TECHNICAL REPORT

ANTIMICROBIAL RESISTANCE CONGRESS

"FACING THE REALITY"

DURBAN ICC – (INTERNATIONAL CONVENTION CENTRE)

DURBAN

SOUTH AFRICA

26-29 OCTOBER 2003

DEPARTMENT OF HEALTH
PRETORIA
SOUTH AFRICA

MEDICINES CONTROL COUNCIL
PRETORIA
SOUTH AFRICA
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<tr>
<td>AMR</td>
<td>Antimicrobial Resistance</td>
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<td>AMRCOC</td>
<td>Antimicrobial Resistance Co-ordinating Committee</td>
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<td>ARV</td>
<td>Anti Retroviral</td>
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<td>CDC</td>
<td>Centres for Disease Control and Prevention</td>
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<td>CAP</td>
<td>Community Acquired Pneumonia</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>DUR</td>
<td>Drug Utilisation Review</td>
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<td>EDL</td>
<td>Essential Drug List</td>
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<td>EU</td>
<td>European Union</td>
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<td>FAO</td>
<td>Food Agriculture Organisation</td>
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<td>GIT</td>
<td>Gastro Intestinal Tract</td>
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<tr>
<td>HIV/AIDS</td>
<td>Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome</td>
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<td>IDDSA</td>
<td>Infectious Disease Society of South Africa</td>
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<tr>
<td>MCC</td>
<td>Medicine Control Council</td>
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<td>MEC</td>
<td>Member of executive Committee</td>
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<td>MEDUNSA</td>
<td>Medical University of Southern Africa</td>
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<td>MRC</td>
<td>Medicine Research Council</td>
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<td>NDOH</td>
<td>National department of Health</td>
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<td>NHLS</td>
<td>National Health Laboratory Service</td>
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<td>NICD</td>
<td>National Institute for Communicable Disease</td>
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<td>NGO</td>
<td>Traditional Healers Organization</td>
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<td>PK/PD</td>
<td>Pharmacokinetics/Pharmacodynamics</td>
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<td>PTC</td>
<td>Pharmacy and Therapeutics Committee</td>
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<td>RTI</td>
<td>Respiratory Tract Disease</td>
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<td>STD</td>
<td>Sexually Transmitted Disease</td>
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<td>STG</td>
<td>Standard Treatment Guidelines</td>
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<td>TB</td>
<td>Tuberculosis</td>
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<td>UTI</td>
<td>Urinary Tract Infection</td>
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<td>WHO</td>
<td>World Health Organization</td>
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ACKNOWLEDGEMENTS

The Department of Health and the Medicine Control Council acknowledge the contribution of the following people towards the success of the Antimicrobial Resistance Conference.

THE AMRC ORGANISING COMMITTEE

Conference Chairperson – Prof Eagles
Conference Organising Committee Chair – Dr R. Misra
Scientific Programme Committee Chair – Ms Precious Matsoso
Scientific Programme Committee Co-Chair – Dr Mbele

(AMRCOC) various MEMBERS at various stages contributed to the success of the congress and we wish to acknowledge their contributions and are unable to mention all the individual persons.

CONFERENCE SECRETARIAT

Conference Project Manager – Dr R. Misra
Conference Operations Manager – Mr R. Bailey
Conference Communications Manager – Dr I. Opfou
(Media & Abstract Enquiries)
Conference Relationships Manager – Mr R. Bailey
(Sponsorship / Donor / Funder / Exhibition Opportunities)
Conference Registrations Manager – Mr R. Bailey
(Participant Registrations)
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(Scientific Programme Enquiries) – Dr I. Opfou
(Registration Enquiries) – Mr R. Bailey
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Dr  C  Butler     Prof Primary Care medicine University of Wales.
Prof  H  Crewe-Brown  NHLS/ University of Wits
Prof  A  Duse      NHLS
Dr  T  Dyke         Australian Pesticides and Veterinary Medicine Authority
Dr  H  Fomundam    School of Public Health MEDUNSA
Dr  A  Franklin    National Veterinary Uppsala Sweden
Prof  A  Hoosen   Microbiological Pathology MEDUNSA
Dr  P  Ive         Wits University
Dr  R  Jobson      MCC/ Medunsa
Dr  S  Kalula      University of Cape Town
Dr  K  Keddy      NICD
Prof  K  Klugman   Rollins School of public health/Emory University/NHLS/MRC/Wits University
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Dr  R  Noorby      Swedish Institute for infectious Diseases
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Prof  G  Swan      MCC/Veterinary Faculty Pretoria University
Prof  P  van Helden  MRC/
Prof  M  van Vuuren  Veterinary Tropical Diseases University of Pretoria
Prof  M  Wierup    Veterinary Faculty/ Swedish University Uppsala Sweden
Prof  S  Essack     School of Pharmacy University of Durban-Westville
Dr  A  Gray       University of natal
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<td>Prof</td>
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<tr>
<td>Dr</td>
<td>A Franklin</td>
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<td>Prof</td>
<td>M Wierup</td>
<td>Veterinary Faculty/ Swedish University Uppsala</td>
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INTRODUCTION

OVERVIEW OF ANTIMICROBIAL RESISTANCE (AMR)

Global Overview of Antimicrobial Resistance:
- Animal
- Human
- Agriculture
- Global

The following issues to be considered in this session:
- Problematic ANTIMICROBIAL (including Antiretroviral)
- Impact of AMR (Public Health & Economic)

GENESIS OF AMR

The following issues to be considered in this session:
- Mechanisms of resistance transfer, resistance detection and methodology.
- Interrelationship between AMR development in humans, animals and use in agriculture.
- PK/PD issues.
- Compliance issues (combined with treatment guidelines).
- Treatment guidelines/protocols/ combination therapies.
- Special populations (demographics, paediatrics, geriatrics, pregnancy related use, environmental, lifestyle and cultural factors).
- Hospital vs. Communities (people exposed to resistance organisms).
- Contribution resulting from antimicrobial environmental pollution, inadequate / inappropriate antimicrobial use and control (health professionals, users, manufactures, registration, availability, farmers, primary health care, essential drug list, pharmacists, nurses).

AMR IN EMERGING & OTHER COMMUNICABLE DISEASES

The following issues to be considered in this session:
- HIV and other opportunistic infections (Antiretroviral)
- TB
- STD
- Malaria
- Common RT, GIT and CNS infections
- AMR in companion and production animals

STRATEGIES & RECOMMENDATIONS FOR CONTAINMENT OF AMR

The following issues to be considered in this session:
- Role of medicines control of antimicrobials & Health Policies (HCP – Health Care Professionals).
- Appropriate strategies for emerging & other communicable disease. (HIV, TB, STD, Malaria, RTI, GIT, UTI, CNS).
Ensuring compliance (dosage/direction for use). Appropriate and prudent use guidelines and updating of EDL / Provision of education to all role players, health care professionals and students.
- Special populations (demographics, paediatrics, geriatrics and pregnancy related use, environmental, lifestyle and cultural factors).
- Strategies in food & companion animals (stock remedies, veterinary medicines and agricultural remedies).
- Specific settings (Hospital vs. Community) / Management of people exposed to R-organisms / Infection control (outbreak management in hospital and community).
- Risk analysis of AMR (risk assessment, risk management and risk communication).
- Model(s) for collaboration between various sectors / groups nationally and internationally.
- Clinical research and antimicrobial resistance.
- Formation of a Special Advisory Group by DOH to advise on the control of AMR.
- Surveillance and monitoring issues.

The Antimicrobial Resistance Congress was an initiative of the MCC and the NDOH National Department of Health. Over 160 delegates, drawn from across South Africa and some International Representatives, attended the Conference.

The theme of the Conference was “FACING THE REALITY.”

THE OBJECTIVES OF THE CONGRESS WAS THE FOLLOWING:

- To update the latest concepts of antimicrobial resistance and development of resistance.
- To establish the extent of knowledge of antimicrobial resistance and use of antimicrobials in South Africa.
- To consider the importance of antimicrobial resistance on Public Health.
- To review the use and impact of antimicrobial resistance in food production.
- To streamline strategies for the containment of antimicrobial resistance.
- To consider the coordination of national programmes for the containment of antimicrobial use in human, animal and agriculture

THE EXPECTED OUTCOMES OF THE CONFERENCE WERE:

At the conclusion of this conference, participants should be able to meet overall conference objectives and session specific objectives for containing antimicrobial resistance.
OPENING CEREMONY

A traditional ceremony, with a cocktail function was organized for the Sunday 26 October 2003. The Honourable MEC for Health for Kwa Zulu Natal, Dr Z Mkhize welcomed all delegates, including the International Representatives and emphasized the importance of such a congress and wished every success to the congress to achieve its objectives.

