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Communicable Disease Surveillance and Response

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A. Introduction

1. The Challenge

Since their introduction, antimicrobials (antibiotics) have played an essential role in decreasing morbidity and mortality due to infectious diseases. However, infectious diseases remain the leading cause of death worldwide. In recent years, infections caused by resistant strains of microorganisms have been increasing worldwide. The alarm bells are sounding. Concern has been echoed by the world’s health community, with the adoption of a resolution on antimicrobial resistance at the World Health Assembly in 1998.

2. Antimicrobial use and resistance

Antimicrobials are used for treatment of infections and for prophylaxis against infections in humans and animals, for growth promotion in food animal rearing, and in agriculture. The widespread use of these compounds is thought to further encourage the emergence of antimicrobial resistance. However, although it is generally accepted that antimicrobial use promotes the emergence and spread of resistance, this acceptance is based primarily on indirect evidence and there are many aspects of the complex interactions between microbes, humans and antimicrobials that are as yet poorly understood. Nevertheless, it is generally believed that if selective pressures related to the excessive use of antimicrobials are eliminated and the opportunities for transmission of resistant organisms from person to person are reduced, the number of drug-resistant infections will decrease.

3. Development of a strategy for the containment of antimicrobial resistance

Since the emergence of resistance is a natural biological response of microorganisms confronted with the selective pressures imposed by the widespread use of antimicrobial agents, complete eradication of resistance is not feasible and the strategic aim must be one of containment, i.e. creating a situation in which both the emergence and spread of resistant micro-organisms are reduced and yet efficacious use of antimicrobials is maximized.

In developing such a strategy it is important to recognize the diversity of the microbes and the complex interactions between the microbial and human biological systems in the presence of antimicrobial agents. Numerous factors have been identified that affect antimicrobial use and any strategy designed to improve the use of antimicrobial agents must take all of these factors into account.

Although some interventions are reported to be efficacious in improving antimicrobial use and reducing the emergence and spread of resistance, there are considerable gaps in knowledge and further interventions need to be formulated and
tested. In addition, the impact of antimicrobial resistance on morbidity, mortality and the costs of treatment need to be further defined.

Since antimicrobial resistance is a global problem, the strategy should be relevant to both developing and developed countries. It is anticipated that governments will be able to use this global strategy as a basis for developing national strategies and that these will reflect different degrees of emphasis on different factors depending on the national situation.

4. The aim of this Workshop Report

The aim of this report is to provide a summary of the discussions and considerations brought forth at an international workshop held at WHO on 4-5 February 1999. The document is arranged in sections, including the literature review provided at the meeting which outlines those factors considered to be of major importance in the misuse of antimicrobial agents and the emergence and spread of antimicrobial resistance (Section B); a listing of those interventions considered by the meeting participants to be of greatest importance in controlling antimicrobial resistance (Section C); and finally, a list of knowledge gaps and research needs (Section D). A complete reference list and a list of the workshop participants can be found in Annexes 1 and 2 respectively.

How this document fits into the process of the strategy development

The workshop held in February 1999 constituted the first phase in the development of the global strategy for the containment of antimicrobial resistance.

This report provides a basis for further expert review and commentary to be used in the next phase of strategy development. Concurrently, a series of technical reviews has been commissioned on specific topics and these will provide additional reference material to strengthen the evidence-base for the global strategy. In collaboration with other partners, WHO is preparing the global strategy document which will be widely circulated for comment prior to a consensus meeting for final consideration.
B. Review of the literature as a basis for strategy development

1. Prescribers and dispensers

1.1. Factors contributing to misuse and/or resistance

1.1.1. Lack of knowledge

As stated in the Rockefeller University Workshop report, the issue of antimicrobial resistance receives limited coverage in medical school curricula (Tomasz 1994). This may result in less informed physicians who lack a defined understanding of antimicrobial resistance. This lack of knowledge is assumed to play a role in irrational prescribing (Kunin 1987). In many countries, the dispensers of drugs also may not be formally trained as dispensers or as pharmacists. In a study of 40 randomly selected health facilities in Ghana, only 8.3% of the dispensers had received formal training and there were no trained pharmacists at any of the facilities. (Ameyaw 1997)

This factor can be extremely important as antimicrobials and other drugs are frequently purchased without visiting a physician. Bruneton et al. (1997) found that drug sellers in 7 countries in sub-Saharan Africa often advised non-essential drugs without adequate explanations and rarely suggested consultation of a physician.

1.1.2. Inadequate diagnosis

In areas where diagnostic facilities are not readily available (or are entirely absent), thus making differential diagnosis, organism identification, and knowledge of antimicrobial susceptibility patterns difficult, greater amounts of antimicrobials are often prescribed to ‘cover any possible infection’ (Bosu 1997). As resistance continues to become more prevalent, prescribers may be more likely to utilize broader spectrum antimicrobials for empiric therapy and prophylaxis of infections (Yu 1991; Goldmann 1997).

In a study of ‘bare-foot’ doctors in a district of Bangladesh, it was found that in areas without diagnostic services, antimicrobials were prescribed in 60% of all patients seen (Mamun 1991). This overuse of antimicrobials is further supported by Hogerzeil et al. (1993). In a study in 12 developing countries, 25% to 63% of all medications prescribed were antimicrobials (Hogerzeil 1993).

1.1.3. Incorrect drug selection for treatment or prophylaxis of infections

In a study conducted in China, 63% of the antimicrobials selected to treat proven bacterial infections were deemed inappropriate (Hui 1997). In another study in Bangladesh, it was determined that 50% of all the prescriptions for antimicrobials in a hospital unit were considered inappropriate (Hossain 1982).
1.1.4. Dose/duration/route incorrectly prescribed

In a retrospective study from Vietnam looking at antimicrobial dosages, it was found that more than 70% of patients were prescribed inadequate dosages of antimicrobials (Chalker 1997). Gumodoka et al. (1996) reported that although one out of every four patients in their medical districts received antimicrobials by injection, approximately 70% of the injections were avoidable. The majority of these treatments were for respiratory, skin and urinary tract infections.

Long treatment duration and sub-therapeutic or sub-optimal dosages have been correlated with increases in selective resistance (Rice 1990; Guillermot 1998).

1.1.5. Prescriptions in response to patient pressures

Patient demand for antimicrobials has been shown to increase unnecessary antimicrobial prescriptions (Bauchner 1997; Bosu 1997; Macfarlane 1997). In a study by Macfarlane et al. (1997), patient pressure was the most common influence in the decision to prescribe antimicrobials even when the physician thought they were not indicated. This type of prescribing can lead to a ‘perpetual’ cycle if patients repeatedly receive antimicrobials even if they are not indicated, which then enhances their belief that antimicrobials are necessary and they continue to request them (Little 1997; Macfarlane 1997)[see also Section 2, patients: the public]. Patient pressure as to the route of administration of antimicrobials has been reported as some patients believe that injections are more efficacious and work faster in treating infections. Health care workers report that patient demand for injections has led to an over-prescribing of injectable antimicrobials (Gumodoka 1996).

1.1.6. Fear of litigation

Fear of litigation has been suggested as one reason physicians over-prescribe antimicrobials (Fidler, 1998).

1.1.7. Financial gain

In countries where physicians are underpaid, pharmaceutical companies have been known to pay prescribers a commission for prescribing their products (Norrby 1996). In addition, pharmacists and dispensers gain financially from over-dispensing and through dispensing more expensive broad-spectrum agents when cheaper narrow spectrum agents would suffice.

