A Strategy for the Control of
Antimicrobial Resistance in Ireland
Report of the Subgroup of the Scientific Advisory Committee of the National Disease Surveillance Centre

S A R I

FOREWORD BY MINISTER FOR HEALTH AND CHILDREN

Antimicrobial agents have played a major role in reducing the threat from communicable diseases. In recent years, however, resistance to these agents has been recognised as a major threat to public health. The widespread use of antimicrobial agents has increasingly resulted in the selection of micro-organisms that are resistant. Across Europe, these resistant organisms are causing disease in the community and hospital setting, resulting in increased morbidity and mortality rates. The spread of antimicrobial resistance means that this is no longer regarded as a national problem but rather a global problem that requires a co-ordinated effort.

It is therefore important to develop high quality surveillance systems that will provide the information that will underpin effective strategies to counter the threat. The successful participation of NDSC in the European Antimicrobial Resistance Surveillance System represents an important step in this effort. It is also necessary to:

- monitor the supply and usage of antimicrobial agents so that they are used in an effective fashion,

- develop and implement guidelines into the appropriate usage of antimicrobials, and

- further develop effective infection control policies in hospital and community settings.

I would like to compliment the National Disease Surveillance Centre for producing this comprehensive report and for doing so in such a timely manner. As well as combating the threat which antimicrobial resistance poses, the advice and recommendations contained in this report will assist in the development of a comprehensive strategy for the health sector in relation to this issue.

Micheál Martin T.D.
Minister for Health and Children

April 2001

CHAIRMANS REMARKS

Antibiotics are regarded as one of the great medical advances of the 20th century and today form a cornerstone for the practice of medicine. Yet this great achievement is under threat by the rapid emergence and development of antimicrobial resistance (AMR). Ireland is not insulated from these changes. Bacteria respect no boundaries, and in this country many hospital and community pathogens are now resistant to commonly used anti-microbials and in some cases to the agents held in reserve.

The Department of Health and Children recognised the importance of AMR and requested the National Disease Surveillance Centre (NDSC) to make recommendations for AMR prevention. As the triggers for AMR emergence are complex and myriad, the Committee set up by the NDSC represents all the professions involved in delivery of care to the infected patient.

The Strategy for the control of Antimicrobial Resistance in Ireland (SARI) constitutes an important and innovative mechanism to combat the problem of AMR. The implementation of the strategy will require significant resources and the support of all stakeholders, including the general public. General practitioners, hospital doctors, infection control nurses, public health physicians, veterinarians and pharmacists all have a very important role to play. For microbiologists, SARI constitutes a central component of their role and it is heartening to see this formalised and resourced. It is evident that SARI will integrate well into the EU approach to AMR and hopefully will have a significant impact on what both the EU and WHO recognise as a major threat to public health.

The Committee is to be congratulated on the efficient and timely production of this comprehensive document. In particular, Dr. Olive Murphy who chaired the Committee has made a very significant contribution.

On behalf of the Scientific Advisory Committee, I am pleased to present this report to the Board of NDSC. I believe the NDSC can, as part of a multidisciplinary team, play a significant role in the implementation process, while continuing to provide the essential surveillance data necessary to support the strategy.

Dr Edmond Smyth
Chairman, Scientific Advisory Committee of the NDSC

TABLE OF CONTENTS

SUMMARY OF RECOMMENDATIONS

SUMMARY OF RECOMMENDATIONS

This committee recognises the need to develop a national strategy for the control of the development and the spread of antimicrobial resistance in Ireland. The committee recommends that the Department of Health and Children (DOHC) considers the control of antimicrobial resistance in humans a priority and makes resources available to ensure that the recommendations of the committee are implemented. All efforts to address the problem of antimicrobial resistance in humans should be considered in parallel with existing and future efforts addressing the problem in animals.

THE DEVELOPMENT OF A NATIONAL FRAMEWORK

This committee recommends the development of a three tier strategy, with local, regional and national tiers. Such a framework will ensure the existing services are developed and strengthened and local ownership of the problem, whilst tackling it within a national setting. The national committee should be co-ordinated by the National Disease Surveillance Centre. This national tier will allow international co-operation, which is an important part of the global strategy.
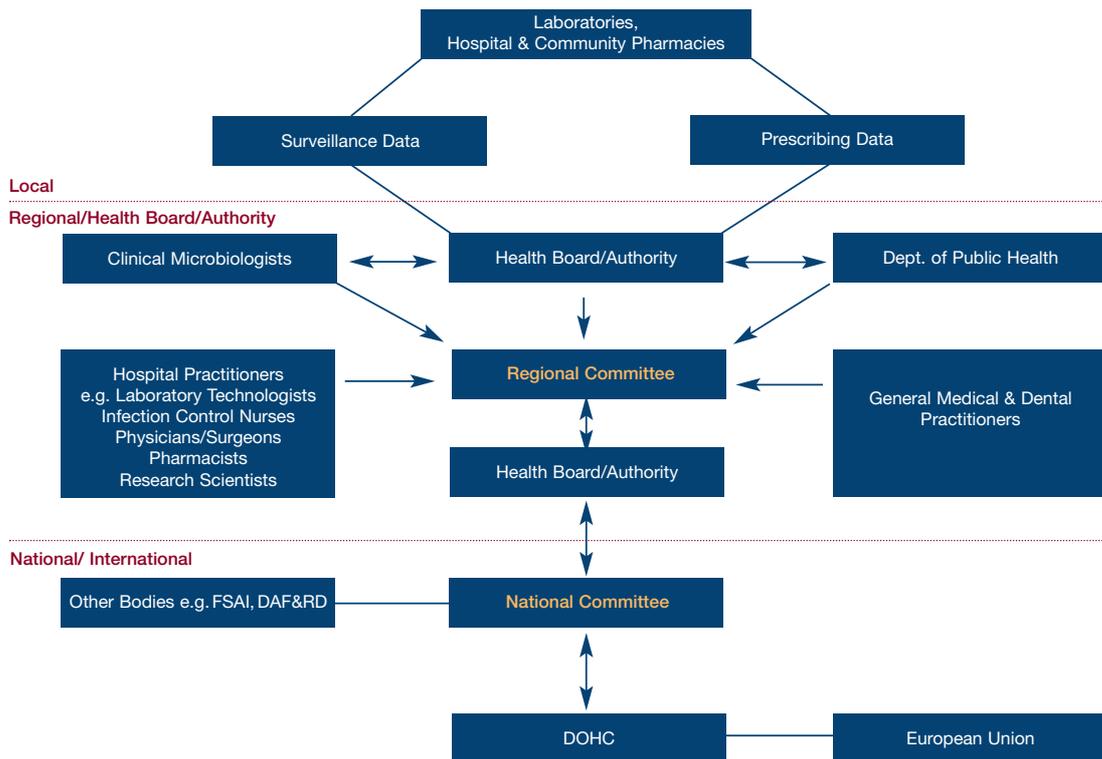
Proposed infrastructure for the antimicrobial resistance strategy*
*please refer to section 3.1 "Recommended infrastructure" when reviewing this flow chart.

The Surveillance of Antimicrobial Resistance

The committee recommends that

i. An infrastructure both at public health and laboratory level is established to ensure that reproducible, standardised, antimicrobial resistance data are collected and analysed locally, regionally and nationally in a timely manner.

ii. The DOHC establishes a network of national reference laboratories as a priority to service routine laboratories, help develop and evaluate new technologies and provide epidemiological data and facilitate research in this area. In addition, these laboratories should provide expert advice on areas of clinical practice and infection control.

iii. Routine laboratories are resourced to enable them to provide reproducible and standardised antimicrobial resistance data in a timely manner. The provision of an electronic data handling system will be an essential element. These laboratories should be managed by consultant clinical microbiologists.

iv. A general practice based sentinel surveillance system is established to ensure adequate geographic sampling for antimicrobial resistance in the community.

v. A hospital based surveillance system is established to detect hospital-acquired infections and ensure adequate sampling for antimicrobial resistance in this population.

The Monitoring of the Supply and Use of Antimicrobials

The committee recommends that

i. The tight legislative controls that exist in the area of antimicrobial prescribing are maintained and enforced.

ii. A system for the collection and analysis of antimicrobial use and prescribing in hospitals and the community is established.

iii. A basic set of data agreed by the committee be collected, i.e. the origin of the prescription, e.g. hospital or community, the agent and dose prescribed, the indication and the length of treatment.

The development of guidance in relation to the appropriate use of antimicrobials

This committee recommends that

i. Expert opinion on the diagnosis, investigation and management of patients with infection is available 365 days a year to all medical practitioners both in the community and hospitals.

ii. National guidelines for appropriate antimicrobial usage are drawn up and introduced in

all aspects of clinical practice both in hospital and the community. These must be evidenced based, exist for both the prescribing and non-prescribing of agents, have adequate information on dose etc. and highlight local variation.

iii. A process by which a reduction in inappropriate use of antibiotics can be achieved should be defined. This will differ in different settings, e.g. hospital versus community and will need to be developed accordingly.

iv. Interventions aimed at changing clinical practice are supported, encouraged and reinforced by a process of regular audit.

v. Methods, which will aid the above processes, are developed, e.g. decision-support systems, computer assisted prescribing or other prescribing aids.

vi. Improvements in vaccine uptake, in particular influenza and pneumococcal vaccine, should be targeted and prioritised.

vii. A monitoring system is established to measure effectiveness of these interventions.

EDUCATION

This committee recommends that

i. Educational programmes form the foundation for implementation of guidance strategies and a comprehensive programme should commence at undergraduate level.

ii. These programmes must be directed at all clinical professional groups providing patient care, the pharmaceutical industry and the general public.

iii. Education on home hygiene, attention to public health issues, and those developing the strategy consider the maintenance and/or improvement of housing and social conditions.

THE DEVELOPMENT OF PRINCIPLES IN RELATION TO INFECTION CONTROL IN THE HOSPITAL AND COMMUNITY SETTING

The committee recommends that

i. National infection control standards and principles are set both for hospitals and the community.

ii. The necessary infection control services to meet the set standards are resourced and established in hospitals and the community.

iii. The education of all health care workers on issues relating to infection control is prioritised.

iv. The importance of well-established preventative measures, e.g. handwashing or equivalent methods of hand decontamination are reinforced and compliance improved.

v. A monitoring system is established to measure the effectiveness of these interventions.

FUTURE RESEARCH IN THIS AREA

This committee recommends that

i. The financial support provided by governmental bodies for research and development in the area of antimicrobial resistance is increased in line with needs and that such funding is prioritised.

ii. Antimicrobial resistance becomes a priority for funding bodies supporting health care and biomedical research.

iii. Pharmaceutical companies are encouraged to continue the development of new agents and their collaboration with academic units in Ireland.

iv. A network of national reference laboratories is established to support the above research structure.

v. Future research should target areas such as:

• the evaluation of interventional strategies to promote appropriate prescribing.

• clinical studies, which evaluate the important constituents of optimal drug regimens for the treatment of infections.

• improved methods for determining and quantifying the impact of antimicrobial resistance on human mortality and morbidity.

• the motivation of physicians to prescribe, and how prescribing behaviour can best be influenced for the better.

• the role of audit and participation in the feedback of data on compliance with guidelines in influencing behaviour needs assessment.

• the study of mechanisms of antimicrobial resistance.

• the development of new vaccines.

• the development of new treatment modalities and new antimicrobial agents.

• the development of effective alternatives to antimicrobials as well as preventive therapies.

• the development of more rapid diagnostic methods for bacterial infections which might allow for better targeting of antimicrobial treatments. Furthermore, research into the use of multiplex PCR and microchips containing resistance gene arrays should provide rapid and accurate data on the presence of antibiotic resistance genes in microorganisms.

• the effectiveness of different strategies and measures to prevent infection.

INTRODUCTION

1. INTRODUCTION

The problem of antimicrobial resistance (AMR) has been identified by many countries world-wide as a major threat to public health[1-5] The World Health Organisation (WHO) has recognised AMR as a cause of prolonged morbidity, increased case fatality and lengthening the duration of epidemics.[6,7] The European Union (EU) has called on its member states to prioritise the development of a strategy to combat this problem.[8,9]

In response to the increasing concerns both in Ireland and abroad, the Department of Health and Children (DOHC) asked the National Disease Surveillance Centre (NDSC) to evaluate the problem of AMR in Ireland and to formulate a strategy for the future. The NDSC was established following recognition by the DOHC of the importance of national disease surveillance.

A subgroup of the Scientific Advisory Committee of the NDSC was established and this report is the response of this committee. The committee is convinced that the evidence presented here supports the conclusion that antimicrobial resistance poses a major threat to public health in Ireland.

1.1 Membership of the Committee

The 15 member multidisciplinary committee comprises representatives from General Practice, Medicine, Infection Control, Pathology, Dentistry, Veterinary Medicine, Paediatrics, Department of Agriculture, Food and Rural Development, Public Health Medicine, the Food Safety Authority of Ireland, Consumers Association and the Irish Pharmaceutical Healthcare Association (Appendix 1).

1.2 Terms of Reference of the Committee

The committee has been requested to consider the following areas:
1. **The surveillance of antimicrobial resistance in the human and animal populations**
2. **The monitoring of the supply and use of antimicrobials**
3. **The development of guidance in relation to the appropriate use of antimicrobials**
4. **The development of principles in relation to infection control in the hospital and community setting**
5. **To advise on future research in this area**

The terms of reference of the committee refer to the issue of antimicrobial resistance (AMR) in both human and animal populations. The importance of monitoring and controlling antimicrobial use in both these areas is recognised by the committee. However, it was felt that this committee could best address AMR in the human context. The Department of Agriculture, Food and Rural Development (DAF&RD) provided a representative to update the committee on the current initiatives in animal populations in Ireland (section 2.2) and the committee welcomed this assistance. The committee is aware that the DAF&RD has enacted a range of legal controls on the manufacture, supply and use of antibiotics in animals in line with European regulations. In addition, an antibiotic residue-monitoring programme in all species used to produce food in Ireland supplements these controls. The committee considered that a broader membership would be required to address comprehensively the issue of AMR in animals and its relationship with humans.[10] **The committee would welcome a detailed review of the problem of antimicrobial resistance in the animal population in the context of its relationship to human practice. Such a review would complement and enhance the impact of this committee's recommendations for human health care.**

It is the clear view of this committee that the implementation of the committee's recommendations for human health care should not await the outcome of such a review. The problem of AMR in the human context needs to be addressed urgently and these recommendations are in their own right an important step towards addressing this issue.

2. The Problem of Antimicrobial Resistance

2. THE PROBLEM OF ANTIMICROBIAL RESISTANCE

The development of antimicrobials is generally accepted as one of the most significant medical advances of the last century. In addition to saving thousands of lives, antimicrobials have enabled advances such as the use of cytotoxic chemotherapy, the use of immunosuppressive drugs, transplantation and other types of surgery.[11,12]

2.1 Antimicrobial resistance in human pathogens

The problem of AMR has been recognised since the introduction of penicillin into clinical practice in the 1940s. In the past, the development of new agents has partially compensated for this problem. However, over the last 10 years the prevalence of AMR has continued to escalate and the number of new classes of antibacterial drug marketed has been limited.

The problem of AMR is complex. Issues such as increased and inappropriate use of antimicrobials, over-the-counter availability of antibiotics, lack of infection control resources in hospitals and the community, overcrowding in child care facilities and other areas, increased travel and an increasing elderly population are thought to contribute to the emergence and spread of AMR.[13-19]

2.1.1 The principles of antimicrobial resistance

The principle of antimicrobial resistance is 'survival of the fittest', i.e. Darwinian selection.[20-23] Genetic variability is essential for survival and antimicrobial agents will favour those organisms capable of resisting them. Microorganisms are either inherently resistant, i.e. resistance determined by the basic nature of the organism or they can develop acquired resistance, i.e. resistance that develops in a previously sensitive strain. Acquired resistance has generally been found to follow use of antimicrobials. In addition, resistance problems are greatest in countries with highest use and in areas where use is concentrated, e.g. intensive therapy units.

