WHO Scientific Working Group on Monitoring and Management of Bacterial Resistance to Antimicrobial Agents

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1. Introduction

Resistance to antibacterial agents is today a major public health problem in both developed and developing countries throughout the world. The incidence of resistance has increased at an alarming pace in recent years and is expected to increase at a similar or even greater rate in the future as antimicrobial agents continue to lose their effectiveness.

Resistant bacteria do not respect national borders; the development of resistance in the most remote locations can have an impact throughout the world in a very short space of time. Resistance to antimicrobial agents is a problem in the community as well as in institutional settings, where transmission of bacteria is greatly amplified within a highly susceptible population in a confined space. While the elderly, the very young, and the chronically ill are at greatest risk from drug resistant infections, they can also strike healthy people in the prime of life.

With the emergence of multiple-drug resistance, physicians are now confronted with infections which only respond to expensive or toxic drugs, or for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections pose an increasing burden on health care systems worldwide, but have the greatest impact on countries with limited resources. WHO recognizes that the pace of development of new antimicrobial agents has slowed dramatically; effective vaccines for many important pathogens will not be available in the near future; and funding for laboratories engaged in basic research in antimicrobial resistance, and preventive and therapeutic modalities, is inadequate.

The time for complacency has passed and there is a need for heightened vigilance and urgent measures.

A WHO Scientific Working Group on the Monitoring and Management of Bacterial Resistance to Antimicrobial Agents met in Geneva from 29 November 1994 to 2 December 1994. Dr G. Torrigiani, Director of the Division of Communicable Diseases, opened the meeting on behalf of the Director-General.

The Scientific Working Group comprised professionals from the fields of clinical medicine, research and public health from 24 countries, representing all WHO regions, including the heads of 11 WHO Collaborating Centres. The meeting was also attended by representatives of the pharmaceutical industry.

Dr J. Acar was elected overall Chairman of the meeting, with Dr J. Hughes and Dr T. O'Brien as Vice-Chairmen.

The objectives of the meeting were:

- to review the current status of the nature and consequences of antimicrobial resistance
- to make recommendations on how to:
  i. minimize the consequences of drug resistance
  ii. influence the complex process of spread of resistance
  iii. monitor resistance locally, nationally and globally.

2. The nature and costs of resistance

Antimicrobial agents have become an integral part of human medicine. However, during the last three decades, many bacteria have become resistant to them. Today, some organisms in both
developed and developing countries are resistant to practically all clinically useful antibacterial agents and antimicrobial resistance is now a major health problem in many countries.

2.1 A brief review of bacterial resistance to antimicrobial agents

Resistance to β-lactam drugs can be mediated either by β-lactamases or by changes in the organism’s penicillin-binding proteins. While β-lactamases are present in both Gram-positive and Gram-negative organisms, resistance mediated by changes in penicillin-binding proteins is primarily important in Gram-positive organisms. Aminoglycoside resistance can be caused by: enzymes that modify the drug; reduced uptake by the bacterium; or changes in ribosomal proteins that reduce or prevent binding of the drug to the active site. Genes encoding aminoglycoside resistance are commonly found on plasmids and transposable elements. Fluoroquinolone resistance is mediated by decreased uptake of the drug into the bacterial cell, or by changes in the DNA gyrase subunits. Dramatic increases in fluoroquinolone resistance in strains of methicillin-resistant *Staphylococcus aureus* have been observed when fluoroquinolones are used extensively for control of staphylococcal infections. Alteration of the target site is an important mechanism of resistance for macrolides (such as erythromycin), clindamycin, tetracycline, glycopeptides (such as vancomycin), and rifampin. Enzymatic inactivation is important for chloramphenicol and eventually in macrolides. Finally, trimethoprim and sulfonamide resistance usually occur through acquisition of new genes that encode alternate metabolic enzymes that are insensitive to the action of these drugs.

Many of the genes that mediate resistance to antimicrobial agents are linked together on plasmids or transposable elements. Thus, selection of one resistance marker through antimicrobial use can result in the presence of multiple resistance genes in the bacterial strain. Clusters of genes mediating resistance have been observed in up to 12 drugs linked together on a single plasmid in enteric bacteria. In staphylococci and in some Gram-negative organisms, resistance genes may be coupled with DNA encoding heavy metal resistance. Thus, the presence of mercury, cadmium or other heavy metals in the environment can also encourage the proliferation of organisms containing antimicrobial-resistance genes.

2.2 The economics of resistance

While our understanding of the mechanisms of resistance seen in bacteria has progressed significantly over the past two decades, our appreciation of the economic impact of resistance on a community, or a nation, is only just beginning. Current data suggest that bacterial resistance to antimicrobial agents is not only a serious threat to human health, but a significant economic threat as well. The number of individuals who develop disease (morbidity), and the number that die from disease (mortality) caused by resistant organisms, is only one part of the economic equation. Other factors to be considered include: the increased cost of health care, longer hospital stays, the need for more expensive drugs for treatment, and the increased number of diagnostic tests; the loss of productive work by individuals or their family members who are ill; and the increasing number of people who will be infected by individuals with resistant organisms who remained infectious while receiving ineffective therapy. Unfortunately, little data is being collected in hospitals on the economic cost of resistance, and even less data collected on the costs associated with community-acquired infections. In addition, the loss of food animals and livestock due to diseases caused by resistant organisms that fail to respond to traditional therapy must also be taken into account.

2.3 Epidemiology of resistance

Today, microorganisms resistant to multiple antimicrobial agents are becoming more common as causes of both hospital-acquired and community-acquired infections. For example, *S. aureus* strains susceptible only to vancomycin, and enterococci resistant to all clinically useful drugs have been isolated from hospitalized patients in many countries. Strains of *Streptococcus pneumoniae* also resistant to all drugs except vancomycin have been isolated from community-acquired infections on several continents. Only experimental drugs, or unproven, often more toxic
combinations of drugs, are available to treat patients with these multiple resistant infections. Since vancomycin resistance is transmissible in enterococci, the potential for development of vancomycin-resistant *S. aureus* strains clearly exists. The pool of genetic information available to microorganisms enabling them to resist antimicrobial agents is quite large, and new genes are continually being discovered. Thus, the continual development of novel multiple resistant bacterial pathogens is inevitable.

2.4 The lack of new antimicrobial agents

The increase in the number of drug-resistant bacteria has not been matched by a parallel increase in the arsenal of antimicrobial agents used to treat infections. On the contrary, development of new antimicrobial agents has slowed dramatically over the past decade. The use of antimicrobial agents for inhibiting bacterial pathogens in animals, plants and fish, and for promoting livestock growth, has led to the use of large quantities of antimicrobial agents outside human medicine. This widespread use has resulted in a very effective global programme of selection for resistance organisms. The key question today is how to dissipate the selective pressure that leads to the development and spread of resistant organisms. Finding an answer to this has now become critical.

2.5 Selective pressure and population genetics

It is assumed that bacteria have to expend extra energy to maintain antimicrobial resistance genes, particularly if they are located on plasmids. This biological cost, or the reduced fitness imposed by carrying additional plasmid DNA, can be estimated in the laboratory, and has been found to vary for different organism/plasmid/resistance gene combinations. While it was once believed that this additional energy burden reduced the pathogenicity of multi-resistant organisms, this is now known to be untrue. However, given the opportunity, bacteria will eliminate at least some types of resistance plasmids that are not under positive selection. Experimental data suggest that, in some cases, even in the total absence of selective pressure, resistance genes on plasmids are not lost immediately from a population because little energy is required for the organism to maintain the plasmids on which the genes reside. Thus, resistance may be maintained for a number of generations, even in the absence of antimicrobial use. However, data gathered on a number of plasmids suggest that this is probably the exception and not the rule. The reduction of selective pressure by the reduction of antimicrobial use may still be of benefit.

Since it is not feasible to withdraw antimicrobial agents entirely from use in human medicine, more selective use must be advocated in order to reduce selective pressure. Similarly, more prudent use of antimicrobial agents should be made in veterinary medicine, animal husbandry, and agriculture and aquaculture.