MONDAY 27 OCTOBER 2003

The Chairperson of Council, Professor Peter Eagles gave a welcome address. He reiterated the Council's message, which was as follows:

MESSAGE FROM THE MEDICINES CONTROL COUNCIL

Antimicrobial resistance is not the domain of a regulator, however it poses interesting regulatory challenges regarding the continuing use of medicines.

The World Health Organisation and International Conference of Drug Regulatory Authority have identified antimicrobial resistance as an issue that Regulatory authorities must act on. It is for this reason that MCC is convening a congress that will have public health, regulatory, and programmatic implications.

We are inviting all of you from the public and private sector, health care workers, scientists, researchers, specialists, veterinarians, nurses, doctors, pharmacists, microbiologists, technologists, public health administrators, to participate in this important congress. This is about-facing the reality of antimicrobial resistance.

PARTICIPANTS

Over 160 delegates, drawn from across South Africa and some International Representatives as per the attendance list, attended the Conference.

SESSION ONE

Global Overview in animals was presented by Dr A Franklin (International Speaker) National Veterinary Uppsala Sweden

Summary

Intensive breeding systems with large numbers of animals housed in limited areas create favourable conditions for the emergence and spread of infectious agents. Although antimicrobials are needed in the control of infections, they exert a selective pressure for development of resistance among pathogenic and commensal bacteria. Due to lack of data, it is difficult to assess the impact on animal health of resistance in animal pathogens. The development of antimicrobial resistance among enteric
Escherichia coli and respiratory pathogens such as Pasteurella, Mannheimia and Actinobacillus has in some countries lead to a situation where the most modern antimicrobials, such as fluoroquinolones and third generation cephalosporins are, at best, the only remaining options. Likewise, the options available for therapy of swine dysentery are in some countries very limited following development for therapy of swine dysentery are in some countries very limited following development of resistance to tiamulin. All in all, the result of increased resistance among animal pathogens will lead to higher costs in animal production.

The use of antimicrobials in farmed animals also contributes to the selection and spread of food borne zoonotic agents. Through the global food trade, such strains spread and cause infections in humans in countries other than where they emerged. Multiresistant Salmonella Typhimurium DT104 has spread like a pandemic clone in both man and animals, and in the US the prevalence of multiresistant S. Newport appears to increase in cattle and so does the number of infection with that strain in man. The emergence of fluoroquinolone-resistant Campylobacter has added yet another controversy and a number of different groups now advocate restrictions or bans of the use of fluoroquinolone in farmed animals.

Antimicrobials also exert a selective pressure on the normal flora of animals. The relationship between uses of antimicrobials in bacteria from the normal flora of animals can be monitored and analysed. The data generated and reported so far from monitoring programmes in different parts of the world have helped to increase our knowledge of the situation considerably. A good example is the result from the Danish monitoring programme, DANMAP, where, for example, the decrease of Vancomycin resistance, following the ban of avoparcin in 1995, among enterococci isolated from broilers and pigs is demonstrated. A survey of resistance in bacteria from pigs and poultry in selected European countries conducted by the European branch of IFAH demonstrated striking differences between the situation in Sweden and some of the other countries. This difference is probably related not only to differences in the intensity of use of antimicrobials, but also to infection containment practices.

The spread of resistance genes is not restricted only to the mammalian and avian flora. Tetracycline resistance genes were isolated from pig excreta from two farms in Illinois, U.S.A., where antibiotics were regularly used for disease control and growth promotion. The same resistance genes were also commonly found in taxonomically and ecologically diverse bacteria isolated in ground water downstream from farm manure deposits. That study serves to illustrate the important role agriculture plays in the spread of resistance genes into wider environment.

Conclusions and perspectives

- still difficult to compare data (but better)
- major differences between countries
- resistance is a problem for animal health
- resistance in animal bacteria is also a risk for public health

▸containment strategies are warranted
Global overview in Humans was presented by Dr R Noorby (International Speaker) Swedish Institute for infectious Diseases

Summary of his talk was as follows:

Resistance to Antivirals
Uncommon
• Anti-herpesvirus drugs (acyclovir, famciclovir, ganciclovir, etc.)
• Ribavirin
Common
• Amantadin
• Neuraminidase inhibitors
• Anti-retroviral drugs

Resistance to Antifungals
• Use (abuse) of azoles has lead to (i) increased resistance to flukonazol in Candida albicans and (ii) selection of Candida tropicalis and Candida krusei as common aetiology of invasive candidiasis.
• New azoles (itraconazole and vorikonazole) have no obvious advantages over flukonazole.

Conclusions
• Resistance major problem in bacteria, fungi and viruses (HIV)
• Major need for new antibiotics against Gram-negative bacteria
• Continuous need for new antiretroviral drugs
• Reduction of overuse of antimicrobials very important

SESSION TWO

1. Interrelationship between antimicrobial resistance in humans, animals and agriculture by Anders Franklin (Department of Antibiotics, Swedish Veterinary)

The use of antimicrobials in production of farmed animals has been questioned since practice began and the selective pressure exerted on bacteria from this use has lead to emergence and widespread of resistance. Thereby, the use increases or maintains the pool of resistance genes in different ecosystems. Today we have clear evidence showing that resistance genes are transferred between the various ecosystems i.e. from animal to human bacteria. The main source for transfer of resistance genes from animal sources is probably food. An obvious and well-known threat to human health is ingestion of zoonotic agents such as multiresistant Salmonella and fluoroquinolone-resistant Campylobacter. Resistance genes can also be directly transferred from commensal bacteria of animal origin. Escherichia coli and Enterococcus spp., which are common to all farmed animals, can be considered as constituting a reservoir of resistance genes, which may be transferred to pathogenic bacteria both in humans and animals. The relative impact on human health from antimicrobial use in animals and the subsequently increased pool of resistance genes is however difficult to assess. Clearly, increasing antimicrobial resistance among bacteria of animal origin negatively influences animal health as the number of available antibiotics and treatment options gradually decrease.
In order to decrease the selective pressure from the antimicrobials used in animal production, the EU commission in 1999 prohibited the use as growth promoters of those antimicrobials that were used for therapy in human or veterinary medicine. Experience from Denmark and more recently other European countries, showed that withdrawal of the glycopeptide avoparcin as a feed additive to animals lead to considerably reduced levels of Vancomycin-resistant enterococci in broilers and pigs. The decreasing pool of Vancomycin-resistance genes in the animal population in Europe will hopefully lead to a similar decrease in the human enterococcal population.

While much remains to be learned and documented as regards an optimal strategy for containment of antimicrobial resistance, reduction of the selective pressure has been shown to be effective in reversing or halting the development. Key elements in a containment strategy are prudent use and education. Not least important is the monitoring of use and resistance preferably in an integrated way in all areas. Control of infectious diseases contributes to reduce the need for antimicrobials.

Conclusions and perspectives

- complex dynamics of resistance
- use in one area can affect resistance in another
- resistance is a shared problem
- scapegoating is futile - we are all to blame
- action needed in all areas:
  - monitoring of use and resistance use only when necessary
  - infection control
- research and education

2. Risk Factors for Antibiotic Resistance in the Pneumococcus K.P.Klugman
(Department of International Health, and School of Medicine, Division of Infectious Diseases Emory University, Atlanta, USA AND MRC/NICD/Wits Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa.)

The relationship between antibiotic resistance and antibiotic use in the community is now established from the level of the antibiotic use of an individual to the antibiotic use of entire regions. The pneumococcus is the most studied community-acquired pathogen in terms of risk factors for antibiotic resistance and serves as a model for community acquired pathogens. This presentation will define the role of clonality in the epidemiology of antibiotic resistance in the community and show how mechanisms of resistance can be used to predict the emergence of resistance. In Africa in particular, the widespread community use of cotrimoxazole is a risk factor for the emergence of penicillin resistance and may play a role in the emergence of fansidar resistance in malaria. We have recently shown that gender may be an important risk factor for resistance and have demonstrated that pediatric serotypes of pneumococci associated with antibiotic resistance are more common in women than men. This difference is particularly found amongst HIV-infected persons who are at increased risk of infection caused by antibiotic resistant strains. Pneumococcal conjugate vaccine has been shown to reduce resistance in children and may also reduce resistance in adults living in the same community.
Future Prospects

- The biological basis of the success of pneumococcal clones is a critical area of study – they are driving the emergence of multiple resistance
- Molecular mechanisms of resistance may predict the likelihood of spread
- Resistance to FQ has appeared in a child
- Pneumococcal conjugate vaccines may interrupt “child to mother” transmission of resistant pneumococci.

