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ORIGINAL: ENGLISH
DISTRIBUTION: GENERAL

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Antibiotic resistance: synthesis of recommendations by expert policy groups

Alliance for the Prudent Use of Antibiotics
JL Avorn, JF Barrett, PG Davey, SA McEwen, TF O'Brien and SB Levy

Boston, MA, United States of America

World Health Organization

A BACKGROUND DOCUMENT FOR THE WHO GLOBAL STRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE

Acknowledgements

The World Health Organization (WHO) and the Alliance for the Prudent use of Antibiotics (APUA) acknowledge the United States Agency for International Development (USAID) for their concern about the issue of antibiotic resistance and their support in producing this report.

Stuart B. Levy, President of APUA, ensured that the report was accurate and comprehensive and that it would benefit both Ministers of Health and health care workers at the local level who can make a difference.

Kathleen Young, the Executive Director of APUA, recognized the contribution that APUA could make to support WHO's Global Strategy through this project. She designed the initial format and assured the quality of the report.

Barbara Souder, the Project Director, coordinated all aspects of this report and Margaret Kruse, a scientist and writer, acted as chief technical writer and production engineer.

APUA gratefully acknowledges the assistance of its support staff: Sarann Bielavitz, for summarizing the reports by the expert policy groups; Brian Price for the graphics; Jennifer Mills-Knutsen for administrative coordination; and Ellen Wells for bibliographic and editorial assistance.

Julia J. Chuang, from Scientific Information Resources, Bristol-Myers Squibb, United States, is gratefully acknowledged for her research work on Chapter IV.

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Designed by minimum graphics
Printed in Switzerland

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List of acronyms

AHRQ	Agency for Healthcare Research and Quality, United States
AIDS	Acquired Immune Deficiency Syndrome
AIEPI	Integrated Management of Childhood Diseases, Pan American Health Organization
APO	Audit Project Odense
AR	antimicrobial/antibiotic resistance
ARM	antimicrobial resistance management/manager/monitor
ASM	American Society for Microbiology
BBSRC	Biotechnology and Biological Sciences Research Council, United Kingdom
BSAC	British Society for Antimicrobial Chemotherapy
CA-SFM	Comite de l'Antibiogramme de la Société Française de Microbiologie, France
CDC	Centers for Disease Control and Prevention, United States
CEM/NET	Centro de Epidemiologia Molecular, Portugal/Network for Epidemiological Tracking of Antibiotic Resistant Pathogens, United States
CISET	Committee on International Science Engineering and Technology, United States
CMO	Chief Medical Officer
CNS	central nervous system
CPD	continuing professional development, United Kingdom
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Program
DDA	Department of Drug Administration, Nepal
DDD	defined daily dose
DHHS	Department of Health and Human Services, United States
DoD	Department of Defense, United States
DTC	Drug and Therapeutic Committee, Viet Nam
DVA	Department of Veterans' Affairs, United States
EARS	European Antimicrobial Resistance Surveillance
EMEA	European Medicines Evaluation Agency
ENT	ear, nose, and throat
EPA	Environmental Protection Agency, United States
ESBIC	European Society for Biomodulation and Chemotherapy
ESCMID	The European Society for Clinical Microbiology and Infectious Diseases
EU	European Union
FDA	Food and Drug Administration, United States
FESCI	Federation of the European Societies for Chemotherapy
GAARD	Global Advisory on Antibiotic Resistance Data
GAO	General Accounting Office, United States
GPs	General Practitioners
HACCP	Hazard Analysis, Critical Control Point, United Kingdom
HCFA	Health Care Financing Administration, United States
HELICS	Hospitals in Europe Link for Infection Control through Surveillance
HGOH	Hospital Gynecology-Obstetric Hanoi, Viet Nam
HIV	Human Immunodeficiency Virus
HMG	His/Her Majesty's Government
HMO	Health Maintenance Organization, United States
HRSA	Health Resources and Services Administration, Department of Health and Human Services, United States

ICARE	Intensive Care Antimicrobial Epidemiology, Centers for Disease Control and Prevention, United States
ICU	intensive care unit
ID	infectious disease
IDSA	Infectious Diseases Society of America
IMF	International Monetary Fund
IND	investigational new drug
IOM	Institute of Medicine, United States
ISC	International Society of Chemotherapy
KOL	key-opinion-leader
MDRTB	multidrug-resistant tuberculosis
MIC	minimal inhibitory concentration, testing method
MRC	Medical Research Council, England
MRSA	methicillin-resistant *Staphylococcus aureus*
MSH	Management Sciences for Health, Boston, United States
NAO	National Audit Office, United Kingdom
NARMS	National Antimicrobial Resistance Monitoring System, United States
NATAC	National Antibiotic Therapeutic Advisory Committee, Nepal
NCCLS	National Committee for Clinical and Laboratory Standards, Europe
NEPI	Network for Pharmacoepidemiology, Sweden
NHS	National Health Service, United Kingdom
NIAID	National Institute of Allergy and Infectious Diseases, United States
NIBSC	National Institute for Biological Standards and Control, United Kingdom
NICE	National Institute for Clinical Excellence, Great Britain
NICE	Nosocomial Infection Control in Europe
NIH	National Institutes of Health, United States
NINSS	Nosocomial Infection National Surveillance Scheme
NISS	Nosocomial Infection Surveillance System
NME	new molecular entity
NSG	National Steering Group
NNISS	National Nosocomial Infections Surveillance System
OIE	Office International des Epizooties
OTA	Office of Technology Assessment, United States Congress
OTC	over the counter
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PHCP/GTZ	Primary Health Care Project/ Deutsche Gessellschaft für Technische Zusammenarbeit
PHLS	Public Health Laboratory Service, England and Wales
PHON	Pharmaceutical Horizon of Nepal
PRP	penicillin-resistant pneumonia
PRSP	penicillin-resistant *Streptococcus pneumoniae*
QC	quality control
RCCDC	Regional Center of Communicable Disease Control, Malmo, Sweden
R&D	research and development
RTI	respiratory tract infection
SIGN	Scottish Intercollegiate Guideline Network
SMA	Scottish Microbiology Association
SMAC	Standing Medical Advisory Committee, United Kingdom
SRH	Smolensk Regional Hospital, Russia
STD	sexually transmitted disease
STRAMA	Swedish Strategic Program for the Rational Use of Antimicrobial Agents and Surveillance of Resistance
TB	tuberculosis
TIGR	The Institute for Genomic Research, Maryland, United States
TSN	The Surveillance Network, California and Virginia, United States
USAID	United States Agency for International Development
USDA	Department of Agriculture, United States
UTI	urinary tract infection
VRE	vancomycin-resistant enterococci
WB	World Bank
WHO	World Health Organization
WMA	Welsh Microbiological Association
WP	Working Party
WTO	World Trade Organization

Executive Summary

In the not too distant past, antibiotics could be counted on to treat a bacterial infection. Those days are almost gone, as bacteria have emerged that are resistant to each of the antibiotics currently on the market. Deaths have occurred as a result of untreatable bacterial infections. This trend is expected to continue unless the problem of antibiotic resistance can be curbed. In response to this threat, the World Health Organization (WHO) has worked with many partners, including the Alliance for the Prudent Use of Antibiotics (APUA), to develop the WHO Global Strategy for Containment of Antimicrobial Resistance (*26*).

As part of the development process of the WHO Global Strategy, WHO commissioned a series of technical reviews. APUA responded to WHO's request to review reports on antibiotic resistance prepared by prestigious scientific and governmental organizations over the last two decades. The purpose of this review is to identify areas of consensus in the experts' recommendations in the selected reports, update the findings, consider the barriers to concerted action and suggest ways to move from recommendations to action.

Twenty-five expert reports (*1–25*—see Table 1, Table 3 and Appendix A) compiled by scientific and medical authorities were selected for this review by APUA because they are highly referenced in the literature and reflect extensive deliberations by a wide variety of key expert policy groups. In developing this synthesis, APUA consulted five medical and scientific experts on antibiotic resistance who reviewed relevant sections of the reports. Their reviews are presented in Chapters I–V and cover the major areas of intervention, i.e., surveillance, education of patient and provider behaviour, prevention (including sanitary and infection control), research and product development, and antibiotic use in animals. Each author focused on those reports with extensive subject matter related to their area of investigation. In addition to summarizing findings from the expert policy reports, updated information, references and authors' insights were added.

APUA also collected information from their international chapters about experiences at the local level; these reports, reflecting the views of APUA Chapters and not necessarily reflecting national policy, are included in Appendix B.

After review, analysis and update, and with additional insights from the authors of the individual chapters of this review, the key recommendations emanating from the 25 expert reports are summarized below under the following headings:

- Increase awareness of the antibiotic resistance problem
- Improve surveillance of antibiotic resistance
- Improve antibiotic use in people
- Regulate antibiotic use in animals
- Encourage new product development
- Increase resources to curb antibiotic resistance in the developing world
- Increase funding for surveillance, research and education.

Under each heading recommendations have been organized on the basis of the suggested level of decision-making necessary for implementation of the intervention i.e., "who can do what".

A more detailed analysis of these recommendations is provided by the author of each chapter.

Increase awareness of the antibiotic resistance problem

For real reforms in the use of antibiotics to occur, individuals in the general public and in public health and provider groups at the international, national, and local levels must take ownership of the problem and provide leadership to reverse this public health crisis.

International organizations

- Obtain worldwide commitments to establish prudent antibiotic use policies.

National and municipal organizations

- **Publicize the outcomes of programmes from other countries**: Communicate global trends in antibiotic resistance with potential local impact, such as the results of the European Union's legislation against use of antibiotics in growth promotion. Collect and publicize the economic consequences, or lack thereof, of Denmark and Sweden's complete ban on growth promoters.
- **Educate the general public**: The United Kingdom's campaign to "cherish and conserve your natural flora" pointed out the beneficial aspects of bacteria which can be obliterated by excessive antibiotic use. A campaign about proper antibiotic use should be aimed at young children, the parents of young children, workers in day care centres, schoolteachers, those who work in agriculture, and policy-makers in all areas.
- **Promote communication**: Facilitate communication among academic institutions, government agencies, those who pay for health care, and pharmaceutical manufacturers to reduce the extent to which such groups act at cross purposes in relation to antibiotic use and infection control. Provide materials to support intervention programmes and utilize communication tools such as the media and the Internet.
- **Evaluate the curricula of universities**: Undergraduate, postgraduate and continuing education programmes at veterinary, medical, pharmacy, and nursing schools should be evaluated to ensure that prudent antimicrobial use and resistance are given high priority. Courses should make students more aware of how to evaluate promotional materials and what questions to ask during a sales presentation.

Health care institutions

- **Use effective teaching methods for educating prescribers**:
  - — Use group problem-solving sessions, role playing, lectures.
  - — Focus on clinical issues one at a time.
  - — Use an educational outreach worker for training at the office.
  - — Use opinion leaders or district-level staff as trainers.
  - — Repeat sessions to reinforce message.
  - — Apply community-based case management interventions.

Health care workers

- **Educate the general public**:
  - — Physicians: Discuss proper antibiotic use with all patients.
  - — Veterinarians: Discuss ways to minimize antibiotic use with animal owners, such as improved farm hygiene and alternatives to antibiotics as growth promoters.

Improve surveillance of antibiotic resistance

The urgent recommendation for surveillance of antimicrobial resistance and plans for performing surveillance have been elaborated upon over the past two decades. Over that same period a succession of unexpected, new and life-threatening resistance problems have emerged and spread throughout the world. These global outbreaks have had little monitoring to support their ultimately failed containment. Only inadequate and fragmentary surveillance systems exist today.

National and municipal organizations

- **Coordinate local surveillance networks**: Public health departments can take the initiative to contact medical centres and develop a surveillance network. If an existing privately-initiated network exists, the public health department should support and help that network to grow.
- **Recruit leaders for surveillance networks**: The public health department cannot pay for all the participants that a surveillance network requires. It has to find leaders within the network and use their help to motivate all the participants to work together on the surveillance network.
- **Support a reference laboratory**: The public health department should support a reference laboratory, hitherto lacking in many surveillance networks. The network initiator's laboratory may become the reference laboratory. With proper support, the reference laboratory can appreciably improve the performance of the network's laboratories and connect, integrate, and interpret their data.
- **Share results of surveillance with international organizations**.
- **Monitor resistance in food animals**: Undertake regular monitoring for resistant bacterial pathogens and commensals in food-producing animal populations and animal-based food products.

- **Monitor sentinel human populations**: Evaluate the usefulness of monitoring sentinel human populations (e.g. farm and abattoir workers) and people in the community for infection and/or colonization with resistant bacteria.

Health care institutions

- **Develop local surveillance networks**: Medical centres can support data gathering within their centre and join or start a local surveillance network.
- **Maintain a laboratory with adequate quality assurance and trained technicians**.

Health care workers

- **Initiate a local surveillance network**: A microbiologist or infectious disease specialist can initiate an antimicrobial resistance surveillance network; most of the networks started in various countries began in this way. The leadership and interest of these individuals and their colleagues can keep these networks functioning.

Pharmaceutical companies

- **Undertake post-marketing surveillance to detect emergence of resistance to new antibiotics**.
- **Support surveillance networks**: Support the work of a local surveillance centre through funding and/or surveillance projects.

Improve antibiotic use in people

National and municipal organizations

- **Enforce the prudent use of antibiotics**: For example, the United States federal government could adopt a strategy making the implementation of state policies to curb the misuse of antimicrobial drugs mandatory before states could receive federal funds earmarked for public health.
- **Create national and regional guidelines**: National standards and guidelines should be created for community infection control management with the following features:
  - — A requirement that every district health authority should have at least one community infection control nurse.
  - — The ability to be adapted at the local level.
  - — An implementation protocol that includes who is being targeted; how to stage the implementation; how to manage the supporters and detractors; how to reach goals, and ways to build on existing audit systems.
- **Update guidelines based on surveillance data**: Regularly update guidelines for antimicrobial use based on resistance surveillance data.
- **Eliminate financial incentives that promote the misuse of antibiotics**: In countries where governments subsidize the purchase of antimicrobial drugs, legislative or regulatory changes in these subsidies could lead to a decline in the use of the drugs. Governments could investigate the effect of changes in reimbursement on the prudent use of antibiotics and on surveillance of prescribing or resistance; for example, the United States Congress Office of Technology Assessment (OTA) identified a potential problem with Medicaid and Medicare reimbursement policies.
- **Monitor advertising**: Develop and enforce ethical standards concerning advertising of antibiotics to the general public to counteract the strong commercial pressures from manufacturers to increase utilization of antibiotics and antibacterials.
- **Consider the impact of new drugs on resistance during the drug approval process**: Consideration of resistance issues should be required prior to drug approval for human, animal, or plant use.
- **Limit general access to new drugs**.
- **Establish post-marketing surveillance accords** with producers to ensure early detection of emerging resistance to new drugs.

Health care institutions

- **Establish an Infection Control Committee** for surveillance of infection; identification of outbreaks; implementation of effective control measures (e.g., hand washing); sterilization and disinfection of equipment and supplies.
- **Establish a Drugs and Therapeutics Committee** to evaluate antibiotic use data, resistance patterns, efficacy and cost; make recommendations for proper antibiotic use that are appropriate to a particular clinical setting and population.
- **Establish guidelines for appropriate antibiotic use**: For maximum benefit, such guidelines should be:
  - — Based on evidence.
  - — Relevant and appropriate to the clinical and microbiological issues of a given population.
  - — Developed with the involvement of the prac-

titioners (and potentially the patients) who will be using them.
  - — Disseminated not simply via printed memoranda, but rather through the use of interactive strategies oriented to change behaviour.

- **Appoint an antimicrobial resistance monitor to**:
  - — Serve as a local resource to follow the current literature on antibiotic resistance.
  - — Analyse local data.
  - — Propose and implement strategies for control and resistance.
  - — Work with clinicians on the care of specific patients.
- **Reduce the spread of infection**: Adopt Centers for Disease Control and Prevention (CDC) recommendations for isolation of patients colonized with resistant bacteria.
- **Create pharmacy reports**: Hospitals should produce regular reports about pharmacy supplies to wards or clinics in the format of defined daily dose (DDD) per 1000 beds. Review the pharmacy reports periodically with the laboratory results to detect problems of resistance early.
- **Establish and disseminate essential drugs lists**: Based on those such as the World Health Organization Model List of Essential Drugs, to help simplify antibiotic choices for practitioners as well as make them more clinically appropriate and cost-effective.
- **Educate employees**: Promote education about the antibiotic resistance problem through:
  - — Providing ongoing supervision and monitoring of practice.
  - — Instituting regular audit and feedback of prescribing patterns.
  - — Teaching through the development of group processes.
  - — Developing standardized treatment guidelines.
  - — Using problem-oriented training.
  - — Providing targeted in-service training of health workers.
- **Maintain a laboratory**: with adequate quality assurance and trained technicians. Use sterile supplies and sterile procedures: Gloves and gowns are important pieces of protective equipment.