1.1.8. Response to promotional pressure

It is recognized that often the main resources of drug information for prescribers are drug representatives and commercially oriented publications. This was confirmed in a study by Bosu (1997). [Also Section 5]
1.2. Interventions related to prescribing and dispensing factors

1.2.1. Understanding drug use patterns

A first step to improving rational use of antimicrobials is to understand prescribing patterns. This will aid in the identification of areas for potential interventions to improve use (Bosu 1997). Using indicators and methods described in the WHO manual “How to investigate drug use in health facilities” (WHO 1993), it is possible to describe drug use patterns and prescribing behaviour. After undertaking interventions to improve drug use, these same indicators can further be used to measure impact.

1.2.2. Education on appropriate use

A combination of national prescribing guidelines and educational campaigns on appropriate use of antimicrobials targeted at prescribers has had some success in reducing specific patterns of antimicrobial resistance (Seppala, 1997). In addition there has also been some success in the use of educational campaigns targeted at prescribers and patients to recognize that not all infections require the use of antimicrobials. Included in this same campaign was a message to parents to discourage them from sending their sick children to day-care to reduce opportunities for transmission of infection (Kristinsson 1995).

In an effort to reduce ‘reconsultation’ of patients, Macfarlane and colleagues (1997) utilized a patient information leaflet regarding coughs. In patients not prescribed antimicrobials, a trend was observed, although not statistically significant, between those given the educational leaflet and the incidence of not reconsulting. The use of delayed prescribing techniques has been proposed when physicians feel ‘pressured’ into prescribing antimicrobials (Cockburn 1987; Butler 1998). Some physicians say that they promise a free return visit if the patient feels that a reconsultation is necessary because they did not receive antimicrobials (Butler 1998).

Because inappropriate prescribing is rarely due to a lack of knowledge alone, many studies have found that the use of only printed material without other forms of supporting interventions are ineffective in altering prescribing behaviours. (Soumerai 1989; Mabadeje 1997)

The use of academic detailing or ‘unadvertisements’ and educational programmes directed to physicians have been shown to decrease antimicrobial usage/misuage (Avorn 1983; Harvey 1986; Molstad 1994; Gani 1997). Unfortunately none of these studies looked at resistance as an outcome or impact indicator.

It has been suggested that increasing the problem-based pharmacotherapy training for medical and paramedical students can have a positive impact on long term good prescribing habits. The use of the WHO “Guide to Good Prescribing” (De Vries et al. 1994), a manual designed to support problem-based learning for medical students, has demonstrated a positive impact on prescribing skills of 219 students in
seven medical schools (De Vries et al. 1995). [Also see Section 5, private industry, for additional educational interventions for medical students]

Improving the drug education of non-physician prescribers and dispensers is also a recommended step in improving drug use. In a study in Ghana, educational interventions aimed at dispensers significantly improved drug use by increasing the percentage of appropriate labelling and patient knowledge of their medications (Ameyaw 1997). In the Philippines as well, interventions targeted at local drug sellers significantly improved their quality of practice (Sia 1997).

1.2.3. Policies to reduce antimicrobial use

Coast et al. (1998) explored economic perspectives of policies used to decrease antimicrobial resistance. They discuss several techniques such as regulation (controlling prescribing via policy/guidelines or by enforcing a global limit to prescribing of antimicrobials), permits (allowing physicians to prescribe up to a certain quantity of antimicrobials per permit) and charges (levy taxes on antimicrobials). In their model, they suggest that the use of permits may offer an economic method of reducing antimicrobial resistance. [See also Section 4].

1.2.4. Maximizing appropriate antimicrobial prescribing

There has been much discussion regarding the appropriate selection, best dosage, or best dosing interval of antimicrobials in the attempt to avoid the selection of resistance as well as which parameters to use to verify various hypotheses (Drusano 1998; Schentag 1998; Thomas 1998). In addition, the use of antimicrobials in combinations has been suggested for some infections, as a trend has been observed of a reduced incidence of resistance when combination therapy has been employed (Milatovic 1987; Hilf 1989).

In general, clinical drug trials have not been designed to determine the most appropriate duration of antimicrobial therapy, and thus the duration of therapy is generally prescribed following package insert recommendations. Many scientists and clinicians believe that shorter treatment courses for many infections are likely to be as equally effective as the longer courses (Pichichero 1997). A potential benefit of shorter course therapies may be to decrease the selective resistance pressures of antimicrobials on microorganisms. In addition, shorter lengths of therapy are more readily adhered to by patients.

The careful selection of antimicrobials is an important factor in the development of resistance as it appears that some antimicrobial agents may be more likely to select or promote resistance (Loulergue 1994; UK Department of Health 1998). [See also Section 7].
2. Patients: The Public

2.1. Factors contributing to misuse and/or resistance

2.1.1. Self medication

Self medication is often cited as a major contributing factor to drug resistance (Vuckovic 1997). In a Brazilian study, it was determined that the three most common types of medication used by villagers were antimicrobials, analgesics and vitamins with the majority being prescribed by a pharmacy attendant or purchased by the patient without prescription (Haak 1988). This is important as many antimicrobials are often inadequately dosed or do not contain adequate amounts of active drug (Kunin 1987).

2.1.2. Poor adherence

In a literature search conducted in 1988, over 4000 English articles were available in the literature on patient adherence/compliance with more than 75% of them having been published within the previous 10 years (Trostle 1988). In a majority of the studies, it was reported that a lack of patient understanding and provider communication led to most instances of non-adherence (Sackett 1979; Buckalew 1986). This factor is critical as often patients who fail to complete therapy (such as in the case of tuberculosis) will relapse and require retreatment. Previous treatment is considered an important factor in the selection of resistant bacteria (Bloom 1992).

2.1.3. High need (poor underlying health)

Malnutrition and poor underlying health can contribute, through increasing susceptibility to infection, to greater usage of antimicrobials.

2.1.4. Misinformation/inappropriate beliefs; patient over-reliance on antimicrobials

In a survey of 3610 patients conducted by Braithwaite and colleagues (1996), over 50% of interviewees believed that antimicrobials should be prescribed for all respiratory tract infections with the exception of the common cold. It was also reported that 81% of patients expected to see a definite improvement of their respiratory symptoms after 3 days, and 87% reported that feeling better is a suitable reason for cessation of antimicrobial therapy. In addition, most of these patients believed that remaining antimicrobials could be saved and used again at a later time.

In the Philippines it is reported that people believe that isoniazid is a ‘vitamin for the lungs’ and many mothers purchase isoniazid syrup for children with ‘weak lungs’ in the absence of documented tuberculosis (Querubin 1986). In another study, patient demand caused one pharmacy in South India to stock over 25 (of the over 100 available) brands of co-trimoxazole. Patients familiar with the brand name of Septrin led physicians to prescribe the same drug under different names (Nichter 1994).
2.1.5. Poverty-associated undertreatment

A lack of access to drugs due to economic hardship has been described as a factor for impacting resistance as appropriate therapy can be interrupted. In many developing countries, for economic reasons antimicrobials are purchased in single doses and may be only taken for a couple of days until the patient ‘feels better’. This action has the potential for impacting the emergence of resistance (Couper 1997; UK Department of Health 1998).

2.1.6. The ‘Expensive is better’ myth

It has been suggested that many patients believe that more expensive medications are more efficacious (a belief also shared by some prescribers and dispensers). This results in the unnecessary use of newer, more costly, broader spectrum antimicrobials and encourages the selection of resistance to these agents. It also results in unnecessary expenditures.