It is generally agreed that the emergence and spread of AMR is determined by (i) the selection pressure exerted by antimicrobials on bacterial flora, both non-pathogenic and pathogenic, and (ii) the intra- and inter-species transmission of resistance genes and organisms. Bacteria can exchange genetic information by several mechanisms, e.g. plasmids, transposable genetic elements, DNA integration elements and a single organism may possess several resistance determinants. Some agents appear to select for resistance more readily than others do and the selection pressure may vary with dosage, route of administration and duration of therapy. Bacterial strains may contain complex aggregations of genes that can be linked together and this may result in the use of one agent selecting resistance to another agent.

2.1.2 Use of antimicrobials

In the USA, 80% of antimicrobials are used in general practice and 20% in hospitals. In hospitals it has been estimated that antimicrobials can account for up to 30% of the drug budget. This pattern is similar to many other countries and it is estimated that up to 50% of antimicrobial use in humans may be inappropriate.[24,25] As already outlined any use will select for

resistance. Although the evidence supporting the hypothesis that inappropriate and excessive use of antimicrobials is responsible for the increasing incidence of AMR is largely circumstantial, it is also described as 'overwhelming'.[5]

2.1.3 Health impact of antimicrobial resistance

AMR is now accepted as a major public health threat and is associated with excess morbidity and mortality, prolongation of hospital stay and epidemics of infection, and increased antibiotic costs.

2.1.4 Strategies for the control of antimicrobial resistance

It is agreed that measures to control antibiotic usage,[26] combined with measures to control spread of bacteria,[27,28] will at least probably slow the emergence and spread of resistant organisms. Some data suggest that different strategies may need to be developed for certain microorganism-drug combinations. It is difficult to identify with certainty which strategies are the most effective in the control of AMR but most countries to date have focused on two main strategies (1) the appropriate and prudent use of antimicrobials both in hospitals and the community and (2) good infection control practices again both in hospitals and the community.

A strategy to control the inappropriate use of antibiotics will require a team approach, the cornerstone of which will be an educational programme. A number of recent studies have shown that antibiotic control policies can reduce the use of antibiotics both in the community and hospitals.[29-39] In addition to reducing the selection pressure for resistance, such practices will reduce the number of adverse effects experienced by patients. In addition to improving patient well-being and benefiting all society, a reduction in the health impact of AMR will reduce expenditure in a cost constrained health service.

2.2 Antimicrobial resistance in animals and food microorganisms

Resistance to antimicrobial drugs is also recognised in bacteria of animal origin. Most EU member states are investigating antimicrobial resistance in bacteria in their animals and are co-operating in EU funded schemes to assess the extent of the problem. The role of non-pathogenic bacterial flora in animals, antibacterial resistance in naturally occurring bacteria in the environment and the role of antibiotics used for plant protection are being investigated in relation to their role in exchange of resistance between non-pathogenic organisms and those pathogenic for animals and man. While resistance development for any reason may increase the risk of resistance being transferred to pathogenic organisms, the role of antimicrobial resistant bacteria from animals in human disease is more difficult to ascertain.[40,41] Some estimates have indicated that resistance in bacteria from animals may only be of minor significance in human disease when compared to other factors but more detailed evaluation of the problem is required. As already stated **this committee would welcome a detailed review of the problem of antimicrobial resistance in the animal population in the context of its relationship to human practice. Such a review would complement and enhance the impact of this committee's recommendations for human health care.**

The procedures adopted by the DAF&RD for a number of years are in line with recommendations of the EU Scientific Steering Committee on Antimicrobial Resistance published in May 1999.[8] The opinion indicated that action needs to be taken promptly to reduce the overall use of antimicrobials in a balanced way in both human and veterinary

medicine. This involves such strategies as the control of antimicrobial usage, elimination of unnecessary and improper use of antimicrobials, improved disease preventive measures, improving the effective use of antimicrobials presently available based on more precise diagnosis of the infectious agent, and on monitoring of antimicrobial resistance.

Data from the 'Federation Europenne de la Sante Animale' (FEDESA) on gross antimicrobial use in the EU which was presented to the European Symposium on Antibiotic Resistance in Bacteria of Animal Origin, held at the Institute Pasteur, Paris on the 29th and 30th of November 1999 indicated that in 1998, 10,000 tonnes of antibiotics were used in the EU - 52% were used on humans; 33% were used therapeutically on animals and 15% were used as feed additives. When calculated on a per kilogram basis this represented an approximate 5 fold greater usage of antibiotics in man than animals (Antibiotics for Animals. FEDESA, December 1999).

2.2.1 The use of antimicrobials in animals in Ireland

Antimicrobials used in animals are controlled by a number of legal instruments supervised by the Minister for Agriculture, Food and Rural Development. The most significant are the Animal Remedies Regulations of 1996 (S.I.179). These regulations include detailed rules regarding the manufacturing, retailing and supply of animal remedies. Every stockowner is obliged to keep an Animal Remedies Record in which details of antimicrobial treatment of his/her animals are recorded. These records must be capable of being cross-checked with those of his Veterinary Practitioner. When treating food animals, Veterinary Practitioners advise on the period of time for which the animal and or its produce must be withheld from the food chain. Inspections of premises associated with the wholesale and retail trade in antimicrobials are carried out by DAF&RD staff. Also, a residue-monitoring programme is carried out by DAF&RD on a number of samples from food producing animals on a random basis at farms and at slaughter.

All Veterinary Surgeons registered in Ireland received a copy of a booklet produced by the Federation of Veterinarians of Europe entitled ANTIBIOTIC RESISTANCE & PRUDENT USE OF ANTIBIOTICS IN VETERINARY MEDICINE in 1999.

As a result of indications that the use of antibiotics as growth promoters may be associated with resistance development in bacteria from animals, a number of these antibiotics have been withdrawn from use as feed additives in the EU. Further evaluation of this area and the impact such use has in human medicine is required.

2.2.2 Surveillance of antibiotic resistance in animal and food pathogens in Ireland

Standardisation of test procedures in private and public laboratories and the development of an appropriate quality control system would make data more comparable. The development of an appropriate computer based system for the Regional and Central Veterinary Laboratory network would greatly facilitate collation of data and the early detection of resistance. Such data could then be easily compared with data obtained on isolates from humans. Broadening the range of organisms being investigated would be of value. The development of more rapid tests for the isolation/identification of pathogens and antibiotic susceptibility testing would favour a more prudent use of antibiotics.

As part of an EU Cost Action Fair Project, the Central Veterinary Laboratory is involved in harmonising testing systems and the collection of epidemiological data in co-operation with other national reference laboratories. Projects in resistance monitoring in zoonotic bacteria are being undertaken. A project to determine resistance in zoonotic bacteria in pigs, in collaboration with colleagues in the Veterinary Faculty of UCD, is also being undertaken.

2.3 Surveillance of antimicrobial resistance in humans in Ireland

In considering the development of future strategies in Ireland, the committee considered it worthwhile to review currently available data in an attempt to quantify the problem of AMR in Ireland. Current data suggest that the Irish experience is similar to that in other countries with increasing levels of antibiotic resistance both in hospitals and in the community.

In 1992, the Maastricht treaty called for improved national and trans-national infectious disease surveillance. The National Disease Surveillance Centre was set up in 1998 conjointly by Ireland's eight health boards and with the approval of the Minister for Health and Children. The aim of the NSDC is to improve the health of the Irish population by the collation, interpretation and provision of the best possible information on infectious diseases.

2.3.1 A national surveillance system

To date in Ireland antimicrobial resistance data have been collected at local and to some extent at regional and national levels. A number of regional infectious disease networks were established during the 1990's e.g. INFOSCAN (Southern, Mid-Western and South-Eastern Health Boards) and the Eastern Health Board I.D Bulletin. Whilst these networks have monitored a number of areas relating to infectious diseases, Infoscan has succeeded in generating data on antimicrobial resistance which have been used to influence local policies. AMR data however, are not available for all geographical areas and have not been collated at a national level. In addition to these networks ad hoc surveys have been performed. The need for a national strategy to provide high quality, relevant and timely data is well recognised.

2.3.2 The European Antimicrobial Resistance Surveillance System

Since early 1999 Ireland, along with EU neighbours and Iceland, has participated in the European Antimicrobial Resistance Surveillance System (EARSS).[42,43] The aim of this project is to collate national antibiotic resistance data and to 'map' resistance in participating countries. During the pilot phase, data have been collected on invasive isolates of *Staphylococcus aureus* (blood) and *Streptococcus pneumoniae* (blood and cerebrospinal fluid). In 1999, twelve laboratories participated in the pneumococcal arm and 11 in the staphylococcal arm of the project. In 2000, sixteen laboratories are participating ensuring a better coverage and geographical distribution of isolates. Two central laboratories are collecting isolates for further susceptibility testing and epidemiological analysis.

2.3.3 Currently available data

i. *Streptococcus pneumoniae*

Streptococcus pneumoniae is a major cause of community-acquired pneumonia, bacterial meningitis, sinusitis and otitis media. Penicillin resistance was first detected in clinical isolates in the 1960's and is now recognised as a serious problem world-wide.[44-46] The incidence of both low-level resistance(minimum inhibitory concentration MIC≥0.1 mg/L and ≤ 1.0 mg/L) high-level resistance(MIC≥2.0 mg/L) varies geographically and continues to increase.

The Alexander project was established in 1992 to examine antimicrobial susceptibilities of bacterial isolates from community-acquired infections of the lower respiratory tract.[47,48] During

the 1996-1997 study two Dublin hospitals participated: 87 isolates of *S. pneumoniae* were examined and a rate of 10.3% high-level penicillin resistance and 13.8% low level resistance in *S. pneumoniae* was found. This compares with levels of 8.3% in 1998 and 17% in 1999 in respiratory isolates in the Southern, Mid-Western and South Eastern Health Boards (Infoscan) (Table 1).

Table 1. *S. pneumoniae* respiratory tract isolate susceptibility data (% resistance). *Source Infoscan*.

S.pneumoniae	1997	1998	1999
Penicillin	15.4	8.3	17
Erythromycin	5.1	2.4	15
Tetracycline	6	2.4	9.8

These data can now be compared with national data obtained during 1999 by EARSS which found penicillin resistance in 18.8% of invasive *S.pneumoniae* isolates (Table 2) confirming that Ireland has a higher level of resistance than previously thought.

Table 2. EARSS Invasive *S. pneumoniae* antibiotic resistance in 1999.

S.pneumoniae	Total [n]	Resistant	% Resistant	95% CI
Penicillin (Oxacillin)	159	29	18.2	12.2-24.2
Erythromycin	121	18	14.9	8.5-21.2
Tetracycline	87	1	1.1	0-3.4.

The majority of isolates were re-examined at a central laboratory (Royal College Surgeons/ Microbiology Dept. Beaumont Hospital) and a rate of 23% was found. All resistant isolates demonstrated low level resistance (Figure 1) and no multi-resistant strains were detected.
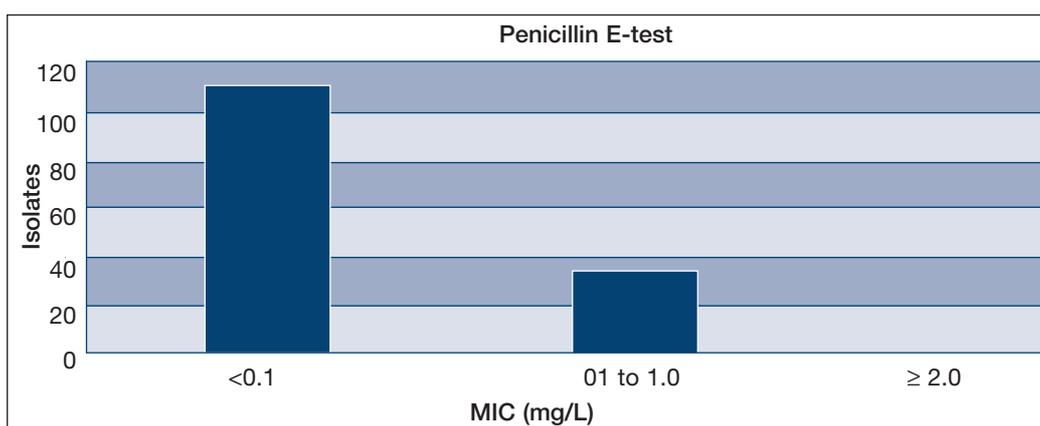
Figure 1. Minimum inhibitory concentration (MIC) of *S. pneumoniae* isolates by penicillin E-test.®

These results compare with previously reported rates of 45% in Spain, 25% in France and 5 to 10% in the UK, Germany, Belgium and Italy. Such strains are rare in Nordic countries and in the Netherlands. Geographical variation within countries has however been reported. In Northern Ireland, Goldsmith *et al* documented an increase in penicillin resistance from < 1% to 10.6% between 1988 and 1995 and a significant proportion of strains demonstrated both high level penicillin resistance and multi-drug resistance.[49]

Although not all participating laboratories had reported at time of writing, preliminary EARSS data (Irish data from 1999) are presented in Table 3.

All *S. pneumoniae* isolates will now be typed, providing epidemiological data for the first time in Ireland. These data will be used to study the pattern of spread, improve our understanding of the epidemiology and ultimately influence policy aimed at prevention and control.

Table 3. EARSS proportion of penicillin resistant *S. pneumoniae* (PRSP) by Country 1998 - 1999.

Country	No. isolates	No. PRSP	% PRSP
Germany	213	4	2
Netherlands	644	14	2
Norway	871	3	0.3
Sweden	745	21	3
Iceland	55	1	2
Finland	213	8	4
Belgium	958	136	14
UK	240	19	7.9
Italy	108	15	14
Portugal	66	9	14
Ireland	160	31	19
Luxembourg	11	2	18
Greece	56	33	59
Spain	1240	418	34
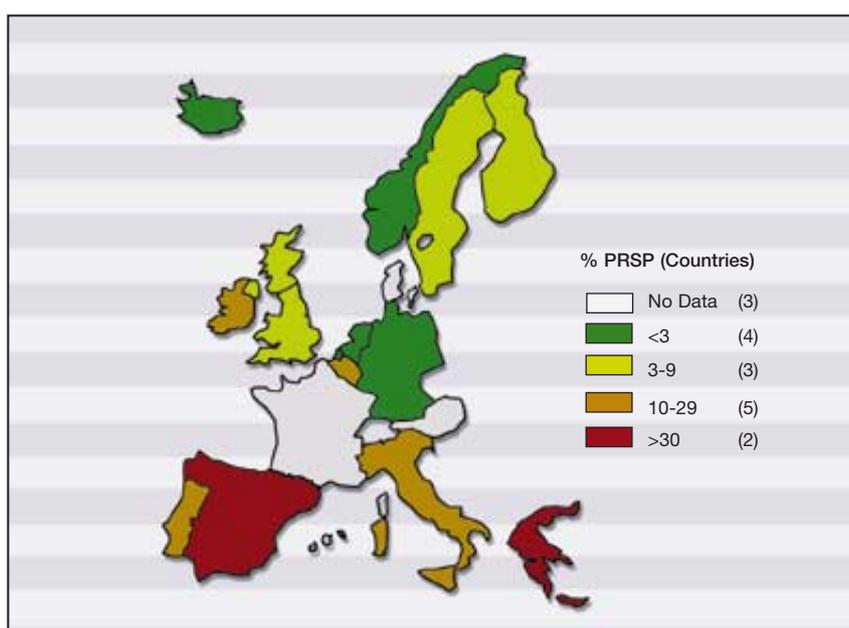
ii. *Staphylococcus aureus*

Staphylococcus aureus is a common cause of infection both in the community and hospitals.[50] Although penicillin resistance developed soon after its introduction, the availability of ß-lactamase stable penicillins overcame this problem. Methicillin resistance however developed quickly and control of the spread of methicillin resistant *Staphylococcus aureus* (MRSA) has been a major challenge for the last 30 years.[51] It is generally accepted that MRSA rates are lower in countries with well resourced, active infection control policies and this is felt to account for the variation in rates seen throughout Europe and world-wide.