Health care workers

- **Prescribe antibiotics prudently through**:
  - — Avoiding antibiotics for simple coughs and colds.
  - — Avoiding using antibiotics for the treatment of viral sore throat.
  - — Limiting antibiotic use in uncomplicated cystitis in healthy women to three days.
  - — Limiting telephone prescription of antibiotics to exceptional cases only.
  - — Avoiding using broad-spectrum antibiotics when narrower-spectrum agents would work as well.
  - — Basing the antibiotic prescription on microbiological culture results whenever possible.
  - — Modifying the regimen over time as required.
  - — Considering cost-effectiveness in choosing an antibiotic regimen.
- **Improve hygiene**: Perform regular hand washing. Failure to cleanse hands after each patient contact spreads infection.

Improve antibiotic use in animals

Antibiotics are used not only to combat bacterial infections in animals but also as growth promoters in animals raised for meat (referred to as food animals). In some countries, about 50% of total antimicrobial production by weight is used in animal agriculture. As in people, the excessive antibiotic use in animals provides intensive training in survival-of-the-fittest to the resident bacteria. A reservoir of antibiotic resistance is building in the bacteria associated with animals which may be transferred to the bacteria living in humans.

National and municipal organizations

- **Increase awareness of the antibiotic resistance problem**: Make veterinarians and animal owners aware of antibiotic resistance impact on humans, and of the costs of resistance to themselves, their families and animals, and to the public. People need good reasons to modify their behaviours and these should be provided to them.
- **Regulate antibiotic prescriptions for animals**: Evaluate the impact of making all systemic veterinary antimicrobials available by prescription only. If sufficient evidence exists that profits from sales negatively impact on prescribing, take appropriate countermeasures. Address the reluctance or inability to regulate prescribing practices of veterinarians at the national level.

- **Restrict growth promoter use in animals**: Stop using antimicrobials of a similar class to those used for treating humans as growth promoters in animals.
- **Regulate antibiotic use in animals**: Establish a regulatory system to oversee the authorization, distribution, sale and the use of antimicrobials in food-producing animals. Establish a system to monitor the type and quantity of antimicrobials given to food animals, similar to that for humans.
- **Set a risk standard for resistance**: Identify the public health risks from antibiotic resistance that are acceptable to society. If acceptable levels for microbial risks (or "risk standards") can be agreed upon internationally, quantitative risk assessment could be used to identify resistance thresholds, beyond which public health impacts become unacceptable. If antibiotic resistance increases above levels of concern, then incremental interventions up to withdrawal of the drug from the market should be considered.
- **Consider human and non-human uses simultaneously**: A single, multidisciplinary government committee should oversee the regulation of antimicrobials in both human and non-human fields.
- **Monitor advertising**: Advertising and promotion of animal health products should comply with national guidelines and codes of practice.

Veterinarians

- **Promote the prudent use of antibiotics in animals**, in accordance with similar strategies for humans. Recommended dosages should be optimal for therapy and minimize the development of resistance. Prophylactic use should be regularly assessed for effectiveness and need.
- **Develop local guidelines for antibiotic use**: Locally derived treatment guidelines should include a list of antimicrobials for conditions commonly presented in various species, and offer a rational treatment choice based on scientific data. These guidelines should address the use of antibiotics important to humans such as fluoroquinolones.

Food animal producers

- **Improve farm hygiene**: Develop and implement standards of practice to ensure that antimicrobials are not used as a substitute for good farm hygiene.
- **Reduce use of antibiotics as growth promoters**: Reduce exposure of animals to low doses of antimicrobials for long periods of time (i.e., growth promoters and prophylactics) if such uses select for resistance to drugs used in human medicine.
- **Improve animal husbandry**: Encourage farming practices that reduce the need for prophylactic and therapeutic use of antibiotics. Alternative ways to reduce infectious disease in animals, such as improved vaccination programmes, enhanced biosecurity measures, and reduced housing density should be promoted when appropriate. This could, however, increase the cost of food production in some countries.

Researchers

- **Risk-benefit analysis of growth promoter use**: Evaluate the nature and magnitude of the impact of antimicrobial growth promoters and use the information to assist in risk-benefit assessments of each use.
- **Environmental impact**: Conduct pilot studies to assess the extent of environmental contamination by antimicrobial residues and resistant organisms that enter the soil or water from human and animal waste.
- **Food processing and distribution methods**: Evaluate the effect of current food processing and distribution methods on the emergence and spread of resistant organisms.

Encourage new product development

As the current tools used against bacteria become less effective, protecting the public from bacterial infections requires new tools. Pharmaceutical companies and related industries must be encouraged to pursue research and development of new preventative and curative measures (such as vaccines and antibiotics) and new screening and surveillance methods.

National and municipal organizations

- **Provide incentives to industry**:
  — Create policies that give pharmaceutical companies an extended patent life in exchange for increased restrictions on the sales of antimicrobials.

— Provide incentives to companies to invest in research and development so as to remove the need to re-coup their investment in a predictably poor selling, but medically needed agent.
— Streamline the regulatory process for drugs and products that are critically needed or which address infection solutions without undermining resistance solutions.
— Provide a mechanism for a government or not-for-profit organization to assume the leadership (and risk) in developing an essential infectious disease therapy product (vaccine or drug or diagnostic test) if pharmaceutical industries choose not to do so.This would be analogous to the strategy of industry licensing-in from academia by establishing the option for the reverse process to occur (license from the industrial concerns).
— Encourage pharmaceutical companies that had developed antibiotics but never commercially exploited them to pursue more antimicrobial research and development if their earlier antibiotics (now without patent protection) were given extra legal protection, either under patent law or a legal regime like the Orphan Drug Act.
— Introduce joint funding arrangement schemes for research work between governmental agencies and industry.

- **Protect intellectual property rights**: International law should provide intellectual property protection rights and enforcement to encourage industry to invest in antibiotic research, development, and delivery in developing countries.
- **Facilitate networking**: Encourage partnerships between industry, academia, and government to better exploit existing and new technologies to combat antimicrobial resistance (drugs, vaccines, diagnostics).

Pharmaceutical companies

- **Increase research and development in several areas**:
  — Vaccine research and drug discovery.
  — Pharmacokinetics, pharmacodynamics, and dosage regimens in relationship to antimicrobial resistance emergence probability.
  — Basic research into the identification and function of novel genes to provide industry with new, defined targets for therapeutic intervention.
  — Screening methods.
  — Surveillance tools, including computer programs for data management and reporting.

Increase resources to curb antibiotic resistance in the developing world

Antibiotic-resistant bacteria are found in industrialized and developing countries alike and with international travel, can pass easily from country to country.

International organizations

- **Share results of surveillance internationally**: International cooperation is needed to disseminate the results of surveillance among all countries, so that even those without the infrastructure can use the results to conduct risk assessment, make policy and manage risk.
- **Secure technical and financial support for developing countries**: Investigate methods for mandating technical or financial support from industrialized countries to developing countries.
- **Invest in a worldwide vaccine strategy to reduce antibiotic use** and combat antimicrobial resistance by preventing infectious diseases in humans.
- **Ensure the availability of vaccines and quality drugs**:
  — Initiate major worldwide programmes relating to formulation and delivery of vaccines.
  — Strengthen national and international capacity to ensure the availability and quality of anti-infective drugs.
- **Facilitate communication among the countries of the world**:
  — Introduce a global alert system requiring national governments to inform worldwide health authorities about outbreaks of resistant infections.
  — Develop a global web site similar to the Nosocomial Infection Control in Europe web site at http://helics.univ-lyon1.fr.
- **Safeguard privacy and human rights**: International human rights law must be taken into account to set effective public health policies.
- **Promote appropriate international laws**: Consultations with experts in international law is important when devising a global strategy for curbing antibiotic resistance.

National and municipal organizations

- **Decrease risk of infectious disease by**:
  - — Improving the quality of life and health with widespread immunizations.
  - — Improving sanitation and water supply systems.
  - — Emphasizing alternate methods of infection control, such as bednets in areas at risk for malaria.
- **Ensure antibiotic availability**: Availability of appropriate antibiotics for treatment of infections will contain the spread of infection in general and resistant strains in particular.
- **Share resources with other countries**: Industrialized countries should help developing countries build a quality infrastructure to address health needs in the long term, including investment in research and development.
  - — Provide support to invest in diseases in the developing world.
  - — Assist in implementing preventive strategies through improving social infrastructure and improving sanitation and water supply systems in developing countries.
  - — Support developing countries in creating reliable supply systems.

Increase funding for surveillance, research and education

Increasing understanding of the bacterial response to antibiotics and increasing operational research into interventions to deal with the antibiotic resistance are two major recommendations to help curb the antibiotic resistance problem.

National and municipal organizations

- **Increase funding for a surveillance network**: Public health departments need funding to build a surveillance network.
- **Increase funding for research**: Basic and clinical researchers need funding to identify new antibacterial targets and to better understand antibiotic resistance mechanisms.
- **Increase funding for education**: Health care providers and the general public need to be educated about the antibiotic resistance problem.

TABLE 1. **REPORTS BY EXPERT POLICY GROUPS (1987–2000)**

Year (ref no.)	Document title	Organization	Study nature, location, and time	Conclusions
1987 (*1*)	Reviews of Infectious Diseases Antibiotic Use and Antibiotic Resistance Worldwide Sponsored by the Fogarty International Center, NIH	National Institutes of Health (NIH), Fogarty Center (USA)	Six Task Forces, comprised of representatives from different disciplines and countries, studied various aspects of antibiotic resistance between 1983 and 1986.	A global, standardized surveillance system is recommended as the best way to track emerging resistance patterns. Expanded studies of the mechanisms of multidrug resistance are supported. The authors also encourage the expansion of central surveillance systems and the development of vaccines and more rapid diagnostic tests.
1990 (*2*)	Healthy People 2000: National Health Promotion and Disease Prevention. Full Report, With Commentary	Public Health Service (PHS) (USA)	Convened consortium in 1987 with 300 national organizations. The 2000 Consortium was facilitated by the National Academy of Sciences and the Institute of Medicine to assist the PHS to convene 8 regional hearings and take testimony from over 750 individuals. Over 10,000 people responded to the review and comment period.	The keys to meeting the government's objectives on infectious diseases include public education about hygiene and infection control, education of health care providers about disease epidemiology and disease prevention, research on the improvement of immunizations, diagnostic techniques and therapies, as well as immunization and efforts to maintain safe food and water supplies.
1992 (*3*)	Emerging Infections: Microbial Threats to Health in the United States	Institute of Medicine (IOM) (USA)	Between February 1991 and July 1992, a multidisciplinary committee convened to identify significant emerging infectious diseases and develop recommendations on how to deal with them.	Surveillance is crucial to the detection and control of infectious diseases. Coordinated efforts of public and private organizations, individuals and government agencies must be expanded and improved.

Year (ref no.)	Document title	Organization	Study nature, location, and time	Conclusions
1994 (*4*)	Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States	Centers for Disease Control and Prevention (CDC) (USA)	Plan developed by CDC in partnership with representatives from public and private health organizations at the local, state, national and international levels.	The creation of a comprehensive strategy is necessary to address the threat of emerging infectious diseases. To be most effective, such a strategy should be integrated with plans for reform of the larger health care system.
1995 (*5*)	WHO Scientific Working Group on Monitoring and Management of Bacterial Resistance to Antimicrobial Agents	World Health Organization (WHO)	Summary of International Workshop held by WHO, Geneva, Switzerland Nov. 29-Dec. 2, 1994.	Heavy usage of antimicrobial agents, poor infection control standards, and environmental contamination with antimicrobial-resistant pathogens are key areas of concern.
1995 (*6*)	Impacts of Antibiotic-Resistant Bacteria	Office of Technology Assessment (OTA) (USA)	Review of scientific literature, exploration of biological mechanisms behind ABR, and research into availability of new antibiotics.	Infection control, the optimal use of existing antibiotics, and the development of new antibiotics should be the primary approaches to antibiotic resistance.
1995 (*7*)	Infectious Disease – A Global Health Threat	National Science and Technology Council (USA)	Report from the CISET Working Group on Emerging and Re-emerging Infectious Diseases Convened December 1994.	In order for a global surveillance network to be realized, it is necessary to coordinate, strengthen and link existing systems. Electronic links would enhance the surveillance capabilities of the US government's field stations.
1995 (*8*)	Report of the ASM Task Force on Antibiotic Resistance	American Society for Microbiology (ASM)	Report of a workshop held on July 6, 1994.	The Task Force stresses the immediate need for surveillance of resistance in humans and animals. They also advise the more prudent use of antibiotics in human and veterinary medicine; improved hospital infection control and guidelines; improvement of infection control curricula for all health care professionals; better consumer education; and more basic research.
1997 (*9*)	The Medical Impact of the Use of Antimicrobials in Food Animals	World Health Organization (WHO)	Report of WHO Meeting Berlin, Germany Oct. 13–17, 1997.	When creating any public health policies regarding the use of antimicrobials in livestock production, it is necessary to take into account the benefits to production versus the potential risks to human health. More prudent use of antibiotics is the key recommendation, especially when viable alternatives exist.
1997 (*10*)	America's Vital Interest in Global Health	Institute of Medicine (IOM) (USA)	Report of a workshop conducted in November of 1995.	The improvement of global health, security and economic viability depends on collaborations among US government health agencies, as well as partnerships with US industry, academia and non-governmental organizations, other governments and NGOs.
1997 (*11*)	New and Reemerging Infectious Diseases: A Global Crisis and Immediate Threat to the Nation's Health. The Role of Research.	American Society for Microbiology (ASM)	Analysis of documents on emerging infectious diseases.	The report recommends increased funding for research efforts to develop improved diagnostic tests, new antibiotics, and vaccines.
1997 (12)	Resistant Organisms: Global Impact on Continuum of Care	Royal Society of Medicine (UK)	Proceedings of a conference sponsored by 3M Health Care and Regent Medical, London September 27, 1996.	The abatement of the problem of antibiotic resistance can only be achieved through cooperation of prescribers, patients, government, pharmaceutical, and agricultural industries. Surveillance, infection control, and improved prescribing practices are all important components of any collaborative effort.