2.6 The search for new anti-infectives

There are a limited number of ways to kill a bacterial cell. Antibacterial agents directed to the enzymes involved in cell wall, protein, and nucleic acid synthesis, or those mediating a variety of metabolic pathways, have, on the whole, been highly successful for five decades in controlling infectious diseases. Unfortunately, subsets of bacteria have developed resistance to all of these agents, and the development of new antibacterial agents based on the mechanism of pathogenicity or molecular modelling of intracellular target sites will not produce new agents for several years. The lack of new ways of inhibiting bacterial growth underscores the importance of preventing disease through increasing immunization coverage with existing vaccines, and through the development of newer, more effective and safer vaccines. In addition, several older forms of therapy, including bacterial interference, serum therapy, and the use of bacteriophages to kill organisms, may be worth reconsidering.
2.7 The clinical impact of resistance

Only recently drug resistance has become a concern to the practising physician. There appears to be little change in the prescribing habits of physicians - even in geographic regions where resistance has been recognized. Researchers and epidemiologists are beginning to understand that resistant organisms increase morbidity and prolong epidemics, primarily because the lack of effective therapy leads to more people being exposed to individuals with disease, which in turn leads to increased colonization and infection, with increased mortality, particularly in immunocompromised patients.

In order to reduce the clinical impact of resistance both in hospitals and the community, the problems that cause delays in placing patients with infectious diseases on effective therapy must be identified and corrected. Lack of laboratory data, when antimicrobial susceptibility tests are not performed on clinically significant organisms; inadequate access to laboratory data by physicians, due to outmoded communication systems or lack of computer terminals on hospital wards; no access to antimicrobial agents with extended-spectrum activity, as occurs in some countries; and, non-compliance of patients, must all be considered and investigated. The need for better education of physicians and hospital administrators about resistance is important if it is going to be reduced in hospitals. The cost of better infection control programmes in hospitals is likely to be much less than the increasing cost of resistance. In the community, a reassessment of therapeutic regimens is in order, since the benefits of empiric therapy (for what may well be non-bacterial infections) do not necessarily outweigh the cost of resistance.

Finally, clinical microbiologists must be educated on the need for rapid, accurate testing and reporting of antimicrobial susceptibility testing data, since these data serve not only to guide therapy but act as a sentinel for the emergence of novel resistance in the hospital and community.

3. Recent increases in resistance

3.1 Beta-lactamases

Since their discovery in 1983, there has been a rapid increase in the number and variety of plasmid-mediated extended spectrum β-lactamases. There are now 26 unique derivatives of the TEM β-lactamases and 5 of the SHV variety. Most of the bacteria involved are *Klebsiella pneumoniae*, frequently isolated from nosocomial outbreaks in many countries where around 15% of such hospital isolates are resistant. New mutant type β-lactamases have appeared in the same institution and sometimes in the same patient. Both single-point mutations and gene recombinations appear to be involved. The threat of incorporation of chromosomal genes for even broader spectrum β-lactamases into plasmids has occurred. In Japan, a strain of *Pseudomonas aeruginosa* with a plasmid-mediated β-lactamase conferring resistance to all β-lactams, including imipenem and meropenem, has been reported. In several hospitals there has been spread to *Serratia*. In France, Scotland and Spain, a new class of TEM-derived plasmid-mediated β-lactamase giving resistance to β-lactamase inhibitors, but not the oxyimino-β-lactams, has been described.

3.2 Aminoglycosides

Aminoglycoside-resistant mechanisms were studied in more than 11,000 resistant isolates from 154 hospitals in North, Central and Southern Europe, Latin America, South America, South Africa and the Pacific area. The phenotypic resistance pattern to 12 selected aminoglycosides was compared with results using 19 aminoglycoside resistance gene probes and the results were compared to earlier studies. Using multiple gene probes, it was shown that multiple mechanisms causing resistance to a range of aminoglycosides occurred. Multiple mechanisms (2 or more) were common in *Citrobacter*, *Enterobacter* and *Klebsiella* (40%) in Europe and Latin America - sometimes 3 (5.7%) or even 4 (0.35%) mechanisms occurred. Similar frequencies occurred in *Providencia* (32%) and *Serratia* (45%) but were less common in *Escherichia* (22%) and *Proteus*. Very high incidence of multiple mechanisms (50%) were found in isolates from Greece, Turkey
and Latin America. In *Pseudomonas* and *Acinetobacter* incidences of 37% and 74% were common. All these results contrast with lower incidence in earlier surveys.

The situation in *Citrobacter*, *Enterobacter* and *Klebsiella* is indicative of the complexity of the problem where, in addition to the older mechanisms ANT (2")-I and AAC (3)-II, the two newer mechanisms AAC (3)-I and AAC (6")-I were found in >40% of strains and usually in multiple combinations. Since AAC (6")-I causes resistance to tobramycin, netilmicin and amikacin, broad spectrum aminoglycoside resistance was common. Similar multiple combinations of mechanisms have been found in *Providencia*, *Serratia* and *Pseudomonas*. In the latter the presence of permeability resistance in over 50% of isolates led to very high broad spectrum resistance rates.

The above phenomena have led to changes in the clinical effectiveness of the various aminoglycosides. Earlier isolates were only resistant to gentamicin and tobramycin but, in the present surveys in many parts of the world, there was increasing resistance to netilmicin and amikacin - as high as 66% to 97% in Greece, Turkey and Latin America.

### 3.3 Trimethoprim

Plasmid-mediated sulphonamide resistance is due to two genes but that for trimethoprim (TMP) has now reached 17 and most of the genes are on transposons. Although there has been a diminished use of sulphonamides in some countries, the genetic determinants of resistance are still very common, probably related to the spread of transposons.

In the 1970s, TMP-resistance in *Escherichia coli* from urine samples was about 10% but by the 1980s had reached 15% to 20% simultaneously in many countries. In the developing countries of Latin America and Asia, over 50% of isolates of *E. coli* and *K. pneumoniae* are resistant whereas in Northern Europe and the USA lower incidence occurs. Very high incidence of TMP resistance has been reported in *Shigella*.

The genetic linkage of SUL- and TMP-resistance genes invalidate the concept of using TMP-SUL combinations to minimise the development of resistance. There are no signs that removal of the sulphonamide or trimethoprim pressure is having any immediate effect.

### 3.4 Quinolones

In 1990-91, a community-based study showed that more than 98% of Gram-negative bacteria in Europe and the USA were fully susceptible to fluoroquinolones, whilst 7 to 14% were resistant in South American countries. Epidemics of fluoroquinolone-resistant strains of *Salmonella* and *Shigella* have not been reported but there have been resistant strains reported from individual patients. High rates of *Campylobacter jejuni* resistance have been detected in some countries, as in Spain. Methicillin-susceptible *S. aureus* (MSSA) are generally susceptible to quinolones. On the contrary, Methicillin-resistant *S. aureus* (MRSA) developed resistance very quickly, and the prevalence of resistant strains is very high, reaching 98% in certain hospitals in France. In *S. pneumoniae*, few resistant strains were reported with dissociated patterns of resistance to different compounds.

For Gram-negative nosocomial pathogens, the range of fluoroquinolone resistance varies from 5% in *E. cloacae* to 33% in *Acinetobacter* and, in general, the incidence is higher in Europe than in the USA. In France, in *P. aeruginosa* the incidence is particularly high (35%), especially in Intensive Care Units. In the last few years the emergence of a high level fluoroquinolone-resistant *Enterococci* has been reported.

The epidemiological observations show a striking difference in the incidence of fluoroquinolone resistance when community acquired infections are compared with nosocomial infections. In the community, epidemics have not occurred, but resistance is emerging in some countries, as in Spain.
However, in hospital settings, outbreaks of resistant strains have been observed. A particular problem which needs evaluation is the impact of the veterinary use of quinolone drugs.

3.5 Methicillin-resistant *Staphylococcus aureus*

Following the introduction of methicillin, the first isolates of methicillin-resistant *S. aureus* (MRSA) were made in 1961 in the UK and reports from other European countries, Asia, Australia and South Africa soon followed. Small outbreaks occurred in individual hospitals where the MRSA were multi-resistant, especially to penicillin and tetracyclines. The strains were mainly phage group III. During the 1970s, the incidence of MRSA decreased in most countries and the decreasing use of streptomycin and tetracycline may have contributed to this, possibly associated with the disappearance of specific phage types.

In the late 1970s and early 1980s, strains which were multi-resistant, often including gentamicin, were isolated in many countries, initially in Australia, Ireland and the USA. Some strains were phage group III but most could not be typed using conventional typing sets. They were highly transmissible and efficient colonisers, but of variable virulence. Previous non-specific antibiotic therapy was an important risk factor in individual patients. However, in Denmark and the Netherlands preventive measures, including well implemented antibiotic policies and early detection of multi-resistant strains, have limited the spread and prevented major outbreaks.