Until now glycopeptides have been the mainstay of treatment for patients with serious MRSA infections.[52] Vancomycin resistance has been detected in a number of countries.[53-55] Spread of vancomycin resistant *S. aureus* may occur and may have serious consequences. The detection of such strains and the control of the spread of these isolates need to be prioritised. The problem of methicillin resistance in *S. aureus* in Ireland has been recognised since the 1970's.[56-61] A considerable volume of data on MRSA from Dublin Hospitals for the last 20-year period is available. MRSA have been endemic in a number of large hospitals in Dublin since the 1980s. The majority of these strains exhibit a multi-antibiotic resistance phenotype as well as resistance to heavy metal ions and constituents of disinfectants. The population dynamics of MRSA in these hospitals is fluid, with the introduction of new strains on an ongoing basis as many of these are introduced by patients following transfer from other Irish and foreign hospitals.[62-65] Outbreaks have been reported from a number of centres.

In 1993, a study examined *S. aureus* isolates from 9 hospitals and found that 15% of isolates were resistant to methicillin.[66] In terms of national data, two hospital-wide prevalence studies have been performed, the first in 1995 was performed prior to the introduction of national MRSA guidelines and confirmed that Ireland has a significant problem with MRSA.[67,68]

The second study was commissioned by the DOHC in 1998 and was performed on an all-Ireland basis in co-operation with the Northern Ireland MRSA working party. The results have now been published by the DOHC ('North/South study of MRSA in Ireland, 1999' published July 2000). The study looked at a number of areas including the epidemiology of MRSA in the North and the South, laboratory methods used for the detection of MRSA, the extent of resistance to antibiotics other than methicillin in MRSA and the current infection control procedures in operation in hospitals. In addition to a two week prospective prevalence survey, the study performed a retrospective review of invasive (blood culture) *S. aureus* isolates during 1998. The incidence and prevalence of MRSA varied geographically. A prevalence of 14.0 / 100,000 population (Figure 2) and an incidence of 6.5 / 100,000 population was found in the South. The retrospective blood culture survey found that 31% of invasive infections during 1998 were MRSA; this compared with 22% in the North. The *S. aureus* bacteraemia rate was 24.5 / 100,000 in the South compared with 20.4 / 100,000 in the North, and the MRSA bacteraemia rate was 7.6 / 100,000 in the South compared with 4.5 / 100,000 in the North.

Important epidemiological information has also been elucidated by the project. In the study isolates were typed by antibiogram-resistogram (AR) typing and phage typing and selected isolates were further investigated by whole cell DNA analysis, using restriction endonuclease digestion followed by pulse-field gel electrophoresis. Further analysis is still required but different strains have been found to circulate and predominate in different areas. A number of unfamiliar types were also found and work on these strains is ongoing. This work underscores the need for epidemiological analysis of MRSA and also the need for international collaboration. The access to reference facilities has been an important and essential part of this work.

Data on the prevalence of MRSA in nursing homes in Dublin confirm that MRSA is not only a hospital problem but is also prevalent in the community.[69,70]

N= Number of cases
Rate=MRSA cases per 100,000 population*
SPR=Standardised Prevalence Ratio

NWHB

N=46
Rate = 21.8
SPR=149

NHSSB

N=43
Rate=10.1
SPR=73

WHSSB

N=40
Rate=14.3
SPR=115

EHSSB
N=92
Rate=13.6
SPR=89

SHSSB
N=17
Rate=5.5
SPR=42

NEHB
N=32
Rate=10.5
SPR=82

WHB
N=38
Rate=10.8
SPR=74

MHB

N=20
Rate=9.7
SPR=74

ERHA**
N=263
Rate=20.3
SPR=176

MWHB
N=37
Rate=11.7
SPR=90

SEHB
N=31
Rate=7.9
SPR=61

SHB
N=41
Rate=7.5
SPR=57
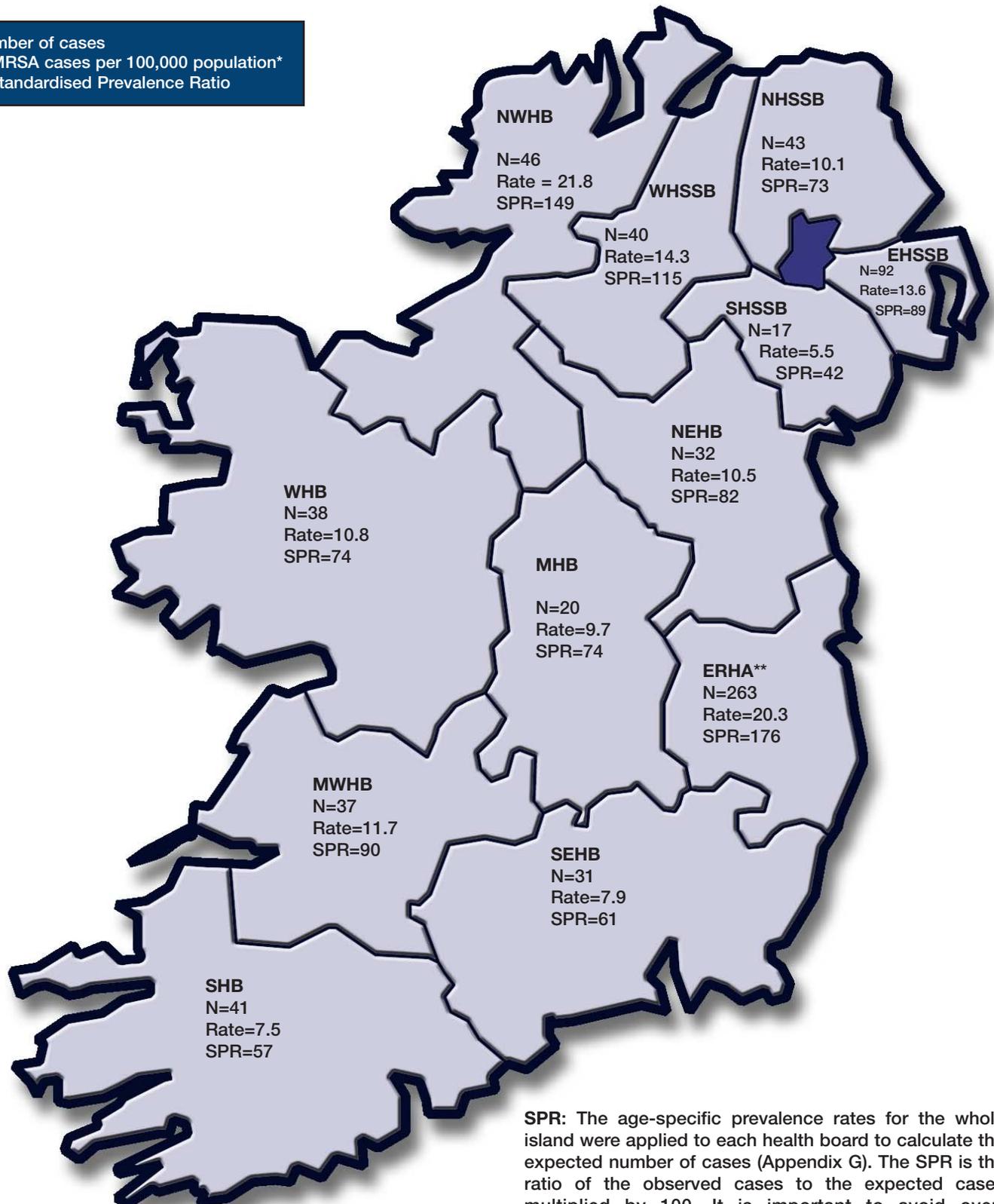
SPR: The age-specific prevalence rates for the whole island were applied to each health board to calculate the expected number of cases (Appendix G). The SPR is the ratio of the observed cases to the expected cases multiplied by 100. It is important to avoid over-interpretation of the SPR as the numbers of cases are small and may change significantly from one period to the next by chance.

Figure 2. MRSA prevalence per 100,000 population by Health Board region for two week period 1999.
(From "North/South Study of MRSA in Ireland 1999", Department of Health and Children.)

* Health board allocation on basis of location of laboratory
** Formerly known as the EHB(Eastern Health Board)

Since 1999, Ireland has participated in EARSS and preliminary data from this project suggest that 39% of invasive *S. aureus* isolates were methicillin resistant in the 1999 which compares with rates of between 0-53% throughout Europe (Table 4).[71]

Table 4. EARSS: Proportion of invasive *S. aureus* isolates resistant to methicillin by Country 1998 - 1999.

Country	No. Isolates	No. MRSA	% MRSA
Denmark	502	0	0
Iceland	41	0	0
Netherlands	1178	10	1
Sweden	1175	14	1
Finland	250	9	3.6
Belgium	305	67	22
Germany	660	57	9
Luxembourg	40	5	12.5
UK	651	219	34
Greece	137	72	53
Italy	687	279	40.6
Ireland	514	202	39
Portugal	190	94	49
Spain	348	127	36

% MRSA (Countries)

No Data (3)
<3 (4)
3-9 (2)
10-29 (2)
>30 (6)
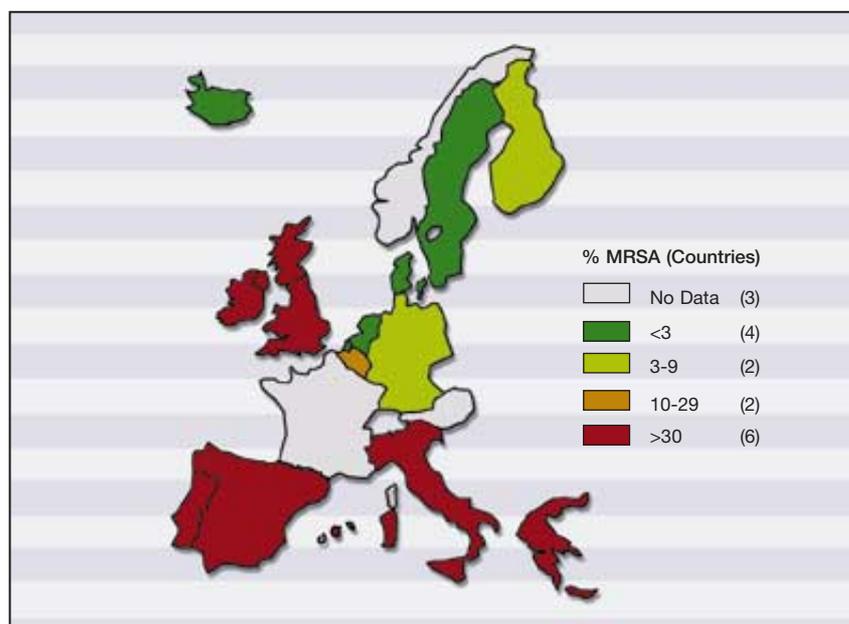
As part of the EARSS project all methicillin resistant isolates are referred to St James's Hospital, Dublin for further analysis. This has allowed confirmation of resistance and examination of susceptibility to a range of other antimicrobials including glycopeptides (Table 5). To date, glycopeptide resistance in *S. aureus* has not been detected in Ireland. There have been reports of teicoplanin resistance in clinical isolates of *S. epidermidis*.[72]

The collection of strains currently underway with EARSS will allow epidemiological analysis of the problem of invasive MRSA in Ireland at a national level for the first time.

Table 5. EARSS MRSA susceptibility data in 1999 for hospitals in Ireland.

Antibiotic	Total [n]	Resistant	% Resistant
Gentamicin	172	99	57.6
Fusidic Acid	172	3	1.7
Erythromycin	172	164	95.3
Vancomycin	172	0	0
Ciprofloxacin	172	163	94.8
Rifampicin	172	2	1.2
Tetracycline	172	1	0.6

iii. Gram negative bacilli

Gram negative bacilli remain an important cause of both hospital and community acquired infection.[73-74] To date, the problem of resistance has been seen mainly in hospital acquired infections, in particular in immunocompromised patients and in those nursed in specialist areas, e.g. intensive care units (ICU), haematology, oncology units and neonatal units.[75-79] In addition, it is generally accepted that extended spectrum ß-lactamase mediated resistance represents a serious problem among gram negative nosocomial pathogens.

Again, national data in Ireland are lacking, however some local data suggest that our problems are similar to those experienced elsewhere. A study of consecutive blood culture isolates in an Irish hospital found that 76% of the gram-negative bacilli (55 enterobacteriaceae and 13 non-fermentative gram negative bacilli) studied were resistant to ampicillin, 46% to co-amoxiclav, 31% to cefotaxime, 16% to ceftazidime, 15% to gentamicin, 13% to piperacillin/tazobactam and 9% to ciprofloxacin. In particular the phenomenon of extended-spectrum ß-lactamase production was noted.[80]

Three Dublin hospitals have been involved in outbreaks of serious infection with a multi-drug resistant strain of *Serratia marcescens*. Dating back to 1984 when the first Dublin outbreak was reported to more recently described outbreaks in an ICU department in 1998 and in a haematology/oncology unit in 1999, the antimicrobial resistance profile of *S. marcescens* has expanded to include, not only chromosomal-mediated cephalosporin resistance but also resistance to aminoglycosides and fluoroquinolones.[81-83]

In addition to the above problems with multi-resistant *Pseudomonas aeruginosa*, *Burkholderia cepacia* and *Acinetobacter* spp. in at risk populations have been identified both here and abroad.[84,85] All of these pathogens can result in serious infections including outbreaks. Containment of these outbreaks and the treatment of infected patients can be difficult. In Ireland the extent of the problem with these pathogens remains largely unknown.

iv. Enteric pathogens

a. *Salmonella* spp.

Salmonellosis remains an important cause of food borne illness in humans. Increasing antimicrobial resistance is a world-wide problem.[86,87] Recent data from the United States support the view held by some that the use of antimicrobial agents in livestock contribute to the problem of AMR in strains causing human disease. [88]

In Ireland, data collected since 1996 has found high levels of resistance among *Salmonella enterica* serotype Typhimurium.[89] Many isolates have been found to be resistant to at least 5 antibiotics, ampicillin, chloramphenicol, streptomycin, sulphonamide and tetracycline (ACSSuT).

Many outbreaks have been described and a recent study has identified the presence of integron-like structures in these isolates, a novel mechanism by which unrelated DNA becomes incorporated into cells.[90,91]

A study funded by the Food Safety Authority of Ireland (FSAI) is currently underway and will allow evaluation of 50-60% of human isolates. Preliminary 1999 data confirm the problem outlined in earlier reports and are presented in Table 6 (Prof. M. Cormican, personal communication).

Table 6. Antibiotic suscepibilities of *Salmonella enterica* serovars isolated in Ireland in 1999.

% resistance (no of isolates)								
	N	Ampicillin	Chloramp-henicol	Streptomycin	Sulphonamide	Tetracycline	Trimethoprim	Nalidixic Acid
S.Typhimurium	150	83(124)	65(97)	68(102)	83(127)	85(127)	23(34)	2(3)
S.Enteritidis	123	3(4)	0(0)	1(1)	1(1)	4(5)	1(1)	7(9)
S.Bredeney	50	0(0)	0(0)	2(1)	2(1)	0(0)	2(1)	0(0)
S.Kentucky	9	0(0)	0(0)	22(2)	44(4)	33(3)	33(3)	0(0)
S.Virchow	4	25(1)	0(0)	0(0)	0(0)	25(1)	25(1)	75(3)
S.Schwarzengrund	4	0(0)	0(0)	0(0)	75(3)	0(0)	75(3)	0(0)
S.Hadar	4	50(2)	0(0)	50(2)	0(0)	50(2)	0(0)	50(2)
Others	25	NA	NA	NA	NA	NA	NA	NA

b. *Campylobacter* spp.

Campylobacter spp. are now recognised as one of the main aetiologic agents of acute diarrhoeal disease. Data on the incidence of this infection in Ireland are lacking. However, in the area covered by Infoscan the number of reported cases doubled between 1993 and 1998. The pattern is likely to be similar elsewhere in the country. In addition to an increasing number of infections, resistance to antimicrobial agents amongst *Campylobacter* spp. is an increasing problem world-wide.[92,93] Irish data on resistance however, are lacking. A recently published study by Lucey *et al* looked at resistance to a number of agents in clinical human cases and isolates from porcine and poultry sources. Although the numbers were small, this study confirmed resistance to ampicillin in 17%, erythromycin in 11.3%, tetracycline in 24.5%, sulphonamide in 62.3% and ciprofloxacin in 1.9%. Seventy seven percent were resistant to three or more antimicrobial agents. This study also identified the presence of integron-like structures in these isolates, a novel mechanism by which unrelated DNA becomes incorporated into cells.[94]

v. *Neisseria meningitidis*

Neisseria meningitidis is an important cause of meningitis and septicaemia and Ireland continues to have a significant burden of morbidity and mortality from meningococcal infection when compared to other EU partners.