Year (ref no.)	Document title	Organization	Study nature, location, and time	Conclusions
1997 (*13*)	Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the Prevention of Antimicrobial Resistance in Hospitals	Society for Health Care Epidemiology of America and Infectious Diseases Society of America	Publication in *Infection Control and Hospital Epidemiology*, Vol.18, No.4, pp. 275–291.	Antibiotic resistance must be considered a global health problem. Responsibility lies with all hospital personnel to control infections and use antibiotics properly, to help prevent its further spread.
1997 (*14*)	Antibiotic Resistance: Origins, Evolution, Selection, and Spread	CIBA Foundation (International and Scientific Charity)	Proceedings of a Symposium (#207) held at the Ciba Foundation, London July 16–18, 1996.	Reversal of antibiotic resistance and return of susceptible organisms are possible. These goals can be achieved through the implementation of rational use guidelines for new antimicrobials and through the cooperation of prescribers and consumers.
1998 (*15*)	The Current Status of Antimicrobial Resistance Surveillance in Europe	World Health Organization (WHO)	Report of WHO Workshop (held in collaboration with the Italian Associaizone Culturale Microbiologia Medica) Verona, Italy, December 12, 1997.	Europe's disparate surveillance networks would benefit from a pan-European coordinating group. Such a group could help to standardize surveillance methodologies at the local, national and international levels.
1998 (*16*)	Emerging Infectious Diseases Special Issue	Centers for Disease Control and Prevention (CDC) (USA)	Peer-review Journal: Proceedings of the International Conference on Emerging Infectious Diseases, Atlanta, GA, March 1998.	Basic research is crucial to the control of emerging and reemerging infectious diseases. Improvements in hygiene and immunization can be very effective methods of infection control, although often difficult to implement because of human nature.
1998 (*17*)	Preventing Emerging Infectious Diseases: A Strategy for the 21st Century	Centers for Disease Control and Prevention (CDC) (USA)	An evaluation and update of *Preventing Emerging Infectious Diseases*.	Implementation of guidelines from *Preventing Emerging Infectious Diseases* resulted in decreases in the prevalence of certain infectious organisms. The authors expect this follow-up plan to be successful in preparing the US public health infrastructure to respond to infectious diseases, whether they are familiar, of unknown origin, or the result of bioterrorist attacks.
1998 (*18*)	Antibacterial Drugs in Animal Feeds. Human Health Safety Criteria, Guideline 18.	Food and Drug Administration (FDA) (USA)	The criteria are suggestions for complying with regulations mandated by Congress and the Food and Drug Administration.	The criteria are meant to keep the agricultural industry within what are thought to be safe levels of antimicrobial use in food-producing animals.
1998 (*19*)	The Path of Least Resistance	Department of Health (UK)	Review of case studies, review of the basis and impact of resistance, commission of an independent review of evidence.	The prescription of antibiotics often depends on the attitudes and expectations of patients; the practitioner's decision must take into account the greater effect of the prescription, in terms of increased selection for resistance. A combined approach of practitioner and public education is recommended.
1998 (*20*)	Antimicrobial Resistance (Entire Journal for September 5, 1998 devoted to Antimicrobial Resistance)	British Medical Journal	Peer Review Journal (7 editorials and 4 papers).	Cooperation on the part of medical professionals, politicians, the pharmaceutical industry, and patients is necessary to improve the problem of antibiotic resistance.
1998 (*21*)	Resistance to Antibiotics and other Antimicrobial Agents	House of Lords (UK)	Between July 1997 and March 1998, Sub-Committee members conducted interviews at the Public Health Laboratory Service and with individual experts in the US and UK. They also gathered evidence from the agricultural and pharmaceutical industries, international and regional health organizations and professional medical and scientific societies.	The problem of antibiotic resistance must be more widely recognized as a serious threat in order to be adequately addressed. Continuing professional education would help to achieve such recognition. Locally-created antibiotic formularies and guidelines, and improved access to microbiological testing, when practical, are other important tools for practitioners. The authors urge caution in the use of antibiotic classes that are prescribed in both human and veterinary medicine.

Year (ref no.)	Document title	Organization	Study nature, location, and time	Conclusions
1998 (*22*)	Antimicrobial Resistance: Issues and Options	Institute of Medicine (IOM) (USA)	Report of a workshop conducted in July of 1997.	The participants stress the need for national and global surveillance of antibiotic resistance in animals and humans; for more prudent use of antibiotics, especially in the area of food production; improved hospital infection control and guidelines; patient education; continuing education for practitioners; and more basic research for new antibiotics and diagnostic tests.
1998 (*23*)	Protecting the Crown Jewels of Medicine: A Strategic Plan to Preserve the Effectiveness of Antibiotics	Center for Science in the Public Interest (USA)	Compilation of statistics and information from other scientific sources.	The authors recommend changes on the part of public and private institutions, as well as consumers, to prevent the further spread of antibiotic resistance. Prevention of infectious diseases is emphasized over the development of new drugs.
1999 (*24*)	The Agricultural Use of Antibiotics and Its Implications for Human Health	General Accounting Office (GAO) (USA)	Review consisting of interviews with representatives from govt agencies, agricultural industry and agricultural associations; also scientific review, and consultations with experts. May 1998–April 1999.	Despite 20 years of discussion among government agencies, consensus on the subject of antibiotic use in agriculture has not been reached. The report recommends restriction of antibiotics as growth promoters in animals.
1999 (*25*)	The Use of Drugs in Food Animals: Benefits and Risks	National Research Council (USA)	The Committee reviewed major classes of drugs used in food animals; reviewed scientific literature; heard testimony on animal drug-related issues and reviewed relevant federal regulations.	The committee's greatest concern is the potential for development of resistance to antibiotics used in human medicine due to misuse of antibiotics in food animals. To avoid any increase in such development, the committee recommends the development of new antimicrobials, with possible restrictions of their use to either human or animal medicine.

Introduction

Stuart B. Levy

The introduction of antibiotics into medical practice in the 1940s revolutionized man's ability to cure infectious diseases. Now, over fifty years later, health practitioners around the world can no longer expect their choice of antibiotic to work. Multidrug resistance has become common in clinical settings. While some antibiotic resistance is a natural consequence of antibiotic use, resistance as a clinical threat to patient care can be prevented. More prudent use of these agents will restore and maintain a bacterial environment where susceptible strains can flourish.

The cavalier use of antibiotics has resulted in the progressive depletion of cost-effective agents from our medical armamentarium. A dangerous pattern has emerged in which, as a new antibiotic is introduced, there is rampant overuse or misuse resulting in accelerated development of resistance (Table 2). In the last quarter of the century, respiratory organisms, including *Haemophilus influenzae*, and agents of sexually-transmitted infections, such as *Neisseria gonorrhoeae*, have emerged as worldwide multidrug-resistant threats. In addition, rapid increases in vancomycin-resistant enterococci and the emergence of vancomycin-resistant *Staphylococcus aureus* have raised concerns that even industrialized countries may be losing this antibiotic of last resort (Figure 1).

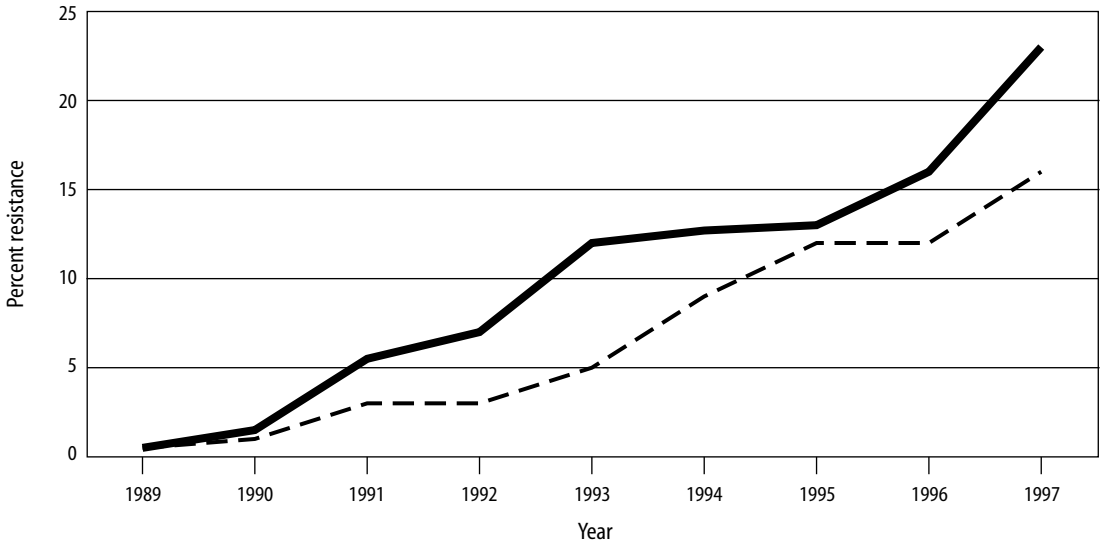
TABLE 2. **ANTIBIOTIC DISCOVERY AND RESISTANCE DEVELOPMENT**

Antibiotic	Discovered	Introduced into clinical use	Resistance identified
Penicillin	1940	1943	1940 (methicillin 1965)
Streptomycin	1944	1947	1947, 1956
Tetracycline	1948	1952	1956
Erythromycin	1952	1955	1956
Vancomycin	1956	1972	1987
Gentamicin	1963	1967	1970

Source: CIBA Foundation (*14*). Reproduced with the permission.

In addition to considering the problem on local and global levels, one must think of resistance in

FIGURE 1. **PROPORTION OF ISOLATES ASSOCIATED WITH A NOSOCOMIAL INFECTION AMONG ICU (SOLID LINE) OR NON-ICU (DOTTED LINE) PATIENTS WHO WERE INFECTED WITH ENTEROCOCCI RESISTANT TO VANCOMYCIN.**



Source: Fridkin S, Gaynes R. Antimicrobial resistance in intensive care units. *Clin Chest Med* 1999;20:306. Reproduced with permission.

terms of the broader environment in which microbes live. Antibiotic resistance is an ecological problem reflecting the fact that antibiotics are societal drugs. Antibiotic use affects not only the individual, but also the individual's environment of microorganisms, which is shared with the rest of society. Susceptible strains are removed and resistant strains replace them. Thus, any national or local strategy to curb antibiotic resistance must stress the prudent use of antibiotics so as to allow restoration of the susceptible flora in a particular community. Recognizing the role that microbial ecology plays in housing and propagating resistant pathogens and commensal organisms will help enormously in developing guidelines for antibiotic use. The microbiologist and clinician, working together as a team, can determine appropriate use in their facility or community.

Selection of reports for this review

As part of the process of development of the WHO Global Strategy for Containment of Antimicrobial Resistance (*26*), a series of technical reviews were commissioned. The Alliance for the Prudent Use of Antibiotics (APUA) responded to WHO's request and reviewed reports on antibiotic resistance prepared by prestigious scientific and governmental organizations over the last two decades. Twenty-five expert reports (*1–25*), compiled by scientific and medical authorities, were selected for this review by APUA because they are highly referenced in the literature and reflect extensive deliberations by a wide variety of key expert policy groups. There are other excellent policy reports which have not been reviewed but which could supplement those considered here, such as those from Canada, Australia, Finland and Denmark.

The review process

In developing this synthesis, APUA consulted five medical and scientific experts on antibiotic resistance who reviewed relevant sections of the selected expert reports. Their reviews are presented in Chapters I–V and cover the major areas of intervention: Chapter I. Improve and Expand Surveillance; Chapter II. Increase Awareness: Optimize Patient and Provider Behaviour; Chapter III. Strengthen Sanitation, Infection Control, and Regulatory Measures; Chapter IV. Encourage Research and Product Development; and Chapter V. Improve Antibiotic Use in Animals. Each author focused on those reports with extensive subject matter related to their area of investigation (see Table 3). For example, only McEwen (Chapter V) reviewed those reports written specifically on antibiotic use in animals and plants. O'Brien reviewed additional reports (*27*,*28*,*29*,*30*,*31*) because they were exclusively about surveillance and introduced important data and principles revisited in later reports. In addition to summarizing findings from the expert policy reports, updated information, references and the author's insights were added where considered appropriate and relevant by the author. The Summary of Reports, with key conclusions from each, is presented in the Executive Summary Table 1 together with the Key Recommendations synthesized under a series of headings:

- Increase awareness of the antibiotic resistance problem
- Improve surveillance of antibiotic resistance
- Improve antibiotic use in people
- Improve antibiotic use in animals
- Encourage new product development
- Increase resources to curb antibiotic resistance in the developing world
- Increase funding for surveillance, research and education.

Each set of recommendations is categorized by the levels of decision-making necessary to initiate action. A resumé of each of the expert reports reviewed, prepared by APUA, is contained in Appendix A.

In addition, APUA collected information from their international chapters about a number of current national and local initiatives, as an illustration of the power of local movements. Each of these programmes chose a particular feature of the antibiotic use and resistance problem and put together a team to address it. Their reports, reflective of APUA Chapters but not necessarily reflecting national policy, are included in Appendix B.

Conclusion—A manageable approach at the local level

Although concerned scientists and prestigious study groups have met to document the problem of antimicrobial resistance and suggest solutions, the key players who can impact the problem have somehow not been engaged. This review highlights the

TABLE 3

Reference No. (year of publication) Short title	General review				Control & prevention		
	Trends in diseases & resistance	Causes & mechanisms of resistance	Antimicrobial use in animals & plants	Economic cost of resistance	Public health promotion & prevention strategies	Public policy strategies	Surveillance
1. (1987) Antibiotic use and antibiotic resistance worldwide: report of a study sponsored by the Fogarty International Center of the National Institutes of Health, 1983–1986	x	x		x	x	x	
2. (1990) Healthy People 2000: National Health Promotion and Disease Prevention					x	x	x
3. (1992) Emerging Infections: Microbial Threats to Health in the United States			x		x	x	x
4. (1994) Addressing emerging infectious disease threats: A prevention strategy for the United States					x		
5. (1995) WHO Scientific Working Group on Monitoring and Management of Bacterial Resistance to Antimicrobial Agents		x				x	
6. (1995) Impacts of Antibiotic-resistant bacteria	x	x	x	x	x	x	x
7. (1995) Infectious Disease– A Global Health Threat	x		x			x	
8. (1995) Report of the ASM Task Force on Antibiotic Resistance		x				x	x
9. (1997) The Medical Impact of the Use of Antimicrobials in Food Animals			x				
10. (1997) America's vital interest in global health: Protecting our people, enhancing our economy, and advancing our interests						x	
11. (1997) New and Re-emerging Infectious Diseases: A Global Crisis and Immediate Threat to the Nation's Health	x				x		
12. (1997) Resistant organisms : Global Impact on Continuum of Care		x				x	
13. (1997) SHEA Position Paper on Prevention of Antimicrobial Resistance in Hospitals		x			x	x	
14. (1997) Antibiotic Resistance: Origins, Evolution, Selection and Spread	x	x	x	x	x	x	x
15. (1998) The Current Status of Antimicrobial Resistance Surveillance in Europe							x

Reference No. (year of publication) Short title	General review				Control & prevention		
	Trends in diseases & resistance	Causes & mechanisms of resistance	Antimicrobial use in animals & plants	Economic cost of resistance	Public health promotion & prevention strategies	Public policy strategies	Surveillance
16. (1998) Papers from the International Conference on Emerging Infectious Diseases	x		x		x	x	x
17. (1998) Preventing Emerging Infectious Diseases: A Strategy for the 21st Century	x			x	x	x	x
18. (1998) Human Health Safety Criteria Guideline 18			x				
19. (1998) The Path of Least Resistance		x					
20. (1998) British Medical Journal special edition on Antimicrobial Resistance			x		x	x	x
21. (1998) Resistance to antibiotics and other antimicrobial agents		x					
22. (1998) Antimicrobial Resistance: Issues and Options	x					x	x
23. (1998) Protecting the Crown Jewels of Medicine: A Strategic Plan to reduce the spread of antibiotic resistance		x				x	
24. (1999) The Agricultural Use of Antibiotics and its implications for human health	x		x			x	
25. (1998)The Use of Drugs in Food Animals: Benefits and Risks			x				

need for action at the national and local levels to break this pattern and to reverse increasing rates of resistance in communities and countries worldwide. It also identifies a number of barriers to be overcome including:

- The complex, and somewhat invisible, nature of the problem;
- Financial incentives which foster misuse of antibiotics;
- Lack of necessary coordination among many disciplines;
- Lack of adequate funding, leadership, and accountability at the national level;
- The complexity and vast number of possible interventions, making prioritization difficult.

Despite these formidable barriers, it is the local nature of the problem which provides optimism that resistance can be contained and curbed if susceptible microbes can be re-established within defined areas. Individual institutions and health practitioners that use antibiotics more prudently will restore bacterial equilibrium in favour of susceptible bacteria and thereby preserve the effectiveness of antibiotic therapy in their communities.

While the WHO Global Strategy (*26*) provides a thorough and comprehensive foundation, it is up to each nation, local institution and local provider to tailor specific initiatives to their particular resistance problems, resources, and practices.

CHAPTER I

Improve and expand surveillance

Thomas F. O'Brien

Abstract

Expert groups advising on control of antimicrobial resistance have repeatedly emphasized the need for surveillance of resistance. This chapter reviews the discussions and recommendations on surveillance of resistance in reports issued by sixteen such groups over the past two decades.

The problem of antimicrobial resistance is enormous because of the magnitude of the interconnecting global bacterial populations it involves. It is intricate because of the diversity of resistance genes and genetic vectors responding to differing usage of antimicrobial agents on different parts of those populations in different parts of the world. It is also peculiarly circular since an attempt to cure one patient may eventually prevent cure of another.

For these reasons, as reflected in these reports, resistance presents different problems to a remarkably wide range of caregivers, policy-makers, and researchers, and they need different kinds of information from surveillance. The reports identify needs for local information to guide local selection of agents for individual patients, infection control in the hospital, public health in the community, and local antimicrobial usage strategy. Different analyses are needed at the national level to overview resistance epidemiology and to set drug policy. Global detection and tracing of emerging problems are also needed.