3. Pharmacokinetics and Pharmacodynamics

**Prof Lynne D Liebowitz**
(Department of Medical Microbiology, University of Stellenbosch)

To achieve maximum efficacy and minimize the emergence of resistant strains, antibiotics should be dosed according to their pharmacokinetic (PK) and pharmacodynamic (PD) properties. Antibiotics kill bacteria in either a concentration-dependent or time-dependent manner. The PD parameter, which best fits concentration-dependent antibiotics is the ratio of the area under the serum concentration curve (AUC) divided by the minimum inhibitory concentration (MIC) of the antibiotic. For antibiotics which act in a time-dependent manner the most appropriate PD parameter is the percentage time the concentration of the antibiotic in the serum is above the MIC against the causative organism, during the dosage interval. New antimicrobial formulations are being designed taking these parameters into consideration.

4. General Perspectives on the Control and Use of Antimicrobial Drugs in Animals in South Africa: Contributing Factors in the Genesis of Antimicrobial Resistance

**G E Swan**
(Department of Paraclinical Sciences, Faculty of Veterinary Science, University of Pretoria, South Africa; and Member of the Medicines Control Council (MCC) and Chairman of Veterinary Clinical Committee (MCC))

Antimicrobial drugs are used extensively for the treatment and prophylaxis of disease, as well as a feed additive for growth promotion, in animals. The use of antimicrobial drugs in animals, in particular food producing animals, may contribute to the emergence of resistant bacterial strains in animals and humans. Transfer of antibiotic-resistant bacteria from animals to humans is well documented for *Salmonella* infections and other food borne zoonotic infections. Regulatory control of antimicrobial drugs; technical guidelines for the prudent and responsible use in animals by the various stakeholders; monitoring of usage in animals, and monitoring and surveillance of resistance following veterinary use are essential elements in the assessment of human health risk and risk management for the containment of resistance development. Breakdown or inadequacies of any of these elements may contribute in the genesis of antimicrobial resistance. A general perspective on the control and use of antimicrobial drugs in animals in South Africa, including the types of drugs and their indications for use; registration and control; availability and extent of usage; and current veterinary and animal production practices, will be discussed. Aspects of abuse and misuse of antimicrobial drugs in animals will be identified.
CONCLUSION

- Human safety risk-assessment should form the basis of approval of veterinary antimicrobials
- An integrated veterinary and human national antimicrobial policy is required
- Abuse of antimicrobials is synonymous to promoting conditions for resistance development
- The risk-benefit of the use of antimicrobials as growth promoters needs to be re-evaluated

**Impact of antimicrobial growth promoter (GP) termination**

- Reduction in total amount of antimicrobials used (54%) and in the duration of exposure (live time exposure to 0.4 days in poultry and 7.9 days in pigs)
- Dramatic reduction in food animal reservoir of enterococci resistant to the GPs and reduction in reservoir of genetic determinants
- Increase in the therapeutic use of some antimicrobials in pigs but not poultry
- Minimal loss in productivity (loss of 1.4% in pigs and 0.4% in poultry per annum)

SESSION THREE

1. The Role of Pharmacovigilance in Antimicrobial Resistance Dr M. Roy Jobson (MEDUNSA/ MCC)

**CONCLUSION** Pharmacovigilance can play a powerful role in the cyclical and dynamic interplay between practitioners and regulatory authorities from the time the first suspicions of antimicrobial resistance arise to the point at which a regulatory action is taken.

2. Medication Compliance and Resistance Henry Fomundam BSP, Pharm. D. (National School of Public Health Medunsa)

One of the greatest 20th century scientific achievements was the development of antibiotics. Antimicrobial resistance has marred this milestone in the history of health care in the world. The problem of antimicrobial resistance is multi-faceted and includes, over reliance on antimicrobials, inappropriate prescribing patterns by health professionals and unskilled practitioners, patient compliance issues and adequate surveillance. The spread of resistant microbes present the clear and eminent danger that requires the combine resolve of every health care discipline including the guiding support of researchers. Medication compliance, also referred to as medication "adherence" or, most recently especially in the United Kingdom, medication "concordance", is an issue of much concern to many health care professionals, consumers, and researchers irrespective of what terminology is used to describe this challenge. Non-compliance may be intentional or involuntary. It may relate to the quality of information given, the impact of the regimen on daily life, the physical or incapacity of patients, or their social isolation. Clinical practice and drug use patterns in both developed and developing countries have contributed to the high levels of antimicrobial resistance. In 2002, WHO stated that Antimicrobial resistance is growing for most major infectious diseases, including bacterial diarrhoea, gonorrhoea, malaria, pneumonia
and tuberculosis. This could also be attributed to the fact that Up to 75% of antibiotics are prescribed inappropriately, even in teaching hospitals in developing countries and the fact that less than 1 in 3 developing countries have fully functioning drug regulatory authorities. Antiretroviral resistance for the treatment of HIV is now quickly rising as a public health concern of global magnitude especially for a disease that currently has no cure.

The Centres for Disease Control and Prevention (CDC) estimates that about 100 million courses of antibiotics are prescribed by office-based physicians each year. CDC claims that about half of those are unnecessary, being prescribed for patients presenting with colds, coughs, and other viral infections. To combat this public health threat, in 1999 the CDC, Food and Drug Administration, National Institutes of Health and many other federal agencies formed an Interagency Task Force on Antimicrobial Resistance.

Researchers found a 76% discrepancy rate between what medicines patients were prescribed, and what medicines (Rx and non-prescription) they actually took. Of those discrepancies, 51% stemmed from patients taking medicines not recorded; 29% were from patients not taking a recorded medicine; and 29% were from differences in dosages (S. Bedell et. al., "Discrepancies in the Use of Medications," Archives of Internal Medicine, Vol. 160, July 24, 2000).

**Conclusion.**

Non-compliance is a multifactorial problem and requires multifactorial responses. We increasingly rely on medicines to sustain good health, but using medicines to best effect is a major challenge. Involving patients and carers as partners in prescribing decisions and supporting them in medicine taking is key to improving patient safety, health outcomes and satisfaction with care (MP 2002). All health care disciplines have a role and responsibility to improve and ensure drug adherence.

**Way Forward.**

DOTs Plus, Compliance plus, Concordance

- Continue to strengthen drug regulation
- Improve infrastructure and human resources constraints.
- Regular community Education that includes ALL or as many people as possible.
  - HIV disease, Prevention and adherence.
- Every district should have teams made up of a least a peer educator and a nurse.
  - Will visit upon patient request or Directed by the Clinician.

**Assessing Adherence**

- Pill counts
- Self-report
- Electronic monitoring
- Home visits

3. Role of STGs in Managing AMR  Gavin Steel Clinical Pharmacology (East London Health Complex / MCC)

Containment of antimicrobial resistance begins with the selection of the appropriate antibiotic dosing regimen followed by tight compliance by the patient. Various
vehicles have been deployed to facilitate the actualisation of these ideals. This discussion explores the current practice and seeks to illustrate potential alternatives. When reviewing the impact of medication adherence behaviour upon therapeutic outcomes, antibiotics introduce the additional consideration of antimicrobial resistance. Though failed outcomes readily observed the impact of resistance at the population level is often insidious or non-compliance is multifaceted and may encomplice one or more of the following:

- Access to medicines
- Missed or incorrect doses
- Administration of the antibiotic at times that are congruent with the dosing interval.
- Premature cessation of the cause of therapy
- Shared medication between family members

Prudent dosing regimen design, clear medication labelling and patient counselling supported by various forms educational materials all contribute toward improving the probability of compliance.

Broad based educational programmes aimed at the community prepare the individual and their support structures for assuming a dosing regimen into their daily life style when they present with an infectious disease often the disease model or patient’s motivation levels require the introduction of additional home based support structures when contemplating ambulatory therapeutic interventions.

Guidelines seek to inform the prescriber as to as to optimal approach when managing their patient. A successful guideline will take cognisance of the following:

- Aetiology
- Prevalent resistance profile
- Safe antibiotic options
- Appropriate dosing regimen based on pharmacodynamic model and pharmacokinetic considerations introduced by the pathophysiology
- Pharmacoeconomics

The essential drug list (EDL) compiles standard treatment guidelines (STGs) based upon submissions prepared by opinion leaders that have been peer reviewed by institutional and provincial pharmacy and therapeutics committee (PTCs). At the national level a reviewer places the supporting evidence into context and applies the principle of evidence based medicine in making recommendations to the national drug list and guidelines.

A consideration of resistance and compliance profiles plays a central role during this review.