2.1.7. Expectation of treatment

Patients commonly expect to receive prescriptions upon a visit to their physician and it has been described that patients’ expectations for a prescription are met approximately 75% of the time by the prescriber. As shown by Macfarlane et al. (1997), 85% of patients thought their respiratory symptoms were caused by infection, 87% believed that antimicrobials would help and one fifth of these patients specifically asked their physician to prescribe an antimicrobial (Macfarlane 1997).

2.1.8. Response to advertising

Direct-to-consumer advertising allows pharmaceutical manufacturers to market prescription drugs directly to the public. Generally, multi-media such as television, radio and print are utilized. The goal of direct-to-consumer advertising is to induce consumers to purchase products that they may not otherwise purchase. This factor is further complicated by the fact that the targeted audience (the public) is rarely the one who prescribes or pays for the medication(s).

Direct-to-consumer advertising has been noted to have “the potential to stimulate demand by playing on the consumer’s relative lack of sophistication about the evidence of that supports the use of one treatment over another” (Shapiro 1997). These advertising methods are quite effective as described in a paper by Vuckovic and Nichter (1997), where pharmacists reported being able to guess the topics of the previous day’s television shows based upon the daily customer requests for medications.

In a telephone survey of consumers regarding direct advertising, 66% believed that advertisements for prescriptions would provide useful information and 88% said that they would seek out more information about a drug that they saw advertised on
television or in print. On the other hand, 63% disagreed with the statement that most people would be able to tell if they were being misled by the advertisements (Morris 1986).

An American study demonstrated that most physicians surveyed (95%) had encountered an average of 7 patients within the previous 6 months who had specifically requested drugs as a result of direct-to-consumer advertising (Lipsky 1997). Over 70% of the physicians reported that patient requests as a result of direct-to-consumer advertisements had lead them to prescribe a pharmaceutical agent that they might not have otherwise chosen.

Recently the United States Food and Drug Administration (FDA) has proposed new guidelines that lift previous restrictions on direct-to-consumer advertising and allow the pharmaceutical manufacturers greater freedom on advertised health claims. A two-year evaluation period has been proposed to assess the impacts and implications of the new guidelines (“T Hoen 1998).

[Also see Section 5, private industry]

2.2. Interventions related to patient factors

2.2.1. Improving adherence

Many methods have been used to ensure adherence to antimicrobial therapy. These include the use of fixed dose combinations (to minimize the number of tablets or capsules to be taken), special calendars, blister packing, directly observed therapy (DOTS) for tuberculosis (Frieden 1995) and more simplified therapy (Cockburn, 1987). DOTS has been shown to significantly decrease acquired resistance in tuberculosis (Weis 1994) and this strategy is currently being studied globally (personal comment, M. Espinal, WHO).

2.2.2. Patient/public education

Education of patients about the name, dosage, description and common adverse effects of their medication(s) has been used to increase adherence (Sharpe 1974). A greater interaction between health providers and consumers for health and drug (antimicrobial) related education has been proposed. As T Hoen (1998) states “Health professionals, including pharmacists, have a responsibility to build partnerships with consumers and patients. This partnership and cooperation is essential in the political arena in which health care policies are set so that sensible arguments can be made against strong commercial pressures…”.

The WHO Action Programme on Essential Drugs (DAP) convened a consultation to address the need for public education in rational drug use (WHO 1994) and since has produced a document “Rational Drug Use: Consumer Education and Information” (WHO 1996). This document discusses the practical issues and dilemmas related to the need for rational drug use education, its priority and content, underlying principles and target population. In a study carried out in Peru, a
multifaceted educational intervention directed at the community using media, face-to-face meetings and training on the use of medicines was successful in decreasing the inappropriate use of antidiarrhoeals and antimicrobials for simple diarrhoea (Paredes 1997).

3. Governments and health systems

3.1. Factors contributing to misuse and/or resistance

3.1.1. National policies poorly communicated, not implemented, or poorly implemented with little or no adherence

A lack of support in actively marketing the Essential Drugs List (EDL) in Ghana has shown that it has had little impact on prescribing (National Drugs Committee 1994) nor is it even available in many government health facilities (Bosu 1997). In a study in two villages in Brazil, around 50% of all medications used were not found on the country’s EDL or on the WHO Model List (Haak 1988).

3.1.2. Regulatory mechanisms ineffective and/or substandard drugs/lack of quality assurance

The Counterfeit Intelligence Bureau estimated that in 1991, 5% of the world’s trade was counterfeit. This percentage is likely to be higher for pharmaceuticals that are easily transportable and are in great demand (WHO 1992). Such counterfeit products have bypassed regulatory controls for quality assurance, thus potentially resulting in medications that contain too little or none, or even entirely different active ingredients.

3.1.3. Sales not regulated, informal sector sales

Although antimicrobials are prescription-only medicines in many countries, there is a wide variation between the law and what is actually practised. In Spain for example, antibacterial agents can be purchased in most pharmacies despite having prescription-only status (UK Department of Health 1998) and in many developing countries antimicrobials can be purchased without prescription (Levy 1987; Hui 1997; Hart 1998). In a study of chemist shops in Nairobi, it was discovered that 64% of chemists sold antimicrobials without physicians’ prescriptions. In addition, most would sell incomplete treatment courses at the request of the patient (Indalo 1997). In a study of a rural village in Bangladesh, 95% of all medications consumed were obtained from pharmacies with only 8% having been prescribed by graduate physicians (one-third of these medications were anti-infectives) (Hossain 1982).

3.2. Interventions related to government and health systems factors

3.2.1. Establishing essential drugs lists and essential drug policies
In 1977 the first WHO Model List of Essential Drugs was developed with the goals of promoting access to and the rational use of drugs. This document contains a selected number of antimicrobials, has been revised regularly and serves as a guide for countries in determining their national drug policies. At present over 120 countries have implemented an EDL.

In a study comparing areas where Essential Drug Policies (EDPs) were and were not functioning, those areas in which an EDP existed had more essential drugs available, with stocks to last three times longer than in the areas without programmes. In addition, significantly fewer injections and antimicrobials were utilized in areas with a national EDP. It was concluded that programmes significantly improved the availability and rational use of essential drugs (Hogerzeil 1989). A retrospective study of prescribing practices in Ethiopia found a significant decrease in the prescribing of non-essential drugs after introduction of an EDL (Lindtjorn 1987). It has been suggested that an EDL is most effective when supported by educational programmes and follow-up (Hogerzeil 1995).

### 3.2.2. Establishing National Standard Treatment Guidelines

It has been suggested that National Standard Treatment Guidelines be developed in connection with the countries EDL. These national guidelines can then be further adapted for local hospital specific use. As is true with the EDL, national guidelines are more effective in combination with supporting interventions such as training and supervision (Kafuko 1997). Such guidelines must be regularly updated and reviewed as well.

[See Section on 4, hospitals, for more information on treatment guidelines]

### 4. Hospitals

#### 4.1. Factors contributing to misuse and/or resistance

##### 4.1.1. Lack of hospital therapeutics committee

While no references were found relating this to misuse or resistance, it is considered a necessary component of an antimicrobial control programme.

##### 4.1.2. Lack of antimicrobial policies, policies not updated with surveillance data and/or poor information flow

Hospitals serve as an important source for learning of prescribing practices for students. Unfortunately, this prescribing is often irrational. In an analysis of prescribing practices in 10 studies from teaching hospitals world-wide, overall 41-91% of all antimicrobials prescribed were considered inappropriate (Hogerzeil 1995).