The reports recognize that information for surveillance of resistance must ultimately begin with data from microbiology laboratories and that these laboratories need to be increased and improved. They look to advancing information technology to link clinical laboratories in networks guided by reference laboratories that would work to both generate and improve the data. They also seek to integrate this information with additional patient information, including patient antimicrobial usage, in order to make better systems for the management of local resistance. Such data from multiple centres would also provide more detailed understanding of the relationship of antimicrobial use to the spread of resistance.

The groups made generally similar recommendations over the two decades, although some of their more recent reports have commented on how little these recommendations have been implemented. An obstacle may be that surveillance of resistance, as noted, requires an unusual degree of cooperation and integration between the efforts of caregivers and public health workers. Caregiving institutions are the predominant producers and users of resistance surveillance data, but public health leadership and support is needed to integrate the data into larger systems and to collaborate in understanding and containing resistance.

Synthesis and summary

Do we need surveillance of antimicrobial resistance?

The groups were nearly all emphatic about the need for surveillance of antimicrobial resistance, as reflected in their statements:

- "without reliable information … it would be impossible to find solutions"(*2*)
- "more systematic surveillance on a much larger scale is needed to provide explanations or remedies"(*4*)
- The US should "take the lead in promoting the development and implementation of a comprehensive global infectious diseases surveillance system."(*5*)
- "Distribute …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."(*6*)
- "There is an urgent need for effective domestic surveillance of antibiotic resistance in animals and humans."(*7*)
- "A surveillance system is essential for understanding the spread of antibiotic-resistant bacteria and

planning interventions so as to preserve the efficacy of currently available antibiotics."(*9*)

- "Establish a system for monitoring bacterial resistance and antibiotic usage."(*10*)
- "Redressing these deficits"[in surveillance] "is crucial in global and national public health terms, and the most powerful case possible must be made for urgent and substantial response."(*12*)
- "Systematic collection of epidemiological data on resistance should be initiated immediately…The costs to the NHS are likely to be modest compared with many other actions."(*13*)
- "Comprehensive surveillance is required to measure the public health impact of antimicrobial resistance and of interventions (including those proposed in this report) to minimize antimicrobial usage."(*14*)
- "A critical elemental in addressing the environmental impact of antimicrobial resistance is effective surveillance…With respect to antimicrobial impact on the environment, surveillance involves not only data on bacterial pathogens, but also data on other microorganisms that are part of the affected ecosystem."(*15*)
- "Surveillance of antibiotic resistance (AR) is critical to provide early warning of emerging problems, monitor changing patterns of resistance, and target and evaluate prevention and control measures."(*16*)

What kind of surveillance do we need?

Systems for surveillance of antimicrobial resistance have many common and interrelated elements, which are mentioned frequently in the reviewed reports. Any one system will be a blend of and a balance between these elements. Report numbers referenced below for each element do not cite all of the reports that touched upon that element, but only some that are representative or most pertinent.

Antimicrobial resistance is an enormously complex subject, dealt with by microbiologists, clinicians, epidemiologists, pharmacists, basic research scientists, infection control workers and public health workers, etc. They see the problem in different ways and, as members of these expert groups, have wanted different kinds of information from surveillance of it. Nonetheless, a general consensus about the elements of surveillance emerges from these reports, and their differences often seem complementary.

Clinical microbiology laboratory information

The essential basic element of surveillance is information from microbiology laboratories. Antimicrobial resistance is ultimately about different kinds of bacteria and their susceptibility to different antimicrobial agents. Microbiology laboratories are the only source of such information, and most of it is generated by routine clinical microbiology laboratories.

The immediate users of such data from any microbiology laboratory are health care workers in the hospital and the community it serves. They need this level of surveillance information to treat individual patients, to update local treatment guidelines, to observe effects of their local interventions and to detect, monitor, and contain local spread of resistant strains (*3*,*6*,*12*,*14*,*15*).

The most direct, responsive, and useful way of providing local health care workers with the surveillance information they need is to file the data from their clinical microbiology laboratory in a user-friendly, local electronic database, which they can query instantly, repeatedly, and in specific detail, as problems arise. The World Health Organization (WHO) provides free software for such a database (WHONET) and additional software (BACLINK) to translate data into the database from existing local computerized laboratory reporting systems that lack database capability (*6*,*7*,*15*).

The need for antibiotic use data. In addition to resistance data there is need for health institutions and governments to collect and review antibiotic use data. This would allow more precise analyses of relationships between antibiotic use and resistance. Much of the antibiotic use data reside within pharmaceutical companies which should be encouraged to share this information with public health agencies. Also, governments could set up their own systems and requirements to collect the use data from health care providers and institutions. In addition, post-marketing resistance surveillance should be routine to detect resistance trends.

Problems with quality of clinical microbiology laboratory information. Several of the groups recognized problems with the existing quality of clinical microbiology laboratory data. Quality of testing may be uneven in many laboratories, and there is often no programme for quality assurance. These limitations may represent lack of funding, supplies, training or oversight. Many regions lack microbiology labo-

ratories altogether, and where they do exist their services may be underutilized or improperly utilized. Information is further diminished if a laboratory reports only the interpretations of susceptibility tests without their actual measurements (*12,16*).

Recognition of these limitations has prompted recommendations in the reports reviewed for development, support, training, improvement and quality assurance oversight of clinical microbiology laboratories, and for more of them in some places. Their improvement is seen as essential for a comprehensive surveillance system and, not incidentally, to improve care for the many patients whose individual treatment is being directly affected by tests done in those laboratories (*6,12*).

Problems with analysis of clinical laboratory information. Another limitation of using only clinical microbiology laboratory reports, cited by several of the reports, is that it relates to an uncertain population base. Prevalence of resistance is commonly expressed as a percentage derived from the number of resistant isolates as the numerator with the number of both resistant and susceptible isolates as the denominator.

This is adequate for many practical uses of surveillance information, including many at the local level such as infection control. It can, however, allow a sampling bias that overstates resistance by ignoring susceptible strains obscured by successful treatment without culture, or by more culturing in places where there is more resistance. It also limits more formal epidemiological studies of resistance and its contribution to disease burden (*14*).

The reports that mention this need for more appropriate denominators do not specify how to get them. Presumably, the microbiology databases would have to be linked to other databases containing demographics, diagnoses, etc., which could better characterize the patients. The microbiology databases could also be linked with pharmacy databases in order to identify those patients who were treated for infection without being cultured before treatment. Advances in informatics are now beginning to make this a real possibility (*14*).

Members of some groups wanted to specify in advance which bacterial pathogens should be included in surveillance, presumably to minimize work or data storage costs. We have been repeatedly surprised in recent decades, however, by resistance problems emerging in species where they had not been expected (e.g., enterococci). We have also come to recognize the importance of early detection of such new problems (called "alert organism surveillance" or "exception reporting" in one report). Over the same period, moreover, the costs of data storage and management have plummeted to near trivial levels (*7,14*).

A similar question about what to include in the database further illustrates differences in viewpoint. Those investigating the evolution or ecology of antimicrobial resistance see resistance as epidemics of resistance genes through vast populations of bacteria that rarely infect. They want surveillance to elucidate and trace how resistance genes emerge, get into vectors and become linked under selection and co-selection in reservoirs of environmental or colonizing bacteria before finally entering a pathogenic strain that may infect someone. Their denominators are bacterial populations. They think that everything important for resistance happens in the bacteria before the infection begins and the epidemiologists start to count people for their denominators.

Advancing information technology has the potential to accommodate such diverse views. It can facilitate entry of data that is well characterized, so the database can be broadly inclusive at little cost and still allow subsequent analyses of any selected subsets of the data to be sharply defined. Your pathogens need not interfere with my commensals, and we may both learn how they interact (*4,12,15*).

The roles of microbiology reference laboratories

The reviewed reports identified multiple roles in resistance surveillance for microbiology reference laboratories (*6,14,15*).

Surveillance by the reference laboratory. Reference laboratories can themselves do surveillance of antimicrobial resistance. The usual way is for a network of clinical laboratories to collect designated types of bacteria from among those they routinely isolate and ship them to the reference laboratory. The reference laboratory then retests the susceptibility of those isolates and may also repeat their identification.

Reference laboratory surveillance has the potential to test the isolates by more uniform methodology and against more agents. Testing against more agents can distinguish fine differences between agents and discriminate more resistance phenotypes. Having all of the isolates in one laboratory

also makes it easier to use newer methods to investigate their genetic relatedness and the molecular bases of their resistance phenotypes.

The limitations of this model of reference laboratory surveillance is that it is expensive and therefore can sample only a tiny fraction of a network's clinical isolates. It is best at answering selected questions or providing general overviews of specific problems. Its information on population denominators for the isolates it tests is no greater and may be less than that of the network clinical laboratories that contributed them. It also lacks the detail needed for surveillance at the local level. Local infection control needs to know the locations of the last hundred patients who had methicillin-resistant *Staphylococcus aureus* (MRSA), and not just of the two whose isolates were sent to the reference laboratory.

It would be valuable, however, for local surveillance to know both the locations of their last hundred patients with MRSA, from their own local database, and also how their local testing of the two MRSA isolates sent to the reference laboratory compared to its testing of them. It would additionally be useful for them to know how their two isolates related to the MRSA sent in from other centres. Conversely, it would be useful for the reference laboratory to know whether the two isolates they tested from that centre represented only a few such isolates at that centre or an extensive outbreak.

For such reasons, the value of integrating the data from routine clinical laboratories and the data from reference laboratories on the isolates they have both tested was recognized by several of the groups reviewed, and characterized as "cross-validating" by one of them. It does not appear to have been much exploited yet (*14*). Most existing reference laboratory surveillance has been proprietary, its large budgets supported mostly by pharmaceutical companies seeking information on particular issues. Cross-validation has thus not been a priority.

It would seem easy, however, to extend the analyses of databases of such proprietary systems to cross-validation and to other questions framed by public health concerns. There will undoubtedly be a need also to develop antimicrobial resistance reference laboratories in the public health sector, not only to do some specialized or "cross-validating" surveillance, but to also have multiple other roles in coordinating multi-centre surveillance networks, as discussed below.

Reference laboratory roles in coordinating multi-centre surveillance networks. Organizing networks of medical centres and merging their individual susceptibility test databases can generate a national resistance surveillance database without great expense. The organized network can then serve as a base for collaborative programmes that use continuing quality control and benchmarking analyses of the shared data to improve its quality, use, and interpretation both locally and nationally.

Several of the groups discussed the roles that a central reference laboratory could play in organizing and coordinating such a surveillance network. It could take the initiative in recruiting and setting up the network. It could train participants in use of the network software. It could develop or be the network distribution point for proficiency testing and other quality assurance programmes for network laboratories. It could give network laboratories training courses shaped, in part, by problems seen in the results of such quality testing results and in the analyses of the data flowing through the network (*6*,*14*).

To the extent that a network reference laboratory also conducted surveillance projects on the reference laboratory model sketched above, it would have the opportunity to further improve routine network data by the kind of cross-validation mentioned above. Finally, the reference laboratory would take the lead in the continuing analysis of total network data and in improving the local analyses ongoing at each centre in the network (*14*).

Active surveillance. "Active surveillance" is a term sometimes used in descriptions of epidemiological studies. Within the context of studies of resistance the term may be applied at a number of levels, for example: the identification and recruitment of a patient or study population; the collection of screening or diagnostic specimens; the performance of non-routine testing; and/or the in-depth analysis of data. Used in this sense, active surveillance can often be accomplished within, and be a valuable complement to, routine clinical practices. For some purposes, however, it may also require special studies.

Special studies. Special studies to provide more surveillance information than is in routine clinical isolate data usually undertake to obtain additional designated specimens for culture, or additional categories of patient information, or to perform more elaborate isolate testing or data analysis.

Such studies might, for example, survey resistance of *E. coli* from stools of untreated healthy people, of *S. pneumonia* in nasopharyngeal swabs from children in a day-care centre, or the urinary isolates of all untreated women presenting with symptoms of urinary tract infection.

Alternatively, they might seek to record all diagnoses, or extensive demographic data or all antimicrobial therapy in a given population of patients. They might also perform extensive analyses of the genotypes of isolates of one species or of the linkages of different antimicrobial resistance phenotypes in different bacterial species in various collections of isolates.

Because such special studies have usually been labour intensive, requiring extra effort and funding, they have tended to be fragmentary and difficult to sustain. They do, however, have the potential to enhance the information obtained from surveillance and improve its epidemiological foundation, especially if they can be linked to one another and to more routine surveillance to develop new kinds of cross-validation (*14*).

Advancing information technology has the potential to eliminate the extra effort required for some of these studies and so make them more widely utilized. Data on patients' demographics and use of antimicrobials are increasingly being filed in electronic reporting systems, along with their microbiology test results. Downloading all three into a common database would routinize and so make widely available analyses previously kept rare by the need for tedious chart review.

Participants interconnected in existing surveillance networks may also be better organized, if not already self-selected, to collaborate in ongoing projects requiring collection and culturing of additional specimens.

Information systems for surveillance

Many of the reviewed reports emphasized how essential for the surveillance of antimicrobial resistance are computerized information systems, but few explored their specifications. The needs seem obvious and advancing information technology should be making it easier to meet them (*3*,*5*,*6*,*7*,*13*,*14*).

Software exists now, as mentioned above, to put any laboratory's susceptibility test results and some basic demographics of the cultured patients into a database dedicated to that application. If software with the same or easily matched codes and file format is used by all the laboratories in a network, merging their databases, after 'hashing' for confidentiality, into a database network costs almost nothing.

Further development of such software could increase its usefulness for infection control data management. Downloading discharge data on each patient's diagnoses and pharmacy data on each patient's antimicrobial usage into additional fields in the same database would make it possible to analyze what kinds of isolates preceded or followed what kinds of antimicrobial therapy in patients with what kinds of diagnoses (*7*,*14*).

Downloading pharmacy data on antimicrobial usage by each patient at each medical centre in a multi-centre resistance network would also allow the network to capture that data for the whole network, as it does the resistance data, by merging the databases of all the centres. This could be one component of a national system for surveillance of antimicrobial usage. Such surveillance has been strongly recommended in several of the recent reviewed reports, but none of them has offered much detail on how to do it (*12*,*16*).

Information technology now makes it easier to implement such integrated information systems. A type of software called a data conversion utility facilitates matching of data fields and translation of codes between the various electronic systems that report and store relevant data sets in different medical centres and a common database that can analyze all of their interrelationships. An example would be BACLINK, which facilitates translations of data from various microbiology reporting systems into common WHONET files.

Research on surveillance data

We can picture how resistance genes may emerge, insert into genetic vectors and spread under selection in one or many strains and species through the world's interconnecting bacterial populations. The picture we have, however, is projected largely from expectations based on the well-studied molecular details of those genes and vectors. Plasmids can transfer, and resistance genes should move in and out of integrons, etc., but only rarely have we been able to observe them actually doing those things in the real world. The microbes' resistance system is operating all around us, but we cannot observe its workings or the rates at which changes occur. If we could, we might manage it better.

The kind of systematic surveillance of resistance

recommended by many of these reports, coupled with advancing molecular technology, should make it possible to do at least some surveillance at the molecular level. We should be able to trace lineages of resistance genes, genetic vectors, and strains of bacteria in different circumstances and under differing selection. The goal would be to improve our ability to predict what will happen and to intervene and avert problems (*3*,*4*,*6*).

Research and surveillance are each recommended in nearly all of the reviewed reports, but only a few make a connection between them. We need research on how best to do surveillance. We need further development of surveillance software and research on how to use it fully. We also need to develop surveillance linked to molecular technology as a research tool to elucidate the real world population biology and detailed epidemiology of antimicrobial resistance.

What have been the barriers to the implementation of surveillance?

The urgent recommendation for surveillance of antimicrobial resistance and basic plans for how to do it were made nearly two decades ago (*2*,*3*). Its urgency has been reemphasized and elaborated upon by each of the expert groups that has met since. Over that same period, a succession of unexpected, new, and very damaging resistance problems have emerged and spread throughout the world. These global outbreaks, one after another, have had only the sketchiest of monitoring to support the ultimately failed attempts at containment. As nearly all of the recent reports agree, only inadequate and fragmentary surveillance systems exist today.

The reports reviewed do not examine the reasons why prior reports' recommendations for surveillance of antimicrobial resistance had been so little implemented, except for one that discusses barriers and resources in one country (*13*). The nature of antimicrobial resistance, the types of recommendations made, and the experiences of those surveillance systems that have been started may, however, suggest some of the barriers.