To date, *N. meningitidis* isolates demonstrating high-level penicillin resistance have been reported from South Africa and Spain. Isolates with low level resistance are more frequently

described, however the clinical significance of such isolates is not fully known. In the UK an upward trend in MIC has been found in the last 15 years and continued monitoring of the situation is underway.

The Meningococcal Reference Laboratory at the Children's Hospital, Temple Street, Dublin in addition to providing important epidemiological data, will also prove a useful source of antimicrobial resistance data in the future.

vi. *Streptococcus pyogenes* **and** *Streptococcus agalactiae*

Penicillin resistance in *Streptococcus pyogenes* has not been reported. Erythromycin resistance is a well recognised problem and clonal spread of such a strain has been reported in Finland.[95] A national reduction in macrolide used was followed by a reduction in resistance levels. In Ireland there are no national data on resistance in both these important pathogens, however some local data are available (personal communication Prof. M Cormican)(Table 7).

Table 7. Results obtained on 64 *S. pyogenes* and 35 *S. agalactiae* collected in 1998/1999 tested in University College Hospital, Galway.

		Sensitive	Intermediate	Resistant
S.pyogenes	Chloramphenicol	64	0	0
	Clindamycin	63	0	1
	Erythromycin	60	2	2
	Ofloxacin	56	4	4
	Penicillin	64	0	0
	Tetracycline	49	1	14
		Sensitive	Intermediate	Resistant
S.agalactiae	Chloramphenicol	35	0	0
	Clindamycin	34	0	1
	Erythromycin	32	2	1
	Ofloxacin	26	6	3
	Penicillin	35	0	0
	Tetracycline	9	1	25

Method: NCCLS disc diffusion, with E-test® penicillin MIC for some strains equivocal on disk diffuson.

vii. *Mycobacterium tuberculosis*

A national surveillance programme of *M. tuberculosis* infection is in operation. However, the collection of susceptibility data has not been a primary aim of this programme. Reporting clinicians are asked to report the presence of resistance.[96-98] Available data have not demonstrated an increase in resistance levels and as yet no outbreak of multi-drug resistance has been reported. A national tuberculosis committee is currently reviewing the control of *Mycobacterium tuberculosis* in Ireland and strategies to control the development and spread of multi-drug resistant strains.

viii. *Enterococcus* **spp**.

Nosocomial enterococcal infections appear to be increasing in incidence world-wide and many strains are multiply resistant. Vancomycin resistant enterococci (VRE) in particular have become a serious problem in some centres.[99] A survey of antimicrobial susceptibility of clinical isolates of *Enterococcus* spp. from Irish hospitals was performed in 1991.[100] Many of the isolates were multiply antibiotic resistant. Ampicillin resistance was detected in 16%. High level gentamicin resistance (HLGR) was found in 7% and glycopeptide resistance in 2%.

Another study was performed in 1994, following an outbreak of vancomycin resistant *Enterococcus faecium* (VREM) in an oncology unit in Dublin. HLGR and penicillin resistance was again demonstrated.[101] A retrospective study of enterococci isolated from blood cultures showed that between 1991 and 1994 ampicillin resistance increased from 22% to 51% and HLGR increased from 17% to 60%. Prior to the outbreak 2% of isolates were vancomycin resistant. An outbreak in Northern Ireland has also been described.[102] The related phenomenon of vancomycin dependence in enterococci was first described in Ireland in 1997.[103] These results suggest that antibiotic resistance in enterococci in Irish hospitals is a significant problem, but further work is again required.

ix. Urinary tract pathogens

A number of surveys of isolates and susceptibility trends have been performed, one of which examined apramycin resistance in common causes of UTI.[104,105] A further study found high levels of antimicrobial resistance in pathogens causing UTI in the community.[106] Of particular concern was the finding of ciprofloxacin resistance and extended spectrum ß-lactamase production in isolates from patients with no history of contact with residential health care facilities.

x. *Haemophilus influenzae* **and** *Moraxella catarrhalis*

The first detailed study of antibiotic resistance in *Haemophilus influenzae* in Ireland (Northern Ireland and Ireland) was performed in 1988.[107] Resistance for ampicillin, chloramphenicol and tetracycline was found to be well established and higher than that found in the UK with 10.2% of strains demonstrating ß-lactamase mediated ampicillin resistance. Comparable data from Northern Ireland are also available.[108] In 1992, a two year study of invasive *H. influenzae* disease was undertaken before the introduction of *Haemophilus influenzae* type B (Hib) vaccine.[109] This study provided useful epidemiological data and also demonstrated that 17% of serotype B strains were ß-lactamase producers, i.e. resistant to ampicillin. More recently the Alexander Study found that 17.3% of 202 isolates were ß-lactamase producers. In addition, 1.5% of isolates were ß-lactamase negative and ampicillin resistant. Of the 65 isolates of *Moraxella catarrhalis*, 96.6% produced ß-lactamase. Infoscan also yields useful data on an annual basis for both these pathogens (Table 8).[110]

Table 8. *Haemophilus influenzae* **antibiotic resistance (%) 1997-1999.** *Source: Infoscan*

Antibiotic	1997	1998	1999
Ampicillin	21.6%	18.6%	15.6%
Co-amoxiclav	1.4%	0.9%	2.4%
Tetracycline	4.8%	0.9%	1.1%
Erythromycin	49.5%	35%	50%

xi. Viruses

Antiviral drugs are important in the treatment and control of a number of viral infections. Resistance to all currently available agents has been demonstrated and can pose therapeutic difficulties for the management of certain groups of patients. Currently, data on antiviral resistance in Ireland are lacking.[111-114]

a. Herpes viruses
Acyclovir resistance in Herpes simplex virus is well documented and can be problematic in AIDS patients and transplant patients. Other problematic herpes viruses include varicella-zoster virus and cytomegalovirus but again resistant isolates are usually isolated from immunocompromised patients after prolonged therapy.

b. Human Immunodeficiency Virus
The problem of anti-retroviral resistance is well documented. The use of highly active antiretroviral therapy (HAART) probably reduces the rate of emergence of resistance however continued monitoring of the problem is essential. In Ireland such data are not yet available, though the Virus Reference Laboratory will collate data on resistance to antiretroviral agents in patients with newly diagnosed HIV in the future.

xii. Fungi
Resistance to currently available antifungal agents is recognised as a significant and increasing problem especially in immunocompromised patients.[115-117] There are two aspects to be considered: (1) the development of antifungal resistance in *Candida* sp., especially *C. albicans* and (2) the selection of inherently less susceptible Candida and other fungal species.

a. *Candida albicans*
Azole antifungal resistance in *C. albicans* has been reported extensively over the last decade, primarily from HIV-infected/AIDS patients treated extensively (including prophylactically) with these compounds, especially fluconazole. The development of resistance is associated with the extended duration of therapy. In Ireland, approximately 3% of AIDS patients with recurrent oral and pharyngeal candidosis have azole-resistant *C. albicans*. A similar percentage of fluconazole-resistance has been found among isolates of *C. dubliniensis* from this patient group.

b. Non-*Candida albicans* Candida species
Over the last decade there has been a dramatic increase in the incidence of infections caused by non-*C. albicans* candida species in Europe and the Americas. This is particularly true of candida septicaemia. These organisms are also becoming increasingly important nosocomial pathogens. Many non-*C. albicans* candida species, such as *C. glabrata* and *C. krusei* are inherently less susceptible to azole antifungal drugs, and these happen to be the species responsible for the recent dramatic increase in the incidence of candida infections. Other species, such as *C. lusitaniae*, are inherently resistant to polyene antifungals.

These organisms are *de facto* antifungal drug resistant in many cases. Non-*C. albicans* candida species (predominantly *C. glabrata*) account for approximately 10% of oral fungal infections in Irish patients (~20% in HIV-infected/AIDS patients).

xiii. Summary
Currently, national data on antimicrobial resistance in Ireland for a number of important pathogens are lacking. The available data suggest that a significant problem exists and these data need to be built on in order to establish the extent of the problem and to monitor the effectiveness of future strategies.

2.4 Antimicrobial use in Ireland

2.4.1 Antimicrobial use in humans
If we assume that increased antimicrobial use correlates with an increased prevalence of antimicrobial resistance, and base future strategies for prevention on the control of prescribing, it is essential that we analyse in detail all aspects of antimicrobial use. Accurate information, however, on patterns and amounts of antimicrobial use, both in Ireland and throughout Europe, is limited.

2.4.2 Over-the-counter availability of antibiotics
In Ireland, all antibacterial agents are prescription only medications. Certain antiviral agents and antifungal agents may be legally sold without a prescription under the supervision of a pharmacist. Antibacterial agents can be bought in some European (failure of enforcement) and developing countries without prescription and such practices have been linked with high resistance rates. The failure of enforcement in some European countries has been described as 'under the counter availability' and is due to antimicrobials being sold by pharmacists without a prescription.

2.4.3 Current Sources of Data in Ireland
Currently in Ireland it is possible to obtain some data on antimicrobial use in the community (see below). None of the data sources listed however give information on antimicrobial use in hospitals.

a. General Medical Scheme (GMS) Data

The GMS Payments Board receives copies of all prescriptions written for GMS patients as part of pharmacists' claims for payments. These data can quantify the number of prescriptions written for a particular antibiotic, e.g. amoxycillin and the number of tablets per prescription. These prescriptions do not provide any information on the source of the script or the indication for treatment.

b. Drugs Payment Scheme Data

The new Drugs Payment Scheme (DPS) which came into force in July 1999 replaced the Drug Refund Scheme and the Drug Cost Subsidisation Scheme. While the DPS is administered at health board level, claims for payment are processed centrally by the GMS Payments Board rather than by individual health boards. In addition, pharmacists submit copies of receipts issued to patients rather than the original prescriptions. These receipts show information such as name and quantity of medicine dispensed and details of the prescriber but do not include details of dose, source of script, indications or periods of treatment. A further limitation on DPS data is that not all private prescription are processed through this scheme - unless an individual patient or family exceeds the threshold expenditure of £42 per month, no claim can be made under the scheme and therefore there will be no record of the prescription(s).

c. Pharmaceutical Industry Data

Pharmaceutical industry data are collected by a commercial company, IMS Health, from a number of sources - wholesalers and doctors. There are basically two key data sets - prescription data (no. of scripts, indications, quantity etc) based on information supplied by general practitioners and sales data based on sales through wholesalers.
IMS data are used by the pharmaceutical industry to measure trends in market growth. A sample of prescription data is collected from 200 GPs and is analysed to give an estimate for the country as a whole. The sampled GPs change from time to time as new GPs agree to collect the data and others opt out.

The following limitations arise with IMS prescription data:

    i. No hospital survey is involved.
    ii. Sample bias applies
    iii. No information is obtained on what is actually dispensed.
    iv. Regional samples may be very small.

In relation to IMS sales data, this service collects information on the sale of prescription products from wholesalers to pharmacy. Reliability of this data is variable.
Limitations arise for the following reasons:

    i. Direct sales from manufacturers to pharmacy are not recorded.
    ii. This service collects data on what is bought but not what is sold by the pharmacy.
    iii. The impact of parallel trade in antimicrobials is not factored into the IMS data.

2.5 Current Irish Infrastructure

The future development of both a successful surveillance and intervention programme in Ireland will require a substantial support structure. The committee felt it was important to document, as a baseline, the level of support currently available in order to establish the resources implications of these recommendations.

2.5.1 Laboratory Support

Although there are approximately 60 laboratories providing diagnostic microbiology services in Ireland, it is estimated that 24% of these laboratories perform in excess of 85% of tests (A. Murray personal communication). Significant variation exists in workloads, methodologies, availability of information technology and participation in external quality assessment schemes.

The North/South study of MRSA, in 1999 found many variations between laboratories in both the North and South for the detection, identification and confirmation of MRSA. This committee made a number of recommendations including the need to define the optimal methods for the identification and susceptibility testing of MRSA.

As will be addressed later, the expertise of consultant clinical microbiologists is not available to all laboratories or health boards.

Laboratories are not currently resourced to comply with the data collection, reporting, isolate collection and dispatch necessary for a surveillance programme. Such a programme will require standardisation of methodologies, an electronic system for data transmission and significant manpower resourcing.

The need for increased support at laboratory level has already been recognised. In June 1999 the NDSC submitted a report to the DOHC from a committee formed to examine the resource requirements for Microbiology Departments and Departments of Public Health in relation to surveillance of pathogenic organisms and antimicrobial resistance (Appendix 2).

The necessity of standardisation of methodologies has been recognised by the Irish Society of Clinical Microbiology and the Academy of Medical Laboratory Science and a working group has being established to look at standardisation in relation to the issue of antimicrobial susceptibility testing. The need for an electronic surveillance system has also been recognised by the NDSC and this area is also currently under review. To date, Irish laboratories have not participated in an accreditation programme, although this issue is currently being addressed by

the DOHC, Faculty of Pathology, Academy of Medical Laboratory Science and individual laboratories.

A network of reference laboratories does not exist for the majority of pathogens. Where such laboratories have been developed and centrally funded, e.g. Meningococcal Reference Laboratory, Virus Reference Laboratory, the benefits accrued in terms of the development of techniques, the provision of epidemiological data and the availability of expert advice have been welcomed. The North/South study of MRSA recommended that there be ready access to reference facilities for MRSA and the work undertaken by the Staphylococcal laboratory in St James's Hospital has yielded important insights into the epidemiology of MRSA infection in this country. There is a well recognised need for similar resourcing of reference laboratories for other important pathogens and the NDSC, Faculty of Pathology, the Academy of Medical Laboratory Science and the DOHC are currently reviewing this issue.

2.5.2 Consultant Medical Microbiology Services

Current consultant microbiology staffing levels are inadequate. A number of health boards do not have any consultant microbiologists employed and there is no doubt that such staffing levels hinder the provision of a quality service. The role of the microbiologist in providing a laboratory, clinical liaison, infection control and educational service is well established.

In response to a manpower document produced by the Royal College of Pathologists, the Faculty of Pathology has reviewed the manpower situation in Ireland. A document was submitted to the DOHC in late 1998 (Appendix 3).

The North/South study on MRSA has again yielded useful information which may reflect the difficulties experienced by microbiologists attempting to deliver a quality service within the current level of resourcing. Only 41% of hospitals surveyed in the South had a written antibiotic policy compared with 95% in the North. The committee recommended that all hospitals have a written antibiotic policy. In addition, only 65% of hospitals in the south, had an infection control committee. The acute hospitals were significantly more likely to have an infection control committee than the district hospitals. All hospitals in the North had an infection control committee.

2.5.3 Infection Control Services

The function of the Infection Control Nurse (ICN) includes activities such as surveillance, investigation, control, liaison, education and research. Most ICNs report on infection control matters to the consultant microbiologist who is generally also the infection control doctor. Some report to the public health specialist, while others, in absence of the two former, report to a clinician.

The ICN has a key role in formulating policy, implementing infection control programmes and improving practice. Well-resourced infection control services have been shown to be cost effective and can reduce the rate of nosocomial infection by up to 33%. In addition the role of the ICN should be extended outside the acute hospital to District Hospitals, Residential Units for the Elderly/Special Needs etc. Together with the microbiologist, the ICN should also have an advisory and educational input in general practice and nursing homes.

To conduct surveillance of 'alert organisms', antimicrobial resistant organisms, communicable disease and surgical site infection, more ICNs are required than the current complement. One ICN per 250 beds is the recommended ratio in the US but this is now considered inadequate for the current scope of work, which continues to increase in complexity, technological advances, specialisation and educational requirements.

In a 500-bed hospital with established infection control programmes, it has been estimated that four ICNs are required at a minimum to provide for targeted hospital surveillance, including surgical and device-related infection. In a 250-500 bed hospital 2/3 ICNs may be required and one ICN is required for a 250-bed hospital, although some specialised acute 250-bed hospitals may require more than this complement. Additional ICNs may be required where infection control programmes are not fully established, during outbreaks and for implementing new programmes that require extra training and education. Excluding acute hospitals, it has been estimated by the ICNA that an additonal four ICNs, with a senior ICN co-ordinating programmes, will be necessary in each health board area.