Guidelines that are not put into practice remain irrelevant, In order to affect changes to prescribing behaviour the guidelines must inform:

- Continuing professional education
- Undergraduate training
- Drug utilisation review (DUR)
- Drug supply management strategies
- Research

The institutional PTC will affect implementation of the STGs through:

- Formulary adjustment
- Medical and pharmacy departments
SESSION FOUR

1. GUIDELINES FOR THE MANAGEMENT OF UPPER RESPIRATORY TRACT INFECTIONS A Brink, IDSSA

There is a growing perception that the worldwide increase in antibiotic resistance is largely related to inappropriate use of antibiotics. Studies in United States of America and elsewhere suggest that inappropriate use of antibiotics for upper respiratory tract infections (URTIs) add to the burden of antibiotic resistance.

The organisms responsible for most bacterial URTIs are well known and are similar in all age groups. *Streptococcus pneumoniae* is by far the most common organism causing otitis media and sinusitis. *Streptococcus pyogenes* is the only significant bacterial cause of pharyngitis. Cochrane reviews have suggested extremely limited benefit of antibiotics for pharyngitis and otitis media in developed countries; however, there are few data from poorer countries where rheumatic fever and supplicative complications such as mastoiditis are likely to be more common. By establishing a simple guideline and using antibiotics with a relatively narrow spectrum, patients can be well-managed and serious complications avoided.

The most frequently recommended 1st line antibiotics remain penicillin and amoxicillin. The recommendations for duration of therapy differ; for example, using 1st line therapy acute otitis media (AOM) should be treated for 5 to 7 days. In this regard, emerging evidence suggests that shorter duration of antibiotic treatment is associated with less emergence of resistant pathogens. The recommendation for frequency of administration varies according to site of infection and favourable PK/PD profiles. For optimal clinical success, the dosages of antibiotics need to be tailored to the individual; the most common cause of failure as well as emergence of resistance is sub-optimal dosing. For example in AOM, 5ml is prescribed as a standard dose for any child weighing anything from 5-15 kg instead of individualising doses by body mass. The dosages in this guideline include both the registered standard doses and higher recommended doses for areas where resistance to antibiotics have been reported.

The guideline is based on best practice, taking into account unique local circumstances and should assist rational prescribing. However, it should be validated and subjected to the rigor of prospective evaluation.

2. Impact of Pneumococcal Conjugate Vaccine on Pneumococcal Infection and Antibiotic Resistance K.P.Klugman (Department of International Health and Division of Infectious Diseases, Emory University, Atlanta, USA and MRC/NICD/Wits Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa)

While better diagnostics and education of both patients and health professionals may reduce inappropriate antibiotic prescribing for respiratory indications, there are few data to show that reduced use in the community will be translated into meaningful reductions in antibiotic resistance of the key pathogen, the pneumococcus. Additional approaches are thus required. We have demonstrated that children in Soweto who received a 9 valent conjugated pneumococcal vaccine PCV9 – CRM had, at 9 months of age, a 50% reduction in the carriage of penicillin – resistant strains compared to controls, following a randomized controlled trial of infant immunization at 6, 10 and 14 weeks of age. Data from other countries have confirmed these findings and shown
that immunized children and their siblings receive fewer antibiotics than children and their siblings who have not received conjugate vaccine. Surveillance conducted by the Centers for Disease Control in the USA has documented a decrease in the antibiotic resistance of pneumococci isolated from both children and adults in that country since the introduction of conjugate pneumococcal vaccine for routine childhood immunization. This reduction in resistance is due to the effect of the vaccine in reducing the prevalence of paediatric serotypes causing invasive pneumococcal disease. In a large study of nearly 40 000 infants in Soweto, recipients of the 9 valent conjugate vaccine had a 67% reduction in invasive pneumococcal disease caused by resistant strains irrespective of the HIV status of the recipients. This observation suggests that pneumococcal conjugate vaccine could significantly reduce the burden of antibiotic resistance in pneumococcal infections in children, and possibly also, by the interruption of child to adult transmission, in adults, in South Africa.

**Conclusions**

- Pneumococcal conjugate vaccine has had a major impact on pneumococcal disease. It reduces CAP in children. It also reduces invasive disease in high-risk children with HIV infection.
- Will serotype replacement reverse the gains?

**Future Studies**

- Will conjugate vaccine given to children or to adults prevent pneumonia in the elderly? – The impact of the existing 23 valent polysaccharide vaccine has been difficult to prove in randomized trials of the at risk elderly
- Trials of immunogenicity in adults – dose ranging – are starting – efficacy trials may follow
- Effectiveness studies of pediatric vaccine to prevent adult pneumonia are needed

3. A Multi-Centre Surveillance Study in Kwazulu-Natal, South Africa Reveals Inappropriate Standard Treatment Guidelines (STGs) and Resistance to Antibiotics on the Essential Drugs List (EDL) Essack, S.Y.1 School of Pharmacy and Pharmacology, University of Durban-Westville

**Objectives:** The applicability of nationally devised and implemented standard treatment guidelines and an essential drugs list for infections were evaluated within the public health care system in Kwazulu-Natal, South Africa in the context of antibiotic resistance.

**Conclusion**

- The study concluded that resistance profiles amongst bacteria vary too much to allow a national antibiotic policy as proposed in the STGs and EDL.
- Guidelines should be directed to specific profiles found at different levels of health care.
- Regular surveillance to adjust such guidelines is essential.
- Antibiotics treatment should be based on local (ideally institution-specific) antibiotic susceptibility profiles of common causative microorganisms obtained from surveillance studies.
Recommendation

- Imperative to implement a surveillance strategy informing strategies within a public healthcare system increasingly fraught with infections partly as a result of a high incidence and prevalence of HIV/AIDS.

THE EVENING OF THE 27 OCTOBER WAS CONCLUDED BY A GALA DINNER AND DANCE.

The Chair of council and the Registrar of medicine addressed the delegates and passed a vote of thanks to the sponsors and organisers.

DAY TWO OF THE CONFERENCE - TUESDAY, 28 OCTOBER 2003

SESSION FIVE

1. Antimicrobial resistance in STD pathogens A. Willem Sturm (Nelson R Mandela School of Medicine)

Conclusions

• Susceptibility surveillance in STD pathogens is restricted to \textit{N.gonorrhoeae} and \textit{H.ducreyi}
  - Surveillance of clinical response essential
  - The problem organism is \textit{N.gonorrhoeae}:
  - emerging quinolone resistance in S.Africa

2. ANTIMICROBIALS AND PREGNANCY: CONCERNS FOR APPROPRIATE USE AND DEVELOPMENT OF RESISTANCE A A HOOSEN (Department of Microbiological Pathology, MEDUNSA)

Antimicrobial agents are used frequently in pregnancy and related conditions such as post abortion sepsis, symptomatic bacteriuria, post-partum endometritis etc. The agents are used for both prophylaxis and therapy. This presentation focuses on the common conditions associated with pregnancy and reviews some of the settings for the use of antimicrobials and implications for development of resistance. Recent work has focused on screening for group B streptococci (GBS) and bacterial vaginosis (BV) for prevention of neonatal infections and preterm labour respectively. Guidelines for routine GBS screening have been developed in the USA with recommendations for use of ampicillin/penicillin intra-partum. Local studies showing the prevalence of GBS colonization are reviewed and implications for antimicrobial intervention. Screening for BV in pregnancy is not universally recommended. However, a study conducted in Durban showed an association with adverse outcome of pregnancy. Local isolates of \textit{Gardnerella vaginalis}, an organism associated with BV have been tested against a range of antimicrobial agents. The minimum inhibitory concentrations to metronidazole show the isolates to be susceptible. The implications of these findings for management of BV remain unclear.
Local studies on the prevalence of asymptomatic bacteriuria in pregnancy show higher prevalences than those reported from developed countries. Whilst the commonest causative agent worldwide is *Escherichia coli*, its antimicrobial susceptibility profile has shown nearly total resistance to the commonly used agents viz. ampicillin and co-trimoxazole. Alternative therapeutic agents need to be used. Data from community and institutional based studies are presented. Trichomoniasis remains the commonest cause of vaginal discharge in pregnant woman with prevalence figures of nearly 50% at some centers in South Africa. Novel non-invasive specimen collection methods and diagnostic techniques are presented. Minimum inhibitory concentrations of local isolates of *T. vaginalis* show them to be uniformly susceptible to metronidazole. Ongoing surveillance and monitoring of antimicrobial susceptibility profiles of common isolates associated with pregnancy and its outcome needs to be conducted regularly.