Compared to other medical problems being brought to the attention of the public and public health officials, antimicrobial resistance is an extremely diffuse subject and difficult to describe. It is not in one organ or one type of patient but carried by all of us and in the environment. It is not a disorder in people as much as it is a disorder of the world's huge but invisible bacterial populations. Attempts to cure people drive a process that ultimately prevents cure of other people. The fact that it is confusing may have been a barrier to focusing attention on recommendations to contain resistance.

The recommendations for surveillance made in these reports require perhaps unprecedented cooperative activity in any country between a small number of public health officials and large numbers of diverse groups of health care workers. Antimicrobial resistance is a public health problem. Most of the people who are causing it, trying to cope with it, and generating nearly all of the information on it, however, are providing services to individual patients. They produce, own, and have the most immediate and varied uses for the data that will have to be recycled into public health surveillance if there is to be any.

The two parties need to help each other. The public health official on whose desk the recommendations arrive may not have a detailed grasp of the workings of the microbiologists, pharmacists, infection control workers, and clinicians in the medical centres and the communities they serve. Conversely, it may not occur often to these busy multi-specialty local health care providers that they are in part public health workers.

Most of the antimicrobial resistance surveillance networks that have gotten started in various countries over the last decade or so were initiated by a microbiologist or infectious disease specialist. He or she began to file and analyse local susceptibility test results in a database in his or her own medical centre, then persuaded colleagues at other centres to do the same. Occasional funds and/or occasional surveillance projects from pharmaceutical companies helped. The leadership and interest of these individuals and their colleagues have kept many of these networks functioning, and some have grown to include thirty or more centres.

Less often, a public health department has taken the initiative to contact medical centres and begin development of a surveillance network. What seems to have worked best has been when a public health department has established a relationship with one of the beginning privately-initiated networks. In two such examples some relationship had existed from the beginning, and the public health division had later expanded its support when it came to realize the value of the growing network.

When a public health department has come to support a surveillance network, substantial im-

provements have followed. Presumably two things have happened. The first is that the network had been built with participants who were motivated, in that they had been self-selected by their interest and belief that a network could help their work locally.

The second is that the public health department could begin to support a reference laboratory, hitherto lacking in those networks. In each of these two cases the network initiator's laboratory became the reference laboratory. With this support, it could begin to perform the reference laboratory functions described above, and the networks improved appreciably.

Each of the two parties has its own barrier. The public health department needs to be given funding and accountability to build a surveillance network. The public health department, however, cannot begin to pay all the participants that a network needs. Therefore, it has to exercise real leadership in finding leaders within the network, and, with their help, motivate all the participants to work together on the network.

Similarly, none of the participants in the network would be able to fully support a reference laboratory. Yet, the improvements in the network from such a laboratory can enhance the work of the participants. Cooperative mutual barrier removal between public health and local health care may be the most important process in implementing surveillance of antimicrobial resistance.

Governments and their public health agencies need to take the lead in removing these barriers and in encouraging clinical laboratories to participate fully in surveillance networks. They have rarely done this because they have been slow to see the epidemic nature and the menace to health of antimicrobial resistance and thus slow to see it as a public health responsibility, deserving priority and adequate support.

Authors' notes on reports

(*27*) WHO International Collaborative Study of Antibiotic Sensitivity Testing (1968–1970)

This study, carried out in 16 laboratories in different parts of the world, was set up in response to a recommendation of the WHO Expert Committee on Antibiotics.(1961) It was sponsored by WHO, initiated at a meeting in Geneva and coordinated by the Karolinska Institute in Stockholm, with financial support for meetings and administrative work provided by WHO.

The study compared, in multiple countries in great quantitative detail, both broth dilution and agar diffusion methods for antimicrobial susceptibility testing. It essentially began the development of the framework for standardizing and interpreting test results and comparing results from different countries, which are essential prerequisites for surveillance of resistance, especially for international surveillance of resistance.

Its 90 page report, published as a supplement to ACTA Pathologica et Microbiologica Scandinavia (Section B 1971, Supplement No. 217) did not use the word "surveillance" which may not then have been applied to antimicrobial resistance, but for which the study began to build a foundation. It did, however, begin by listing as one of three purposes for standardizing the measurement of the sensitivity of microorganisms to antibiotics (along with rational use and evaluation of new agents) as "for epidemiological studies."

(*28*) WHO Scientific Working Group on Antimicrobial Resistance, Geneva, 23–27 November 1981. WHO/BVI/PHA/ANT/ 82.1

The Working Group outlined the current situation of antimicrobial resistance. It emphasized that the increasing frequency of acquired resistance to antibiotics among bacteria of medical importance is a worldwide health problem that demands international attention. Its report concluded that without reliable information about the susceptibility to antibiotics of important bacteria, it would be impossible to find solutions to the problems created by antibiotic resistance.

The Working Group therefore recommended promotion of surveillance activities at both national and international levels and suggested that WHO could play an important role in promoting these activities. It stressed the necessity of extending the WHO activities in establishing a system for surveillance of antibiotic resistance, and concluded that there was a need for unification of methodology used for the surveillance.

(*29*) WHO Consultation Group for Surveillance of Antimicrobial Resistance, Geneva, 22–26 November 1982. WHO/BVI/PHA/ ANT/ 82.5

This meeting was convened to respond to the recommendations on surveillance of the previous year's Scientific Working Group (above). Its purpose was to discuss the approaches to and objectives of national and international surveillance of antibiotic

resistance, and to make recommendations as to how such a surveillance programme might be designed and implemented on a global scale.

The plan proposed was to:

1. Develop systems to produce reliable data on resistance in all parts of the world.
2. Develop systems to ensure that the data are of good quality and comparability.
3. Analyse the resulting data in many different useful ways on a continuing basis.
4. Use the analyses to monitor, understand and control the spread of resistance.

The Consultation Group identified three general sources of data for surveillance. One was the susceptibility test result data generated in enormous volume by the world's clinical microbiology laboratories. A second was the more specialized data generated by reference laboratories. A third would come from special studies with epidemiologically planned sampling not just of selected patient populations but also of healthy people in different settings and of the environment. The group emphasized that planning in advance to integrate analyses of data from these three general sources would allow cross-referencing enhancement of the value of each.

The report made general recommendations for methods of susceptibility testing, and also for quality control of that testing and for what antimicrobials to test, drawing upon an earlier WHO report on "Guidelines for Antimicrobial Testing (WHO, Ref, LAB/79.3 in Annex)". It pointed out the need to record the actual measurements of susceptibility, such as diameters of zones of inhibition around susceptibility test discs or minimal inhibitory concentrations, rather than the interpretive categories derived from them.

The Consultation Group also examined in some detail the management of the data from such surveillance. It recognized that nearly a dozen categories of data, such as type of sample, date of sample, and the identified species and susceptibility measurements of each isolate were recorded in most laboratories.

Planning in advance a common software format for filing the data in these categories and common codes for the terms and measurements of that data would thus greatly simplify the merging, managing and analysis of data from many laboratories and sources.

The report noted also that once such data are electronically filed, it is easy and cheap to analyse and reanalyse it in many ways to fully extract from it practical understanding of the emergence and spread of resistance. For illustration, it sketched out nine different types of such analyses. It went on to explain how results from these analyses could be extrapolated to insights about prevalence or resistance in different places and different subpopulations, about prevalence of resistance genes and about the evolution and epidemiology of resistance plasmids. It summarized this with a table (below) offering three examples of the kinds of observations that might be made from such

Level	Observation	Use
Local	Frequency of resistance to each antibiotic	Aid selection of antibiotics for individual patients
	Frequency of resistance to each combination of antibiotics	Identify cross-infecting strains, locally endemic resistance plasmids
	Local trends in resistance	Aid re-evaluation of local antibiotic usage and infection control practices
National	More resistance to one antibiotic than usual in other countries	Decrease use of the antibiotic, introduce alternative agents
	Variation in antibiotic resistance in different regions of the country	Seek regional differences in usage, vehicles of resistance spread, e.g., food or water, hygienic practices
	General level and trend of national resistance overall in comparison with other countries	Review, revise national antibiotic usage strategy to increase its effectiveness, reduce resistance
Global	Global trends in resistance to various antibiotics, prevalence of different genera	Guide development, use of new antibiotics, ways of preserving older ones. Compare countries' practices
	Early detection of new resistance to an antibiotic in a particular strain in a particular area	Global warning to detect, contain, treat the emerging strain, examine circumstances preceding emergence
	Global trends in prevalence of distinctive combinations of resistance or resistance genes	Detection, prevention of international spread of particular resistance plasmids of resistant strains

surveillance at each of three levels, local, national, and global, and then of the kind of corresponding practical responses that might be made by caregivers and policy-makers at each level.

Even though this Consultation Group was meeting within about a year after the introduction of the IBM personal computer (PC), at a time when applications of the PC were only beginning, the group noted its potential significance. "Now, however, rapid improvement and reduced costs of small computer technology may soon make it possible to enter the data directly on cassette tape or disc at the testing laboratory." They further observed that this would make possible local analysis of the data for local management of resistance at each medical centre in addition to the more centralized multicentre analysis, which was all that had been practical previously with the big, expensive mainframe computers.

(*1*) Antibiotic Use and Antibiotic Resistance Worldwide, A study sponsored by the Fogarty International Center of the National Institutes of Health, 1983–1986

Nearly all reference to surveillance of antimicrobial resistance in this study performed by five task forces comprised of international experts was in the report of Task Force 2, entitled "Resistance of Bacteria to Antibacterial Agents." The 13 members of that Task Force came from 5 continents, with only 2 of its members from the same country. Many of the members brought available data on resistance from their own medical centres, from colleagues in their countries, or from published literature. Data were also presented from a computerized and isolate-based international surveillance system supported by the US Food and Drug Administration (FDA), which was then ongoing but discontinued later when FDA found an international study inappropriate.

The work of Task Force 2 was to piece together from this available information an overview of the current distribution and apparent trends of antimicrobial resistance throughout the world. Their particular emphasis was to try to integrate what data they had with growing understanding of the molecular basis of resistance and of its spread, so as to be able to interpret one in terms of the other. Their report attempts to do this by examining resistance to agents grouped according to their being inactivated by the same families of resistance mechanisms.

The first recommendation of Task Force 2 was: "The available data on global prevalence of resistance to antibacterial agents were barely adequate to sketch ranges and suggest trends. More systematic surveillance on a much larger scale is needed to provide explanations or remedies. The World Health Organization has developed detailed recommendations for such surveillance and is now beginning integrated surveillance programmes in several regions of the world…This initiative should be exported and expanded."

Their second recommendation began by noting the growing understanding of the genetic elements of resistance. It then stated: "What are particularly needed now are broadly based studies of the deployment of these genetic elements in natural populations of bacteria that will provide an explanation of the phenomena observed in surveillance and suggest practical strategies for containment and reduction of resistance."

(*3*) Emerging Infections. Microbial Threats to Health in the United States. Report of the Institute of Medicine. National Academy Press (1992)

This report called attention to a whole group of recently observed or recently worsening infectious disease problems by creating a new category for them, Emerging Infections, and setting forth their special features and similarities and the growing seriousness of their threat to human health. It amplified the perceived importance of antimicrobial resistance by including it in this category of Emerging Infections.

The report repeatedly emphasizes the importance of surveillance for the control of all emerging diseases. They constitute such a large and diverse set of problems, however, that the report did not attempt to delineate the special needs for the surveillance of each, let alone for antimicrobial resistance, which probably differs most from the others in surveillance methodology. Surveillance of resistance is, however, mentioned in several places.

1. Additional resources are recommended for the Centers for Disease Control and Prevention (CDC) to enhance its National Nosocomial Infections Surveillance System (NNISS) in five ways. The first is to "include data on antiviral drug resistance." The fifth is "to determine the reliability of antimicrobial susceptibility testing performed in NNISS member hospitals." No description is given of the current status of NNISS data on antimicrobial resistance.
2. Under "Agricultural Conditions and Practices" is the somewhat tentative sentence: "It is con-

ceivable that surveillance of feedlot animals for the development of resistant organisms might be a means of early warning for the emergence of newly drug-resistant pathogens."

3. In a section on Access to Surveillance Information, emphasizing that access to surveillance databases is needed by many types of health care workers and researchers, it is noted that there are now no such databases for many problems, including antimicrobial resistance.

4. In a later section is a recommendation that the US Public Health Service develop a comprehensive, computerized infectious disease database that includes all of these components and ensure appropriate access to it.

5. It later recommends that the US "take the lead in promoting the development and implementation of a comprehensive global infectious diseases surveillance system." Another sentence later in the report says that: "Should a global infectious diseases surveillance system be put in place, such as the one suggested in this report, tracking antimicrobial resistance worldwide may be possible."

(*5*) WHO Scientific Working Group on Monitoring and Management of Bacterial Resistance to Antimicrobial Agents. Geneva (1994). WHO/CDS/BVI/ 95.7

This Working Group added several new insights. Meeting at this time, they were able to look back and recognize that resistance had worsened greatly over the previous decade due to an array of surprising new problems, which they reviewed in detail. They warned also that this was happening at a time when pharmaceutical companies, represented at the meeting, appeared to have under development few new antimicrobials to address these new problems.

For surveillance of resistance, a particular insight and emphasis of this group was the primary importance of local surveillance linked to local management of resistance for each medical centre and its community. The group introduced the idea of a local antimicrobial resistance management (ARM) team comprised, to the extent available, of infection control workers, microbiologists, pharmacists and infectious disease clinicians. They would work together, applying their diverse skills to the ongoing analyses of local resistance data, to treat patients and retard spread of resistance optimally within the special circumstances of their time and place.

The report noted that such local monitoring and management was now possible because local resistance databases could be maintained on local personal computers. Previously, local results had to be sent to a single remote centre for multi-centre analysis on a mainframe computer, with standardized printed overview results returned to the centre later. In contrast, local databases can be queried locally, frequently and very specifically on an *ad hoc* basis as specific local problems arise. The technology was seen capable of inverting the older "top-down" surveillance into a "bottom-up" model. In this newer "grass roots" model, actively used local databases could, if they shared common file formats and codes, be easily merged without loss of detail to produce higher level regional, national or international databases, as an inexpensive byproduct.

Software dedicated to supporting such local but combinable antimicrobial resistance databases was demonstrated for the Group. This shareware, called WHONET, had been developed to meet the needs set forth by the WHO Consultation Group for Surveillance of Resistance of 1982 (see above).

Another emphasis of this Scientific Working Group relating to surveillance was the need to build professional infrastructure to support the monitoring and management of resistance. Well-trained microbiologists in adequately supported microbiology laboratories were essential because they were the ultimate source of all of the surveillance data and its quality, and of the information for treating individual patients. The microbiologists, in addition to infection control workers, infectious disease clinicians and pharmacists, would constitute the ARM teams.

The report made separate recommendations for each of three levels of organization. Those related to surveillance of resistance are quoted verbatim below.

Recommendations for WHO

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 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.

Recommendations for individual countries

Same as for WHO plus:

- 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 share with them their shared surveillance database.
- Assess the quality, geographic distribution and professional microbiological support of existing microbiology laboratories, improve them where needed, and open new laboratories in underserved areas.
- Integrate the work and data of reference laboratories with that of other laboratories monitoring the spread of resistance.

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.

(*8*) Report of The ASM Task Force on Antibiotic Resistance (1995)

This report emphasized the need for surveillance of resistance in the US. It pointed out that: "There is currently no national or global surveillance system for monitoring antibiotic resistance in animals or humans. In fact, the amount being expended is totally inadequate." It reviewed available figures from 1992 and could find, outside of private-sector investment in proprietary systems, only $55,455 from all sources dedicated to antibacterial and antiviral drug resistance, out of a total of $76.4 million of federal, state and local funds for surveillance activities of all kinds.

The first recommendation of the report is for a National Antimicrobial Surveillance System. It begins with a list of things the surveillance system should do. The first block of suggestions includes focus on prevalent pathogens from clinical disease cases and routine isolates, attention to upward "creep" of minimal inhibitory concentration (MIC) levels, monitoring of animal products at the supermarket level, inclusion of *Salmonella* as reflecting antimicrobial usage in the animal world and *Shigella* usage in the developing world, and monitoring of soil waste on farms.