The current level of infection control support both in hospitals and in the community is inadequate (Appendix 4). This has also been demonstrated by the recent North/South study on MRSA. As outlined above only 65% of hospitals in the South have an infection control committee and 15% of hospitals did not have access to an infection control nurse. Less hospitals in the South had isolation facilities available. The committee again made a number recommendations in terms of training, the availability of facilities and laboratory and infection control resources.

2.5.4 Public Health Departments

The Director of Public Health is responsible for the surveillance and control of infectious diseases and for monitoring the uptake of immunisations in each board. A specialist in public health medicine delivers this function. The specialist, with the medical microbiologists, and GP unit pharmacist could play a key role in monitoring the regional antimicrobial resistance profiles, and co-ordinating and disseminating the regional prescribing data and policies. The current structure however is not resourced to the level necessary to allow antimicrobial surveillance and control strategies to be put in place (Appendices 2 and 5).

2.5.5 General Practitioners

General practitioners are responsible for up to 80% of antibiotic prescribing and therefore will play a pivotal role in future strategies in this area. At present GPs are not resourced to allow participation in antimicrobial surveillance and educational programmes. Current data available to GPs on local antimicrobial resistance patterns are patchy and inadequate. Publications such as Infoscan provide useful information in their annual respiratory and urinary pathogen surveys. However, these data are only available for part of the country, do not distinguish between hospital and GP isolates (approx 50/50) and are only available annually on a retrospective basis. Additional information on antimicrobial resistance is obtained by sending samples on particular patients. However, again such data cannot be used to formulate guidelines and policies.

To date, GP prescribing has been influenced by general sources of information such as:

i. Drug formularies, e.g. B.N.F. or GP formularies R.C.G.P. Northern Ireland faculty publication.
ii. Bulletins from The National Medicines Information Centre and the Drug and Therapeutics Bulletin (UK).
iii. Journals and textbooks.
iv. Continuing Medical Education meetings, either I.C.G.P. or local hospital-based.

In practice, GPs tend to generalise this information to the rest of the practice population when deciding which antibiotic to prescribe in a given situation.

2.5.6 The Pharmaceutical Industry

The pharmaceutical industry has played a central role in the development of therapeutic agents to fight infectious diseases. Notwithstanding the fact that it currently costs $500 million to bring a new medicine to market, research investment in antimicrobials has grown steadily with particular emphasis on antiviral agents in recent years. In addition to research and development, the industry has also been involved in resistance surveillance programmes such as the Alexander project.

The industry is actively developing ways to optimise and sustain the utility of existing drugs in the environment of antimicrobial resistance. There is an increasing focus on determining optimal conditions of use for antimicrobials, i.e. what is the most appropriate dose, duration of treatment etc., to maximise efficacy and tolerability but also to minimise the risk of developing resistance. Much of this information emerges during the development of antimicrobials. Significant attention is also being paid to simplifying regimens to improve compliance.

All of this information is reflected in the summary of product characteristics (SPC) which accompanies the product. The precise wording of the SPC is agreed with the regulatory authority (e.g. the Irish Medicines Board) at the time the product is first licensed. The company must submit evidence to the regulatory authority to substantiate the statements in the SPC, which is then subject to independent review by the authority and its external experts.

In relation to the advertising and promotion of antimicrobial agents to medical practitioners, pharmaceutical companies are entitled by law to do so. However, such promotion is undertaken within a tight legal framework and must comply with an industry Code of Practice (the IPHA Code of Marketing Practice) which is recognised and approved by the Minister for Health & Children.

2.5.7 Other services

While it is not the brief of this committee, other problems such as overcrowding, lack of nursing staff, consultant staffing levels in other disciplines, junior doctor training and the degree of pharmacy support will impact on the problem of antimicrobial resistance.

3. Recommended Future Strategies and their Implementation

3. RECOMMENDED FUTURE STRATEGIES AND THEIR IMPLEMENTATION

The development of an Irish strategy to combat this problem is essential. Consideration must be given as to how the following recommendations are implemented in an Irish context. This committee recommends that the DOHC considers the control of AMR a priority and that resources are made available to ensure that the following recommendations are implemented.

The following sections will consider future strategies and are the recommendations of the committee.

3.1 Recommended Infrastructure

This committee recommends that currently available resources, i.e. regional infectious disease networks, are developed and strengthened. The development of a three tier strategy, with local, regional and national tiers, would suit the Irish healthcare system (Figure 3). The local tier should comprise the hospital laboratories and pharmacies and the hospital(s) / general practitioners serviced by them. The regional tier should collate data on the area covered by a Health Board/Authority. The national tier should comprise the National Committee, which should be co-ordinated by NDSC, and will collate national data and have responsibility for the development of guidelines, policies and strategies. These can then be adopted and implemented at regional and local level. Expert advice on issues such as educational programmes should be made available; this is particularly important when designing programmes aimed at the general public. The National Committee may wish on occasion to liase with other bodies such as the Food Safety Authority of Ireland and the DAF&RD on issues relating to antimicrobial resistance. The National Committee will be responsible for the communication of national data to the European Union and the World Health Organisation if it is required.
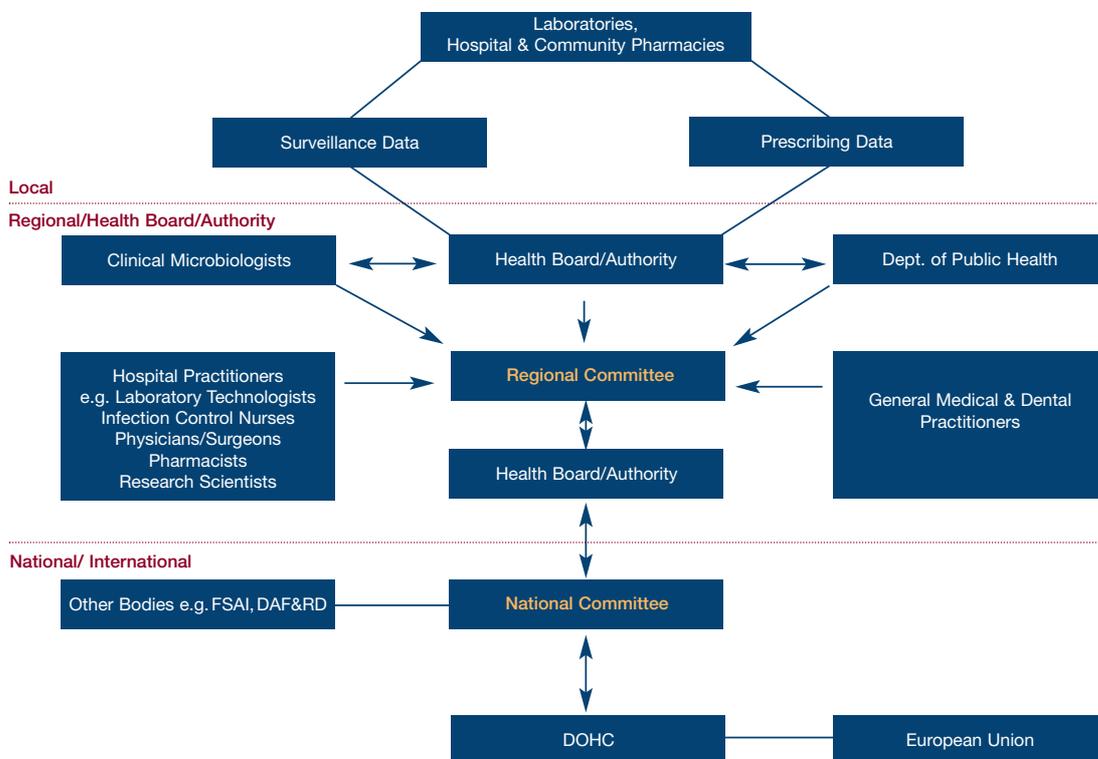

Figure 3. Proposed infrastructure for AMR strategy *

This strategy should be multidisciplinary with clinical microbiologists, laboratory technologists, infection control nurses, infectious disease physicians, physicians/surgeons, general practitioners, GP units, pharmacists, research scientists and public health specialists involved at local and regional levels. The regional committee should be established and co-ordinated by the health board/authority. The Director of Public Health (or representative) or a microbiologist should act as chairman of the regional committee and the committee should nominate two representatives for the National Committee.

It is recommended that surveillance and prescribing data are collated by each board/authority at a regional level and these data are then forwarded to the NDSC. This structure will require an identified person (a microbiologist or specialist in public health) to oversee the collection/collation and local interpretation of data at the local and regional levels. A designated person(s) will also be required to co-ordinate the national tier.
Such a structure will ensure ownership of the problem is devolved to those making the decisions and local data and practices can then be developed quickly to address local problems.

It is important that mechanisms are put in place to ensure that all interventions are evaluated and critically assessed in a timely manner. Such practices will ensure that the strategy is continuously developed and improved.

3.2 The surveillance of antimicrobial resistance

Surveillance data have certain biases that reflect the population surveyed, method of data collection and the underlying purpose of data collection. The ideal surveillance system should provide accurate incidence and prevalence rates in a timely manner. Such a system however requires numerator and denominator data and exclusion of repeat isolates. It is generally accepted that the collection of routine good quality data supplemented by special surveys, the use of sentinel laboratories and general practices will provide the necessary data for the surveillance of AMR. Such a system, supported by Reference laboratories, will enable a timely response to emerging pathogens and current concerns.

3.2.1 The surveillance of antimicrobial resistance in the human population
i. Establishment of an infrastructure

The surveillance of antimicrobial resistance at a national level will require the establishment of an infrastructure to ensure that reproducible standardised antimicrobial resistance data is collected for relevant clinical pathogens and analysed locally, regionally and nationally in a timely manner. Currently, susceptibility data are available within laboratories but this information is not routinely collected. **This committee recommends that such an infrastructure be resourced by the DOHC.**

ii. National reference laboratories

Although most surveillance data will be generated in routine laboratories, this committee recommends that a network of reference laboratories be developed. Such laboratories will provide epidemiological data and facilitate research in this area including the study of mechanisms of resistance, the typing of organisms, the development of rapid diagnostic strategies etc. In addition, these laboratories will be able to provide expert advice on areas of clinical practice and infection control. **This committee recommends that the DOHC establishes a network of national reference laboratories as a priority.**

iii. Routine laboratories

As already discussed, routine laboratories will act as the principle source of routine surveillance data necessary for the development of this strategy. Again it is important that these laboratories are resourced to enable them to provide quality information. **This committee recommends that all laboratories involved in the provision of clinical data participate in surveillance and that laboratories participating in surveillance:**

  a. **have a designated member** of staff with responsibility for the surveillance programme.

  b. **have an electronic system** for the downloading of susceptibility data and appropriate information technology support.

  c. **have standardised methods** for identification and susceptibility testing of microorganisms and provide quantitative data.

  d. **meet set quality standards** by participating in external quality assessment and accreditation schemes.

  e. ensure all staff **participate in ongoing continuous professional development**.

  f. **be managed by a consultant microbiologist** to ensure that tests received in the laboratory are clinically appropriate; to allow interpretative assessment of results; to allow the development of antimicrobial reporting strategies and the provision of clinical liaison and infection control services.

  g. **participate in the evaluation and development of rapid diagnostic tests** and continually strives for an improvement in turn-around times for results.

iv. Surveillance in general practice

This committee recommends that a general practice based sentinel surveillance system should be established to ensure adequate geographic sampling for antimicrobial resistance in the community. To promote better prescribing of antimicrobials in general practice it will be necessary to analyse general practice prescription data against local antimicrobial resistance patterns and communicate this information to GPs.

It will be necessary to:

  a. **improve the methods for the diagnosis of infections** in general practice.

  b. **develop general practice surveillance systems** based on sentinel practices to provide local, regularly updated sensitivity data for common infections and acts as an early warning system for influenza outbreaks and other infections e.g. *Mycoplasma* spp.

  c. use the surveillance data to **develop national evidence based guidelines on antimicrobial prescribing in Irish general practice**.

  d. **ensure that any information** gathered from GP surveillance systems although collated centrally, is reported back to the providers of the information **so that it can be used effectively**.

  e. **assure confidentiality of the data.**

v. Surveillance in hospitals

This committee recommends that a hospital based surveillance system be established at national and local levels to detect hospital-acquired infection based on nationally agreed definitions of infection. Adequate sampling from patients with hospital acquired infection will help in the diagnosis of infection, the detection of the emergence of antimicrobial resistance and the occurrence of outbreaks. Evaluation, review of data and recommendations should take place at a national as well as local level. Timely feedback of information to stakeholders should be a priority to create ownership and improve practice. The infection control team members are key people in the development and co-ordination of such a surveillance system.

3.3 The monitoring of the supply and use of antimicrobials

In the first instance **this committee recommends that the tight legislative controls that exist in the area of antimicrobial prescribing are maintained and enforced.** The establishment of a system to monitor the use and supply of antimicrobials will be necessary to monitor the effects of any interventions.

This committee recommends the development of a system to monitor the use and supply of antimicrobials. It is important that a system is developed for both hospitals and the community. Once available, data should be collated and analysed as previously described.

This committee recommends that a basic data set is collected and should include information on:

  i. the agent prescribed
  ii. the dose prescribed
  iii. the source, e.g. GP versus hospital
  iv. the indication
  v. the length of treatment.

Systems already in place should be built on and developed. Every advantage should be taken of the benefits of computerisation in hospital and community pharmacies. In addition to the routine collection of prescribing data, it may be necessary to undertake survey or sentinel studies in specific areas, e.g. patient compliance.

3.4 The development of guidance in relation to the appropriate use of antimicrobials

This is an essential part of the strategy and guidance must be developed both in hospitals and in the community. Such a strategy requires the promotion of prudent use via education of all prescribers, patients, manufacturers, and other users. **This committee recommends**:

  i. **Expert opinion on the diagnosis, investigation and management of patients with infection is available 365 days a year to all medical practitioners both in the community and hospitals.**

  ii. **National guidelines for appropriate antimicrobial usage are drawn up and introduced in all aspects of clinical practice both in hospital and the community.** The guidelines should:

   a. be evidence based to the greatest degree possible and regularly reviewed.

   b. exist for both the prescribing and non-prescribing of antimicrobials and recommend treatment options for each clinical situation.

   c. be group specific, i.e. different bodies of experts should draw up guidelines for different groups of patients.

d. include information on the most appropriate antibiotic and information on each antibiotic such as dosage, duration of treatment, effect of alcohol consumption, reactions with other medication, etc. This information should reflect the licensed particulars for the product as set out in its summary of product characteristics (SPC).

e. highlight areas where antibiotics are often used but not clinically indicated.

f. highlight local variation, if any, from national susceptibility data which may influence local recommendations.

g. include guidance for the non-antibiotic therapies for infection, e.g. symptomatic therapies for viral respiratory tract infections.

iii. **A process by which a reduction in inappropriate use of antibiotics can be achieved is defined**. This will differ in different settings, e.g. hospital versus community and will need to be developed accordingly.

iv. **Interventions aimed at changing clinical practice are supported, encouraged and reinforced by a process of regular audit**.

v. In the future the **possibility of computer assisted prescribing, decision support systems or other prescribing aids should be considered**. This would allow the timely use of local data and could be adapted regularly depending on trends.

vi. **Improvements in vaccine uptake should be striven for and the development of new vaccines prioritised.**

vii. **A comprehensive monitoring system should be established** to ensure that these measures are in place and to measure effectiveness.