In the late 1980s, a new phage type (16) appeared which has now acquired ciprofloxacin resistance controlled by transposon. The spread of MRSA might be explained by the influence of antibiotic selective pressure on a naturally resistant strain initially present in one or a few countries. A more likely explanation is the occurrence of genetically similar strains in all or most countries, with antibiotic therapy selecting epidemic strains and subsequent horizontal spread. It is unlikely that inter-country or inter-continental spread was a major factor; the spread of the organism, and not genetic transfer of resistance between organisms, was the relevant factor.

3.6 Beta-haemolytic *Streptococci*

A recent resurgence of group A streptococcal infections - for example, acute rheumatic fever in North America since the mid 1980s and the apparently increasing incidence of serious systemic group A infections including toxic shock syndrome - has focused attention on the possibility of antimicrobial resistance. To date, there has never been a penicillin-resistant group A streptococcus from a clinical source. However, the reports of failure to eradicate the organism from the upper respiratory tract generated concern, although many of the reported failures occurred in carriers. In the USA, between 1983 and 1992, a study was made of 300 clinical isolates from patients in 31 states. The strains belonged to more than 20 different group A serotypes and included 43 isolates from patients with severe systemic infections. The MIC$_{90}$ for penicillin was 0.012 mg/ml, indicating no major change in the *in vitro* effectiveness of penicillin. Less than 5% of strains were "resistant" to erythromycin and this should be compared with a report from Finland of over 30%. None of the strains showed resistance to clindamycin. Macrolide resistance is not of clinical importance in most countries. The erythromycin resistance was not associated with specific serotypes. Resistance to tetracyclines was 10%, which is much less than reported several decades ago, and no true resistance to the cephalosporins was found. The results showed that quinolones should not be used for group A streptococcal infections. Studies on the strains from severe or invasive disease suggest that the clinical course is not related to antimicrobial resistance and that this is not a problem for the treatment of group A streptococcal infections, even though some outbreaks have occurred due to resistant strains.

*Streptococci* of group B (*S. agalactiae*) remain a cause of serious infections in neonates and less commonly in adults, but reports of antimicrobial resistance are few. In one study a high incidence (90%) of resistance to gentamicin was found, as well as "intermediate susceptibility" to erythromycin, clindamycin and cefoxitin. One fifth of strains were said to be multi-resistant.
Another, more recent, study in Spain has found 2% of strains with "intermediate sensitivity" to penicillin and 8% to ampicillin. The clinical relevance of these data remains to be substantiated.

Whilst group C and G streptococci tend to have higher MICs for penicillin than do Group A strains, there has not been a significant amount of resistance in clinical isolates.

Antimicrobial resistance in group A streptococci does not yet constitute a major problem either in clinical practice or epidemiological settings but it is prudent to continue surveillance.

3.7 *Streptococcus pneumoniae*

The first clinical isolate of *S. pneumoniae* resistant to penicillin was described in 1967 in New Guinea and, from then until 1977, sporadic resistant isolates were identified in various parts of the world. In 1977 outbreaks due to *S. pneumoniae* resistant to penicillin and also chloramphenicol, tetracyclines, erythromycin, clindamycin and sulphonamides occurred in hospitals in South Africa. Some strains were also resistant to rifampin. The mechanism of penicillin resistance was due to the reduction in the affinity of the penicillin binding proteins (PBP) on the bacteria. Molecular studies showed that the resistant isolates represented genetically distinct clones of pneumococci. Most resistance genes are chromosomal and very stable even in the absence of selective antibiotic pressure.

Following the 1977 outbreaks in South Africa, penicillin resistant *S. pneumoniae* have been isolated on a global basis. Such strains have an increased resistance level to penicillin, exhibit multiple resistance, spread widely, possess high carrier status and maintain their stability in the absence of selective antibiotic pressure. In the 1990s, the current penicillin-resistant isolates frequently show resistance to other antibiotics such as chloramphenicol, trimethoprim, sulphonamides, tetracyclines, erythromycin and aminoglycosides.

At least two epidemiological scenarios have occurred. In the first, the bacteria have increased their penicillin-resistance levels through sequential genetic events which involved the acquisition of multiple drug resistance. The second scenario involved the importation of a resistant clone from a geographically distant location. An example was the appearance and increase of capsular type 6B *S. pneumoniae* in Iceland at the end of the 1980s, apparently by travellers returning from Spain. The extensive global spread of serotype 23F has also been demonstrated and again Spain has been proposed as the origin of this particular clone.

More recently, strains of penicillin-resistant *S. pneumoniae* with resistance to third generation cephalosporins have been reported; vancomycin is still effective, but is used in more serious infections. The possibility of *S. pneumoniae* becoming resistant to vancomycin is of great concern. The appearance of multiple drug resistance in a major Gram-positive pathogen, associated with a very limited understanding of the pathogenesis and epidemiology of the disease, presents a major problem.

3.8 *Enterococci*

Enterococci are an increasing cause of nosocomial infections and high-level resistance to penicillins, aminoglycosides or glycopeptides has been recognized. An overall increase in the incidence of penicillin resistance in enterococci has been reported and it is mainly due to the spread of *Enterococcus faecium*. Resistance may be due to over production of PBP5 or production of β-lactamases which may be combined with a high-level resistance to aminoglycosides. Such strains have occurred in Argentina, Lebanon and the USA. Aminoglycoside resistance is due to a bifunctional modifying enzyme and high incidence (20% or more) has been reported in various countries.
Resistance to glycopeptides occurs in two phenotypes (Type A and Type B). Type A, mainly *E. faecium*, is inducibly resistant to high levels of vancomycin and teicoplanin. This resistance is due to self-transmissible plasmids and has a major epidemic potential. The genes are on a transposon (Tn 1546) and synthesis modified peptidoglycan precursors. Genetic studies indicate that, in Europe, the problem is not due to the clonal dissemination of a single strain but that transposon plays a major role in the spread of glycopeptide resistance in enterococci. The strains occur widely in human carriers, farm animals and waste water. The high incidence of Type A resistance in some countries and hospitals in the USA is partly due to epidemic spread of resistant strains. Some strains cannot be classified as Type A or B and in some outbreaks more than one strain is involved. Type B phenotype strains may be *E. faecium* or *E. faecalis* and are inducibly resistant at various levels to vancomycin, but not to teicoplanin.

The combination of penicillin resistance and glycopeptide resistance in a single enterococcal strain is a major concern and may cause infections increasingly difficult to treat and to control.

3.9 *Neisseria*

The incidence of penicillin-resistant *Neisseria gonorrhoeae* may be as high as 50% in some countries (Taiwan and the Philippines) but in the USA and North Western Europe it is low (5%). Tetracycline-resistant strains have spread in some countries in South America and Africa but this drug is not used in Europe for gonorrhoea. Spectinomycin was the drug of choice for penicillin-resistant infections and, although resistance was first reported in 1981, it is still rare. Resistance to the quinolones (ciprofloxacin) is uncommon, usually of low level and treatment failures are rare. Ceftriaxone, ciprofloxacin and spectinomycin remain efficient for the treatment of gonorrhoea worldwide. WHO has established a global surveillance network.

*Neisseria meningitidis*. Most recent epidemics were due to strains resistant to sulfonamides. Less susceptible strains to penicillins (and other β-lactamases) have been reported from different countries, MIC being 4 to 16 times higher than usual strains. Changes in PBP were documented.

3.10 Anaerobes

Multiple resistance has been reported in several epidemiological settings - such as individual hospitals and different geographic areas. *Bacteroides fragilis* is most frequently involved. The patterns have also been related to antibiotic prescribing regimes and include resistance to β-lactam antibiotics, tetracyclines, clindamycin and 5-nitroimidazole. Metronidazole and chloramphenicol remain highly effective.

Beta-lactam resistance may be due to penicillinases, cephalosporinases and metallo-β-lactamases which hydrolyse carbapenems. In bacteroides, tetracycline resistance is by ribosomal protection encoded by tetQ, whilst in *Clostridium perfringens* it depends on tetracycline efflux encoded by tetP. Clindamycin resistance is mediated by ribosomal modification and nitroimidazole resistance is multi-functional. Many resistance determinants are located on mobilizable or self-mobilizable plasmids, and transposons which can integrate into plasmids or chromosomes may be involved. All this increases the likelihood of the appearance of multi-resistant organisms, and new antimicrobial agents will certainly be needed.