The list further includes use of concurrent patient demographic profiles, the ability to flag organisms with certain phenotypic or genotypic resistance patterns for further study at reference laboratories and for molecular typing, and the use of surveillance to target areas for intervention or epidemiological investigation, mostly at the local but also at national or international levels. It also suggests devising different benefits for different sets of participants, making data available to pharmaceutical companies and having a system that could be modified to address new areas of concern.

Under "monitoring of organisms", the report discusses how to update the list of pathogens to monitor, frequency of analyses, the need for significant numbers of isolates, and the need to include species that may not be pathogens but may be a source of transfer of resistance genomes to prevalent human pathogens.

Sections on geographic representation discuss choosing participant laboratories by US population distribution, suggesting one site per one to two million people with stratification by medical centre size, type, and services, and with supporting help from local and state laboratories, possibly in coordinating data from laboratories supporting community practices.

A section on methods recommends following Europe's National Committee for Clinical and Laboratory Standards (NCCLS) documents, using where possible the disc-diffusion method with alternative special tests including molecular testing, some at reference laboratories, guided by expert advisory panels and with rigid quality control. It also states that: "all data should be expressed as quantitative endpoints regardless of method. This dictates measurement of disc diffusion tests by calipers to the nearest whole millimeter and the use of MIC endpoints in micrograms per millimeter for dilution methods." "Qualitative interpretations shall be applied objectively by computer programs based on current NCCLS tables. Similarly, quality control guidelines found in the NCCLS tables should also establish the validity of each participant's/ referee's data."

A section on data entry and analyses emphasizes that all surveillance systems need well-structured computer systems. It cites the CDC's NNISS and the WHO's WHONET as examples of such software used for resistance surveillance, available and modifiable. It also suggests that networks using such systems or others such as CDC's sexually transmitted disease programme, Veteran Administration (VA) networks, or SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance, Medical College of Virginia and University of Iowa) might serve as working models and that these international programmes might provide possible collaborations. Another section sketches guidelines for analysis of and access to the data, which would be audited by the oversight panel or study administrators.

A section on organization of the surveillance system recommends that funding should be sought from all parties that would benefit from the system, including CDC, FDA, NIH, USDA, VA, DoD, pharmaceutical and health supply industries, drug and health care delivery companies, academic institutions, professional societies, and university medical centres. An oversight panel should include representatives of the organizations plus members of the scientific community who are experts on antimicrobial resistance, specialists in infectious diseases and *in vitro* susceptibility testing or experienced in multi-laboratory surveillance, hospital/ health care epidemiologists, and computer and statistical analysts conversant with antimicrobial issues. Location of the programme within CDC would allow integration with other surveillance activities.

A final section on immediate recommendations calls for an expert panel to develop a surveillance protocol and establish an annual budget, for which the ASM outline might serve as a preliminary or tentative plan. Federal funding should be immediately identified, with federal agencies and other sources involved in funding decisions. It calls also for appropriate expertise in statistical and computer support and for an immediate search for earlier resistance surveillance databases from the US or worldwide surveillance, if available.

(7) Report of the US National Science and Technology Council Committee on International Science, Engineering, and Technology Working Group on *Emerging and Reemerging Infectious Diseases*. Washington (1995)

This US government interagency Working Group, chaired by the Undersecretary for Global Affairs of the Department of State and established under the aegis of the Committee on International Science Engineering and Technology (CISET) of President Clinton's National Science and Technology Council, had members representing more than 17 different Government agencies and departments. Its

charge was to review and make recommendations on the US role in detection, reporting and response to outbreaks of new and re-emerging infectious diseases.

The Working Group considered the entire range of emerging infections and emphasized the important role of surveillance for the whole group. The 2 of its 19 recommendations that mention surveillance for antimicrobial resistance specifically are reproduced below.

- **Assisting WHO to establish surveillance of antibiotic resistance and drug use, as a first step towards the development of international agreements on antibiotic usage**.

  WHONET, an international reporting system for antibiotic resistance, provides WHO with a starting point for this significant work. Taking advantage of its overseas networks US Agency for International Development (UASID) can provide support for surveillance of drug resistance that hinders the treatment of internationally important diseases. In addition CDC can contribute technical support and data management resources (*5*).

- **Identifying and strengthening WHO Collaborating Centres that serve as unique reference centres for diseases whose re-emergence is feared**.

  WHO Collaborating Centres operated in the United States by Government agencies or by American universities require support to build or rebuild their capacity to serve as reference laboratories within a larger, more active infectious diseases network (*8*).

(*6*) Report of the Office of Technology Assessment of the Congress of The United States on Impacts of Antibiotic Resistant Bacteria (1995)

The report does not use the word "recommend", that presumably being the prerogative of the Congress, but instead presents "issues and options", usually expressed as "the Congress could." Under the first of these in its summary (A. Surveillance) it says that "Congress could support the establishment of a national surveillance system, including providing funding."

It goes on to explain: "A surveillance system is essential for understanding the spread of antibiotic-resistant bacteria and planning interventions so as to preserve the efficacy of currently available antibiotics. Because of these public health considerations, and the likelihood that a surveillance system would decrease medical costs, including costs to medicare, Congress could consider funding a nationwide surveillance system."

"The features of the current, limited systems can be incorporated and combined to produce a system of desired size, complexity and cost. It may be advantageous to begin with a less complex system (such as some of the operating systems described in this report), and then add more features. Any system must have a strong advisory group that includes diagnostic laboratory and computer experts, clinicians, hospital administrators, pharmaceutical company researchers, academic scientists, and federal and state regulatory and health officials. The advisors could work to assure that the surveillance system collects and disseminates the information in the forms for its best use."

(*13*) Society for Healthcare Epidemiology of America and Infectious Disease Society of America Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the Prevention of Antimicrobial Resistance in Hospitals. (SHEA Position Paper) (1997)

The first two of the report's seven recommendations for hospitals large and small are: "Establish a system for monitoring bacterial resistance and antibiotic usage" and "Establish practice guidelines and other institutional policies to control the use of antibiotics, and respond to data from the monitoring system."

(*15*) WHO Workshop on the Current Status of Antimicrobial Resistance Surveillance in Europe. Verona (1997). WHO/EMC/BAC/98.1

Participants in resistance surveillance networks in Europe filled out questionnaires in advance, and their responses constitute the descriptions printed in this report. Twenty-nine surveillance activities or networks are described, approximately half of which targeted a single bacterial species. In the workshop the participants reviewed, elaborated upon and discussed these systems.

They found need to improve communication of results to decision-makers; to improve and harmonize quality assurance standards throughout Europe; to have adequate support for microbiology and epidemiology training, laboratory infrastructure, data analysis and communication; and to provide adequate funding for regional partnerships. Lack of funding was the principal obstacle for existing systems. They concluded that further

discussions were necessary to develop collaboration between existing programmes.

(*22*) Antimicrobial Resistance: Issues and Options. Institute of Medicine Workshop Report (1998)

The report's section on surveillance begins by stating that its purpose is to provide information for action and that the information is "for several purposes at every level where health care is provided. Each level has different needs and all are critical." Examples are given of the many kinds of questions that need to be asked and a review of the problems that have historically restricted efforts to monitor antimicrobial resistance.

The report makes the statement in its summary that: "No country, including the United States, has a reliable, longitudinal, full-service antimicrobial resistance surveillance programme with comprehensive focus, nor is there a comprehensive database for monitoring trends in antimicrobial usage."

A section on characteristics of an ideal resistance surveillance system indicates that it should be prospective, active, timely and affordable, with the broadest possible access. It should also provide accurate incidence and prevalence rates, exclude repeat isolates, distinguish infecting and colonizing organisms, and categorize data by location as well as by hospital or community, urban or rural. In addition, it should gather information on antimicrobial use and treatment outcomes (especially failure); detect new resistance markers; and use reliable, standardized test methods on appropriate specimens with validation. It should be a national network representing inpatients and outpatients in all regions with all participating laboratories computerized to collect, process, and report electronic data continuously, with all such databases integrated nationally, and regional and local data made available to practitioners. A separate section reemphasizes the need for local-level surveillance.

A section follows which describes several existing national surveillance systems, including: CDC's, The Surveillance Network (TSN), Canada's, Iceland's, and as international systems CEM/NET, WHO initiatives, and SENTRY. This partially overlaps with a lengthier inventory added as Appendix A.

Another section points out that surveillance data are laboratory-dependent. It proceeds to give an overview, based on extensive experience with quality control surveying largely in the US, of the kinds of problems encountered in laboratory susceptibility testing. It emphasizes that there are few laboratories, even when central laboratories are included, where testing cannot stand improvement, and an alarming number where improvement is essential. The need to improve is not just for surveillance, but for the patients whose therapy is being guided by these tests.

In addressing what is needed the report summarizes why no single global or national antimicrobial resistance surveillance system has the qualities outlined here. Few of the multiple existing surveillance activities have been longitudinal and as a group they are almost totally uncoordinated and unstandardized, so the magnitude and impact of resistance remain poorly understood and, "…the most powerful case possible must be made for urgent and substantial response."

The report refers to the ASM Task Force of 1995 (see above), the recommendations of which it includes as Appendix B. It comments that even though those recommendations are straightforward, their elaboration and implementation will require much coordination and compromise. "No single system is likely to be able to perform the full range of necessary surveillance, so that harmonization of multiple systems and guidelines for the production of comparable data will be ongoing challenges." "Real partnerships will be essential as people and institutions with varying priorities try to achieve goals that may be similar in many ways but divergent in others."

(*21*) The British House of Lords Select Committee on Science and Technology Report on Resistance to Antibiotics and Other Antimicrobial Agents. London (1998)

Chapter 5 of the report is on surveillance. Its first 9 paragraphs are on general reporting requirements for infections and on liaison between agencies. Paragraphs 10–13 emphasize importance of information technology, citing NNISS and Intensive Care Antimicrobial Epidemiology (ICARE). Paragraphs 14–17 discuss recent problems with professional infrastructure and its funding in the UK, including declining financial support for the Public Health Laboratory Service (PHLS).

The last 5 paragraphs cover a national strategy for surveillance. Many groups agree that there is no adequate systematic surveillance of resistance in the UK now. Costs for such a system would be modest but no source has provided funding. There needs to be a consensus with PHLS, NHS,

academia and clinicians. The British Society for Antimicrobial Chemotherapy (BSAC) has set up a Working Party on Resistance Surveillance, which has proposed a multi-level approach and is seeking collaborative arrangements. The Minister for Public Health said, "We support a strategic approach to this," but was unable to make any commitment as to resources.

In concluding their report, the Committee declares surveillance of resistance to be vital to the fight against resistance. It makes multiple recommendations for surveillance, most of which are addressed to specific agencies or organizations in the UK about resource allocation rather than to elements of system design. It does, however, stress the importance of information technology in speeding up exchange of compatible data locally, nationally, and internationally. It also expresses approval of the UK's NNISS system, hopes that it can acquire data on use of antimicrobials, and suggests it consider the ICARE model.

(*19*) Report of the British Department of Health Standing Medical Advisory Committee Subgroup on Antimicrobial Resistance: The Path of Least Resistance (1998)

This incisive and comprehensive report visualizes a multi-level surveillance system that integrates multiple methods of surveillance, "each cross-validating the other." It summarizes and critiques what exists at each level in the UK now and makes realistic suggestions about their improvement. It is extracted, at times nearly verbatim, below.

"Alert organism surveillance," the detection of organisms with significant new features, has a role as an early warning system. It is in place now only to the extent that such isolates find their way to reference laboratories.

Reference laboratory elaboration of species or of resistance mechanisms is often elegant now, but interpretations of epidemiological significance are beset by sampling problems and lack of a denominator.

Sentinel laboratory monitoring, meaning the prospective collection of selected organisms for testing with standard methodology by a central laboratory, offers a high level of control but also lacks a denominator population and can test only small numbers of isolates.

Special surveys are a good tool, particularly if they have prospective selection with a clinical case definition in a defined population, but cannot be performed for every organism and the costs are considerable.

Compilation of routine susceptibility testing data can be a measure of public health impact because these data do have a population denominator, but there remains the problem of non-standard testing methodology. Such routine data represent a huge untapped source of inexpensive, accessible results, which could be analyzed at local, national, and regional levels to give a measure of the public health impact of antimicrobial resistance. The system envisaged is one fed by regular downloads from laboratory computers of routine susceptibility data on a wide range of organisms and specimen types. The aim would be to encompass the whole; an essential facet would be linking the data to population denominators. Although this is a new area of work, the burden on individual laboratories would be relatively low. Electronic downloading of data directly from microbiology computer systems is the ideal, and has been done in other places.

(*30*) Report from the American Academy of Microbiology: Antimicrobial Resistance, An Ecological Perspective (1999)

This report seeks to take a broad, ecological view of antimicrobial resistance and its distribution in the environment. This emphasis is given to much of the discussion and to most of the recommendations for future scientific research. The ecological approach is reflected in the section on surveillance by the statements that "with respect to antimicrobial impact on the environment, surveillance involves not only data on bacterial pathogens but also data on other microorganisms that are part of the affected ecosystem." The report also states "Different types of surveillance are needed for each component of the biosphere."

In discussing different existing types of surveillance it mentions sentinel surveillance for detecting rare or important events. An ecological dimension might be added to this if instead of noting only strains categorized resistant by existing clinical breakpoints resistance could also be defined by lower "thresholds" of change in susceptibility that would "provide a selective advantage to a microorganism or risk for evolution toward greater resistance."

The report continues its discussion of resistance surveillance methods by recognizing that special studies conducted with prospectively defined populations, e.g., surveying pharyngeal carriage of

pneumococci in a defined group of children, is desirable but expensive because the survey has to pay for the culturing.

The same is true for surveillance of clinical isolates by sending them to a remote reference laboratory for uniform testing.

It acknowledges that the bulk of surveillance data will thus come from clinical isolate susceptibility test results downloaded from routine clinical laboratory files. This approach has the potential disadvantage of variable test quality, but it costs little, is rich in local epidemiological detail, and so supports local management of resistance while being a component of regional or national surveillance. Analysis of the resulting stream of test results, moreover, "can serve to continuously improve the quality of the laboratory sampling and testing."

Implicit, but not stated in this discussion, are two ways to enhance the value of such clinical isolate data for generating ecological or environmental insights. One would be to not screen out non-pathogens from surveillance databases, as is sometimes suggested, but only exclude them from particular analyses. The other, as supported above for many other reasons, would be to file only full range measurements of isolate susceptibility (inhibition zone diameters or full-range MICs) rather than just the interpretive categories derived from those measurements. This would allow continuous monitoring of the small increments in resistance (e.g., creeping resistance by accumulating mutations to fluoroquinolones) that may "provide a selective advantage….or risk evolution toward greater resistance."

(*31*) US Interagency Task Force for a Public Health Action Plan to Combat Antimicrobial Resistance (2000)

Based on a public meeting held in Atlanta, Georgia, in July 1999, with representatives of CDC, FDA, NIH, AHRQ, USDA, DoD, DVA, EPA, HCFA, and HRSA and many other groups, the plan lists issues, goals and actions that apply mostly to human (as opposed to non-human, such as agricultural) antimicrobial resistance (AR) issues. For each action item "coordinator" and "collaborator" agencies/departments are specified. Its Executive Summary lists under 4 major headings 11 top priority action items to combat antimicrobial resistance. The first of the 4 headings is "Surveillance", with 2 priority items under it:

"With partners design and implement a national AR surveillance plan that defines, national, regional, state and local surveillance activities; the roles of clinical, reference, public health, and veterinary laboratories; and is consistent with local or national surveillance methodology and infrastructure that currently exist or are being developed".

"Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, in agriculture, and in consumer products."

The section on surveillance in the report states: "At present the United States lacks a coordinated national plan for AR surveillance" and "Improved AR surveillance depends upon enhanced epidemiologic and laboratory capabilities at local, state and national levels, use of standardized and reliable laboratory testing methods, and enhanced use of informatics."

The remainder of the section is an extensive outline of the general needs for developing and implementing such a comprehensive system. The first block deals largely with allocation of general categories of tasks to specific coordinators and collaborators.

The second block is on the development of standards and methodologies. It includes "standardized laboratory methodologies and data elements that allow susceptibility test results and AR surveillance data to be compared across geographic jurisdictions. Similarly, use standardized definitions and methodology to create an electronic surveillance system that health care institutions can use to compare AR data from other local facilities."