3.5 Education in relation to the appropriate use of antimicrobials
This committee recommends that:

i. **Educational programmes form the foundation for the implementation of the guidance strategies.**

ii. **The educational programmes encompass all aspects of AMR,** including mechanisms, strategies, prescribing practices, infection control aspects etc. These programmes must be directed at all clinical professional groups providing patient care, the pharmaceutical industry and the general public. Again, programmes should be developed and targeted at the different groups.

a. *Medical and Dental personnel*: In terms of medical education the programme should commence at undergraduate level and should continue during postgraduate training and throughout professional life. These programmes should be co-ordinated by the relevant professional registration body or the Postgraduate Medical and Dental Board. The ICGP have prepared an overview of strategies used to influence prescribing practice in General Practice (Appendix 6)

b. *Pharmacists*: Pharmacists are an important source of advice for patients and are an important link in the prescribing chain. Pharmacists have a significant role to play in educating the public on the importance of compliance.

c. *Nurses*: Nurses in hospitals and the community also have a key role in helping patients understand the relevance and use of antibiotics. They are also important in the prevention of spread of infection through good hygiene practices. The use of antimicrobials and the understanding of the development of resistance should be prioritised in their undergraduate and postgraduate training.

d. *Pharmaceutical industry*: The pharmaceutical industry has a role to play in ensuring that all activities in relation in the advertising and promotion of medicinal products to healthcare professionals are undertaken responsibly and do not breach industry standards of practice. The pharmaceutical industry will continue to be an important source of information about the correct use of its products (i.e. usage in accordance with the terms of its licence) through the provision of summaries of product characteristics to healthcare professionals, patient information leaflets to patients and other educational activities.

e. *General public*: Education of the general public will be essential if the interventions outlined are to be successful. The level of awareness of antimicrobial resistance must be increased among the general public, particularly regarding the correct use and misuse of antibiotics. Public education campaigns should focus on the fact that antibiotics are a valuable resource if used properly rather than conveying messages such as "antibiotics don't work" or are dangerous. The concepts of 'cherishing your flora' and 'sustaining a valuable resource' must be emphasised. An aggressive publicity campaign should form part of a strategy however it is essential that such a strategy is carefully planned and professionally delivered. Other self-help methods should be encouraged, e.g. the provision and maintenance of an internet site on antimicrobial resistance by the NDSC could provide a valuable resource for educating the public about antimicrobial agent resistance in Ireland. This resource in a multimedia format could be used to explain why antibiotics are not always the answer for sore throats, colds and the flu etc. Surfing the net is a routine pastime for many members of the public and this practice will increase in the future. Children, parents and teachers should be properly educated about general hygiene as a measure to avoid infection. It is also important to educate the general public on the possible over use of antimicrobial detergents, cleaners and toiletries.

iii. **In addition to promoting appropriate prescribing other issues that play a role in the prevention of infection and may contribute to the reduction in antibiotic use are considered.** Education on home hygiene, attention to public health issues, and the maintenance and/or improvement of housing and social conditions may be important in an overall strategy.

3.6 The development of principles in relation to infection control in the hospital and community setting

Establishing an adequate infection control service will be a fundamental part of this strategy. Such a service will reduce the spread of infection, with both susceptible and resistant organisms, and hence reduce the requirement for antimicrobials. ICNs are essential personnel in the development of surveillance strategies, formulation of policy, the provision of education at all levels of service and the setting of standards for best practice. This committee recommends that:

i. **National infection control standards and principles are set both for hospitals and the community.**

ii. **The necessary infection control services to meet the set standards are resourced and established in hospitals and the community.**

iii. **The education of all health care workers on issues relating to infection control is prioritised** and the Infection Control Nurses Association and Irish Society of Clinical Microbiology should advise other educational bodies of the educational requirements.

iv. **The importance of well established preventative measures,** e.g. handwashing or equivalent methods of hand decontamination **be reinforced and compliance improved**.

v. **A comprehensive monitoring system is established** to ensure that these measures are in place and to measure effectiveness.

3.7 Future research in this area

As already discussed much of what is recommended is based on circumstantial evidence and it is important that all these strategies are evaluated fully. **This committee recommends that:**

i. **the financial support provided by governmental bodies for research and development in the area of antimicrobial resistance is increased in line with needs and that such funding is prioritised.**

ii. **the area of AMR becomes a priority for funding bodies supporting health care and biomedical research.**

iii. **pharmaceutical companies are encouraged to continue the development of new agents and their collaboration with academic units in Ireland.**

iv. **a network of national reference laboratories is established to support research in this area.**

Future research should target areas such as:
- the evaluation of interventional strategies to promote appropriate prescribing.

- clinical studies, which evaluate the important constituents of optimal drug regimens for the treatment of infections.

- improved methods for determining and quantifying the impact of antimicrobial resistance on human mortality and morbidity.

- the motivation of physicians to prescribe, and how prescribing behaviour can best be influenced for the better.

- the role of audit and participation in the feedback of data on compliance with guidelines in influencing behaviour needs assessment.

- the study of mechanisms of antimicrobial resistance.

- the development of new vaccines.

- the development of new treatment modalities and new antimicrobial agents.

- the development of effective alternatives to antimicrobials as well as preventive therapies.

- the development of more rapid diagnostic methods for bacterial infections which might allow for better targeting of antimicrobial treatments. Furthermore, research into the use of multiplex PCR and microchips containing resistance gene arrays should provide rapid and accurate data on the presence of antibiotic resistance genes in microorganisms.

- the effectiveness of different strategies and measures to prevent infection.

APPENDIX 1: MEMBERSHIP OF THE COMMITTEE

Dr Olive Murphy, Bon Secours Hospital, Cork.
(Chairman).

Mr Tony Murray, Mater Hospital, Dublin
(representing the Academy of Medical Laboratory Science).

Dr Nola Leonard, Veterinary College, Dublin
(representing the Faculty of Veterinary Medicine).

Dr Lynda Fenelon, St Vincent's Hospital, Dublin
(representing the Faculty of Pathology).

Dr Mary Cafferkey, The Children's Hospital, Temple Street, Dublin
(representing the Faculty of Paediatrics).

Ms Eilish Creamer, Beaumont Hospital, Dublin
(representing the Infection Control Nurses Association).

Prof. David Coleman, Trinity College, Dublin
(representing the School of Dental Science).

Prof. Conor Keane, St James's Hospital, Dublin
(representing the Royal College of Physicians).

Dr Nuala O'Connor, Cork
(representing the Irish College of General Practitioners).

Dr Ann Shannon, North Western Health Board
(representing the Faculty of Public Health Medicine).

Prof. Martin Cormican, National University of Ireland, Galway
(representing the Food Safety Authority of Ireland).

Co-opted members:

Dr Michael Gunn, Department of Agriculture, Food and Rural Development.

Ms Celine Murrin, Consumers Association of Ireland.

Ms Leonie Clarke, Irish Pharmaceutical Healthcare Association.

Dr Michael Barry, Dept. Pharmacoeconomics St James's Hospital, Dublin.

APPENDIX 2: REPORT TO THE DOHC ON THE SURVEILLANCE OF PATHOGENIC ORGANISMS AND ANTIMICROBIAL RESISTANCE

Republic of Ireland surveillance for pathogenic human microbes and antimicrobial resistance

Background

We are encouraged that the Department of Health and Children have recognised the importance of national disease surveillance by establishment of the National Disease Surveillance Centre. Adequate surveillance of communicable diseases requires integration of data from medical practitioners, clinical microbiology laboratories and Departments of Public Health. It is a prerequisite for the success of the NDSC that each of these strands is adequately resourced.

The standard workload of the clinical microbiology laboratory has increased dramatically in recent years. Major factors contributing to the increase include:-

i. Emergence of new infectious diseases e.g. *E.coli* O157, vCJD, cryptosporidiosis, *C. difficile*, hepatitis C, HIV, etc.

ii. Change in epidemiology of endemic organisms, e.g. current hyperendemnicity of meningococcal disease, increased prevalence of hepatitis B and C etc.

iii. Emergence of multi-drug resistant organisms both at community and at hospital level.

iv. Evolution in medical practice with increased numbers of compromised patients - advances in critical care, haematology oncology, transplantation etc.

v. Increased frequency and rapidity of travel with resultant rapid dissemination of microorganisms and importation of infectious diseases not typically found in this geographic area.

vi. Population shifts.

vii. Globalisation of the market economies with global distribution of both fresh produce and prepared foods - again facilitating rapid dissemination of organisms if produce is contaminated (this might not be immediately recognisable at the local level unless good national surveillance is present).

The real impact of these factors and need for vigilance is evidenced by the:-

i. Lethal outbreak of *E.coli* O157 in Scotland.

ii. Emergence of vCJD in the U.K.

iii. Outbreak of *E.coli* O157 in children at a day care unit in the Republic of Ireland.

iv. Recurrent outbreaks of salmonellosis.

v. Local outbreaks of meningococcal infection.

vi. Hospital based outbreaks of *C. difficile*, vancomycin resistant enterococci. (VRE) MRSA, viral gastroenteritis etc.

Impending problems include:-

i. The next (overdue) influenza pandemic.

ii. Dissemination of highly resistant pneumococci.

iii. Further dissemination of VRE and MRSA.

iv. Emergence of VISA (vancomycin intermediate susceptibility *S. aureus*) and VRSA (vancomycin resistant *S. aureus*).

v. Dissemination of highly multi-drug resistant gram negative organisms (*P. aeruginosa*, *A. baumanii*, *B. cepacia*).

vi. Further dissemination of multi-drug resistant T.B.

Some of those listed above have the potential to reach catastrophic proportions. Extreme vigilance needs to be maintained if the emergence of such problems are to be recognised promptly and contained.

In addition to the timely reporting of designated conditions and alert organisms, it is essential that specified isolates are submitted for detailed epidemiological typing and/or antimicrobial susceptibility testing if the full potential of a national surveillance programme is to be realised.

Currently in the Republic of Ireland the microbiology laboratories are not resourced to comply with the data collection, reporting, isolate collection and dispatch that are the keystones on which any surveillance programme is built. Specifically there is a need for the appointment of a surveillance officer within each laboratory/group of laboratories with responsibility for this. With regard to Public Health Departments, an additional half-time Specialist in Public Health Medicine is required by each Department to provide the additional epidemiological expertise to co-ordinate each region's surveillance activity. In addition to the half-time Specialist an additional half to one whole-time equivalent Clinical Officer is required in each Community Care Area to follow up on the surveillance information required at local level. Following the discussion with the Directors of Public Health it was recommended that flexibility would be allowed in each region as to the type of clinical officer in each Community Care Area who would be recruited. Some area of strengthening and/or re-organisation of the Area Medical Officer duties is required. In other areas Clinical Surveillance Officers with a nursing background were recommended.'

In addition, the resourcing of a standard I.T. system with links in each Community Care office, local laboratory and the regional Public Health Department is an urgent requirement. An additional clerical resource of one clerical officer at regional Public Health Department is required to support the system.

APPENDIX 3: CONSULTANT MICROBIOLOGY STAFFING LEVELS.

Table 9. The calculations of projected/ideal consultant staff levels based on the Royal College of Pathologists' guidelines, in relation to workload and population.

Health Board	Present Consultant Staff Microbiology/Virology	Projected/ideal Consultant Staff Microbiology/Virology
North Western	1	2
North Eastern	0	3
Eastern	9.5	21.5
Midland	0	2
Mid Western	0*	2**
Western	2	4
South-Eastern	1	2
Southern	2	5.5
Total	**15.5**	**41**

Submitted by the Faculty of Pathology.
*Consultant pathologist with an interest in microbiology in post
** Initial Faculty of Pathology recommendation was 1 post, however based on population and the service needs two posts now recommended by the Mid-Western Health Board.

APPENDIX 4: INFECTION CONTROL NURSE STAFFING LEVELS.

Total beds represents acute hospital beds, psychiatric hospitals and intellectually disabled beds. Data for total and psychiatric hospitals are based on figures for 1997, acute hospitals and intellectually disabled on 1996 figures. This represents major specialties, but not all beds may be included.

Table 10: The total and acute hospital beds in health board areas, the number of ICNs currently in post and the recommended ratio of ICNs.

Health Board	Beds Total	Beds AcuteHospital	No. ICNs In Post	No. ICNs Ratio 1/250 Beds
Eastern	8445	4947	14	34
Midland	1259	473	2	5
Mid-Western	1915	752	0	7
North Eastern	1669	911	3	6
North Western	1477	662	2	6
South Eastern	2908	1114	3	12
Southern	3546	1771	5	14
Western	2791	1231	2	11
Total	24010	11861	31	95

Submitted by the ICNA.

APPENDIX 5: PUBLIC HEALTH SPECIALIST STAFFING LEVELS.

Table 11. Current Public Health Specialist with responsibility for Infectious Diseases staffing levels

	WTE Public Health Specialists	Population
EHB	2.5	1,300,000
SHB	1.5	500,000
NEHB	0.25	310,000
MHB	0.4	205,000
MWHB	0.8	320,000
SEHB	1.0	390,000
NWHB	0.4	212,000
WHB	0.5	352,000

Submitted on behalf of the Faculty of Public Health.

APPENDIX 6: EDUCATION OF GP PRINCIPALS WITH A VIEW TO CHANGING ANTIBIOTIC PRESCRIBING BEHAVIOUR.

Prepared by Prof. Colin Bradley University College Cork on behalf of the ICGP.

A variety of educational approaches to changing the prescribing behaviour of established general practitioners have been tried in many different countries. Among the approaches that have been tried and systematically evaluated are:

- Sending out of written material advising doctors on 'good/rational prescribing'

- Traditional lectures/seminars and other types of postgraduate courses

- Feedback to practitioners of their own prescribing data with or without comparator data on their peers' prescribing and with or without opportunities to meet and discuss the data and its implications with either/or peers and/or experts

- Opportunities to discuss prescribing and/or clinical practice more broadly with peers and/or external (to the practice) 'experts', e.g. 'quality circles'

- Academic dealing i.e. one-on-one visits to practitioners from 'experts' with specialised knowledge and/or training in prescribing/therapeutics

- Decision support software including software built into GP information systems designed to offer information/decision support at the point of issuing a prescription

Broadly speaking, the more traditional educational approaches (e.g. lectures) and approaches which fail to actively engage the learner (e.g. dissemination of written advice alone) have little or no impact on prescribing behaviour. More elaborate schemes which aim to engage doctors in active learning (e.g. 'quality circles') and schemes which personalise messages in relation to the doctor's own prescribing behaviour (e.g. academic detailing and feedback of prescribing data) have been shown in studies to be capable of changing prescribing behaviour. However, there remain doubts about whether behavioural change can be sustained unless the educational endeavour, including feedback and peer discussion is maintained over time. A system of postgraduate education for general practitioners in Ireland already exists in the form of the ICGP continuing medical education (CME) network. Although it has not yet been specifically deployed with a view to changing prescribing behaviour of participants, it seems ideally configured to deliver effective education on better antibiotic use in peer discussion groups. The GP Units of Health Boards also have access to the kind of data that would be useful for providing individualised feedback of prescribing information. Furthermore, although 'academic detailing' as such is not carried out in Ireland, this is a function that could also be developed by GP Units (given some extra resources) and would greatly enhance the value of CME and provide outreach to non-participants in CME.

Specifically in relation to antibiotic prescribing, it has been shown that doctors' preferred choices of antibiotics for use in common infections in general practice can be changed towards greater use of antibiotics advocated by expert advisers, i.e. more appropriate antibiotics. However, an effective means of persuading doctors to reduce their overall level of antibiotic prescribing has not yet been adequately demonstrated. It has been shown that doctors who prescribe fewer antibiotics have fewer patients attending with minor respiratory infections and vice versa. In addition, the proportion of patients (about 10%) seen with minor respiratory infection return within the same illness episode for a further consultation but that this proportion is the same regardless of whether or not the patient received an antibiotic at the first consultation. Another study has shown that if patients are given a prescription for an antibiotic but are advised to hold off using it until symptoms either persist for a few more days or get

markedly worse a high proportion (about one third) of such prescriptions will not be dispensed. An educational exercise for established GPs to assist them in declining inappropriate requests/pressure from patients to prescribe unnecessarily (reported to be a major driver of GP antibiotic prescribing) has been devised. This exercise, rather than focusing on which is the right antibiotic for a particular infection, focuses on the conduct of the consultation by the doctor. Particular emphasis is placed on the issue of patients' expectations and how these might be more skilfully managed by GPs. It is hypothesised that this exercise, if taken up by a large proportion of GPs, and offered in a sustained way to support behavioural change by GPs in consultations, would lead to a reduction in the total volume of antibiotics prescribed. A trial of this style of intervention specifically in the area of antibiotic prescribing is about to be instigated by the Department of General Practice, University College Cork. It is intended that the trial will be implemented through the existing ICGP CME network. The Wellcome Trust has expressed an interest in possibly sponsoring the trial.