[Also see Section 3, governments and health systems regarding EDL and STG]
4.1.3. Lack of infection control committees, procedures or guidelines

As the principles of hand-washing and/or changing of gloves before and after contact with patients are often disregarded (Albert 1981; Graham 1990; Larson 1995; Goldmann 1997), dissemination of resistant bacterial strains in hospital and health care facilities is increased. The spread of resistance is widening as patients move from intensive care wards to general wards and then to the community, or between hospitals and nursing homes (Riley 1984; Ayliffe 1997; UK Department of Health 1998).

4.1.4. Lack of sterile supplies

As it has already been documented, especially in light of HIV/AIDS, infections can be transmitted via non-sterile injection equipment. In a study of health facilities in Tanzania, it was also shown that 40% of the supposedly sterilized needles and syringes were bacterially contaminated (Gumodoka 1996).

4.2. Interventions related to hospital factors

4.2.1. Multi-faceted/interdisciplinary approach

Multi-disciplinary and integrated approaches to reduce antimicrobial use in hospitals have been proposed as a solution by many experts (Goldmann 1997; Hughes 1997; Acar 1998; Struelens 1998). Hospital administrators, clinicians, infectious diseases specialists, infection control teams, microbiologists and hospital pharmacists all have a role and their coordination is vital. The integrated responsibilities that can be undertaken include formulary-based guidelines, monitoring and evaluating drug use, surveillance and reporting of hospital resistance patterns, detection and appropriate care of patients with resistant commensal organisms, and promotion and monitoring of basic infection control practices (Struelens 1998).

Although there is little information regarding the impact of a hospital therapeutics committee (also called pharmacy and therapeutics committee) in developing countries, their beneficial role in the promotion and monitoring of drugs as well as cost containment has generally been established in developed countries (Soumerai 1984; Weekes 1996). Therefore, it is recommended that hospital therapeutics committees be established in developing country hospitals.

4.2.2. Use of formularies/control policies/treatment guidelines

The use of formularies has been suggested as a method for decreasing inappropriate prescribing and generally reducing expenditures. It has been suggested that a formulary should be ‘flexible’ and depend on cost-effectiveness and patterns of resistance (Levy 1987). If antimicrobial control programmes are to be effective, it is important to ensure consistent longterm monitoring. Although, decreases in resistance were observed with the use of control programmes as soon as monitoring was relaxed, resistance quickly increased (US Congress Report 1995).
In a review of clinical guidelines (Grimshaw 1993), it appeared that they can improve decision-making and as a result, improve patient care. It has been suggested that programmes utilising clinical guidelines that are supported by other interventions such as education, peer review, etc, are more effective than those without support (Goldmann 1996). In an observational study of one hospital with a computerized prescribing guideline system that encouraged appropriate use of antimicrobials, trend analysis showed that hospital resistance patterns stabilized over a seven-year period (Pestotnik 1996).

In a study by Recco et al. (1979), although prescriber education combined with hospital antimicrobial control policies led to decreased antimicrobial costs and improved prescribing, resistance was not reduced. In fact, resistance increased in many common gram-negative infections.

It has been suggested that hospital formularies may be a contributing factor in the selection of resistance by being very restrictive (Schentag 1995). In a survey in the USA, although a great majority of the hospitals had implemented formularies as a method for decreasing antimicrobial costs, most replied that expenditures had actually increased. The most commonly cited reason for this increase was the problem of drug resistance (Rifenburg 1996).

Clinical guidelines focused on use of injectable antimicrobials necessary to treat infections and the proper sterility of needles and syringes, as well as health education programmes, were used to raise awareness about the effectiveness of oral medications and the possible adverse effects of injected medications. This resulted in greater knowledge of health care workers on the appropriate use of injectable antimicrobials, decreased contamination of syringes and needles and a reduction in patient demand for injections (Vos 1998).

Targeted antimicrobial control policies in combination with improved hygiene (often including education) have reduced antimicrobial resistance in some settings (Barber 1960; Giamarellou 1997).

Antimicrobial order forms have been used with success in improving antimicrobial prescribing in some hospitals (Avorn 1988; Gyssens, 1997) but other studies have documented that orders had no effect on improving antimicrobial prescribing (Aswapokee 1992).

The cycling of antimicrobials within a health care institution has been suggested as a possible intervention to decrease drug resistance. This technique alternates formulary antimicrobials between drug classes every several months and theoretically reduces the selective pressure of one antimicrobial class (Schentag 1998). However, this hypothesis is challenged by a study that showed that cycling can replace one resistance problem with another (Urban 1993).

Therapeutic selection of antimicrobial agents has been proposed as a method for decreasing resistance. A study by Betts and colleagues (1984) examined the impact
of changing the hospital formulary aminoglycoside (from gentamicin to amikacin) on development of resistance in various gram-negative bacteria. In the 5 years following the intervention, gram-negative resistance rates to gentamicin decreased with little development of amikacin resistance.

In a mathematical modelling study, Bonhoeffer et al. (1997) evaluated various types of interventions that have been widely discussed for reducing antimicrobial resistance in hospitals. They compared antimicrobial cycling, combination therapy and 50-50 therapy. 50-50 therapy is also known as ‘switch back therapy’, where one of two antimicrobials are alternately selected each time a new patient is treated. For example patient 1 receives antimicrobial A, patient 2-antimicrobial B, patient 3-antimicrobial A, patient 4-antimicrobial B and so forth). They determined that although 50-50 therapy was equal to or better than antimicrobial cycling, combination therapy was better than both of these other methods (except when the resistance genes of the two drugs are carried on the same plasmid).

4.2.3. **Emphasis on better handwashing techniques**

It has been suggested that interventions such as education and motivational programmes, improvement of equipment, performance feedback (among others) can increase adherence to improved handwashing (Larson 1995). The basic aspects of hygiene have been shown to be important in reducing infection transmission rates (and thereby the spread of resistance); Mayer et al. (1986) showed that improved handwashing and/or use of gloves and gowns did lead to decreased infection rates.
5. **Private industry**

5.1. **Factors contributing to misuse and/or resistance**

5.1.1. **Industry/wholesaler/retailer pressure to sell and/or over-promotion/misleading promotion**

In a number of sources, it is clearly described that advertising and promotion by the pharmaceutical industry is a major and powerful source of information for prescribers (Avorn 1982; Zarate 1995). In a review of the literature on the interactions between physicians and the pharmaceutical industry, it was concluded that there was strong evidence that these interactions influence prescribing behaviour (Lexchin 1993).

It has been suggested that physicians may not even be aware of these influences. In a study by Avorn et al. (1982), although most prescribers believed that drug advertisements and detail men played a role of ‘minimal importance’ in influencing prescribing patterns and academic sources of information were ‘very important’, it appeared that the opposite was actually true. This finding was further confirmed by a study of prescribing habits of physicians in Peru (Zarate 1995). Although over two-thirds of physicians surveyed claimed their primary source of drug information came from medical literature, the study concluded that advertising materials distributed by pharmaceutical companies appeared to be a key source of information for prescribers. The authors went on to say that this factor “tended to promote irrational drug use.”

In a study by Wilkes et al. (1992) investigating the quality of advertisements in medical journals, experts were asked to evaluate the appropriateness of advertisements for publication in the form in which they actually appeared. They concluded that 28% of the advertisements should have been rejected and another 34% should have had major revision before publication.

5.2. **Interventions related to private industry factors**

5.2.1. **National or local guidelines**

Many countries have instituted guidelines and codes for pharmaceutical companies to deter them from misleading promotion. As reported by Lexchin (1997), not only do these codes vary between countries but they also vary as to the manner in which they are executed.