It also calls for development of "standards for reporting quantitative data (e.g., MICs or zone diameters) in ways that will detect decreased susceptibility." This is necessary because numerical AR test results reported non-quantitatively (e.g., as susceptible, intermediate or resistant) as "susceptible" may mask an emerging AR problem (i.e., microbes with a small decrease in susceptibility may still be classified as susceptible).

A block is devoted to the need, little mentioned in previous reports, to allow the data within such a surveillance system to comply with patient confidentiality policy. Subsequent sections recommend work to ensure that this is possible and to develop new policy if needed.

Other recommendations follow, such as: "Link human drug-use data to clinical information (e.g., diagnosis, severity of illness and outcome). "Work with accrediting agencies to address antimicrobial

drug-use monitoring as part of quality control assurance in health care delivery systems." "Evaluate the performance of licensed, automated AR testing devices in the context of changing resistance patterns and update their labeling where appropriate (e.g., changes in quantitative resistance that may make a test result invalid)."

Under a section on state health and agricultural agencies is the recommendation that they "maintain the capacity to test the drug-susceptibility patterns of resistant organisms of public health importance, especially for drug-microorganism combinations for which testing methods are not routinely available at hospital and commercial laboratories."

A section on dissemination of surveillance data recommends: "Provide an accessible, centralized source of AR data from major surveillance systems involving animal and human populations. In consultation with stakeholders determine how to report AR data in a way that is useful to interested parties (e.g., clinicians, public health officials, veterinarians, and researchers). Include sufficient detail in surveillance reports to permit local analysis and comparison with trends in drug use and medical and agricultural practices."

A final section on monitoring AR in agricultural settings recommends expansion of the National Antimicrobial Resistance Monitoring System (NARMS) and extension of its sampling to monitor transmission of resistant infections. It also recommends monitoring of fruit and vegetable production and of environmental contamination by antimicrobial drug residues and drug-resistant organisms that enter the soil from human and animal waste.

CHAPTER II

Increase awareness: optimize patient and provider behaviour

Jerry L. Avorn

Abstract

Considerable evidence points to widespread problems in knowledge, attitudes, and behaviour relating to antibiotic use among both patients and prescribers in the industrialized and the developing worlds (*19*,*32*,*33*,*34*). Such evidence is drawn from numerous sources:

- Inappropriate patterns of antibiotic use for a variety of specific clinical conditions:
  - — Use of antibiotics to treat symptoms that are clearly viral in nature
  - — Reliance on excessively broad-spectrum antibiotics when narrower-spectrum agents would be more appropriate
  - — Errors in the timing and duration of antibiotic prophylaxis at the time of surgery
  - — Poor adherence by patients to prescribed antibiotic regimens, including premature cessation of therapy and "hoarding" antibiotics for future unsupervised use
- In the developing world, widespread use of antibiotic injections when not clinically indicated
- Erroneous responses by patients and physicians to surveys concerning antibiotic knowledge and attitudes
- Under-use by physicians and consumers of proven non-antibiotic means of infection control, such as hand washing
- Growing consumer demand for "antibacterial" cleaning preparations which can actually increase bacterial resistance
- Low levels of use of products that can provide safe, effective alternatives to antibiotic use to combat infection, such as condoms, bednets in malaria-prone areas, vaccines.

The causes of such educational and behavioural deficits have also been well identified (*8*,*35*–*38*). They include:

- Inadequate training of health professionals in rational antibiotic use (and non-use)
- Minimal or nonexistent training of children at all levels of education in relation to health habits
- Aggressive marketing of antibiotics and antibacterials to both physicians and patients
- Inadequate or nonexistent continuing education requirements concerning infection control and antibiotic utilization for most health professionals.

This chapter reviews the barriers for changing physician and patient behaviour and suggests effective intervention strategies.

Disincentives and barriers to overcome

A number of specific problems have been identified that present obstacles to the development and dissemination of effective programmes of prescriber and patient education concerning the prudent use of antibiotics (*7*,*21*,*22*,*39*). These include:

- Inadequate support for publicly financed educational programmes for either professionals or lay people
- Strong commercial pressures from manufacturers to increase utilization of antibiotics and antibacterials
- Low levels of literacy in the developing world, limiting the impact of verbally-based public education messages
- Fear of litigation in the United States which encourages the practice of "defensive medicine", often leading to prescription of an antibiotic when one may not be necessary
- Pressures to shorten the length of a physician visit, which in turn increases pressure for antibiotic utilization as a time-efficient means of ending the visit
- Poor regulation in the developing world of claims made in promotional materials for antibiotics
- Physicians' desire for autonomy, which can make

them disinclined to accept guidelines or antibiotic restrictions.

Educational strategies which have been shown to be ineffective

One approach stands out as having remarkably little effect in altering antibiotic use. This approach, the simple dissemination of printed guidelines or educational messages, without other reinforcement, is unfortunately among the most commonly used. This has now been studied in a variety of randomized controlled trial settings with strikingly consistent results: physicians who are mailed printed information on proper prescribing, but who do not receive any other kind of intervention, in general do not change their practice any more than physicians randomized to a control group (*40*). The fact that this finding has been so consistently reported makes it even more disturbing that this approach is probably the single most frequently employed strategy for changing antibiotic prescribing. Another common approach, that of having an expert lecture a passive audience with minimal opportunity for interaction, has also been reportedly shown to result in little or no change in medication use behaviour.

Fortunately, other methods of improving antibiotic utilization have been well studied and found to reliably improve the appropriateness of prescribing. These are described in the section that follows. While the term "appropriate antibiotic use" will be used consistently, it should be pointed out that such broadly-defined education would also include such topics as the appropriate use of vaccines and the use of alternative methods of infection control, such as hand washing.

Strategies which have been demonstrated to be effective in improving the appropriateness of antibiotic use

Most studies and published recommendations have considered education and behaviour change interventions separately by the audience targeted: patients, prescribers, or (in the developing world) non-physician drug vendors. These categories will be used in the sections which follow. However, it is evident that the ideal approach would constitute a combination strategy aimed at both the prescribers and the users of antibiotics. In fact, some recent research has shown that such a "double-barrelled" targeting of both audiences can produce a synergistic effect much greater than that achieved by addressing either audience separately.

Another overarching principle evident in many studies and policy recommendations on improvement of medication use is the concept that education/behaviour change interventions should be tailored to the specific circumstances and needs of the audience, rather than presenting a "one size fits all" formula which may not resonate with the individual experience of the targeted prescriber or patient.

Ideally, programmes to change behaviour of patients, physicians, or lay caregivers should be grounded in solid behavioural science theory and experience, as well as (equally practically) the theory and experience of marketing (*41*). Specific theories relevant to the reduction in antibiotic misuse include the PRECEDE model, which considers factors that encourage or prevent behaviour change, and the Transtheoretical Model, which takes into account the various cognitive and behavioural stages associated with adopting changes in a specific area (*42*,*43*).

While it is not easy to reduce inappropriate antimicrobial use, some encouraging data exists about the efficacy of some programmes in improving problematic practices. Overall, there is good news about the efficacy of such programmes in improving drug use. In a review of 59 studies of interventions to improve medication use (primarily antibiotics) in the developing world, Ross-Degnan (*44*) found that among studies which had an evaluation design adequate to permit comparison of outcomes, 43% of studies had an impact classified as "large" (>25% improvement compared to controls), and 36% had a moderate impact (10–25% improvement compared to controls). Only 21% of the studies had low or no impact (<10% improvement). The most common approach in this latter group of minimal impact was the dissemination of printed materials recommending rational utilization.

Interventions directed at prescribers

In that review (*44*), the following types of interventions were found to produce significant improvements in prescribing, as measured in randomized intervention trials:

- Multiple training modalities applied together (group problem-solving, role playing, lectures, opportunity to practice skills)
- Focusing on one clinical issue at a time

- Training at the work site
- Use of opinion leaders or district-level staff as trainers
- Repeated sessions focusing on reinforcement of the message
- Community-based case management interventions (their use in acute respiratory infections and diarrhoea was so effective that a mortality benefit could be demonstrated).

Administrative interventions were found to work well in improving antibiotic utilization if they had the following attributes:

- Were based on group process
- Involved ongoing supervision and monitoring of practice
- Provided regular audit and feedback of prescribing patterns.

In a similar evaluation, Laing and Hogerzeil (unpublished) reviewed the experience of a number of programmes in the developing world and concluded that the following strategies had strong records of success in improving prescribing of antibiotics and other drugs:

- The development and effective dissemination of lists of essential drugs and standardized treatment guidelines
- The creation and empowerment of pharmacy and therapeutics committees in hospitals
- Problem-oriented training
- Targeted in-service training of health workers.

In addition to these observations about effective strategies, consensus has also developed concerning the clinical content of programmes to improve antibiotic use. Some of these are quite straightforward, such as the basic British recommendations advocated as a simple starting-point for reducing inappropriate antibiotic use (*20*):

- Avoid antibiotics for simple coughs and colds
- Do not use antibiotics for the treatment of viral sore throat
- Limit antibiotic use in uncomplicated cystitis in healthy women to three days
- Limit telephone prescription of antibiotics to exceptional cases only.

Other recommended content areas for such antibiotic education programmes are equally straightforward, and contain messages such as the following:

- Do not use broad-spectrum antibiotics when narrower-spectrum agents would work as well
- Base the antibiotic prescription on culture results whenever possible
- Modify the regimen over time as required
- Consider cost-effectiveness in choosing an antibiotic regimen.

In the industrialized world, computers have been put to good use in guiding choices of antibiotics for hospitalized patients. In one system, a computer "consultant" is given all pertinent facts concerning a patient's infection and clinical condition, and then offers antibiotic recommendations. These have been found to have a very high degree of clinical accuracy when compared with the "gold standard" recommendations of infectious disease specialists (*45*).

The ordering of all medications, including antibiotics, on computer terminals will become common in many institutions in the industrialized world over the next few years. Initial experience with such systems in hospitals where they are already in place indicates that they can be used to good advantage in reducing antibiotic utilization by reminding the ordering physician *at the time the order is being written* that such a choice is not in conformance with available evidence and/or institutional guidelines, and offering more reasonable alternatives. Such systems can also be used to flag orders which require further consultation or approval by an infectious disease consultant (*46*,*47*).

Other educational approaches less dependent on technology have also been demonstrated to be effective in improving antibiotic use. In the 1980s, researchers in the United States began to apply the powerful behaviour change interventions employed by the pharmaceutical industry, but put in the service of restrained prescribing rather than promotion of sales of a given product. In this approach, which came to be known as "academic detailing," clinician/educators were trained from a medical school base to become expert in the drug therapy required for specific conditions, and also received training in strategies of "social marketing" and behaviour change. These educational outreach workers were then sent to visit with physicians in their offices at a convenient time, much as industry sales representatives do. They presented the need for appro-

priate prescribing in terms which were concise, clinically relevant, and behaviourally appropriate; the presentation was supplemented by engaging, well-designed, graphic print materials. Initially, such educational outreach workers were primarily pharmacists, but this role has also been filled effectively by physicians, nurses, and—in the developing world—by lay people as well. The communication is designed to be interactive rather than didactic, which offers the educator an opportunity to understand the specific informational and attitudinal situation of the targeted prescriber and to modify the educational session accordingly. Following its initial demonstration in the United States, this approach has spread throughout the world, and has been found to be equally effective in both industrialized countries and the developing world. In April 1997, a four-day conference in Chiang Mai, Thailand, focused on improving medications in the developing world; a number of such successful programmes were described in detail. Cost-benefit analyses have demonstrated that such programmes can save more than twice their expenses in terms of reduction of unnecessary prescribing (*44*).

Education of students in the health professions

Current training about rational antibiotic use is widely regarded as inadequate in most pre-professional settings throughout the world. More relevant and critical education about infection control and treatment has been called for not just for medical students, but also for students of nursing, pharmacy, and veterinary medicine. Beyond the specific scientific content in pharmacology and microbiology that must be taught, students also need to be taught to critically evaluate promotional materials for medications to become more "media savvy" in evaluating printed advertisements and prepared to ask the right questions during sales presentations for antibiotics. Problem-based education has been found by many health professions educators to be a useful and powerful method of communicating such information.

Interventions directed at patients, families, and consumers

The patient is a vital link in the pathway of antibiotic utilization; it is often patient demand which triggers inappropriate antibiotic prescribing in the first place. Because of this, and because of the central role played by the patient (or parent of a pediatric patient) in the implementation of antibiotic regimens, strategies directed at consumers can be of particular importance in reducing antibiotic use (*48*). Such education can take numerous forms:

- In pediatrics, caregivers can be educated to recognize patterns of symptoms that can indicate whether a child should be brought in for medical care and potentially for an antibiotic prescription. Such education encourages appropriate utilization and discourages inappropriate use.
- Better recognition of the symptoms of malaria can allow for earlier referral to a health care professional, earlier diagnosis, and treatment.
- Education about the non-drug management of routine diarrhoea in children (e.g., with oral rehydration solutions) can replace unnecessary referrals to scarce medical resources, as well as inappropriate requests for antibiotics.
- In adults, conditions susceptible to such education about appropriate health-seeking behaviour include viral upper respiratory symptoms, vaginitis, and recognition of the early symptoms of Human Immunodeficiency Virus (HIV), among others.

Public education programmes have focused on broad themes, such as the lack of utility of antibiotics in viral conditions and the need to adhere carefully to the prescribed regimen if an antibiotic is ordered, rather than starting or stopping therapy on an as-needed basis.

A particularly interesting approach has been taken in the United Kingdom to encourage the public to "cherish and conserve your natural flora," pointing out the beneficial aspects of bacteria which can be obliterated by excessive antibiotic use. Other groups have advocated the education of the public concerning the risks of unnecessary antibiotic use in animals and agriculture as well as humans; the Alliance for the Prudent Use of Antibiotics (APUA) has been particularly active in this regard.

Other audiences for interventions

Beyond the obvious targets of physicians and patients, other important groups have been identified as appropriate audiences for education about antibiotic use, including workers in day care centres, schoolteachers, those who work in agriculture, and policy-makers in all these areas as well as health care.

System-wide interventions

In addition to strategies directed at prescribers and patients, a number of effective educational strategies have targeted the health care delivery system itself, whether in the form of governmental health care services or private sector health practices or systems. This section will not deal with regulatory approaches to improve the antibiotic use, which are discussed elsewhere in this report (See Chapter III). Rather, it will focus on means of educating the participants and leaders of such systems in order to encourage them to adopt more enlightened policies at a systems level (*31*,*49*).

- The creation of drugs and therapeutics committees (or pharmacy and therapeutics committees) can be a very useful strategy at the level of individual health centres as well as at the level of national health care programmes. Such groups can evaluate all available evidence concerning utilization data, resistance patterns, efficacy, and cost, in order to make recommendations for proper antibiotic use which are appropriate to a particular clinical setting and population.
- Dissemination of essential drug lists, such as those promulgated by the World Health Organization (WHO), can help simplify antibiotic choices for practitioners as well as make them more clinically appropriate and cost-effective.
- Facilitation of communication among academic institutions, government agencies, those who pay for health care, and pharmaceutical manufacturers can sometimes reduce the extent to which such entities act at cross purposes in relation to one another in relation to antibiotic use and infection control.
- Beyond the drug lists themselves, guidelines for the use (or non-use) of antibiotics in particular situations can improve the rationality of prescribing. For maximum benefit, such guidelines should be:
  - — Evidence-based
  - — Appropriate to the clinical and microbiological issues relevant to a given population
  - — Developed with the involvement of the practitioners (and potentially the patients) who will be using them
  - — Disseminated not simply via printed memoranda, but rather through the use of interactive strategies oriented to changes in behaviour, as described elsewhere in this section.

A number of strategies for improving the knowledge base of physicians and the public concerning antibiotic use have pointed to the need for capacity building on a number of fronts to make such programmes possible. Such infrastructure requirements fall into several categories. First among these is the capacity to devise, validate, and modify evidence-based guidelines on rational antibiotic use, since this is necessary to provide the content needed to drive any educational programme. These programmes can be governmentally sponsored, as is the case with the British National Institute for Clinical Excellence (NICE), or the guidelines development process of the US Agency for Health Care Policy and Research before it was disbanded under political pressure several years ago. Similar activities have been conducted by the US Centers for Disease Control and Prevention as well as WHO, and antibiotic guidelines have been widely disseminated in Australia. In addition, professional societies have also developed their own evidence-based guidelines for appropriate antibiotic use. These have included the American Society for Microbiology, and a variety of specialty societies (e.g., the American Heart Association guidelines for the use of prophylactic antibiotics in patients with valvular heart disease, or the American College of Gastroenterology recommendations concerning regimens for the eradication of *H. pylori* infection).