3.11 Tuberculosis

Dramatic outbreaks of multi-drug-resistant tuberculosis (MDR-TB) have occurred in HIV-infected patients in the USA, and high mortality and significant nosocomial transmission have been features often associated with delayed diagnosis, inappropriate therapy and poor isolation facilities. Indications are that MDR-TB is a problem in both immunocompetent and HIV-infected populations. Poor surveillance data and laboratory facilities do not allow an accurate assessment of the problem in many countries, but the evidence suggests that resistance is emerging worldwide. The highest incidence of resistance to isoniazid plus rifampin, often with resistance to other drugs,
has been reported in Los Angeles (11%), New York City (30%), Argentina (10%), Chile (12%) and Korea (14%). In many countries, resistance to the drugs singly may be as high as 21% for isoniazid in Los Angeles or 42% in Korea, 14% for rifampin in Korea and 19% for streptomycin in Korea. In contrast, in England and Wales, the incidence of resistance to all drugs is low. Improved therapy of MDR-TB requires novel compounds to support current second-line drugs. If worldwide control is not effective, worsening drug resistance and high morbidity and mortality will occur. WHO is seeking to enhance worldwide surveillance of MDR-TB.

3.12 Enteric infections

Antibiotics are frequently used unnecessarily for the treatment of diarrhoea. Antibiotic therapy is indicated for invasive bacterial disease such as typhoid, shigellosis, and infections due to invasive *E. coli*. In cholera, antibiotic treatment shortens the purgation stage, reduces the bacterial excretion, and hence diminishes transmission.

In South-East Asia, the incidence of *Salmonella typhi* strains which are resistant to chloramphenicol, and often to tetracycline and ampicillin as well, may be high (50% or greater in some countries). The drugs of choice are now the fluoroquinolones, except in young children, where alternate drugs such as ceftriaxone may be necessary.

The problem of antimicrobial resistance is most acute for shigellosis. Multi-antibiotic resistance is now at a high incidence in many developing countries and the problem is most worrying in *Shigella dysenteriae* type 1 (Shiga's bacillus). Naldixic acid became the drug of choice but resistance now often occurs. The fluoroquinolones are the only effective agents but these are also expensive and are not yet formally approved for use in children. Mecillinam is appropriate for children, but is not generally available.

Over the past several years, multiple drug resistance has developed in *Vibrio cholerae* serogroup 01 in Asia and Africa. Whereas tetracycline was previously indicated, a high percentage of strains in some areas are now resistant and other agents, such as cotrimoxazole, furazolidone or erythromycin are needed. *V. cholerae* O139 remains sensitive to tetracycline, but all strains are resistant to cotrimoxazole. In cholera, antibiotic use is only adjunctive to adequate rehydration.

Antibiotic treatment is not needed for mild cases of travellers' diarrhoea due to enterotoxigenic *E. coli*. For severe cases in adults, antimicrobials are useful. Because of increasing antibiotic resistance, doxycycline is no longer recommended. The drugs of choice now are the fluoroquinolones. The need for the use of antibiotics in campylobacter infections is questionable, but erythromycin has been used. In some countries of Northern Europe, strains resistant to the fluoroquinolones have been reported and this may be related to their use in food animals, particularly poultry.

The indiscriminated use of antimicrobial drugs for diarrhoeal disease has led to a high incidence of multi-resistant strains and caused a great problem, especially in the developing world. Since most resistance in enteric bacteria is plasmid-mediated, multi-resistance will continue to spread as long as this selective pressure remains.

4. How to modify conditions to limit resistance

4.1 In bacteria of human populations

Infectious diseases are the leading cause of death worldwide. Mankind continues to confront new diseases and syndromes caused by infectious agents and to be challenged by the evolution of microbes. Today, antimicrobial resistance is one of the major global threats.

Recent examples of important outbreaks of bacterial infections include the cholera epidemics in South America and South Asia, an epidemic of multi-drug resistant (MDR) *S. dysenteriae*
(Shiga's bacillus) infection in addition to cholera in refugee camps in Rwanda, and the recent plague epidemic in India. Examples from the United States include a multi-state outbreak of foodborne *E. coli* O157, the waterborne outbreak of cryptosporidiosis in Wisconsin, detection of a new rodent-borne hantavirus, continued challenges of MDR tuberculosis, the increase of drug-resistant *S. pneumoniae*, and nosocomial infections caused by vancomycin-resistant *E. faecalis*. In the future, it is likely that the clinical manifestations of diseases will continue to change, diseases will appear in new geographical areas, microorganisms will continue to evolve, and drug resistance will increase.

The disease prevention strategies of the US Centers for Disease Control and Prevention include: (1) rapid national and international detection and response to new, reemerging, and drug-resistant diseases; (2) applied research in disease diagnosis and prevention; (3) better communication and implementation of prevention strategies; and (4) stronger links between local, state, federal, and international public health agencies to support disease tracking and prevention and control programmes.

Addressing the increasing challenges posed by drug-resistant organisms is a major focus of the plan and is addressed under each of the four goals. Strategies include strengthening national and global surveillance, development of improved diagnostic techniques, improving antimicrobial usage, development of new antimicrobial agents, development of new and improved delivery of existing vaccines, development and evaluation of prevention strategies, and professional and public education.

4.2 In bacteria of animals and other reservoirs

In veterinary medicine, antimicrobial agents are used for therapy, prophylaxis and nutrition. In each case selective pressure is imposed on bacteria and antimicrobial resistance is selected. This increase has been found for example in *Salmonella* spp. after prophylactic use of gentamicin in turkey rearing and the therapeutic use of quinolones in cattle and poultry.

In order to prevent the spread of resistant microorganisms from animals into the environment and to man, the use of antimicrobial agents for nutritional purposes should be restricted to those agents not used in human medicine, and not causing cross-resistance to those used in human medicine. Prophylaxis should not replace good animal care, and antimicrobial therapy should be based on accurate diagnosis of infections.

In the UK, implementation of the 1969 recommendations of the Swann Committee led to a temporary drop in the number of MDR Salmonella cases. However, overuse of prophylaxis in animals is still a concern.

It was suggested that WHO should organize the monitoring of antimicrobial resistance in animal husbandry. Research was also needed on the prophylactic use of bacteriophages in the treatment of bacterial infections.

4.3 In bacteria in special environments

Hospitals worldwide are facing an unprecedented crisis due to the rapid emergence and dissemination of antibiotic-resistant bacteria. Strains of *S. aureus* resistant to methicillin are endemic in numerous hospitals, leaving vancomycin as the sole effective agent. Now, strains of enterococci resistant to vancomycin have appeared, due, in part, to the intensive selective pressure of vancomycin use.

The reasons for this development include improper use of antimicrobial agents and failures in hygienic measures, such as handwashing and the use of gloves. The key problem in developed countries is how to present this problem to hospital managements. In developing countries, there
is still a lack of basic infection control systems and major problems are caused by the inappropriate use of antimicrobials.

Although it may appear that many infection control measures are suitable only for industrialized countries, in fact, the most critical measures are inexpensive and can be applied even in hospitals where resources are severely limited.

There is a need for competent people to train hospital personnel. Meanwhile, close cooperation is needed between staff in the clinical microbiology laboratory, infectious disease control and hospital infection control in order to improve hospital hygiene measures.

4.4 Perspectives on chemotherapy

The pharmaceutical industry has responded to the development of antimicrobial resistance in three principal ways: continued chemical modification of existing agent classes; interference with resistance mechanisms to increase target access; and searching for agents with novel mechanisms of action.

Synthetic chemistry has yielded improvements in nearly all existing classes of agents used clinically. Beta-lactamase inhibitors are a good example of interference with resistance mechanism. However, other clinically useful agents have not yet emerged. Most agents with other mechanisms of action have not been pursued due to lack of advantages over existing classes. In addition, potential new classes of agents would not necessarily supplant existing classes.

Carbapenems are still the antibacterial agents with the widest in vitro spectrum. New narrow spectrum agents, such as aztreonam, have not been very successful, and are therefore not very attractive for development. Immunomodulators may offer a possible way forward. A helpful improvement in the increasing problem of multi-drug resistance would be closer links between research carried out by universities and that of the pharmaceutical industry. It was pointed out that the lack of effective antimicrobial agents leads to the use of more toxic compounds.