**SUMMARY**

- Anti-microbial usage in pregnancy
- Focus on prophylaxis – screening and management of infections / colonisation
- GBS
- Asymptomatic bacteriuria
- BV

**3. Antimicrobial Resistance in the Geriatric Population: Special Considerations**

Dr S Kalula. *(The Walter and Albertina Sisulu Institute of Ageing in Africa, University of Cape Town, Groote Schuur Hospital)*

Infectious diseases have remained a major cause of death and disability through out the history. Although there has been a significant reduction in infection related mortality and morbidity since the beginning of the “antibiotic era,” complications from infectious diseases remain a serious problem for older persons. Pneumonia remains the major infection related cause of death in older persons, and urinary tract infection is the most common bacterial infection seen in geriatric patients. Other serious and common infections occur frequently in this age group, making frequent prescribing of antibiotics common practice. The large volume of antibiotics prescribed has contributed to the emergence of highly resistant pathogens among older patients. Antimicrobial resistance, which is an increasing problem, contributes to the increased morbidity, mortality and increased health care costs. Resistant pathogens previously seen only in acute care settings are becoming increasingly common in long term care facilities where control-of-infection measures are mostly minimal. The development of newer antibiotics may have modestly improved therapeutic options for treatment of infections due to resistant pathogens in industrialised countries, but for developing countries these therapeutic options are unaffordable. Therefore, the best strategy in the prevention of the emergency of antimicrobial resistance is to limit the potential for development of resistance and transmission of these pathogens. This can best be achieved by minimising misuse of antibiotics and maximizing adherence to basic hygiene standards.
Drug resistance to antimalarials has a major impact on case management resulting in increased morbidity and mortality of individual patients. An increase in gametocyte carriage as a result of failed therapy leads to increased transmission, adversely affecting malaria control in endemic areas. Antimalarial drug resistance develops as a result of drug overuse, under dosing, poor compliance and the use of drugs with long half-lives. Chloroquine resistance is widespread globally, and resistance has developed relatively rapidly to sulfadoxine pyrimethamine. Quinine resistance has developed in South East Asia, but the drug remains effective in Africa. To prevent this ongoing resistance to sequential monotherapy, combination therapy, preferably using an artemisinin compound together with a second effective drug is the recommended policy. The development of resistance is dependent on parasite load. The artemisinins are highly effective drugs that rapidly decrease parasite load. Drug resistance has dictated treatment policy in South Africa. The emergence of chloroquine resistance in KwaZulu Natal (1987) and Mpumalanga (1997) necessitated a change to sulfadoxine pyrimethamine (SP) as first line treatment for uncomplicated malaria. The development of SP resistance in KwaZulu Natal necessitated a further change to artesunate in 2002, and artesunate is used together with SP in order to prevent further resistance developing. InMpumalanga. In vivo monitoring of parasitological and clinical responses is critically important to provide evidence for drug resistance and the need for further treatment changes. While mechanisms of resistance have been well characterised for selected drugs, notably the antifolate drugs, in vitro drug resistance has only limited use in formulating drug policy. National drug policies, compliance with recommendations, and wide coverage with artemisinin combination therapy are important in retarding development of further drug resistance.

SESSION SIX

1. Susceptibility Patterns of Respiratory Pathogens in South Africa
Lynne D. Liebowitz, (Department of Medical Microbiology, Tygerberg Hospital and University of Stellenbosch)

Worldwide the incidence of infections caused by antibiotic-resistant strains of bacteria is increasing. There are three studies in which the antibiotic susceptibility patterns of respiratory tract isolates have been reported. The Alexander study was performed on isolates collected in 1996-1997 from patients in the public sector, while the Libra and Protekt studies assessed isolates collected in 2001-2002 from patients in the private sector.

In the Alexander study less than 5% of the pneumococcal strains were fully resistant to penicillin, while in the Libra and Protekt studies the percentage of resistant isolates was much higher. In the LIBRA study, strains of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis isolated from specimens submitted to 14 private laboratories in South Africa were sent to the Microbiology Laboratory at Tygerberg Hospital for minimum inhibitory concentration (MIC) determinations. MIC determinations were performed according to NCCLS recommendations. According to the NCCLS breakpoints 24% of 729 S.pneumoniae isolates were sensitive, 30% intermediate and 46% resistant to penicillin. Macrolide
resistance was high with 61% of the pneumococci being resistant to clarithromycin and azithromycin. Cotrimoxazole resistance was also high with 28% of strains being sensitive, 21% intermediate and 51% resistant. β-lactamase was produced by 8% of 718 H.influenzae, and 91% of 253 M.catarrhalis isolates respectively. None of the pneumococci, H.influenzae or M.catarrhalis isolates tested were resistant to the quinolones moxifloxacin and levofloxacin. The results of the Protekt study were virtually identical.

2. HIV-1 subtype C drug resistance in South Africa  aLynn Morris ( aAIDS Virus Research Unit)

The emergence of HIV drug resistance is a major obstacle to effective anti-retroviral (ARV) treatments. For many patients, HIV-1 viremia is initially suppressed by ARV therapy but may rebound due to the emergence of drug resistant variants. Monitoring of drug resistance is therefore an integral part of managing patients on ARV therapy and for determining future treatment options. ARV therapy in South Africa is limited and there are no published studies on drug resistance patterns in viruses found in this region. This study was aimed at looking at drug resistance profiles of HIV-1 subtype C patients failing therapy in South Africa. Samples were obtained from 61 patients most of who had received at least 2 nucleoside reverse-transcriptase inhibitors and either one non-nucleoside reverse-transcriptase inhibitor or a protease inhibitor. All patients were infected with HIV-1 subtype C viruses. The most frequent mutations detected were M184I/V (38%), followed by D67N (31%), T215Y (28%), K70R (23%), M41L (21%), K65R (15%), K219Q and Q151M (10%) reflecting the heavy use of 3TC and AZT in this cohort. K103N (53%), G190A (36%), V106M (30%), Y181C (13%), Y188C (13%) and M230L (10%) were found among patients failing NVP or EFV containing regimens. Of the 32 patients who received protease inhibitors, the most common mutations were M46I (18%), V82A (16%), L90M (16%), I54V (13%), N88D/S (9%) and D30N (6%). These data indicate that HIV-1 drug resistance develops in South African patients failing ARV therapy and that mutations are similar to those found among treated patients infected with subtype B viruses.

3. HIV Resistance in SA Dr Prudence Ive (Clinical HIV Research Unit Wits Health Consortium)
Conclusions
• 3TC → M184V → ddI
• NNRTI → PI
• d4T → AZT
• (do not want combination ddI/d4T)

Resistance Testing
• To enable to recycle nucleosides after both the first and second line regimens.
• PCR point testing for NRTI’s → looking for TAMS (41L, 67N, 70R, 210W, 215Y/F, 219Q)

For the Future
• Tenofovir (TDF) – once daily dosing potent nucleotide. (K65R)
• Atazanavir (ATZ) – protease, once daily dosed. Excellent tolerability. I50L mutation conferring hypersusceptibility to e.g. Kaletra.
• Emtricitabine (FTC) – once daily nucleoside with 50% of M184V mutation.

Possible new regimens
• d4T/3TC/EFV → TDF/3TC/EFV or TDF/FTC/EFV
• AZT/ddI/Kaletra → ATZ/ddI/ATZ (possibility of recycling Kaletra)

4. Drug Resistance in Tuberculosis PD van Helden* (MRC Centre for Molecular and Cellular Biology and Department of Medical Biochemistry, Faculty of Health Sciences, Stellenbosch University, South Africa)