Glossary of Terms

GLOSSARY OF TERMS

Acquired resistance: resistance to antimicrobial agents that develops in microorganisms that were previously sensitive

Aetiology: the cause of a specific disease

Antibacterial: a substance produced by or derived from a microorganism that inhibits or destroys bacteria

Antibiotic: a substance produced by or derived from a microorganism that inhibits or destroys other microorganisms

Antibiotic policy/Antibacterial policy: written guidance that recommends antibiotics and their dosage fortreatment of specific infections

Antifungal agent: an agent that can be used to treat infections caused by fungi

Antimicrobial agent: any compound that at low concentrations exerts an action against microbial pathogens and exhibits selective toxicity towards them

Antimicrobial resistance: see resistance

Antiseptic: a non-toxic chemical that can be used to clean skin before an operation so as to prevent infection or applied to skin to cleanse dirty wounds

Asymptomatic: not showing any symptoms of a disease, although it is present

Audit: organised review of current practices and comparison with predetermined standards. Action is then taken to rectify any deficiencies identified in current practices. The review is repeated to see if the predetermined standards are met

Bacteraemia: presence of bacteria in the bloodstream

Bacterium: a microscopic organism with a single chromosome of a circle of single stranded DNA

Blood culture: sample of blood taken from a patient with a serious infection

ß-lactamase: an enzyme produced by some bacteria which is capable of antagonising the effect of a ß-lactam antibiotic thereby making the bacterium resistant to treatment by the antimicrobial

Chromosome: the structure containing nucleic acid (DNA) that carries the genetic information of an organism

Chemotherapy: the prevention or treatment of disease by the use of chemical substances

Clinical microbiologist: a person who studies the science of the isolation and identification of microorganisms that cause disease in humans and applies this knowledge to treat, control and prevent infections in humans

Colonisation: the ability of some pathogens to live on or in a host without causing disease

Commensal: a member of the normal bacterial flora

Communicable disease: a disease caused by a microorganism that can be passed from a person, animal or the environment to another susceptible individual

Community: populations, diseases or health services outside of hospitals

Compliance: the degree to which patients follow the instructions for taking a course of treatment

Contact: a person who has been exposed to a source of infection

CSF: Cerebrospinal fluid: the clear watery fluid that surrounds the brain and spinal cord

Denominator: the population considered being at risk, e.g. the total number of people admitted to a hospital or receiving a particular antimicrobial agent. This is used to calculate rates such as incidence and prevalence

Disinfectant: a chemical that destroys or removes bacteria and other microorganisms.

DNA: deoxyribonucleic acid: the genetic material of most living organisms

Efficacy: the effectiveness of an agent or a preparation or a treatment

Empirical treatment: treatment based on past experience or observation rather than the result of laboratory investigations

EMRSA: epidemic methicillin resistant *Staphylococcus aureus*

Endemic: present in a community or common among a group of people; a disease prevailing continually in a community

Epidemic: the occurrence in a community or region of a group of illnesses of similar nature, clearly in excess of normal expectancy

Epidemiology: the study of the occurrence, cause, control and prevention of disease in populations

Fatality: see mortality

Flora: see normal bacterial flora

Formulary: a compendium often used in hospitals to list the drugs readily available for prescribing. Some indicate the seniority of medical staff who may prescribe individual drugs

Fungus: member of a class of primitive organisms but is an eukaryote

Gene: the basic unit of genetic material

GP: general practitioner

Gram stain: a dye that is used to stain bacteria to aid identification when viewed with a microscope

Gram-negative: bacteria that are stained red by Gram stain

Gram-positive: bacteria that are stained violet by Gram stain

ICU: intensive care unit

Immunocompetent: a person who has normal immune responses

Immumocompromised: Immunosuppressed: a person who has impaired immunity due to disease (e.g. cancer) or treatment (e.g. corticosteroid drugs or radiotherapy)

Incidence: the number of episodes of a disease that occur in a specified period of time in a specified group of people,

Inflammation: the response of tissues to damage caused by physical, chemical or biological agents

Inherent resistance: resistance to an antimicrobial agent that is due to the basic nature of the organism, e.g. all gram-negative bacteria are impermeable to glycopeptides and are therefore resistant to them

IT: information technology such as computers

Meningitis: inflammation of the membranes (meninges) that envelop the brain and spinal cord.

Microorganism: any organism that is too small to be visible to the naked eye, e.g. bacteria, fungi, viruses and protozoa

Morbidity: the state of having a disease

Mortality: death

Multi-resistance: a microorganism that is resistant to two or more unrelated antimicrobial agents

Mutation: a change in the genetic material of an organism, or the resultant change this causes in a characteristic of the individual, caused by an alteration to the nucleic acid structure

Nosocomial infection: infection acquired during hospitalisation that is neither present nor incubating at the time of admission

Normal bacterial flora: the bacteria that normally live on and in the skin, gut, mouth and upper respiratory tract of humans. Also called commensal organisms, they do not normally cause disease, and provide some protection from infection. When antimicrobial agents are used to treat infectious disease they can affect the normal bacterial flora and their ability to provide protection from infection

Opportunist: a pathogen that infects immunocompromised people but rarely infects immunocompetent people

Optimum duration: the best duration of treatment, not too long or too short

Otitis media: inflammation of the middle ear

Pathogenicity: capacity to cause disease

Pathogen: a microorganism capable of causing disease

PCR/Polymerase Chain Reaction: laboratory procedure that produces millions of copies of DNA from one or few molecules

Phenotype: entire physical, biochemical and physiological makeup of an individual which is both genetically and environmentally determined

Plasmid: a piece of genetic material (DNA) often found in bacteria that is independent of the chromosome

Prevalence: the number of instances of a particular disease or other condition at a particular time, e.g. the number of people with tuberculosis, or the number infected with a pathogen resistant to antimicrobial agents

Protozoan: a single-celled microorganism, that is more complex and usually bigger than a bacterium and may be free living or parasitic

Quality issues: issues about the quality of health services delivered to patients in hospitals and the community

Reference laboratory: a laboratory that carries out more specialised tests on samples received from other laboratories and is usually involved in research relating to its particular area of interest

Resistance: the ability of a microorganism to withstand an antimicrobial agent.

Respiratory tract infection: infection of the respiratory tract including upper respiratory tract infections such as colds, sinusitis, and lower respiratory tract infections such as pneumonia

Selection pressure: environmental conditions that favour the survival and replication of certain individuals, e.g. the presence of an antimicrobial agent favours the survival of micro-organisms that are resistant to it

Susceptible/Sensitive: organisms that are unable to replicate or are killed by an antimicrobial agent

Septicaemia: severe general infection caused by pathogens and their toxins

Sinusitis: inflammation of the sinuses of the nasal cavities that is commonly caused by infection

Surveillance: the systematic collection and evaluation of data on all aspects of a disease that are relevant to its prevention and control

Transmission: passing infectious disease from one person to another or a plasmid from one bacterium to another

Vaccine: a preparation that can be used to stimulate the development of immunity against one or more pathogens to prevent infections including measles, mumps; polio, rubella, whooping cough, diphtheria, hepatitis A, hepatitis B and rabies

Virulence: the ability of a pathogen to cause disease

Virus: a very small microorganism that can only survive and multiply within a living cell

REFERENCES

REFERENCES

1. Hawkey PM. Action against antibiotic resistance: no time to lose. *Lancet* 1998; **351**: 1298-1299.

2. Cunney R, Smyth E. Controlling antibiotic use: protecting an endangered medical resource. *Irish Medical Journal* 1998; **91**(1):14-15.

3. O'Brien TF. The global epidemic nature of antimicrobial resistance and the need to monitor and manage it locally. *Clinical Infectious Diseases* 1997; **24 (Suppl 1)**: S2-S8.

4. Baquero F. Antibiotic resistance in Spain: what can be done? Task Force of the General Direction for Health Planning of the Spanish Ministry of Health. *Clinical Infectious Diseases* 1996; **23**: 819-823.

5. Scientific Medical Advisory Committee: Subgroup on Antimicrobial Resistance 'The Path of Least Resistance'. Department of Health, UK. 1998.

6. World Health Organisation. Antimicrobial resistance Monitoring Programme. *WHO Drug Information* 1997; **11**; 248-249.

7. Tenover FC, Hughes JM. WHO Scientific Working Group on monitoring and management of bacterial resistance to antimicrobial agents. *Emerging Infectious Diseases* 1995; **1**: 37.

8. Report of the EU Scientific Steering Committee on Antimicrobial Resistance. May 1999.

9. The Copenhagan Recommendations: Report from an Invitational European Union Conference on 'The Microbial Threat'. Copenhagan, Denmark, September 1998.

10. Advisory Committee on the Microbiological Safety of Food. Report on microbial antibiotic resistance in relation to food safety. Department of Health, UK. 1999.

11. Hogberg U. Effect of introduction of sulphonamides on the incidence of and mortality from puerperal sepsis in a Swedish county hospital. *Scandinavian Journal of Infectious Diseases* 1994; **26**: 233-238.

12. Mosdell DM, Morris DM, Volturs A et al. Antibiotic treatment for surgical peritonitis. *Annals of Surgery* 1991; **214**;543-549.

13. Munoz R., Coffey TJ, Daniels M et al. Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae*. *Journal of Infectious Diseases* 1991; **164**: 302-306.

14. Arason VA, Kristinsson KG, Sigurdsson LA et al. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children. *British Medical Journal* 1996; **313**; 387-391.

15. Afzal-Shah M, Livermore D. World-wide emergence of carbapenem-resistant *Acinetobacter* spp. *Journal of Antimicrobial Chemotherapy* 1998; **41**: 576-577.

16. Gaynes R. Antibiotic resistance in ICUs: a multifaceted problem requiring a multifaceted solution. *Infection Control & Hospital Epidemiology* 1995; **16**: 328-330.

17. Hoiby N, Jarlov JO, Kemp M et al. Excretion of ciprofloxacin in sweat and multiresistant *Staphylococcus epidermidis*. *Lancet* 1997; **349**: 167-169.

18. London N, Nijsten R, Mertens P, v. d. Bogaard A, Stobberingh E. Effect of antibiotic therapy on the antibiotic resistance of faecal *Escherichia coli* in patients attending general practitioners. *Journal of Antimicrobial Chemotherapy* 1994; **34**: 239-246.

19. Rao GG, Ojo F, Kolokithas D. Vancomycin-resistant gram-positive cocci: risk factors for faecal carriage. *Journal of Hospital Infection* 1997; **35**: 63-69.

20. Schaberg DR, Zervos MJ. Intergeneric and interspecies gene exchange in gram-positive cocci. *Antimicrobial Agents & Chemotherapy* 1986; **30**: 817-822.

21. Lipsitch M, Levin BR. The population dynamics of antimicrobial therapy. *Antimicrobial Agents & Chemotherapy* 1997; **41**: 363-373.

22. Levin BR, Lipsitch M, Perrot V et al. The population of genetics of antibiotic resistance. *Clinical Infectious Diseases* 1997; **24**(Suppl 1): S9-S16.

23. Hall RM, Collis CM. Mobile gene cassettes and integrons: Capture and spread of genes by site specific recombination. *Molecular Microbiology* 1995; **15**: 593-600.

24. U.S. Congress, Office of Technology Assessment. *Impacts of Antibiotic Resistant Bacteria OTA-H629*. Washington D.C.: U.S. Government Printing Office; 1995.

25. Cohen ML. Antibiotic use. In Antimicrobial Resistance: Issues and Options. *Workshop Report*. National Academy Press. Washington D.C. 1998

26. Couper MR. Strategies for the rational use of antimicrobials. *Clinical Infectious Diseases* 1997; **24** (Suppl 1): S154-S156.

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

28. Scheckler WE, Brimhall D, Buck AS et al. Requirements for infrastructure and essential activities of infection control and epidemiology in hospitals: a consensus panel report. *Infection Control and Hospital Epidemiology* 1998; **19**: 114-124.

29. Goldmann DA, Weinstein RA, Wenzel RP et al. 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* 1996; **275**: 234-240.

30. Macfarlane JT, Holmes WF, Macfarlane RM. Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomised controlled study of patients in primary care. *British Journal of General Practice* 1997; **47**: 719-722.

31. Bradley CP. Factors which influence the decision whether or not to prescribe: the dilemma facing general practitioners *British Journal General of Practice* 1992 ; **42**; 454-458.

32. Holmes WF, Macfarlane JT, Macfarlane RM, Lewis S. The influence of antibiotics and other factors on reconsultation for acute lower respiratory tract illness in primary care. *British Journal of General Practice* 1997; **47**: 815-818.

33. Macfarlane JT, Lewis SA, Macfarlane R, Holmes W. Contemporary use of antibiotics in 1089 adults presenting with acute lower respiratory tract illness in general practice in the UK: implications for developing management guidelines. *Respiratory Medicine* 1997; **91**: 427-434.

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

35. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *British Medical Journal* 1997; **315**: 1211-1214.

36. Evans RS, Pestotnik SL, Classen DC et al. A computer-assisted management program for antibiotics and other anti-infective agents. *New England Journal of Medicine* 1998; **338**:232-238.

37. Purves I. Prodigy, a computer assisted prescribing scheme. Interim data show that it is worth taking the scheme further. *British Medical Journal* 1996; **313**: 1549.

38. Weingarten SR, Riedinger MS, Hobson P et al. Evaluation of a pneumonia practice guideline in an interventional trial. *American Journal of Respiratory Critical Care Medicine* 1996; **153**:1110-1115; .

39. Stephenson J. Icelandic researchers are showing the way to bring down the rates of antibiotic-resistant bacteria. *Journal of the American Medical Association* 1996; **275**: 175.

40. Piddock LJV. Does the use of antimicrobial agents in veterinary medicine and animal husbandry select antibiotic resistant bacteria that infect man and compromise antimicrobial chemotherapy? *Journal of Antimicrobial Chemotherapy* 1996; **38**: 1-3.

41. Bates J, Jordens JZ, Griffiths DT. Farm animals as putative reservoir for vancomycin resistant enterococcal infection in man. *Journal of Antimicrobial Chemotherapy* 1994; **34**; 507-514.

42. Bronzwaer SLAM, Goettsch W, Olsson-Lijequist B et al. European Antimicrobial Resistance Surveillance System (EARSS): objectives and organisation. *Eurosurveillance* 1999; **4**(4); 41-4.

43. O'Flanagan D. Development of a strategy to control antimicrobial resistance in Ireland. *Eurosurveillance Weekly* 1999; **3**.

44. Centres for Disease Control and Prevention. Defining the public health impact of drug resistant *Streptococcus pneumoniae*: report of a working group. *Morbidity and Mortality Weekly Reports* 1996; **45**; no. RR-1.

45. Appelbaum PC. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clinical Infectious Diseases* 1992; **15**:77-83.

46. Soares S, Kristensson KG, Musser JM, Tomasz A. Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *Journal of Infectious Diseases* 1993; **168**: 158-163.

47. Felmingham D, Gruneberg RN and the Alexander Project Group. The Alexander Project 1996- 1997: latest susceptibility data from this international study of bacterial pathogens from community acquired lower respiratory tract infection. *Journal of Antimicrobial Chemotherapy* 2000; **45**:191-203.

48. Goldstein FW, Acar JF. Antimicrobial resistance among lower respiratory tract isolates of *Streptococcus pneumoniae*: results of a 1992-93 western Europe and USA collaborative surveillance study. The Alexander Project Collaborative Group. *Journal of Antimicrobial Chemotherapy* 1996; **38**(Suppl A): 71-84.

49. Goldsmith CE, Moore JE, Murphy PG. Pneumococcal resistance in the UK. *Journal of Antimicrobial Chemotherapy* 1997; **40**(Suppl A): 11-18.

50. Keane CT, Coleman DC, Cafferkey MT. Methicillin-resistant *Staphylococcus aureus*-a reappraisal. *Journal of Hospital Infection* 1991; **19**(3): 147-52.