4.5 Small peptide antibiotics

There are over 100 small cationic antibacterial peptides which have been described at the present time. These peptides have been found in bacteria, plants, insects, amphibians, crustaceans, mammals and humans. A variety of different peptides have been produced using recombinant DNA technology. They demonstrate a rapid bacterial killing, a self promoted uptake as well as enhanced uptake of lysozyme and certain antibiotics. The studied peptides also bind bacterial endotoxin. In addition to bacteria, they are also effective against fungi.

4.6 Anticipation of future patterns of drug resistant infections

The spread of microbial drug resistance has always been faster than the progress of research in the area. The Minax Research Center will explore methods for better prediction of future trends and emergence of novel resistance determinants through the study of potential pathogens selected under controlled experimental conditions.

5. How to monitor and manage resistance nationally and locally

A series of reports was presented from selected countries on the surveillance, monitoring and management of antimicrobial resistance.
5.1 Reports from selected countries

Algeria

The Pasteur Institute of Algeria is a national reference laboratory, where drug resistant strains from private and public hospitals are sent. Communication with health authorities is conducted by telex or fax and periodic reports are published. A computer-based surveillance system has not yet been introduced.

It was reported that, up to September 1994, eight resistant strains of *V. cholerae* *el tor* had been seen in 1970, 1979, 1980 and 1986. All the strains identified harboured a group C plasmid. Since September 1994, an epidemic of *V. cholerae* *el tor* resistant to streptomycin, chloramphenicol, tetracyclines, trimethoprim, sulfonamides and fusidic acid has been identified in eastern Algeria.

Two strains of *S. typhi* harbouring group N plasmids were identified in 1993. However, twelve resistant strains identified between 1972 and 1992 harboured plasmids which belong to different incompatibility groups. Recent isolates of nosocomial strains like *Salmonella* subsp mbdata and *Salmonella kedougou* have shown β-lactamase activity, including ESBL.

Resistance to oxacillin in *S. aureus* rose from 5.4% in 1991 to 20.3% in 1992. Increased resistance to aminoglycosides and macrolides has also been seen. No resistance to vancomycin or quinolones has been reported.

Canada

A national drug resistance survey was conducted in Canada from 1 February 1993 to 31 January 1994. Strains of *Mycobacterium tuberculosis* from a representative sampling were submitted by provincial laboratories to the National Reference Centre for Tuberculosis at the Laboratory Centre for Disease Control in Ottawa. Anti-tuberculosis drug resistance was confirmed in the national laboratory, using standardized methodologies. Of 520 strains examined to date, 34 were resistant to one or more drugs for an overall resistance of 6.6%. For single drugs, 2.9% were resistant to streptomycin and 1.2% to isoniazid. For multiple drugs, 1.7% were resistant to isoniazid and streptomycin, 0.4% to isoniazid and ethambutol, 0.2% to isoniazid, streptomycin and rifampin, and 0.2% to isoniazid, streptomycin, rifampin and ethambutol.

People's Republic of China

Since 1988, the People's Republic of China has been a member of the Surveillance System of Bacterial Resistance to Antimicrobial Agents of the WHO Western Pacific Region. In 1993, 6286 bacterial clinical isolates were collected from Shangai hospitals. Susceptibility testing was made using the Kirby-Bauer method. The indicator organisms and antibiotics used were those recommended by the WHO meeting of the Working Group on the Surveillance of Sexually Transmitted Diseases and Bacterial Resistance to Antimicrobials in 1991. It was found that:

- 95% of the *S. aureus* and 83% of the coagulase negative staphylococci produce β-lactamase. All staphylococci are highly susceptible to vancomycin, but 5% of the enterococci are resistant to it

- Rate of resistance to fluoroquinolones in *Shigella* spp is under 5%. More than 90% of *Salmonella* spp are still susceptible to chloramphenicol, ampicillin and contrimoxazole; very few fluoroquinolones-resistant strains are isolated

- Strains of *E. coli* are more resistant to gentamicin and quinolones than other Enterobactericeae. Strains of *N. gonorrhoeae* resistant to norfloxacin were reported.
Czech Republic

Regular monitoring of antibiotic resistance in the Czech Republic started in 1988. Data from 14 hospitals and 3000 strains are seen each year. An annual report is published by the National Reference Centre. The report contains information on the resistance of particular species to a standard set of antibiotics broken down by hospital, ward and specimen. Current data suggest overall that drug resistance is not yet a serious problem. Since 1989 there have been no restrictions on the import of antibiotics. Antibiotic centres have been established at most of the laboratories, in hospitals and at public health laboratories. The use of antibiotics is regulated through consultation with antibiotic centres, which are coordinated by the National Reference Laboratory.

Hungary

Since 1974, the National Institute of Hygiene has established a surveillance system, involving laboratories of the public health centres of 19 counties and the Central Hospital for Infectious Diseases. Data on drug resistance based on disk diffusion tests indicate that resistance to penicillin in pneumococci is between 20% and 40% and resistance in S. sonnei to the combination TMP-SXT is very high (over 80% in 1993). It was suggested that levels of drug resistance in Hungary are related to the inappropriate use of antibiotics. Efforts are made to involve hospital laboratories in the surveillance system.

India

In India, periodic reports are made on the extent of drug resistance. Current data include:

- *S. pneumoniae*: no resistance to penicillin reported between 1983 and 1994

- *Haemophilus influenzae* type b: 54% resistance to chloramphenicol, 46% resistance to penicillin and no resistance to cefotaxime

- *N. meningitidis*: no resistance to penicillin or chloramphenicol

- Group A streptococcus: no resistance to penicillin, erythromycin or chloramphenicol

- Multi-drug resistant strains of *S. pyphi*, resistant to ampicillin, chloramphenicol and trimethoprim, have emerged since 1989 with a maximum of 68% MDR strains observed in 1992. Since 1993, the prevalence of MDR has declined and currently is about 40%

- Slight decrease in resistance to ampicillin and nalidixic acid was seen in *Shigella* between 1983 and 1993

Russian Federation

The Russian National Centre for Surveillance of Antimicrobial Resistance has been functioning at the Central Research Institute of Epidemiology (CRIE) since 1986, in collaboration with specialized burns, septic, obstetrical and surgery-based hospitals in various regions of the former USSR. The Centre is responsible for: monitoring, staff training, collation and analysis of data using the WHONET, conducting genetic research and maintaining feedback with collaborating hospitals.

Analysis of the data base revealed that high activity towards *P. aeruginosa* was retained by amikacine (<1% of resistant strains); not more than 7% of *K. pneumoniae* were resistant to amikacine and cefotaxime; and no *E. coli* strains were found to be resistant to cefotaxime, polymixine and nalidixic acid.
Sweden

Annual surveillance of antimicrobial resistance is carried out in Sweden under the auspices of the Swedish Reference Group on Antibiotics. The majority of microbiology laboratories in Sweden participate in the surveillance studies and all use the disk diffusion method for susceptibility testing of clinical isolates. The 1994 surveillance includes 92,661 susceptibility test results from the 32 participating laboratories.

No penicillin resistance was noted among group A streptococci. This species showed 4.5% resistance to erythromycin, 0.2% to clindamycin and 6% to tetracycline. Among pneumococci, 3.4% were resistant to penicillin using the 1μg oxacillin disk. No vancomycin resistance was noted.

H. influenzae showed β-lactamase production in 10.5%. In addition, 2% of the strains showed chromosomally mediated resistance to β-lactams. Among K. pneumoniae strains, 11% were resistant to cefuroxime, 1% to cefotaxime and 7.7% to ciprofloxacin. P. aeruginosa was resistant in 1.8% to ceftazidime, 4.7% to imipenem, 1% to aminoglycosides and 11.4% to ciprofloxacin.

United Kingdom

Surveillance of key pathogens is carried out by individual reference laboratories in the Public Health Laboratory Service (PHLS). The Meningococcal Reference Unit has observed a trend in 11,000 isolates tested over the last decade for a decreased penicillin susceptibility (without occurrence of resistance such as would demand a change of treatment policy), consistent levels of sulphonamide resistance (30%), but rare occurrence of rifampicin resistance and no quinolone resistance. The Gonococcus Reference Unit correlates antibiotic resistance in referred isolates with their geographical origin. New cases of tuberculosis are notified to the National TB Reference Laboratory, which checks the results in isolates showing primary resistance; such strains are still uncommon in the UK. The Anaerobe Reference Unit tests isolates submitted by 12 "sentinel" laboratories, in a rolling programme. Bacteroides spp. have shown consistent susceptibility to metronidazole and imipenem; C. perfringens isolates have been generally susceptible to favoured drugs (except tetracycline - 40% resistance).