Management of TB is complicated by the emergence of drug resistant strains of Mycobacterium tuberculosis and this pose a threat to the success of TB control programmes. Drug susceptibility testing by culture is time-consuming and technically difficult. It is known that resistance to drugs is due to a number of genomic mutations in specific genes of M. tuberculosis. These mutations can be used as markers to rapidly predict drug resistance, since drug susceptible isolates lack the corresponding gene mutations. A number of molecular-based methods have been developed to exploit the observation that specific mutations found in drug resistant strains are absent in susceptible organisms. Many of these methods are complex and not always applicable for routine use. We have developed a PCR-based screening method, which allows batch analysis of samples via dot-blot hybridisation with allele specific probes to detect resistance to a variety of drugs. The method is reproducible, not technically demanding and takes about two normal working days to obtain results from the start of amplification (done in batches of 30-40 samples) to final detection (batches of up to 150 samples and controls). Mathematical modelling predicts cost savings of 40% for rapid diagnosis of drug resistance compared to the traditional culture susceptibility test and shows clearly the necessity for proactive case finding and rapid diagnostic techniques. The method has now been established alongside the TB control programme and the results (sensitivity, specificity, repeatability) obtained directly from sputum (n = 2470) compares favourable to the routine culture method. In another approach a longitudinal reference database containing geographic, phenotypic and genotypic characteristics of all drug resistant isolates (n = 519 patients) collected over 19 months from 72 clinics in 2 of the 4 health districts in the Western Cape Province of South Africa has been established and analyzed. The results showed that 41% of the isolates are MDR and a further 47% are resistant to INH only. The large pool of INH mono resistant isolates have similar genotypes in the MDR group and
may by further selection develop into MDR-TB. DNA fingerprinting showed that 88% of all isolates shared a common pattern of 30 distinct types. Four major families, classified according to specific spoligotype signatures, are responsible for the drug resistant epidemic. The families are the Beijing/W-like (27%), F11 (13%), F28 (5%) and the IS6110 Low-Copy-Clade (27%) and represent 72% of the drug resistant isolates in the study. This suggests that the drug resistant epidemic is driven by transmission of an already drug resistant strain. The strain families are spread throughout the region. Most of the MDR isolates are found in the IS6110 Low-Copy-Clade and are predominantly from one town in the region. This is mainly due to an outbreak of an emerging highly drug resistant strain (now called DRF150), which recently have evolved by clonal expansion. Strain characteristics and the molecular approach described in this study can be used for the rapid identification of outbreak drug resistant Mycobacterium tuberculosis strains in an attempt to combat further transmission.

SESSION SEVEN

1. A Four Year Global Evaluation of the Susceptibility of Candida spp to Fluconazole by Disk Diffusion. Lynne D Liebowitz (University of Stellenbosch)

Conclusion: Fluconazole resistance is presently not a problem in the South African isolates of Candida spp, excluding C. krusei and C. glabrata.

2. INCREASING ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHIMURIUM BACTERAEMIA AT CHRIS HANI BARAGWANATH HOSPITAL

H.H. Crewe-Brown

Department of Clinical Microbiology and Infectious Diseases, Chris Hani Baragwanath Hospital, Soweto

Conclusions: The continued escalation in the rate of non-typhoidal Salmonella bacteraemia parallels the increasing HIV-seroprevalence and spread of the AIDS epidemic in South Africa. S. Typhimurium is the predominant serotype causing invasive infection; rates of resistance and multiresistance in S. Typhimurium strains are increasing progressively. The emergence of ESBL-producing S. Typhimurium in adults in 2002 is a cause of concern, leading to greater difficulty in treating patients effectively. Pulsed-field gel electrophoresis of multiresistant strains showed a high degree of clonality. An external source for these strains needs to be sought.

3. Pneumocystis jiroveci: Evaluation of Molecular Diagnostic techniques and Cotrimoxazole Resistance Surveillance in Cape Town FJL Robberts

Department of Medical Microbiology, School for Basic and Applied Health Sciences, University of Stellenbosch, Tygerberg.

Laboratory diagnosis of Pneumocystis jiroveci relies primarily on microscopic identification, however molecular techniques are proving superior. Long-term prophylactic treatment with cotrimoxazole has resulted in emergence of resistant strains in first world countries.

Conclusions. Of the PCR primers investigated the mt LSU rRNA nested primer technique was the most suitable. PCR was seen to be an important adjunct to IF,
which appeared prone to false-positive and -negative results and should be considered complementary. No mutations conferring resistance to cotrimoxazole were detected and it was evident that surveillance of resistance development is severely limited due to low sensitivity of the DHPS/DHFR primers.

4. Resistance in *Streptococcus pneumoniae* from Blood Cultures and Relationship to HIV status at Chris Hani Baragwanath Hospital HH Crewe-Brown (Department of Clinical Microbiology and Infectious Diseases, NHLS.)

**CONCLUSIONS**

- The increasing numbers of severe invasive pneumococcal infections in HIV-infected patients are of concern
- Increasing numbers of adult women with *S. pneumoniae* bacteraemia reflect the HIV prevalence rate in women
- Intermediate penicillin resistance has not continued to increase, but is significantly higher in HIV-infected compared with uninfected children
- Many HIV-infected patients, particularly adults, have fully susceptible strains
- Strains, which are resistant to penicillin and/or have intermediate resistance to third generation cephalosporins, are uncommon

**Co-trimoxazole resistance**

- Has increased significantly in adults and total numbers of patients over the past four years
- Is significantly higher in HIV-infected compared with uninfected children
- Is associated with a higher rate of multi-resistance in HIV-infected versus uninfected children
- Is significantly higher in HIV-infected women compared with HIV-infected men

Used excessively, co-trimoxazole may be associated with increased resistance to other antimicrobial agents. Increasing co-trimoxazole resistance will render its use suboptimal as a prophylactic agent for opportunistic infections in adults and children.

5. Antimicrobial Resistance in Companion and Production Animals, with Special Reference to Southern Africa Dr. M. Van Vuuren Department of Veterinary Tropical Diseases Faculty of Veterinary Science University of Pretoria

**Conclusion**

- A national veterinary antimicrobial resistance surveillance and monitoring programme coordinated by the University of Pretoria with financial support *inter alia* from the National Dept. of Agriculture and with the participation of a network of regional private and government veterinary laboratories should be encouraged and given a high priority

6. Antibiotic Resistance Patterns of *Salmonella* and *Enterococci* Isolates from Selected Foods and Food Handling Environments in Botswana. Mpuchane, S.
**Recommendations**

- Improvement of farm hygiene to reduce the number of pathogens present on farms and in slaughterhouses.
- Improvement of animal husbandry There is need to collaborate extensively on research efforts and results pertaining to resistance mechanisms and ways to produce food without using the quantity of antimicrobials currently being used.
- There is a need for national governments to collaborate with farmers, relevant NGO’s, consumers, veterinarians, clinicians and researchers in addressing the problem
- There is need to regulate on the use of antibiotics in Agriculture

- Fruits and vegetables should be washed thoroughly to remove resistant bacteria and antibiotic residues.
- Since cockroaches have been shown to carry and spread resistant microorganisms on their bodies and faeces, all efforts should be made to eradicate them from our homes.
- Proper herd management to reduce faecal shedding that contributes to the spread of faecal microorganisms
- Avoid the common use of antibiotics for humans and for animals

7. **Emerging antibiotic resistance in bacterial gastroenteritis in South Africa**

South Africa – Two Years On Karen Keddy (Enteric Diseases Unit NICD National Health Laboratory Service)

**Conclusion**

Surveillance for enteric pathogens is an important tool for combating enteric disease in the developing world. Ongoing surveillance is critical to our understanding of these pathogens and to controlling them through appropriate health policy, including education, vaccination and antibiotic recommendations. Antibiotic usage in humans and animals use needs to be carefully monitored and documented to prevent the development of further resistance in enteric pathogens.

**SESSION EIGHT**

1. **Developing a model and methodology to contain AMR country pilot projects**

Kathleen Holloway Essential Drugs & Medicines Policy WHO Geneva

Presented by Andy Gray on behalf of WHO

**Background:** The WHO Global Strategy to contain antimicrobial resistance (AMR) recommends a multidisciplinary approach of 67 interventions. There is little evidence on which interventions would be most effective or feasible and probably this would vary across and within countries and health systems. Furthermore, there is little capacity in many countries to undertake the multi-disciplinary approach needed.

**Aim:** WHO is initiating pilot projects in several sites to develop a new locally applicable model to contain AMR that can be used in developing countries? This involves (1) developing a new methodology for the integrated surveillance of AMR and antimicrobial use, (2) evaluating interventions to contain AMR and (3) building local capacity in a multidisciplinary approach to the containment of AMR.

**Methods:** The projects will occur in 3 phases. The first phase is to set up an integrated surveillance system for AMR and antimicrobial use, the second phase to use this
surveillance system to evaluate the impact of interventions to contain AMR and the third phase to expand to other sites and use the data for advocacy in-country. The AMR surveillance is of 1-2 selected organisms in patients with pre-defined clinical condition in hospital outpatient and primary health care facilities on presentation before treatment. The antimicrobial use surveillance is at all levels of the health care system in the same geographical area as the clinical specimens for resistance testing were taken.

**Progress:** Two projects have been started in S.Africa undertaken by the Universities of Natal/Durban Westville in Durban and MEDUNSA in Pretoria. In Durban, the surveillance is focused on S.Pneumoniae and H.Influenzae in patients with productive cough and in MEDUNSA the surveillance is focused on E.Coli in patients with uncomplicated urinary tract infection. The process of starting these projects took more than 1 year and involved a multi-disciplinary team developing a satisfactory proposal and site visit by WHO. Other WHO-supported pilot projects have started in India and are under discussion in 3 other countries.

