	$8,576 (H), (K)	(A) Floyd *et al* 1997 (H) Moore *et al* 1996	(E) Costs derived from Floyd *et al* 1997. Uses cost estimate for hospitalization for initial CON therapy (2 months). (G) Costs derived from Floyd *et al* 1997. Uses cost estimate for hospitalization for initial DOTS therapy (17.5 days). (K) Costs derived from Moore *et al* 1996. Uses cost estimate for hospitalization for initial CON/DOT therapy
ONGOING MDR-TB	Have to repeat therapy (assume DOTS for MDR-TB)	$1,9436 (F)	$1,9436 (F)	$12,874.35 (L)	$12,874.35 (L)	(F) Based on Floyd *et al* 1997 and Bastian *et al* 2000 (L) Based on Moore *et al* 1996 and Bastian *et al* 2000	
ONGOING STB	Have to repeat therapy (assume DOTS for STB)	$1,775.70 (A)	$649.30 (A)	$10,528(H)	$11,371.00 (H)	(A) Floyd *et al* 1997 (H) Moore *et al* 1996	

Table A14.7 Estimated costs for the alternative treatment regimens for MDR-TB

Regimen	**Ethambutol**	**Pyrazinamide**	**Kanamycin**	**Ciprofloxacin**	**Ethionamide**	**Cycloserine**	**Para-aminosaliclic acid**	**Total cost**
(USD/month)	$2.60	$2.63	$13.50	$7.34	$16.05	$318.05	$239.40	
3KetZQE/18EtQE	$54.68	$7.90	$40.50	$154.22	$1,597.05			**$1,854.35**
3KetZQC/18EtQC		$7.90	$40.50	$154.22	$1,597.05	$6,678.97		**$8,478.64**
3KetEQC/18EQEt	$54.68		$40.50	$154.22	$1,597.05	$954.14		**$2,800.59**
3KetQCP/18EtQC			$40.50	$154.22	$1,597.05	$6,678.97	$718.20	**$9,188.94**

Source: Bastian *et al* 2000.

Notes: How to read table A14.7: the estimated drug cost of treating MDR-TB with associated ethambutol and pyrazinamide resistance is USD9,188.