The Antibiotic Reference Unit in the PHLS Laboratory of Hospital Infection monitors the levels and mechanisms of resistance in referred isolates, with currently a particular emphasis on methicillin-resistant S. aureus, S. pneumoniae, Streptococcus pyogenes and Enterococcus spp. These data are supplemented by surveys of referred unselected isolates by the PHLS network of 53 laboratories. In addition, clinical laboratories notify their susceptibility test results on isolates from bacteraemia and meningitis, to provide a large and geographically representative database for analysis. These data receive the validation that is essential for acceptance of such information from the results of the PHLS National External Quality Assurance Scheme (NEQAS), to which almost all UK laboratories subscribe (as well as many others in Europe). Typing data and antibiotic data are being merged in the databases. The spread of specific epidemic clones, especially for certain epidemic MRSA, is well-established but will be enhanced.

Venezuela

Since 1988, a National Surveillance system has been in operation to monitor bacterial resistance to antimicrobial agents. By 1994, 19 hospitals were participating. Data are obtained from the laboratories using the disc diffusion method, according to NCCLS guidelines, and the results are published once a year. The objectives of the programme are: to report on drug resistance in Venezuela; to identify the underlying mechanisms of resistance; and to make recommendations on the use of antimicrobials on a local and regional basis.

Data for 1993 revealed that: oxacillin resistance is 18% for S. aureus and 47% for coagulase negative staphylococcus. 3% of S. aureus were resistant to vancomycin (NOT CONFIRMED by a reference laboratory). 53% of strains of E. coli were resistant to ampicillin, 17% to the
combination sulbactam-ampicillin and 35% to TMP-SXT. Introduction of ESBL was suggested by the marked increase of resistance to third generation cephalosporins in *K. pneumoniae*, between 1988 and 1993. Recent observations include 7% resistance to penicillin in *S. pneumoniae* and 26% in *N. gonorrhoeae*. In early 1994, a small outbreak of *N. meningitidis* group C with diminished susceptibility to penicillin (MICs 0.25 to 0.75), was observed and reported.

**Western Pacific Region**

Throughout 1990 and 1991, data on bacteria resistance to antimicrobials were obtained from focal point laboratories in 12 countries and areas, collated and distributed to focal point laboratories and all the laboratories participating in the international or regional quality assessment programme. This two-year exercise identified the technical and operational problems in the existing system of surveillance of antimicrobial resistance. On the basis of these findings, a restricted list of the most important pathogens causing community and hospital-acquired infections was formulated, and the most relevant antimicrobial drugs to be tested and reported for each category of bacteria was also compiled. Recommendations were made for improving the reliability and clinical usefulness of the regional surveillance system for antimicrobial resistance and the guidelines were updated.

Since 1992, the surveillance data from all participating countries have been collated and distributed. This feedback serves as a guide for the participating countries in the appropriate use of antibiotics.

The gonococcal surveillance scheme involves the participation of 15 countries in the Region and the establishment of a Regional Reference Centre for *N. gonorrhoeae* in the Microbiology Department of the Prince of Wales Hospital in Sydney, Australia. In 1992, a total of 600 strains was examined at the Reference Centre and the data were analysed and distributed. While the data received so far are useful, they represent a point of prevalence of the status of antibiotic resistance in the *gonococcus* within the Region. This information will become even more valuable when the study becomes continuous and the trends in antibiotic susceptibility patterns can be monitored and identified.

5.2 Information on WHO antimicrobial policy

WHO policy on drugs is based on the essential drug concept. Currently the WHO model list contains 22 well-established antimicrobial substances which are considered to cater for the health needs of the majority of the population. Additionally, there is a chapter on the need for reserve antimicrobials which are defined as those useful for a wide range of infections but, because of the need to reduce the risk of development of resistance and because of their relatively high cost, it would be inappropriate to recommend their unrestricted use. In order to promote the safe, effective, economic and rational use of these drugs and to prevent resistance to them, it has become crucial to develop a strategy on their use. This strategy should include:

- Information and prescribing guidelines - the WHO model prescribing information series
- Monitoring of patterns of drug resistance - prevalence of antimicrobial resistance and the usage of antimicrobials - should be encouraged
- Quality of antimicrobials must be reliably assured - priority being given to ensuring that available drugs conform to specified good manufacturing practices and comply with recognized quality specifications
- Continuing education of prescribers and the public must be assured - by the provision of treatment guidelines to the former, through responsible reporting in the lay press and accurate product labelling in the latter
- Control of promotional activities must be strengthened - national markets must be controlled through systematic registration of products and by adherence to WHO's ethical criteria for medicinal drug promotion.

5.3 WHONET

WHONET is an integrated system for collaborative surveillance of bacterial resistance to antimicrobial agents at local, national and global levels. It is based on a network of laboratories linked by a common software for analysing and sharing descriptions and susceptibility test measurements of each of their isolates and quality control test strains. A laboratory which does not have a computerized reporting system may enter such results into the WHONET programme on a personal computer. A laboratory which already enters its results into a laboratory information system may export them by a translation programme directly into the WHONET programme.

The WHONET software enables each laboratory to configure its result entry format to its own testing practices and to the specific patient locations it serves. The file format for all laboratories, however, is universal so that one analytical programme analyses results from any of the laboratories. The analytical programme has also been made microbiologist-friendly to make it easy for each participating centre to analyse its own results continuously and in multiple ways. WHONET thus empowers each user to understand and manage resistance locally.

The WHONET software also makes it easy for each laboratory to analyse the results of any or all other laboratories with which it shares data diskettes. Such networks are now being formed by local initiative in a number of countries, the most advanced being in Argentina and Venezuela. Such groups are encouraged to use the software to initiate their own research, to organize multi-centre testing of new antimicrobials, and to publish their own surveillance results.

As experience with WHONET has grown, its use for continuing local surveillance at each participating centre has come to be viewed as its major function, and large scale surveillance more a by-product. A high prevalence of resistance to an agent at a centre usually proves to be due to the spread of specific strains resistant to that agent, as well as to varying combinations of other agents. These need to be traced by local analyses, addressed by local infection control measures and antimicrobial usage practices. WHONET seems best used, not just to build a database, but to build a network of interested parties, sharing and interpreting a database and managing the problems it delineates.

The WHONET system was demonstrated at the meeting. Using computers provided at the meeting, participants were able to study details on the computer programmes and the different methods of analysis used.

5.9 The need to monitor and manage resistance locally

The need to manage and monitor resistance locally is based on the obligation of the clinician to provide the best treatment for the patient and to protect patients from resistant bacteria. To do this requires understanding of resistance, detailed information on current resistance problems locally, and the efforts of many health care workers coordinated to that information and understanding.

This need was not served by earlier concepts of surveillance. Each laboratory summarized its results and sent them to a centre for collation. Neither the local laboratory nor the centre had a database containing information about individual isolates. Now both may have such databases. Personal computers (PCs) make it easy to build a database on a PC in any laboratory. Copies of local databases using a common file format may be forwarded to a centre and aggregated for combined analysis effortlessly and without loss of detail.
Use of a common file format allows all the laboratories to use the same software to analyse their local results. Effort can thus be concentrated on designing and revising the one set of analytical programmes as experience grows to make it more user-friendly and its analyses more useful.

Experience with a network of clinical laboratories building and merging local PC-supported, isolate-based, test measurement-filing databases with a common format (see WHONET above) is generating additional insights into the surveillance of resistance. The analyses by each medical centre of its own results is emerging as more important than overview analyses of the aggregated database by the project centre. Each centre can see its results in terms of its susceptibility test performance, which needs continual review and quality control, its patient mix, its community, its nosocomial infection problems and its antimicrobial use. Local medical centres are in the best position to monitor and interpret their local results and to intervene and correct their problems.

Experience is also showing that it is not enough to have easy access to detailed information about resistance at a medical centre. Someone still has to watch, interpret and respond to it. This task involves several disciplines (e.g. microbiology, infection control, pharmacy, clinical services) and may fall between them and be overlooked at a busy centre. Antimicrobial resistance monitor/manager (ARM) is a term proposed for one or more individuals appointed by the centre responsible for monitoring and (to the greatest extent possible) managing antimicrobial resistance at a medical centre. The ARM's duties would be to:

- follow and understand current publications on antimicrobial resistance
- analyse and interpret local results continuously and thoroughly
- work with, coordinate efforts of the involved disciplines to elaborate, propose and implement strategies on issues such as antimicrobial usage and strain containment
- help the clinician provide the best treatment for the infected patient

The aim of redefining these tasks would be to realign and refocus attention on the details of the resistance problem locally and to mobilize new support for this mission.