Education of medical students in the Philippines showed that the group of students who underwent a four hour course in evaluation of drug promotional materials scored significantly better than those students in the control group when questioned on ‘violations of existing guidelines’ on drug promotion (Alvero 1997).
6. Non-medical uses of antimicrobials

6.1. Factors contributing to misuse and/or resistance (impacting human health)

6.1.1. Growth promoters in food animals, treatment and disease prevention in food animals, agriculture and aquaculture

Most of the factors affecting emergence and spread of antimicrobial resistance and misuse of antimicrobials already described in previous sections also apply to the non-medical use of antimicrobials. For prescribers and dispensers, education is lacking on antimicrobial resistance and appropriate antimicrobial therapy. In many countries, therapeutic antimicrobials are dispensed by inadequately trained individuals. By far the largest amount of antimicrobials is applied to animal flocks and herds through feed with inherent problems of accurate dosing and inevitable treatment of all animals irrespective of health status. Empiric treatment predominates because of the widespread lack of diagnostic services (particularly in developing countries) and may often be, from the producers' viewpoint, economically contraindicated. Sales of drugs constitute 40% of the income of veterinarians in some countries (ACMSF report, 1999).

As noted in Section 3, inefficient regulatory mechanisms or poor enforcement of regulations, with lack of quality assurance and marketing of substandard drugs, are also important contributory factors. Discrepancies between regulatory requirements and prescribing/dispensing realities are often even wider than in human medicine. In some countries, even injectable antimicrobials for disease treatment in animals are sold over the counter (World Health Organization, 1997). Antimicrobial growth promoters are not considered as drugs and are licensed, if at all, as feed additives.

Marketing of antimicrobials and growth promoters by private industry influences prescribing behaviour and use patterns of veterinarians, feed producers and farmers.

Reports from North America and Europe estimate that about 50% (in tonnage) of all antimicrobial production is used in livestock production (including poultry) (FEDESA, 1998). Antimicrobials are used as growth promoters (in sub-therapeutic doses), prophylactically for disease prevention (e.g. after co-mingling of animals from different farms), and therapeutically, for treatment of infections in animals. The increasing production of food of animal origin under 'industrialized' conditions has contributed to the increased use of antimicrobials.

The consequences of selecting resistant bacteria in animals include:
- An increase in the prevalence of resistant bacteria in animals;
• The increased potential for transfer of resistant pathogens to humans by direct contact with animals or through the consumption of contaminated food or water. The transfer of resistance genes from the animal to the human bacterial flora;
• The potential for resistant infections and therapeutic failures in animals and humans. The increased prevalence of foodborne disease from pathogens of animal origin suggests that the risk of human acquisition of resistant zoonotic pathogens is increasing.

In addition, the impact of the widespread distribution of non-metabolized antimicrobials through sewage into the environment and other ecosystems is unknown.

6.1.2. Problems with specific pathogens or drug classes: salmonella, campylobacter, enterococci

There is direct evidence that antimicrobial use in animals selects for antimicrobial-resistant non-typhoid Salmonella serotypes (Glynn et al., 1998; Holmberg et al., 1987). These bacteria are transmitted to humans mainly through food or direct contact with animals. Resistance limits the therapeutic options available for the small subset of clinical cases of invasive non-typhoid Salmonella infections which require antimicrobial treatment. A recent example is a clone of S. typhimurium DT104, resistant to ampicillin, tetracycline, streptomycin, chloramphenicol and sulphonamides, which has become prevalent in many countries including the UK, Germany and the USA (Glynn et al., 1998).

Following the introduction of fluoroquinolones for use in food-producing animals, the emergence of Salmonella serotypes with reduced susceptibility to fluoroquinolones in humans has become a cause for particular concern. This phenomenon has been observed in countries such as France, Germany, Ireland, the Netherlands, the Russian Federation, Spain and the UK (WHO Report, 1997). There has been little documented impact of this resistance on human health to date, but there is concern about the potential human health consequences if resistance were to increase and spread. This has been substantiated by a recent outbreak of quinolone-resistant S. typhimurium DT104 resulting in treatment failures in hospitalized patients in Denmark (Moelbak et al., 1999).

Following the introduction of fluoroquinolones for use in poultry, there has been a dramatic rise in the prevalence of fluoroquinolone-resistant Campylobacter jejuni isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals without previous exposure to quinolones (WHO Report, 1997). Because of their broad antibacterial spectrum, fluoroquinolones are often used in humans for empirical treatment pending laboratory results. The effect of fluoroquinolone resistance in Campylobacter on the clinical outcome of treatment with a fluoroquinolone is not clear.

The use of avoparcin as a growth-promoting feed additive in animal husbandry has contributed to the reservoir of transferable resistance genes to glycopeptides,
including vancomycin, in the commensal enterococci of animals. Glycopeptide-resistant enterococci from animals can reach humans via the food chain. Although glycopeptide resistance genes have been shown to be widely disseminated, the extent to which the gene pool in animals contributes to the prevalence of glycopeptide-resistant commensal enterococci in humans has not been quantified. Glycopeptide-resistant enterococci cause serious infections in hospitalized immune-impaired patients. In this setting, they contribute to increased morbidity and mortality, in part because of limited therapeutic options.

There is concern that there will be increased dissemination of glycopeptide resistance genes among Enterococcus faecalis and their spread to other gram-positive bacteria, particularly to multi-resistant Staphylococcus aureus for which vancomycin is the drug of last resort. Due to the limited number of agents available for the treatment of glycopeptide-resistant enterococcal infections in humans, antimicrobial agents not previously used in human medicine are being investigated, including drugs from classes currently used as growth promoters in animals. Therefore the selection of further resistance in enterococci in animals is undesirable, e.g., streptogramin resistance due to use of virginiamycin as a feed additive in animals.

6.2. Interventions related to ‘non-medical’ factors

WHO has recommended that those antimicrobials that select for resistance to agents used for human treatment should not be used in animal husbandry. It was re-emphasized that antimicrobials should not be a substitute for healthy hygiene in animals and that excessive use of antimicrobials should be reduced (WHO 1997). However, in an editorial of March 1998, it was noted that no changes in antimicrobial use in animals in the USA have resulted from these recommendations (Levy 1998). In Europe in 1998, four major growth promoters (bacitracin, tylosin, spiramycin, virginiamycin) were banned. Limited studies from Germany and Denmark have shown that ban of avoparcin in animals in Europe has led to a reduction in the prevalence of vancomycin-resistant enterococci in poultry and in healthy individuals (Wegener 98, Klare et al. 97). Sweden banned the use of growth promoters in livestock and poultry in 1987 and subsequently there has been a marked reduction in antimicrobial consumption in animals. Prevalence of antimicrobial resistance in Salmonella isolated from animals in Sweden has fallen significantly since 1985.

Improvements in animal production hygiene have also been recommended to reduce the need for antimicrobials (WHO, 1997) and some studies (Wierup 1997)) have shown that such improved hygiene and reduced use can be achieved without loss in productivity.
7. Microbial determinants

7.1. Factors causing emergence and augmentation of resistance

Bacteria have evolved many different mechanisms of resistance. These can be classified as: a) alteration in, or addition of, the target site of antimicrobial binding; b) alteration in access to the target site (e.g. decreased permeability of cell wall; efflux mechanisms); and c) inactivation of the antimicrobial (e.g. beta-lactamases). Furthermore, resistance may arise through mutation or by acquisition of resistance genes (horizontal transmission) from another bacterial species.