**Concluding remarks**
- Pilot projects have been successfully initiated in a variety of resource-constrained settings
- Where data have already been generated, barriers to setting up such co-ordinated surveillance systems are immediately apparent, but not insurmountable:
  - Time and effort required – personnel, training, access to data in the private sector
  - Costs
  - Limitations of available data
  - Future plans
- That most of the pilot sites already chosen + those in development will proceed to Phase 2 - development, implementation and evaluation of interventions to promote more rational use of antimicrobials

**2.Antimicrobial Resistance in Developing Countries: Challenges for Infection Control** Adriano G Duse (Department of Clinical Microbiology and Infectious Diseases NHLS and Wits School of Pathology)

Anti-microbial Resistance Within The South African Context: *S. pneumoniae*
- Successful global spread of Spanish serotype 23F pneumococcal clone (Spain 23F-1) including to South Africa
- Two pneumococcal clones of serogroup 19A identified in South Africa (PIRP South Africa 19A-7, and MDR South Africa 19A-13)
- Unique PR serotype 6B clone has emerged locally in South Africa (South Africa 6b - 8)

**3.Hospital v community exposure to multiple antibiotic resistance** Prof Shaheen Mehtar Head of Unit for Infection Control (Department of Community Health Tygerberg Hospital & Stellenbosch University)
There is no escape from multiply antibiotic resistant bacteria either in communities or in hospitals. Antibiotic usage in communities are widespread and are indiscriminately used in
1) General medical practice
2) Over the counter usage from pharmacies
3) Animal husbandry

In hospitals the use of antibiotics is extensive; up to 25% of in-patients at any one time will be administered at least one antibiotic—in high care units this number may increase to five or six antibiotics being administered at the same time. In the UK hospitals have reported the antibiotic budget being almost one third of the pharmacy budget for the hospital. There is even more use reported from other countries such as the United States.

In hospitals antibiotics are prescribed empirically and therefore the samples taken for microbiology do not reflect the true pathogens causing the disease—the outcome is that colonising bacteria which rapidly replace sensitive ones, are isolated, reported from the laboratory with antibiotic sensitivity patterns and inevitably are treated with very expensive and usually broad spectrum antibiotics.

Antibiotics are widely used in hospitals for some of the following reasons
1) surgical prophylaxis
2) medical prophylaxis
3) peri-operative cover
4) empiric therapy
5) targeted therapy

There is a misconception that antibiotics are wonder drugs that rectify all wrongs including poor surgical technique. This has led to the abuse of antimicrobial agents in many countries. Essentially, over use of antibiotics leads to the emergence or acquisition of resistance—while poor infection control practices lead to spread of such multiply antibiotic resistant bacteria.

There is much pressure to prescribe antibiotics upon the general practitioner from the patients attending the clinic. Equally, pharmaceutical companies driven publications, peer publications and cost of the antibiotics influence prescribing. The prudent use of antimicrobial agents should be considered for both community and hospital use—BUT, antibiotic policies are no substitute for good infection control practice.

Lessons we can learn

■ Indiscriminate use of antibiotics leads to resistance levels which renders antibiotics as life saving drugs ineffective.
■ Should we look for new antibiotics or use the current ones more prudently?
■ Where resistant strains are present, spread can be retarded by routine good IC practice.
■ Contain both hospital and community spread of resistant bacteria

PRELIMINARY RECOMMENDATIONS

The evening of the Tuesday 28th the chairs of the sessions had a working supper in which the recommendations from each presentation was summerised.
Preamble:

Antimicrobial resistance (AMR) is a recognised problem both globally and nationally. The extent and impact of the problem in South Africa must be quantified. There are risks that have been identified that are associated with AMR in humans and animals, which pose a burden both economically and clinically. Programmatic and policy approaches to contain AMR that have been undertaken internationally have included the following components:

- Effective regulation
- Communication (including adherence)
- Infection control
- Monitoring and surveillance
- Research
- Cost related measures

RECOMMENDATIONS

**Session One: Chair Dr Khomo and Prof Klugman**

1. Surveillance and monitoring systems needs to be customized to meet country requirements (e.g. private and public sector)

2. Risk assessment as well as regulatory control of human and veterinary medicines.

3. Review antimicrobial consumption and the identification of key pathogens.

4. Utilize structures that already exist and facilitate coordination with all stakeholders (e.g. involvement of TB and malaria control programmes).

5. Identify the gaps in the already existing surveillance systems and correct the deficiencies.

6. Review the contribution of current infection control guidelines

**Session Two: Chair Prof Wierup and Prof Dangor**

- Relationship between antibiotic usage in food-producing animal and resistance.
- Interrelationship between animal and human antimicrobial resistance

**Session Three: Chair Mrs Hela and Prof Banoo**

1. The importance of adherence/compliance must be reflected in a revised definition that includes short- and long-term goals.

2. Appropriate pharmacovigilance systems need to be supported by surveillance, monitoring and laboratory data.
3. Drug decision-making must be informed by resistance profiles and PKT/PKD data.

4. Design of antimicrobial studies must consider implications of AMR.

5. Guidelines need to be associated with a strong implementation plan.

Session Four: Chair Prof Liebowitz and Dr Butler

1. Non antimicrobial agents / pneumococcal vaccination can improve antimicrobial resistance by reducing the need for antibiotic use.

2. Targeted surveillance required to guide empirical therapy

3. Reassess the use of prophylactic regimens (e.g. cotrimoxazole, INH)

Session Five: Chairs Dr Dyke and Dr Steel

Overlap with previous session

1. Highlight was certain organisms and populations

2. Recommendation was that a comprehensive perspective surveillance is essential to get a more complete insight in the problem

3. Surveillance needs to be followed with an intensive appropriate intervention and it is critical to be different for various problems

Session Six: Chairs Dr Khomo and Dr Mbelle

HIV Surveillance

A) General Surveillance

Eg for incident infections with primary resistance

i) ANC Survey using Bed Elisa (showing infections in last six months) on all positives and looking for key mutations

ii) Looking for incident (primary) infections at STD clinics and resistance patterns

B) Programmatic Monitoring on annual basis at treatment facilities for ARV roll out

i) Drug supply (pharmacists)
ii) Drug administration
iii) Clinic visits
iv) Adherence assessments
v) Number of patients with consecutive viral loads and resistance testing on those which increase

Resistance task group to be formed if resistance testing is done as part of therapeutic monitoring and to include Virologist, Epidemiologist, Statistician and Clinician

Session Seven: Chairs Prof Sturm and Dr Franklin

1. Quality control systems (HACCP) to be applied in animal production.
Session Eight: Chairs Dr Misra and Prof Swan

1. Harmonisation with WHO and FAO/OIE
2. Infection control strategies and interventions including agriculture and veterinary.
3. WHO has proposed a model for Antimicrobial resistance containment including multiple interventions that could be made
4. Monitoring drug usage and microbial surveillance was identified as the priority interventions.
5. The other interventions should be prioritized within the countries
6. Prudent use of antiseptics and disinfectants
7. Usage of other methods to control infections beside usage of antimicrobials

Session Nine: Chairs Prof Eagles and Prof Swan

1. Good disease control measures, increasing the health status, improved management systems and a focus on hygiene factors are alternative ways and will go a long way in reducing the need for Antimicrobials in animals and therefore in the containment of resistance
2. The use of antimicrobial as a growth promoter does not have any scientific merit
3. Surveillance is the key to a national Antimicrobial resistance containment programme. Aspects of definition, technical considerations, including aspects such as denominators, choice of populations, numbers and types of samples and responsibility are important issues to consider.
4. Communication and reporting back to persons and organizations supplying data is essential
5. In developing guidelines all stakeholders need to be involved and documents to be continuously reviewed.

DAY THREE WEDNESDAY 29 OCTOBER 2003

SESSION NINE

1. Role and strategies for the use of antimicrobials in animals
   Martin Wierup, Professor, Faculty of Veterinary Medicine Swedish University

With the focus on effective control of infectious diseases and the containing of antimicrobial resistance the basic strategies for the use of antimicrobials in animals are outlined. In addition is presented the principals of disease preventive methods and examples of their application as alternatives and complements to the use of antimicrobials.