51. Speller DC, Johnson AP, James D, Marples RR, Charlett A, George RC. Resistance to methicillin and other antibiotics in isolates of *Staphylococcus aureus* from blood and cerebrospinal fluid, England and Wales, 1989-1995. *Lancet* 1997; 350: 323-325.

52. Cafferkey MT, Hone R, Keane CT. Sources and outcome for methicillin-resistant *Staphylococcus aureus* bacteraemia. *Journal of Hospital Infection* 1988; **11**(2):136-43.

53. Woodford N, Morrison D, Johnson AP, Speller DCE. Current perspectives on glycopeptide resistance. *Clinical Infectious Diseases* 1997; **24**: 211-215.

54. Ploy M, Gre'land C, de Lumley L, Denis F. First isolates of vancomycin-intermediate *Staphylococcus aureus* in a French hospital. *Lancet* 1998; **351**: 1212.

55. Hiramatsu K, Hanaki H, Ino T et al. Methicillin Resistant *Staphylococcus aureus*: Clinical strains with reduced vancomycin susceptibility. *Journal of Antimicrobial Chemotherapy* 1997; **40**; 135-6.

56. Cafferkey MT, Hone R, Coleman D, Pomeroy H, McGrath B, Ruddy R, Keane CT. Methicillin-resistant *Staphylococcus aureus* in Dublin 1971-84. *Lancet* 1985; **28**(2):705-8.

57. Cafferkey MT, Hone R, Falkiner FR, Keane CT, Pomeroy H. Gentamicin and methicillin resistant *Staphylococcus aureus* in Dublin hospitals: clinical and laboratory studies. *Journal of Medical Microbiology* 1983; **16**(2):117-27.

58. Dowd G, Cafferkey M, Dougan G. Gentamicin and methicillin resistant *Staphylococcus aureus* in Dublin hospitals: molecular studies. *Journal of Medical Microbiology* 1983; **16**(2):129-38.

59. Coleman DC, Pomeroy H, Estridge JK, Keane CT, Cafferkey MT, Hone R, Foster TJ. Susceptibility to antimicrobial agents and analysis of plasmids in gentamicin- and methicillin-resistant *Staphylococcus aureus* from Dublin hospitals. *Journal of Medical Microbiology* 1985; **20**(2):157-67.

60. Mulvey M, Arbuthnott JP, Coleman DC. Molecular typing of methicillin and gentamicin resistant *Staphylococcus aureus* in Dublin. *European Journal of Clinical Microbiology* 1986; **5**(6):719-25.

61. Morgan MG, Harte-Barry MJ. Methicillin-resistant *Staphylococcus aureus*: a ten-year survey in a Dublin hospital. *Journal of Hospital Infection* 1989; **4**(4):357-62.

62. Humphreys H, Carroll JD, Keane CT, Cafferkey MT, Pomeroy HM, Coleman DC. Importation of methicillin-resistant *Staphylococcus aureus* from Baghdad to Dublin and subsequent nosocomial spread. *Journal of Hospital Infection* 1990; **15**(2):127-35.

63. Cotter L, Lynch M, Cryan B, Greer P, Fanning S. Investigation of a methicillin-resistant *Staphylococcus aureus* (MRSA) outbreak in an Irish hospital: triplex PCR and DNA amplification fingerprinting. *Journal of Hospital Infection* 1997; **36**(1):37-47.

64. Carroll JD, Pomeroy HM, Russell RJ, Arbuthnott JP, Keane CT, McCormick OM, Coleman DC. A new methicillin- and gentamicin-resistant *Staphylococcus aureus* in Dublin: molecular genetic analysis. *Journal of Medical Microbiology* 1989; **28**(1):15-23.

65. Rossney AS, Pomeroy HM, Keane CT. *Staphylococcus aureus* phage typing, antimicrobial susceptibility patterns and patient data correlated using a personal computer: advantages for monitoring the epidemiology of MRSA. *Journal of Hospital Infection* 1994; **26**(3):219-34.

66. Moorhouse E, Fenelon L, Hone R, Smyth E, McGahon J, Dillon M. *Staphylococcus aureus* sensitivity to various antibiotics-a national survey in Ireland 1993. *Irish Journal of Medical Science* 1996; **165**(1):40-3.

67. Rahman M, et al. Revised guidelines for control of MRSA in hospitals: finding the most useful point. *Journal of Hospital Infection* 1999; **42**(1): 71-2.

68. Johnson Z, Fitzpatrick P, Hayes C, Sayers G, Pelly H, McDonnell B, Thornton L, Buttimer J. National survey of MRSA: Ireland, 1995. *Journal of Hospital Infection* 1997; **35**(3):175-84.

69. O'Sullivan NP, Keane CT. The epidemiology of methicillin resistant *Staphylococcus aureus* (MRSA) in Dublin Nursing Homes. *Irish Journal of Medical Science* 1999; **38**:135-141.

70. Shuhaibar MN, Falkiner FR. The prevalence, antibiotic susceptibility and phage-type of nasally carried *Staphylococcus aureus* in the Dublin community. *Irish Journal of Medical Science* 1992; **161**(10):589-92.

71. Veldhuijzen I, Bronzwaer S, Degener J et al. European Antimicrobial Resistance Surveillance System (EARSS): susceptibility testing of invasive *Staphylococcus aureus*. *Eurosurveillance* 2000; **5**(3): 34-36.

72. Nourse C, Kaufmann M, Byrne M, Byrne C, Moylett E, Murphy H., Butler K. Clinical isolates of *Staphylococcus epidermidis* with reduced susceptibilities to teicoplanin in a paediatric hospital in Ireland [letter]. *Journal of Antimicrobial Chemotherapy* 1998 ; **42**(1):118-9.

73. Livermore DM, Yuan M. Antibiotic Resistance and production of extended-spectrum ß-lactamases amongst *Klebsiella* spp. from intensive care units in Europe. *Journal of Antimicrobial Chemotherapy* 1996; **38**: 409-424.

74. M'Zali FH, Heritage J, Gascoyne-Binzi DM, Denton M, Todd NJ, Hawkey PM. Transcontinental importation into the UK of *Escherichia coli* expressing a plasmid-mediated AmpC-type beta-lactamase exposed during an outbreak of SHV-5 extended-spectrum beta-lactamase in a Leeds hospital. *Journal of Antimicrobial Chemotherapy* 1997; **40**:823-831.

75. Falkiner FR, Keane CT, Dalton M, Clancy MT, Jacoby GA. Cross infection in a surgical ward caused by *Pseudomonas aeruginosa* with transferable resistance to gentamicin and tobramycin. *Journal of Clinical Pathology* 1977; **30**(8):731-7.

76. McHale PJ, Keane CT, Dougan G. Antibiotic resistance in *Providencia stuartii* isolated in hospitals. *Journal of Clinical Microbiology* 1981; **13**(6):1099-104.

77. Falkiner FR, Jacoby GA, Keane CT, McCann SR. Amikacin, gentamicin and tobramycin resistant *Pseudomonas aeruginosa* in a leukaemic ward. Epidemiology and genetic studies. *Journal of Hospital Infection* 1982 ; **3**(3):253-6.

78. Griffin HG, Foster TJ, Falkiner FR, Carr ME, Coleman DC. Molecular analysis of multiple-resistance plasmids transferred from gram-negative bacteria isolated in a urological unit. *Antimicrobial Agents & Chemotherapy* 1985; **28**(3):413-8.

79. McConkey SJ, Coleman DC, Falkiner FR, McCann SR, Daly PA. *Enterobacter cloacae* in a haematology/oncology ward-first impressions. *Journal of Hospital Infection* 1989; **14**(4): 277-84.

80. Cormican M, Corbett-Feeney G, Kelly S et al. In-vitro activity of piperacillin/tazobactam relative to other antibiotics against blood culture isolates. *Irish Journal of Medical Science* 1998; **167**(3); 155-159.

81. Herra CM, Knowles SJ, Kaufmann ME, Mulvihill E, McGrath B, Keane CT. An outbreak of an unusual strain of *Serratia marcescens* in two Dublin hospitals. *Journal of Hospital Infection* 1998; **39**(2):135-41.

82. Coleman D, Falkiner FR, Carr ME, Dowd G, Dougan G, Keane CT. Simultaneous outbreaks of infection due to *Serratia marcescens* in a general hospital. *Journal of Hospital Infection* 1984; **5**(3):270-82.

83. Knowles SJ, Herra CM, Devitt E, O'Brien A, Mulvilhill E, McCann SR, Browne P, Kennedy MJ, Keane CT. An outbreak of multiply resistant *S. marcescens*: the importance of persistent carriage. Bone Marrow Transplantation (in press).

84. Pitt TL, Kaufmann ME, Patel PS, Benge LC, Gaskin S, Livermore DM. Type characterisation and antibiotic susceptibility of *Burkholderia (Pseudomonas) cepacia* isolates from patients with cystic fibrosis in the United Kingdom and the Republic of Ireland. *Journal of Medical Microbiology* 1996; **44**(3):203-10.

85. Humphreys H, Towner KJ. Impact of *Acinetobacter* spp. in intensive care units in Great Britain and Ireland. *Journal of Hospital Infection* 1997; **37**(4):281-6.

86. Threlfall EJ, Ward LR, Rowe B. Spread of multiresistant strains of *Salmonella typhimurium* phage types 204 and 193 in Britain. *British Medical Journal* 1978; **2**: 997.

87. Threlfall EJ, Frost JA, Ward LR, Rowe B. Increasing spectrum of resistance in multiresistant *Salmonella typhimurium*. *Lancet* 1996; **347**: 1053-1054.

88. Cormican M, Butler C, Morris D, Corbett-Feeney G, Flynn J. Antibiotic resistance amongst *Salmonella enterica* species isolated in the Republic of Ireland. *Journal of Antimicrobial Chemotherapy* 1998; **42**(1):116-8.

89. Fey PD, Safranek TJ, Rupp ME et al. Ceftriaxone resistant Salmonella infection acquired by a child from cattle. *New England Journal Medicine* 2000; **342**: 1242-1249.

90. Grein T, O'Flanagan D, McCarthy T, Bauer D. An outbreak of multidrug-resistant *Salmonella typhimurium* food poisoning at a wedding reception. *Irish Journal of Medical Science* 1999; **92**(1):238-41.

91. Daly M, Buckley J, Power E et al. Molecular characterisation of Irish *Salmonella enterica* serotype Typhimurium: detection of class 1 intergrons and assessment of genetic relationships by DNA amplification fingerprinting. *Applied Environmental Microbiology* 2000; **66**(2); 614-619.

92. Gaunt PN, Piddock LJV. Ciprofloxacin resistant *Campylobacter* spp. in humans: an epidemiological and laboratory study. *Journal of Antimicrobial Chemotherapy* 1996; **37**: 747-757.

93. Bowler I, Connor M, Lessing MP, Day D. Quinolone resistance and *Campylobacter* species. *Journal Antimicrobial & Chemotherapy* 1996; **38**: 315.

94. Lucey B, Crowley D, Moloney P, Cryan B et al. Integron-like structures in *Campylobacter* spp. of human and animal origin. *Emerging Infectious Diseases* 2000; **6**(1); 50-55.

95. Seppala H, Klaukka T et al. Effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *New England Journal of Medicine* 1997; **337**; 441-446.

96. Logan J. Symposium on drug resistant tuberculosis. Clinical drug resistance in Ireland 1964-68. *Journal of the Irish Medical Association* 1970; **s63**(393):79-82.

97. Cormican MG, Flynn J. Tuberculosis in the west of Ireland 1986-1990. *Irish Journal of Medical Science* 1992; **161**(3):70-2.

98. Shannon A, Kelly P, Lucey M, Cooney M, Corcoran P, Clancy L. Isoniazid resistant tuberculosis in a school outbreak: the protective effect of BCG. *European Respiratory Journal* 1991; **(7)**:778-82.

99. Woodford N, McNamara E, Smyth E, George RC, High-level resistance to gentamicin in Enterococcus faecium. *Journal of Antimicrobial Chemotherapy* 1992; **29**(4):395-403.

100. McNamara EB, King EM, Smyth EG. A survey of antimicrobial susceptibility of clinical isolates of *Enterococcus* spp. from Irish hospitals. *Journal of Antimicrobial Chemotherapy* 1995; **35(1)**:185-9.

101. Lavery A, Rossney AS, Morrison D, Power A, Keane CT. Incidence and detection of multi-drug-resistant enterococci in Dublin hospitals. *Journal of Medical Microbiology* 1997; **46**(2):150-6.

102. Rizkalla EA, Moore JE, Marshall SA, Murphy PG. Glycopeptide-resistant enterococci in Northern Ireland: first reported outbreak [letter]. *Journal of Antimicrobial Chemotherapy* 1997; **40**(4):607-8

103. Rossney AS, McConkey SJ, Keane CT. Vancomycin-dependent enterococcus. *Lancet* 1997; **349**: 8.

104. Cunney RJ, McNally RM, McNamara EM, al-Ansari N, Smyth EG. Susceptibility of urinary pathogens in a Dublin teaching hospital. *Irish Journal of Medical Science* 1992; **161**(11):623-5.

105. Cormican M, Morris D, Corbett-Feeney G, Flynn J. Extended spectrum beta-lactamase production and fluoroquinolone resistance in pathogens associated with community acquired urinary tract infection. *Diagnostic Microbiology & Infectious Disease* 1998; **32**(4); 317-9.

106. Johnson AP, Malde M, Woodford N, Cunney RJ, Smyth EG. Urinary isolates of apramycin-resistant *Escherichia coli* and *Klebsiella pneumoniae* from Dublin. *Epidemiology & Infection* 1995; **114**(1):105-12.

107. Howard AJ, Williams HM. The prevalence of antibiotic resistance in *Haemophilus influenzae* in Ireland. *Journal of Antimicrobial Chemotherapy* 1989; **24**(6):963-71.

108. Murphy PG, Craig I, Lafong C. The prevalence of antibiotic resistance in *Haemophilus influenzae* in Ireland. *Journal of Antimicrobial Chemotherapy* 1990; **25**(6):1025-6.

109. Moloney AC, Fogarty J, Clarke P, Musser JM. Invasive *Haemophilus influenzae* in the Republic of Ireland. *European Journal Clinical Microbiology & Infectious Diseases* 1997; **16**(5):377-80.

110. Lynch M, Cryan B. Respiratory pathogens: resistance patterns [editorial]. *Irish Medical Journal* 1995; **88**(3):90.

111. Drew W, Buhles W. Antiviral Drug Resistance. In: Richman D, ed. London: Wiley, 1997.

112. Reyes M, Grabber JM, Weatherall N et al. Acyclovir-resistant herpes simplex virus; preliminary results from a national surveillance system. *Antiviral Resistance* 1998; **37**: A44.

113. Slavin MA, Bindra RR, Gleaves CA, Pettinger MB, Bowden RA. Ganciclovir sensitivity of cytomegalovirus at diagnosis and during treatment of cytomegalovirus pneumonia in marrow transplant recipients. *Antimicrobial Agents & Chemotherapy* 1993; **37**: 1360-1363.

114. Japour A, Welles S, D'Aquila R. Mutations in human immunodeficiency virus isolated from patients following long-term zidovudine treatment. *Journal of Infectious Disease* 1995; **171**: 1172-1179.

115. Moran GP, Sullivan DJ, Henman ME, McCreary CE, Harrington B, Shanley DB, Coleman D. Antifungal drug susceptibility of oral *Candida dubliniensis* isolates from human immuno-deficiency virus (HIV)-infected and non-HIV-infected subjects and generation of stable fluconazole-resistant derivatives in vitro. *Antimicrobial Agents & Chemotherapy* 1997; **41**:617-623.

116. Moran GP, Sanglard D, Donnelly SM, Shanley DB. Sullivan DJ. & Coleman DC. Identification and expression of multidrug transporters responsible for fluconazole resistance in *Candida dubliniensis*. *Antimicrobial Agents & Chemotherapy* 1998; **42**:1819-1830.

117. Pfaller MA, Messer SA, Gee S, Joly S, Pujol C, Sullivan DJ, Coleman DC & Soll DR. In vitro susceptibilities of *C. dubliniensis* isolates tested against the new triazole and echinocandin antifungal agents. *Journal of Clinical Microbiology* 1999; **37**(3):870-872.