Given that there are different classes of antimicrobials each with a different molecular target site and the fact that a single bacterial species may exhibit more than one of these mechanisms against a single class of antimicrobial (e.g. change in penicillin binding protein target site and production of beta-lactamase is a common feature of methicillin-resistant *Staphylococcus aureus*), the genetic basis and the phenotypic expression of resistance is extremely complex.

It appears that some bacterial species more readily develop (or acquire) resistance than others when exposed to apparently similar selective pressures. *Shigella* spp. and *Staphylococcus aureus* developed resistance rapidly as each new class of antimicrobial was introduced (with some exceptions, e.g. vancomycin resistance in *S. aureus*). In contrast, *Streptococcus pneumoniae* infections have been treated with penicillin for many years but only relatively recently has this species developed penicillin resistance. This may be because the mechanism of penicillin resistance in *S. pneumoniae* is complex and has taken a long time to evolve. Meanwhile, *S. pyogenes*, a human pathogen in the same genus that must have had exposure to penicillin similar to that of *S. pneumoniae*, remains completely susceptible to penicillin. However, erythromycin and tetracycline resistance are widespread, in *S. pyogenes*. Among opportunistic hospital pathogens, *Enterobacter* spp., for example, have a great propensity for becoming resistant due to beta-lactamase production to expanded spectrum cephalosporins, leading to treatment failure (Chow 1991, Olsen 1983). *Pseudomonas aeruginosa* behaves similarly. Little is known about why these different bacterial species develop antimicrobial resistance at such different rates.

It is reported that some antimicrobial agents may be more likely to select or promote resistance (Loulergue 1994; UK Department of Health 1998) than others. Recently, concern has been expressed about the impact of long half-life antimicrobials on the development of selective bacterial resistance. Although these agents may improve compliance because they can be dosed less frequently, their long half-life may expose bacteria to prolonged periods of sub-therapeutic concentrations of a given agent and thus lead to the selection of resistance (Baquero 1997; UK Department of Health 1998). Despite widespread use for more than 40 years, resistance to nitrofurantoin among *E. coli* being treated with this antimicrobial has not developed.
C. Interventions to contain antimicrobial resistance

The following items were identified by the workshop participants for consideration as potential components of a comprehensive programme for containment of antibiotic resistance. The components are not prioritized here nor are they ranked as to the quality of evidence supporting their effectiveness. Some recommendations were made by several groups and are thus relevant in several different discussion areas but to avoid redundancy have been listed only under one category.

1. Prescribers and dispensers

1.1. Description of current antimicrobial use practices and identification of the determinates of those practices.

- Determine current antimicrobial use practices and the determinants of those practices within each institutional, local or national setting.

1.2. Behaviour change strategies and interventions.

- Prioritize for intervention those conditions and circumstances in which the majority of antimicrobial use and misuse occurs.

- Evaluate the impact of these programmes once implemented.

- Target specific programmes for each category of provider and dispenser, including trained providers (physicians, midlevel providers, physician assistants, nurses, medical aids); authorized dispensers (pharmacists); and unauthorized dispensers (drug sellers, traditional healers, others).

- Utilize elements of behaviour change theory to develop programmes to modify inappropriate antimicrobial prescribing and dispensing within each of these groups of providers.

1.3. Education and Clinical Practice Guidelines.

- Ensure enhanced education of providers regarding appropriate antimicrobial use by implementing specific training on this topic at all levels, including professional school, post graduate in-service education, and exposure to opinion leaders or peer educators in small groups.

- Encourage use of problem-oriented decision making, clinical practice guidelines, and clinical algorithms that foster appropriate management and use of antimicrobials.
• Develop educational programmes for dispensers that enhance their understanding of appropriate and inappropriate use of antimicrobials and encourage them to educate patients regarding the importance of compliance with prescribed antibiotic regimens.

• Formulate evidence-based guidelines for relevant infections and syndromes that can be used in practice, in teaching and in monitoring adherence to recommended policies.

• If developed nationally, modify guidelines to make them relevant at the local level.

• Actively promote the use of guidelines and teaching materials to enhance their adoption.

1.4. Peer review and monitoring

• Improve provider performance and appropriate antimicrobial use by ensuring ongoing supervision of clinical practices, especially the diagnostic and treatment strategies used.

• Regularly monitor drug use practices and utilize peer comparisons or comparison with external standards to gauge performance. Feed back information regarding level of performance to individual providers.

• Link physician/prescriber licensing requirements and continued authority to prescribe to requirements for defined training and specific continuing education on antimicrobial use.

1.5. Other measures

• Identify and eliminate economic incentives (i.e. reimbursement practices) that encourage inappropriate antimicrobial use.

• Encourage the development and use of essential drug lists and formularies relevant to each practice setting.

• Control antimicrobial use by restrictive formularies that limit prescription to selected agents. Such formularies must provide appropriate antimicrobial choices, however, and must be appropriate for the level/place of care.

• Consider holding selected newer antimicrobials in ‘reserve’ at certain levels of care in order to slow the development of resistance to these newer agents.
• Consider further limiting access to antimicrobials by restricting prescribing authority to selected categories of health care worker.

2. Patients and the general public


• Educate patients regarding the inappropriate and appropriate uses of antibiotics.

• Modify patient expectations as to when antibiotics should be used in conjunction with the above.

• Empower patients to participate in optimal medical decision making.

• Utilize behaviour change theory to most effectively modify patient behaviour with respect to antimicrobials.

2.2. Levels of Intervention

• Employ marketing skills and approaches to achieve these ends.

• Focus initially on specific target groups where antimicrobial misuse may be high (i.e. mothers of young children).

• Improve communication skills of providers to teach the above messages; motivate providers to deliver the message.

• Foster interest and participation in patient education by all relevant involved parties, including government, industry, NGOs and CBOs, professional associations, foundations, health care institutions/centres and individual providers.

• Develop levels of intervention, consistent with the above, that are international, national, local and institutional and individual.

2.3. Adherence to antimicrobial regimens

• Educate patients regarding the importance of adherence to prescribed antimicrobial regimens and the consequences of partial or intermittent therapy.

• Encourage the use of medical strategies that foster adherence (simplified and shorter regimens, directly observed therapy, blister packaging, special calendars, fixed dose combinations) and the like.
• Discourage patient self initiation and use of antimicrobials.

3. Governments & health systems

The following recommendations include actions by WHO, by national governments and their respective departments of health, and by health professionals who are involved in advising on health care.

3.1. Global advocacy of antimicrobial resistance

• Target WHO-coordinated advocacy for action towards relevant international organisations (e.g. WTO, WB, IMF).

3.2. Legal framework

• Adapt for national use an internationally-applicable WHO-developed model legal framework for tightening and aligning legislation surrounding the licensure, manufacture, sale, supply, distribution and promotion of medicinal products.

• Adapt to the national situation a WHO-developed framework for the enforcement of all legislation which relates to these matters.

• Introduce legal requirements for the collection of data on antimicrobials which relate to production, distribution, sales and consumption in all spheres of antimicrobial use (human, veterinary, agricultural).

• Introduce formal training and registration schemes such that drugs may be distributed only to nationally recognized and certified dispensing outlets (e.g. via registered pharmacies in hospitals and the community staffed by qualified personnel and via dispensing health professionals).

3.3. National Policies

• Make the containment of antimicrobial resistance a national priority.

• Adapt, and apply as possible, a WHO-derived model system for antimicrobial resistance surveillance. By this means, contribute to the global database.