Conclusion

Antimicrobials our best drug to treat infections but:
• Infectious diseases are best controlled by Prevention
• Disease prevention, health control, is a necessity In animal production
• Always focus on improving health status
• Use antimicrobials first when preventive actions Have failed – not as a replacement
• Use antimicrobials properly based on diagnosis And knowledge
• Follow up and evaluate clinical result, usage and Antibiotic resistance

2. Surveillance and Monitoring of Antimicrobial Resistance. S. R. Norrby, Swedish Institute for Infectious Disease Control

Surveys of antibiotic resistance are commonly performed but the results presented may be misleading. The following prerequisites should be considered for such surveys:
• They should be prospective
• The denominator should be defined, i.e., one should gather information on the numbers of patients, samples and strains that will be examined. For a given type of infection, data should be collected on number of patients with the infection and number of patients from whom samples were obtained.
• Outpatient data should be separated from inpatient data
• Results should be correlated to antibiotic consumption in the population under study.

Unfortunately most surveys are based on routine samples sent to a laboratory. It is then very likely that these samples come from patients with abnormal courses of their infections, i.e., the patients have not responded to empirical treatment as expected and/or they have more serious symptoms than normally seen. Other common mistakes in surveys are inclusion of multiple isolates from one and the same patient. For some species, e.g. *Pseudomonas aeruginosa*, inclusion of multiple patients from one and the same ward is likely to result in registration of multiple isolates of one and the same strain.

All of the above possibilities for bias in the surveillance of antibiotic resistance are likely to result in falsely high frequencies of resistance. The consequence of that is often recommendations for increased use of broad spectrum antibiotics for empirical treatment, a waste of resources.
Issues to consider when assessing resistance surveillance data

• How was “resistance” defined?
• Was the denominator defined?
• From which population(s) were samples obtained?
• Was more than one sample/patient accepted?

Conclusions

• How was “resistance” defined?
• Was the denominator defined?
• From which population(s) were samples obtained?
• Was more than one sample/patient accepted?
Interpret data with caution!

3. Promoting evidence-based antibiotic prescribing in primary care
Professor Chris Butler, Professor of Primary Care Medicine, University of Wales College of Medicine

Over 80% of all antibiotics are prescribed in primary care and more than 50% are probably unnecessary. Unnecessary antibiotics waste resources, expose patients to unnecessary risk from side effects and contribute to resistance-related treatment failure in the community as well as in hospital settings. Antibiotic prescribing is influenced not only by the clinical problem (biological factors). Patients’ and clinicians’ personal and contextual factors are also influential. It is not surprising therefore that attempts to solve the problem of inappropriate antibiotic prescribing with simple solutions have largely failed. These attempts have generally focussed on persuading clinicians ‘why’ they should change. Effective behaviour change interventions need to take into account the full complexity of the clinical situation by incorporating effective strategies for ‘how’ to change. However, it is not only the content of clinician behaviour change interventions that is crucial. Without effective ways for clinicians to acquiring new skills, the best interventions will be ineffective.

This presentation will focus on promoting evidence based antibiotic prescribing, especially in primary care. It will cover relevant findings from the field of clinician behaviour change. Specific interventions aimed at changing antibiotic prescribing will be reviewed, including guidelines, enhanced diagnostic techniques, patient directed strategies, and strategies for enhancing clinician-patient communication. Strategies for dissemination and uptake of interventions will also be reviewed. Recommendations will be made for developing, evaluating and implementing interventions aimed at enhancing evidence-based antibiotic prescribing, especially in primary care.

Summary

- Complex problem
- Single, simple solutions not effective: e.g. unsolicited guidelines through the post
- Law of diminishing returns; smaller changes now might require big investments
- Interventions need to respond flexibly to ‘why’ and ‘how’ of change and have potential to address both dimensions’
- E.g. diagnostic and communication skills synergistic
Communication final common pathway
SDM in acute conditions as well as in chronic serious conditions such as HIV

4. Risk analysis of AMR' Dr Timothy M Dyke, Principal Scientist - Veterinary Medicines Australian Pesticides and Veterinary Medicines Authority

Risk analysis is a critical success factor in the management of antimicrobial resistance, along with 4 other critical success factors (infection control, research, communication and education, and monitoring and surveillance). International experiences in conducting risk assessments and risk management strategies for new and registered antibiotics demonstrate that risk analysis within a regulatory framework has an important role to play in resistance management. However, risk analysis of antimicrobial resistance is an extremely complex endeavour as there are many contributing factors, uncertainties and sparse data.

The way forward?

■ Risk assessment on all new antibiotics and registered antibiotics of public health importance
■ Better surveillance data on local, national and international level
  – Keep asking Why?, Why?, Why?
■ Identify expertise in quantitative risk assessment
■ Identify data gaps and beware of conclusions based on minimal or aggregated data
■ Coordination of human and animal health efforts – bacteria don’t see the difference, why should we?

After tea the finalisation of the summaries of the nine sessions were debated and the following conclusions were arrived

FINAL RECOMMENDATIONS

Risks that are associated with antimicrobial resistance in humans and animals, pose an economic, social as well as clinical burden on the country and its resources.

Programmatic and policy approaches to contain antimicrobial resistance that have been undertaken internationally have included the following components:

➤ Effective regulation
➤ Communication and education (including adherence)
➤ Infection control
➤ Monitoring and surveillance
➤ Research
➤ Cost related measures.

The recommendations from the different sessions of the congress included the following:

1. Surveillance and monitoring systems to contain antimicrobial resistance need to be customised to meet country requirements. The WHO has proposed a
model for containment including multiple interventions that could be made. Monitoring of drug usage and microbial surveillance was identified as the priority interventions, and the others interventions should be prioritised within countries. Surveillance is the key to a national antimicrobial resistance containment programme. Different aspects of definition, technical considerations, including aspects such as denominators, choice of populations, numbers and types of samples and responsibility are important issues to be considered. The communication and reporting back to persons and organisations supplying data is essential

2. Risk assessment strategies as well as regulatory control of human and veterinary medicines based on scientific data are essential. Strategies to contain antimicrobial resistance should integrate and harmonise with international efforts and initiatives, including with those of WHO and FAO

3. Initial programmes for containment of antimicrobial resistance should utilise existing infrastructure and coordination with all stakeholders (e.g. involvement of TB and malaria control) should be facilitated as a matter of urgency. In this regard, deficiencies and gaps in the already existing surveillance systems should be identified and corrected.

4. The contribution of current clinical infection control guidelines and strategies including interventions in agriculture and veterinary health should be reviewed. The prudent use of antiseptics and disinfectants must be advocated. The use of other methods to control infection, in addition to antimicrobials, needs to be emphasised. In this regard, good disease control measures, increased health status, improved management systems and a focus on hygiene factors are alternatives that will go a long way in reducing the need for antimicrobials in animals and therefore in the containment of resistance.

5. Appropriate Pharmacovigilance systems need to be supported by surveillance, monitoring and laboratory data. Quality control systems need to be applied in animal production.

6. Targeted surveillance is required to guide empirical therapy (surveillance need to be followed by intensive appropriate intervention and it is critical to be different for various problems)

7. In developing guidelines, all stakeholders need to be involved and a system for continuous review of documents needs to be instituted. Professional and public education and information requirements need to be developed and implemented as part of a coordinated containment strategy.

8. Surveillance and monitoring of viral resistance needs to be integrated as an essential component of an antiretroviral treatment programme. Resistance testing should be done as part of therapeutic monitoring. To this end, the establishment of a focused task group, which includes a virologist, epidemiologist, statistician and clinician, should be considered.
CLOSING REMARKS

The Chair of the Medicine Control Council, Prof Peter Eagles, officially closed the Conference on 29 October 2003 at 13.00 hrs

The following points were highlighted.

The interrelationship between antimicrobial resistance in humans and animals was emphasised in the use of antibiotics in food-producing animals as well as the transfer of resistant strains from animals to humans. In this regard, the meeting stressed the importance developing sustainable surveillance systems to detect resistant pathogens and monitor the patterns of use of antimicrobials in both humans and animals.

In considering the public health impact of antimicrobial resistance, the meeting stressed the need to encourage the appropriate and cost-effective use of antimicrobials; to prohibit the dispensing of antimicrobials without a prescription from a qualified healthcare professional; to improve practices to prevent the spread of infection and thereby prevent the spread of resistant pathogens; to strengthen legislation to ensure the availability of antimicrobials of good quality, safety and efficacy; and to reduce the irrational use of antimicrobials in food-animal production. Non-antimicrobial agents (vaccines) can improve antimicrobial resistance by reducing the need for antibiotics.

The meeting also examined the influence of resistance in relation to the global epidemic of HIV/ AIDS as well as its impact on the provision of safe and effective treatment interventions, which are also cost-effective. Its role in the prophylaxis and management of opportunistic infections in HIV/AIDS in the South African population was also debated.

The recommendations were noted and will be forwarded to the Honorable Minister of Health.