6. Conclusions and Recommendations

6.1 General conclusions

Antimicrobial resistance represents a crisis at the present time. It stems from a wide range of problems, but there are a number of key factors. A primary one is the heavy usage of antimicrobial agents. Patients often have a poor understanding of the indications for antimicrobial therapy and unrealistic expectations. Sometimes drugs that have been appropriately prescribed are subsequently misused by the patient. The intense selective pressure resulting from antimicrobial overuse has been an important factor in the rapid emergence of resistance. The dissemination of resistant strains in hospitals and other institutional settings is largely attributable to person-to-person transmission, due to the inconsistent application of basic infection control techniques and treatment of patients not guided by susceptibility testing. Meanwhile, environmental contamination with antimicrobial-resistant pathogens adds another dimension to the problem of prevention and control. The impact of resistant organisms is sometimes exacerbated by the inappropriate and excessive use of invasive medical technology, which is often introduced without careful attention to infection control policies and procedures. In addition, in some countries, availability of antimicrobial agents without prescription is a major factor in their misuse. Elsewhere, the use of antimicrobial agents in animal husbandry, particularly for growth promotion and prophylaxis of infection, provides an additional selective pressure which encourages the emergence of drug-resistant organisms. Laboratory systems for detecting antimicrobial resistance
are inadequately controlled, understood and monitored. Finally, crude reporting systems often delay effective responses to emerging problems.

A coordinated multidisciplinary approach is required to tackle this problem. Prevention and control of the emergence and dissemination of antimicrobial-resistant organisms must be established as a strategic priority for international and national public health agencies, as well as for individual institutions and health care practitioners. Leadership and accountability must be assigned, and initiatives to control antimicrobial resistance linked to quality assurance activities. Appropriate resources must be allocated to those who have the responsibility to monitor and control resistance, and basic education provided for health care workers and the public.

Addressing the many challenges posed by emerging antimicrobial resistance requires a strategy at institutional, community, regional, national, and international levels. Partners in the development and implementation of such a strategy should include representatives from clinical and veterinary medicine, public health, microbiology, animal husbandry, the pharmaceutical, agriculture and aquaculture industries, as well as the behavioural sciences.

6.2 Recommended Plan of Action

Recommendations for WHO

a. Communicate the importance of the problem of antimicrobial resistance to developed and developing countries and other international health agencies:

- Use the *Weekly Epidemiological Record* and the *WHO Drug Information Bulletin* to report activities and updates from various programmes, and issue periodic reports of global trends in antimicrobial resistance and on specific emerging resistance problems

- Improve communication and collaboration among WHO programmes that address the issue of antimicrobial resistance, including hospital performance, quality assurance, specific diseases, essential drugs

- Facilitate interaction between government agencies, academic institutions, and the pharmaceutical industry to improve surveillance activities

- Encourage sharing of data among country-level agencies and organizations, and facilitate linkage of existing surveillance systems (WHONET, NNIS, SCOPE, CEMNET, etc.) using WHONET software

- Issue teaching materials and press releases on topics relating to antimicrobial resistance

b. Improve systems for surveillance of antimicrobial resistance:

- Assist nations in assessing status and specific needs of their laboratories for performing adequate identification and susceptibility testing of bacterial pathogens

- Distribute and facilitate the installation of WHONET software in laboratories to enable them to monitor their own results for test quality, for infection control problems, and for local trends in resistance, and to enable them also to merge their results into same-format isolate-based databases for detailed national and international surveillance of resistance

- Assist laboratories, through WHO Regional Offices, in the development of quality control and quality assurance programmes to help improve the accuracy of antimicrobial susceptibility testing methods
- Provide support and facilitate coordination between reference laboratories for better strain typing and other specialized procedures in order to better characterize the epidemiology of resistance

- Encourage the prompt reporting of culture and resistance data and analyses to clinicians, infection control personnel, and public health authorities, and prompt transmission of selected isolates to reference laboratories when appropriate

- Call attention to patterns of resistance in species of bacteria that may represent emerging epidemics, such as vancomycin-resistant enterococci, penicillin-resistant pneumococci, fluoroquinolone-resistant *Shigella*, multi-resistant *Salmonella typhi*, and others less obvious

- Develop an action plan for appropriate response to outbreaks of resistant organisms

- Identify funding sources to help implement the above recommendations

c. Develop recommendations to improve clinical use of antimicrobial agents and decrease selection of resistant bacteria

- Develop educational material including model guidelines to assist countries and their medical centres in developing and gaining acceptance for guidelines for appropriate selection and use of antimicrobial agents

- Promote policies for controlling the dispensing of antimicrobial agents, including designation by individual countries, of the categories and qualifications of health care workers allowed to prescribe antimicrobial agents

- Call attention to ethical standards for the promotion and advertising of antimicrobial agents as promulgated in WHO's ethical criteria for medicinal drug promotion

- Develop information systems for monitoring antimicrobial use and for providing feedback on individual prescribers and institutions

- Promote administrative systems for improving antimicrobial use, such as antimicrobial order forms and automatic stop orders, for prophylactic or empirical treatment

- Recommend that medical centres appoint antimicrobial resistance managers (ARMs) responsible for monitoring and integrating publications on resistance, local susceptibility test results and local antimicrobial usage, and for coordinating the efforts of pharmacy, microbiology, infection control and clinicians to improve use of antimicrobials locally

- Recommend that countries monitor and ensure the quality and potency of both imported and locally-produced antimicrobial agents

- Educate the public to modify attitudes to, and expectations of, health care workers to dispense unneeded antimicrobial drugs

d. Develop strategies to decrease the selection and transmission of resistant microorganisms in medical centres

- Establish the necessary programmes, authority and accountability, and provide appropriate resources to ensure that the detection, prevention and control of antimicrobial-resistant microorganisms is an integral part of national and institutional strategic goals
- Link the prevention and control of antimicrobial resistant organisms in hospitals to national and local quality assurance efforts; consider using infection control as a model in establishing quality assurance programmes.

- Develop methods and standards, as appropriate, for evaluating hospital infection and antimicrobial resistance control programmes, leading ultimately to a national accreditation systems for hospital infection control programmes.

- Establish policies and procedures for the prevention of transmission of resistant microorganisms in hospitals including hand hygiene, barrier precautions, and environmental control measures.

- Develop systems for detecting, transferring, discharging and readmitting patients with specified antimicrobial resistant microorganisms, that are applicable to both extended care and acute care settings.

- Develop educational programmes and hygienic standards for day-care and extended-care facilities.

- Develop programmes to train infection-control personnel emphasizing organization and responsibilities of infection-control programmes.

e. Develop strategies to decrease transmission of resistant microorganisms in the community and plans for responding to outbreaks of bacterial pathogens.

- Promote standards of hygiene in the community, including safe water and food hygiene.

- Support programmes to improve access to treatment and thus earlier detection and interruption of outbreaks of resistant bacteria.

- Emphasize the importance of early and continuing susceptibility testing during outbreaks of bacterial pathogens in order to select and facilitate delivery of the optimal antimicrobial agents and to revise them when needed.

- Encourage monitoring of the prevalence of resistant bacteria in the community, as in day care centres or in healthy untreated people.

f. Develop strategies to decrease the emergence and dissemination of resistant organisms in veterinary medicine and the environment.

- Require that antimicrobial agents for treatment of infections in animals be prescribed by qualified veterinary personnel.

- Ensure that antimicrobial agents are not used as a substitute for adequate hygiene in animal husbandry.

- Prohibit the use for growth promotion in animals of any antimicrobial agents used in human therapeutics or potentially selecting cross-resistance to antimicrobial agents used in human medicine.

- Discourage the unnecessary use of therapeutic antimicrobials for prophylaxis in food animals.