• Create Intersectoral Task Forces (ITFs), with memberships which encompass health professionals, pharmaceutical manufacturers, government, media representatives and consumers.
• Use ITFs to raise awareness of antimicrobial resistance, to organize the collection and assimilation of data on manufacturing, distribution, sales, consumption, and resistance, and to oversee the creation of local task forces.

• Allocate resources for specific activities, including research.

• Implement public health and institutional hygiene measures aimed at the prevention of the spread of infections, and thereby the spread of resistant pathogens.

• Establish Essential Drugs Lists (EDL) and Essential Drugs Policies (EDPs) to improve the availability and use of essential drugs; these could be based on the WHO Model List of Essential Drugs.

• Maximize the effectiveness of an EDL by introducing supportive educational programmes and follow-ups.

• Establish National Standard Treatment Guidelines in connection with the EDL, with further modification for local hospital use. Support such interventions with training and supervision.

4. Hospital

4.1. Control of antimicrobial use

• Establish an effective Hospital Therapeutics Committee within each hospital, with formal links to the Infection Control Committee (ICC).

• Implement an antibiotic utilization review programme based on written guidelines for appropriate treatment and prophylaxis of infections. The programme should be locally developed with wide input and consensus and should utilize local surveillance data whenever possible.

• Utilize regular audits to provide practitioners with feedback on their antibiotic practices.

• Restrict access of industry sales representatives within the hospital environment.

• Integrate to the extent possible the activities of the hospital therapeutics committee, the infection control committee, the microbiology laboratory, and infectious disease specialists with respect to control of antimicrobial use.
4.2. **Infection control committee (ICC)**

- Establish an effective (adequately staffed and trained) infection control programme within the hospital.

- Ensure that essential components of the ICC include active surveillance of infection, identification of outbreaks, and implementation of effective control measures such as barrier precautions (handwashing, gloving, gowning, isolation) and sterilization and disinfection of equipment and supplies.

4.3. **Laboratory factors**

- Ensure that hospital laboratories can perform appropriate diagnostic testing and reproducible antimicrobial susceptibility testing of key organisms.

- Analyze laboratory data to produce surveillance reports for clinicians of patterns of antimicrobial resistance among common pathogens.

- Identify and control outbreaks of infection due to antimicrobial-resistant organisms.

- Utilize the hospital laboratory to undertake specialized microbiological testing as needed to support epidemiological investigations of hospital or community outbreaks of infection.

5. **Pharmaceutical industry**

The following recommendations for action are directed to governments and their health departments, to Licensing Authorities, and/or to the pharmaceutical industry itself:

5.1. **The legal classification of antimicrobial agents**

- Limit the legal classification of antimicrobials to prescription only medicines (POM) wherever possible within the framework of individual national health provision systems.

- Link the POM category to regulations controlling sales, supply and dispensing of medicines and to the scope of allowable promotional activities.

5.2. **Control of promotional activities with the aim of reducing the inappropriate use of antimicrobials**
• Align all aspects of the promotion of antimicrobials within an internationally-agreed Code of Practice; this could be broadly based on the existing Code of Practice produced by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

• Adapt this internationally-agreed standard to develop country-specific codes in accordance with national regulations.

• Institute systems for the monitoring of compliance with legislation on promotional activities and with relevant voluntary codes of practice.

• Apply a regulatory pyramid to the framework of control of promotional activities, based on interventions which are easy for regulators and the regulated to implement but with scope for increasing regulatory intervention as the degree of contravention of accepted practice increases.

• Subcontract some of the responsibility for monitoring of compliance to Non-Governmental Organizations (NGOs) in situations where the Licensing Authority itself is not able to carry out this function comprehensively.

• Work with professional medical associations to limit the scope of inducements (e.g., event tickets, hospitality, travel and direct payments) to health professionals to prescribe antimicrobial agents regardless of clinical need.

5.3. Drug promotion to prescribers and patients

• Educate prescribers regarding the evidence that promotional activities and inducements may markedly influence their prescribing habits.

• Make prescribers aware that promotion by companies in strict accordance with a datasheet may not necessarily constitute prudent use of antimicrobials.

• Ensure that prescribers have access to approved prescribing information on individual drugs and provide impartial sources of information on the relative benefits and risks of antimicrobial therapy such that prescribers do not have to rely solely on the information (e.g., detail aids) presented by company representatives.

• Draw up a code of practice specific to the control of direct-to-consumer advertising of POM preparations in countries where this is allowed.

• Educate patients regarding the appropriate use of antimicrobials, and the role of symptomatic relief medications for milder infections, in order to
counteract the potentially adverse influence of direct-to-consumer advertisements.

5.4. New drug discovery and development

- Encourage co-operative discovery efforts between industry and academia (public-private partnerships) with respect to new drugs and other modalities of preventing and managing infection.

- Introduce joint funding arrangement schemes between government grant-giving bodies and industry to support fundamental research programmes.

- Provide incentive schemes to companies to invest in research and development so that they do not have to rely on sales alone to recoup their R&D costs. Identify funding sources for such programmes.

- Amend and align international patent laws as necessary to provide better protection of intellectual property rights; consider extension of patents for truly innovative medicines.

- Make available and agree on qualifying criteria for fast-track schemes for obtaining marketing authorisation for novel agents.

5.5. Availability of essential drugs

- Encourage co-operation between governments, health care delivery systems and the pharmaceutical industry to improve the availability of essential drugs in all countries.

- Consider incentive schemes along the lines mentioned above which might facilitate such co-operative efforts.

6. Non-human uses of antimicrobials

- Develop and facilitate implementation of global guidelines for containment of antimicrobial resistance from use of antimicrobials in livestock to reduce the risk for selection and dissemination of antimicrobial resistance to humans. This should include production, licensing, distribution, sales and use of antimicrobials and should facilitate close coordination between authorities licensing drugs for animals and humans.

- Growth promoters which select for resistance to antimicrobial agents used for human treatment should not be used in animal husbandry.
• Ensure that education of prescribers and farmers should include prudent use of antimicrobials in animal husbandry and the risks of selecting resistant bacteria in food-producing animals.

• Develop and implement standards of practice to ensure that antimicrobial agents are not used as a substitute for adequate hygiene in animal husbandry.

• Encourage the development of production practices to reduce antimicrobial use in food animals. This may include animal health-oriented management systems and disease prevention measures to make the best possible use of the genetic potential for animal performance, and utilization of alternatives to antimicrobial agents for infectious disease prevention and control, such as vaccines and probiotics.

• Ascertaining and monitor the prevalence of resistant bacteria in food-producing animal populations and animal-based food products. The antimicrobial resistance monitoring programme must allow for correlating with similar data from human isolates. Collaboration of the medical, veterinary and agricultural sectors is vitally important due to the wide variety of laboratories and logistics involved in sample procurement and transport. Joint working groups at national level, including researchers and decision makers from all involved sites, should be established, agree working plans and coordinate activities. Surveillance of antimicrobial resistance serves as an important tool to develop guidelines for antibiotic use for practising veterinarians.

• Establish programmes for monitoring the consumption of antimicrobials by food animals to identify misuse and trigger investigations for identification of factors leading to overprescribing or other forms of misuse. Quantitative data on the use of antimicrobials are essential for assessment of the association between drug use and the selection and spread of resistance. Such data should be available to the appropriate authority.

D. Knowledge gaps & research needs

The knowledge gaps and research needs listed below were presented by the rapporteurs of each working group and further items were extracted from the written text provided by each of the groups.

1. Prescriber behaviour

1.1 How can policies be translated into practice in a sustained manner to improve: a) clinical diagnosis and disease management; b) prescribing practices (antimicrobial use patterns); c) patient care practices (handwashing, catheter insertion, etc.); d) adverse effects monitoring and reduction.
1.2 What are the most appropriate and cost-effective training strategies to achieve the above?

1.3 Do these practices result in improved antimicrobial use and infection control and in reduction in the emergence and spread of antimicrobial resistance?

2. Patient/public behaviour

2.1 Why are certain antimicrobials so popular; for example, injections rather than oral formulations; why some particular products rather than others (e.g. capsule rather than tablet; some colours rather than others)?

2.2 What factors influence patients’ expectations from antimicrobials?

2.3 What satisfies a patient in lieu of a prescription for an antimicrobial at every consultation?

2.4 What is the impact of gender on antimicrobial use?

2.5 In what circumstances do large and small group campaigns (designed to reduce antimicrobial use) lead to behavioural change?

2.6 Can health educators employ better marketing techniques?

2.7 What patient educational materials and other supportive tools impact optimally on patient behaviour (with respect to antimicrobial use)?

3. Laws and regulations

3.1 What would be the impact on antimicrobial resistance of enforcement of existing laws and regulations?

3.2 What are the effects of health sector reform and health care policy with respect to antimicrobial use and antimicrobial resistance?

3.3 Do economic and regulatory strategies have an impact on changing prescribers’ behaviour?

3.4 What are the effects of reimbursement, patient charges, and health insurance on antimicrobial resistance? For example, a) is there an impact on these on inappropriate antimicrobial use?; b) to what extent does a patient’s economic situation lead to overuse of antimicrobial?; c) do cost control policies have an impact on inappropriate antimicrobial use prescribing?

3.5 Are the effects of rigid formularies, antimicrobial use approval and treatment guidelines positive or negative with respect to antimicrobial resistance?
4. Pharmaceutical industry: promotional activities and research and development

4.1 How can key information on safety and efficacy of antimicrobials best be presented so that it is retained by the target audience?

4.2 What are the effects (positive and negative) of medical representatives of drug companies and industry incentives in general (advertising, seminars, travel, free lunches, etc) on the problem of antimicrobial resistance?

4.3 What incentives are needed for pharmaceutical companies to expand research in discovery of new molecular entities and new modalities of preventing and managing infection (such as vaccines and immune modulators) that will provide new, affordable treatments in the future?

4.4 What criteria/data can be used to predict, at an early stage of drug development, the dosage regimens that should be explored in major clinical trials to minimize the risk of selecting resistance while achieving favourable outcome? [licensing authorities should consider requiring that such investigations are carried out as part of the drug development process]?

4.5 Can clinical trial protocols be designed so that the role of resistance in determining clinical and microbiological outcome can be assessed?

4.6 What incentives are needed for companies to expand research into improved rapid diagnostics for infections, including simple, affordable, field-adapted diagnostics?

5. Pharmacological and clinical issues

5.1 What are the most appropriate pharmacokinetic and pharmacodynamic factors which determine the maximum efficacy and minimum emergence of resistance for an antimicrobial? (require disease- and antimicrobial-specific studies).

5.2 What is the dose and duration of therapy that maximizes efficacy and minimizes emergence of resistance (Will require disease- and antimicrobial-specific studies; resistance should be included in evaluation of the outcome).

5.3 What is the effect of patient adherence to prescribed therapy on emergence of resistance?

5.4 What is the impact of oral versus injectable therapy on resistance?

5.5 What are the effects of combination antimicrobial therapy on resistance (and on efficacy)?
5.6 What are the effects of antimicrobials with long half-lives on the development of resistance both in pathogens and in the normal flora?

5.7 Does inferior drug quality impact the selection of resistance?

5.8 What are the clinical implications of resistance detected in vitro (must be assessed by specific site and pathogen)?

5.9 What is the impact of interventions that are designed to change antimicrobial use on patient outcome? For example:
   a) How do symptom scores and patient satisfaction compare when respiratory infections (e.g. purulent rhinitis/common cold or cough/bronchitis) are treated with symptomatic therapy, antimicrobials or placebo?
   b) What is the impact of deferring antimicrobial therapy for acute otitis media? (since up to 80% of infections will resolve within 2-3 days without antimicrobial therapy).
   c) Do case management criteria for fever and rash in non-malarious areas (e.g. incorporated into guidelines for the integrated management of childhood illnesses) improve antimicrobial use?

6. **Microbial genetics and ecology**

6.1 What is the biological price in terms of reduced virulence that microorganisms pay for antimicrobial resistance?

6.2 What is the impact of antimicrobial cycling on this biological price?

6.3 Why do some antimicrobials have a greater tendency to select for resistance than others (both within and between antimicrobial classes)?

6.4 What are the clinical implications and other effects of cross resistance?

6.5 How do the antimicrobial concentrations in phagocytes impact the selection of resistance?

6.6 What are the links and interactions between antimicrobial resistance in hospitals, nursing homes and the community?

6.7 What is the impact of vaccines on the problem of antimicrobial resistance in general and on the carriage of resistant strains (specifically serotypes)?
7. Detection and surveillance of resistance

7.1 What are the essential quality assurance procedures required to ensure meaningful antimicrobial resistance data?

7.2 What is the role and cost-effectiveness of culture and antimicrobial susceptibility testing in specific patient care circumstances (including managed care settings)?

7.3 Can rapid methods, applicable to international surveillance systems, be developed to identify resistant bacteria?

7.4 What are the key surveillance networks for combating antimicrobial resistance?

8. Non-human uses of antimicrobials

Many of the above-mentioned knowledge gaps and research needs related to prescribers’ behaviour, effects and enforcement of laws and regulations, results of pharmaceutical industry promotional activities, and detection and surveillance of resistance are also valid for non-human use of antimicrobials.

8.1 Clinical trials to optimize dose, dose interval and duration of antimicrobial treatment in animals to improve prescription use of antimicrobials;

8.2 Prevention and control of foodborne and zoonotic diseases at the animal production level to reduce the risk of transmission of resistant bacteria to humans;

8.3 Non-antimicrobial alternatives for the control of infectious diseases and syndromes in animals, particularly multifactorial diseases in young animals;

8.4 Development of more rapid diagnostic methods for bacterial infections to reduce need for empirical treatment;

8.5 Interspecies transfer of antimicrobial resistance (plant, animal, humans, environmental organisms);

8.6 Rate of development of medically important bacterial resistance in food-producing animals, in relation to duration of exposure to and concentration of antimicrobial (especially concentrations below the MIC) and including the resistance selection potential of antimicrobials at permitted minimum residue levels;

8.7 Effect of cessation of use of specific antimicrobials on the prevalence and persistence of resistant bacterial in food-producing animals and their immediate environment;
8.8 Means to re-establish the normal antimicrobially susceptible flora following antimicrobial usage;
8.9 Information on the stability of important antimicrobials and their metabolites in the environment;
8.10 Impact of the use of antimicrobials in domestic pets and birds on the development and persistence of resistance bacteria in the farm environment;
8.11 Alternative approaches for growth promotion that do not require antimicrobials;
8.12 Risks from the presence of resistance genes in bacteria used as probiotics;
8.13 Appropriate risk assessment models and data needed to allow the models to be implemented;
8.14 Appropriate post-approval monitoring schemes to complement pre-approval risk assessment models.
ANNEX 1

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7. **Microbial**