- Ensure that the general public is informed of the potential risks to humans of antibiotic use in animal husbandry, agriculture and aquaculture.
- Define acceptable levels of antimicrobial agent residues in food from animal sources and ensure compliance with national standards

- Develop national policies prohibiting the use of resistance reporter genes for deliberate release of genetic modified organisms

6. Support the development and evaluation of new preventive and curative modalities

- Seek funding for the development and evaluation of vaccines for a variety of bacterial pathogens

- Encourage the development of new antimicrobial agents

- Encourage further evaluations of alternative or augmentive therapeutics (non-antimicrobial agents) such as immunomodulators and anti-adhesion molecules

6.3 Recommendations for individual countries

   Acknowledge the global problem of resistance

- Encourage medical centre laboratories to develop isolate-based computer databases of their susceptibility test measurements in a common file format such as WHONET which can easily be monitored at each centre and aggregated into a national surveillance database

- Designate one or more laboratories to help other laboratories install and use the common software, to provide them with test strains and other support for improving their testing, and to manage and interpret with them their shared surveillance database

- Assess the quality, geographical distribution and professional microbiological support of existing microbiology laboratories, improve them where needed, and open new laboratories in underserved areas

- Integrate the work and the data of reference laboratories with that of other laboratories monitoring the spread of resistance

- Develop guidelines for use of antimicrobial agents, and encourage review and adjustment of these, and of antimicrobial formularies, to meet patients' needs as resistance changes

- Develop policies for use of antimicrobial agents in veterinary medicine and animal husbandry, and extend surveillance of resistance to animal isolates

- Adopt and promote, at a national level, the recommendations for WHO outlined in 6.2 above, particularly those under c, d, e and f

6.4 Recommendations for local hospitals and reference laboratories

Develop a plan to monitor and control resistance

- Implement a user-friendly, multi-analysis isolate-based computer system, such as WHONET, which allows detailed monitoring of local resistance and flags isolates or clusters of isolates that may represent emerging outbreaks of resistant strains

- Appoint an antimicrobial resistance manager (ARM) responsible for monitoring and interpreting local resistance and local antimicrobial use and for alerting and working with infection control, pharmacy, administrators and clinicians to refine and optimize antimicrobial therapy and to focus containment efforts
6.5 Research priorities for addressing the problem of resistance

- Develop simple and inexpensive tests to identify types of resistance that are difficult to detect, and animal models and clinical trials to establish their significance and treatment

- Devise for various indications new antimicrobial regimens with alternative dosages and durations of therapy that cure patients but select less resistance

- Define and validate outcome and process measures for strategies to reduce the transmission of resistant organisms

- Characterize resistance mechanisms and correlate with clinical outcome and antibiotic usage pattern

- Locate and characterize the reservoirs of resistance genes

- Develop rapid diagnostic tests for discrimination between viral and bacterial infections with an emphasis on respiratory tract infections

- Develop and validate methods for the efficient evaluation of institutional infection-control programmes

- Study the effect of antimicrobial-control programmes on resistant bacteria

- Define the factors that are most important in selecting antibiotic resistant organisms

- Study transmission of resistant organisms between animals and humans

- Study the factors that encourage the persistence and elimination of resistant organisms in human microflora

- Assess the importance of normal flora as a reservoir for antimicrobial-resistance genes

- Explore methods for better prediction of future trends and the emergence of novel resistance determinants

- Evaluate alternative strategies for the use of antimicrobial agents in intensive care units and other high risk settings

- Explore novel approaches for the elimination of resistant determinants

- Improve our understanding of the protective effect of normal flora

- Determine whether probiotics containing resistance genes pose a public health risk

- Identify factors influencing antimicrobial prescribing decisions
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WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

WHO SCIENTIFIC WORKING GROUP ON
MONITORING AND MANAGEMENT OF BACTERIAL
RESISTANCE TO ANTIMICROBIAL AGENTS

Geneva, 29 November 1994 to 2 December 1994
Location: Salle C

Coffee breaks: 10h30 and 15h30
Lunch break: 13h00-14h00

AGENDA

Tuesday 29 November 1994

09h00: 1. Opening of the meeting Dr Torrigiani

2. Chairman's opening remarks

3. Adoption of Agenda Dr Tikhonitov

4. Introduction

09h30: PLENARY SESSION I: Chairperson: Dr J. Acar
Co-Chairperson: Dr J. Hughes
Rapporteur: Dr F. Tenover

5. The nature and costs of resistance

5.1 Epidemics of progressively linked resistance genes through global networks of bacterial populations under selection Dr O'Brien

5.2 The population genetics of antibiotic resistance Dr Levin

5.3 Consequences of resistance to patients, medical centres, nations: greater costs to poorer nations Dr Acar

5.4 Discussion: What do we need to know about the process of resistance to devise strategies to control it
6. Recent increases in resistance

6.1 Old β-lactamases persist and new extended spectrum β-lactamases emerge

6.2 Aminoglycoside resistance - multiple genes, multiple enzymes and changing resistance patterns

6.3 Trimethoprim resistance increases

6.4 Progressive intercontinental spread of methicillin-resistant Staphylococcus aureus (MRSA)

6.5 Resistance of streptococci changes

6.6 Resistance to fluoroquinolones emerges

6.7 Enterococci acquire new kinds of resistance

6.8 Penicillin-resistant pneumococci

6.9 Drug resistance in tuberculosis: Global situation and WHO’s approach to surveillance

6.10 Resistance in pathogenic Neisseria

6.11 Resistance and diarrhoeal diseases

6.12 Antimicrobial resistance in anaerobes

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Wednesday 30 November 1994

08h30 PLENARY SESSION 3: Chairperson: Dr J. Hughes
Co-Chairperson: Dr G. Ayliffe
Rapporteur: Dr P. Huovinen

7. How to modify conditions to limit resistance

7.1 In bacteria of human populations  Dr Hughes
7.2 In bacteria of animals and other reservoirs  Dr Helmuth
7.3 In bacteria in special environments  Dr Goldmann
7.4 Perspectives in chemotherapy  Dr Kessler
7.5 Small peptide antibiotics  Dr Hancock
7.6 Anticipation of future patterns of drug resistant infections  Dr Citri

Discussions on items 7.1 - 7.6

14h00: PLENARY SESSION 4: Chairperson: Dr O'Brien
Co-Chairperson: Dr Schindler
Rapporteur: Dr Guzman

8. How to monitor and manage resistance nationally and locally

8.1 Reports from selected countries on surveillance, monitoring and management of antimicrobial resistance (useful practical experience, particular projects): Algeria, China, Czech Republic, Hungary, India, Iraq, Russia, Sweden, Venezuela *

8.2 Information on WHO antimicrobial policy  Dr Couper
8.3 Demonstration of WHONET  Dr Stelling
8.4 The need to monitor and manage resistance locally  Dr O'Brien

Discussions on items 8.1 - 8.4

* Additional reports from Canada, the United Kingdom and the Western Pacific Region were presented at the meeting
Thursday 1 December 1994

08h30: WORKING GROUPS (Development of comments and recommendations on 5, 6, 7, 8)

SECTION 1:
Chairperson: Dr Acar
Co-Chairperson: Dr Kaplan
Rapporteur: Dr Tenover

How to minimize consequences of resistance
- at clinical level
- at epidemiological level
- at economical level

SECTION 2:
Chairperson: Dr Hughes
Co-Chairperson Dr Goldmann
Rapporteur Dr Huovinen

How to modify conditions to limit resistance
- identifying factors in particular environments
- strengthening appropriate infection control practice
  (isolation, hygienic measure, etc.)
- testing new strategies of antibiotic usage (rotating, reserving and diversifying)
- developing new antibiotics, vaccines and biological modifiers

SECTION 3:
Chairperson: Dr O'Brien
Co-Chairperson Dr Schindler
Rapporteur: Dr Guzman

How to monitor resistance locally and nationally
- improving surveillance and rapid laboratory identification
- promoting an adequate detection of antimicrobial resistance
- transferring appropriate technology (training courses, workshops, educative materials)
- setting up WHONET system locally, nationally and internationally
Friday 2 December 1994

08h30: PLENARY SESSION 5. Chairman: Dr Acar
Vice-Chairmen: Dr Hughes and Dr O'Brien
Rapporteur: Dr Tenover

Presentation and discussion of Working Group statements and recommendations

14h00 Preparation of Strategic Plan for Management of Antimicrobial Resistance
- Local
- National
- Global

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WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

SCIENTIFIC WORKING GROUP ON MONITORING AND MANAGEMENT OF BACTERIAL RESISTANCE TO ANTIMICROBIAL AGENTS

Geneva, 29 November to 2 December 1994
Location: Salle C

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