WHO has identified a number of other infrastructure-related issues that bear directly on the capacity to mount successful educational programmes concerning antibiotics. These include:

- Control of the promotional activities of drug manufacturers
- Training of a new category of health professional, the antimicrobial resistance manager/monitor (ARM), to serve as a local resource to follow the current literature on antibiotic resistance, analyse local data, propose and implement strategies for control and resistance, and work with clinicians on the care of specific patients
- Development and enforcement of ethical standards concerning advertising of antibiotics
- Analysis of data on local resistance patterns
- Communication of global trends in antibiotic resistance with potential local impact
- Development of information systems to monitor and feed back data on utilization and resistance patterns.

Similarly, the US Agency for International Development (USAID) (*39*) has also focused on the need to build local capacity in developing countries to provide the infrastructure needed to encourage rational antibiotic use. This includes training of personnel and creation of systems to:

- Perform surveillance
- Manage data
- Conduct educational programmes
- Choose which antibiotics to purchase
- Develop policies concerning regulation, reimbursement, and financing of antibiotic purchases
- Provide unbiased drug information
- Establish field sites for innovative demonstration projects (e.g., tuberculosis surveillance and control)
- Train microbiology laboratory personnel
- Prepare training and advocacy materials for local government officials on the burden of disease related to resistance and the need for specific programmes to combat it
- Develop and enforce quality control standards for drug manufacturing and microbiology laboratories.

Internet access makes it possible for patients and practitioners throughout the world to have instantaneous access to current information about medications, patterns of resistance, and other data relevant to appropriate antibiotic use. One such guide has been made available on the Internet through WHO (http://www.who.int). For other relevant web sites see the section, Some Useful Web Sites.

Conclusions

Just as considerable progress has been made in microbiology and clinical infectious diseases in the last two decades, similar progress has been made during this period in understanding why antibiotics are misused by prescribers and by patients, and, equally important, which strategies are most effective in preventing such misuse. Rigorous data are available describing the effect of such innovative programmes in patient and caregiver education, computer-based prescribing guidelines, academic detailing of prescribers, and community-oriented educational programmes; such studies have amply demonstrated their utility and, for some, even their cost-effectiveness. Similarly consistent data are available describing the poor track record of many conventional practices in changing practice patterns, such as the mailed transmission of expert guidelines. It is unfortunately true that such older, conventional practices remain the norm, while more innovative programmes, though becoming more widely adopted each year, still form the minority of intervention programmes. This is probably the combined result of habit and tradition, as well as the lower costs required to conduct programmes that are print-only in nature, and skepticism concerning the cost-effectiveness of more interactive person-based programmes. As the stakes become higher each year in terms of the clinical and economic consequences of antibiotic misuse, it is to be hoped that educational interventions in this arena are subjected to the same critical evaluation and evidence-based use as are the medications whose utilization they attempt to improve.

CHAPTER III

Strengthen sanitation, infection control, and regulatory measures

Peter G. Davey

Abstract

Governmental and private health management systems, at national, regional, and local levels provide the basis for the delivery of health care. These systems are critical to the curtailment of antimicrobial resistance because they help determine the availability and usage of antimicrobials. They also play a role in developing and enforcing programmes to reduce the spread of microbial infections, whether in hospitals or in the community.

Limiting microbial infections is a key step towards the goal of reducing the current prevalence of antimicrobial-resistant organisms. The responsibility of carrying out the daily routines of infection control and sanitation programmes falls to hospital management and health care providers. These routines range from proper hand washing to reporting surveillance data.

This chapter reviews the expert groups' (*1*,*5*,*6*,*7*, *11*,*13*,*19*,*20*,*21*,*22*,*24*) findings and strategies relating to 1) sanitation and infection control, and 2) government and health system regulation. This review outlines what is covered in previous expert policy reports, and provides guidelines from the expert policy groups on a global strategy. The review also designates specific programme components and models that countries might consider in developing their national strategies for infection control and regulation of antibiotics. Areas of concern from previous reports and additional recommendations from the expert policy reports are noted.

I. Sanitation and infection control

Control and prevention of microbial infections and improved sanitation in the health care setting are imperative to decrease the spread of resistant organisms and minimize the need for antibiotics. As cited in the expert reports reviewed (*1*,*5*,*6*,*7*, *11*,*13*,*19*,*20*,*21*,*22*,*24*) (Table A), the major factors contributing to the spread of infection and antibiotic resistance transfer in health care settings are:

- Failure to cleanse hands after each patient contact
- Limited use of gloves and gowns
- Lack of sterile supplies and poor sterilization practices
- Increased movement of patients within and between hospitals.

There is a broad consensus among the expert policy groups (see Table B) on the need to establish an infection control programme in order to more effectively control hospital infections. Elements of such a programme identified in the reports are:

- Surveillance of infection
- Identification of outbreaks
- Implementation of effective control measures (e.g., hand washing, gowns)
- Sterilization and disinfection of equipment and supplies.

Most of the reports reviewed recommended some form of a committee or programme to be responsible for the improvement of infection control. The general statements about infection control improvements within hospitals need to be supplemented by the specific recommendations for improvement of infection control which were addressed in some of the previous expert reports (see Tables C and D). Developing countries in particular face the challenge of improving their public health infrastructure, community sanitation and health education in order to decrease the emergence and spread of infections. This is a priority need in order to decrease the spread of resistant organisms. All countries could improve education of health care and day care workers (*5*,*49*). The previous expert reports also make strong recommendations about mandating hospital infection control within purchasing and commissioning agreements (see Tables C and D).

Other national models for antibiotic resistance intervention

Several programmes and guidelines related to health care management and the control of infections have been developed after most of the policy reports were published. Since infection control is a key strategy in containing antibiotic resistance, local governments and professional societies could consider adapting the following programmes to their own needs, within the limits of available resources (other examples of local initiatives are outlined in Appendix B).

- The *epic* project: Developing National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections. The *epic* project has developed guidelines, approved by the UK Department of Health, which include the following topics: standard principles (hospital environmental hygiene, hand hygiene, the use of personal protective equipment, and the use and disposal of sharps); short-term indwelling urethral catheters in acute care; and central venous catheters. The guidelines are targeted at the United Kingdom and are thought to be practical and affordable within that context. However, the structure of the guidelines would facilitate adaptation to other countries, including developing countries. The second phase of the *epic* programme will concentrate on control of infection in the community. More information can be found at the following web site: http://www.epic.tvu.ac.uk/
- The HELICS project: (Hospitals in Europe Link for Infection Control Through Surveillance). HELICS has produced infection control recommendations for hospitals in the European Union (EU), annexes describing various national infection control programmes, and the current national policies concerning antibiotic resistance from each EU member state. This information can be found at the Nosocomial Infection Control in Europe web site (http://helics.univ-lyon1.fr).

Summary and conclusions: infection control experiences

The statements about hospital infection from the various expert reports discuss important actions at the local and national level to curb antibiotic resistance. This author suggests that they should be followed by these specific actions:

- **Adapt for local use the HELICS Methodology for Measuring the Status Quo for National Initiatives in Infection Control**

  This is consistent with the recommendation from the WHO Scientific Working Group (*5*): "Develop methods and standards for evaluating hospital infection and antimicrobial resistance control programmes, leading ultimately to national accreditation systems."

- **Adapt the *epic* Evidence Based Guidelines (http://helics.univ-lyon1.fr) for implementation in other countries**

  The evidence reviewed in these guidelines is a comprehensive review of the published world literature. However, there may be existing local guidelines that could be reviewed and incorporated into country-specific guidelines. These would also need to take account of existing clinical practices and facilities.

- **Encourage governments to accept accountability for infection control at the national level by making hospital management accountable for local implementation**

  This direction is consistent with the recommendation from the WHO Scientific Working Group (*5*): "Link the prevention and control of antimicrobial resistant organisms in hospital to national and local quality assurance efforts."

  The concept of clinical governance is having considerable impact in the United Kingdom. The UK Government has put infection control and antimicrobial resistance into the list of national priorities for public health, and used initiatives on clinical governance to make it clear to hospital management that they are responsible for action in their hospitals. This approach is now being extended to managers responsible for community health services.

- **Emphasize the importance of infection control in the community**

  In addition to the recommendations of the WHO Scientific Working Group (*5*), development of related interventions to contain antimicrobial resistance in the community include educational programmes and hygienic standards for day care and extended-care facilities, and promotion of hygiene in the community, including safe water and food hygiene.

  As noted in the UK House of Lords report (*21*), infection control beyond the hospital is an area of particular weakness. Communities should

consider improvements in antibiotic use and infection control in nursing and residential homes, which can act as reservoirs of methicillin-resistant *Staphylococcus aureus* and other resistant organisms which are carried back and forth between the hospital and the community.

II. Regulatory measures

The regulations developed and enforced by governmental and health organizations can have a very large impact on the use of antibiotics and the prevalence of antibiotic-resistant bacteria. The need to develop strong national health system regulations is mentioned in many of the expert reports (see Table E). Major issues cited by the WHO report (*50*) include the following:

- Lack of regulation and informal sector sales of antibiotics
- Absence of lists of essential drugs
- Absence of national standard treatment guidelines
- Poor communication and implementation of national policies
- Ineffective regulatory mechanisms.

A helpful classification of regulatory mechanisms and their implementation is given in "Task Force Reports on Antibiotic Use Worldwide."(*1*). The

TABLE 1. **LAWS AND REGULATIONS PERTAINING TO ANTIBIOTICS (ADAPTED FROM *19*)**

Category and designation	**Basis for assignment**
A. Comprehensive	1. No free sale allowed. 2. Professional limits placed on prescription practices by law. 3. Statutory control of advertising; no advertising allowed to lay public. 4. Content of advertising limited by law.
B. Partial	1. No free sale allowed. 2. At least one of controls 2-4 above.
C. Minimal	1. No free sale allowed. 2. None of controls 2–4 above.
D. None	1. Free sale allowed without any restrictions.
Application in practice and enforcement of compliance with regulation	
A. Complete	Tightly controlled availability; regulations rigorously enforced.
B. Partial	Incomplete enforcement of controls, associated with limited availability of antibiotics to the public for other reasons, such as economics and/or logistic factors.
C. Minimal	Incomplete enforcement of controls, associated with widespread availability of antibiotics as a result of failure to apply regulations in practice, and absence of other constraining factors.
D. None	No restrictive legislation; widespread availability.

TABLE 2. **GROUPING OF 35 COUNTRIES[a] BY LAWS/REGULATIONS AND ENFORCEMENT/COMPLIANCE ASSESSED BY QUESTIONNAIRE IN 1986.**

Laws/Regulations[b]	**Enforcement/compliance 1986**			
	1. Complete	2. Partial	3. Minimal	4. None
Comprehensive	11 (31.4%)	2 (0.6%)	5 (14.3%)	1 (0.3%)
Partial	2 (0.6%)	1 (0.3%)	3 (0.9%)	1 (0.3%)
Minimal		2 (0.3%)	1 (0.3%)	
None				6 (1.7%)

Source: Levy SB, Burke JP, Wallace CK (*1*)

[a] Countries were selected from Eastern and Western Europe; North, Central and South America; Africa; Asia and Oceania. Data were reported anonymously (locality within each category not reported).

[b] See Table 1 for an explanation of categories of Laws/Regulations and Enforcement/Compliance.

report reviewed policies about antibiotics in thirty-five countries and found that only eleven (31%) had comprehensive laws and regulations that were completely enforced (Tables 1 and 2). This evidence supports the need for more effective regulatory mechanisms. The data in "Task Force Reports" are nearly fifteen years old; nonetheless, there is broad consensus among the experts on the need to address the five problems listed above (see Table E). There is also broad historical consensus in support of effective national regulation of antibiotic quality, dissemination, and promotion.

Elements of a national policy to combat antibiotic resistance

Additional regulatory recommendations proposed in the recent WHO report (*50*) are also repeatedly suggested by previous expert reports (see Table F) and suggest a basic framework that each country should establish to minimize the emergence and spread of antibiotic resistance in their country:

- Adopt the WHO model legal framework for antimicrobial licensing, sale, supply, distribution, and promotion
- Introduce legal requirements for collection of data on antimicrobial production, distribution, sales, and consumption in human, veterinary, and agricultural use
- Introduce formal training for personnel in antimicrobial dispensing outlets and registration schemes for such outlets.

Additionally, the WHO document (*50*) makes the following recommendation: "identify and eliminate economic incentives (i.e., reimbursement practices) that encourage inappropriate antimicrobial use." This recommendation was apparently overlooked by the other expert policy groups and is only endorsed by one of the other documents (*6*, Table F). Nonetheless, it is an important global issue and a key consideration for national governments attempting to control antibiotic use.

Finally, the importance of involving international organizations is noted in the WHO recommendation: "Target advocacy for action encouraging prudent use of antimicrobials among relevant organizations, such as the World Trade Organization, the World Bank and the International Monetary Fund" (*50*).

Additional issues concerning government and health management systems

Additional specific issues and recommendations from individual expert reports fall into two main areas (detailed in Tables G and H). The first area concerns suggestions for additional legislation to improve the prudent use of antimicrobials, for example, granting antimicrobial use licenses contingent upon implementing antimicrobial-use monitoring programmes, or, where applicable, adjusting subsidies for antibiotics to encourage a more prudent use (*20*,*51*).

The second area concerns legal issues that may impact implementation of infection control or antimicrobial use measures. One example is improving personal human rights laws, especially in developing countries, so that they have a positive impact on a population's public health (*19*,*51*). The document by Fidler (*51*), is a particularly rich source of issues about legislation, encompassing trade regulations, patient rights, data privacy, and patent protection.

Another example is creating economic incentives for pharmaceutical companies to develop new antimicrobial medications (*51*). The listed statements also include good practice guidelines for antimicrobial use, such as assisting poorer countries to gain supplies of appropriate antimicrobials, as well as creating international alert systems concerning antimicrobial resistance (*7*,*49*,*51*).

Conclusions: Regulatory measures

In the management of distribution, availability and use of antimicrobials, several factors—legal, economic, and scientific—should be considered, as summarized below:

- **Development of guidance documents by government and health systems on policies for antimicrobial use**

  Local ownership of guidelines adds to their success. Guidelines can be applied to infection control and can also be part of general antibiotic policies, where local microbial epidemiology can justify variations in prescribing and where there are legitimate concerns about the selection pressures created by uniform national prescribing policies. These guidance documents should be readily adaptable for use in developing countries.

- **Assessment of policies, laws, and regulations and their implementation**

  The 1987 report by the US Department of Health and Human Services (*1*) could be up-

dated. The original report did not reveal the identity of the countries that submitted data. This author would query whether secrecy about such an important global issue either necessary or justifiable.

- **Review opportunities for improving prudent use of antibiotics by changing the licensing process**

  Extend patents in exchange for industry support of programmes to limit the use of antibiotics and support license extension of older drugs with activity against resistant pathogens through fast tracking or orphan drug programmes.

- **Investigate the effect of changes in reimbursement policies on prudent use of antibiotics and on surveillance of prescribing or resistance**

  This is an important recommendation in "Containing Antimicrobial Resistance"(*50*) but does not appear in the other WHO documents. It is endorsed by US Congress Office of Technology Assessment (*6*), which identifies a potential problem with Medicaid and Medicare reimbursement policies. This issue deserves wider consideration in a global context. In addition to considering reimbursement for prescribing, the extent to which privatization of laboratories threatens the surveillance of antibiotic resistance or infection control should be investigated.

- **Consider recommendations (*51*) about trade restrictions against countries that systematically neglect recognized principles and practices for antimicrobial use**

  In the context of environmental protection, trade restrictions seeking to change a production process in another country, rather than to protect against health dangers from a particular product, have been ruled incompatible with international trade law. As part of a general strategy to combat antimicrobial misuse, legitimate trade restrictions against countries that systematically neglect recognized principles and practices for antimicrobial use might be considered; such a move would elevate the status of Codex's Code of Practice for Control of the Use of Veterinary Drugs and Guidelines for the Establishment of a Regulatory Program for Control of Veterinary Drug Residues in Foods (*52*), in the same way as the Sanitary Phytosanitary (SPS) Agreement has elevated the importance of Codex's Maximum Residue Levels for Veterinary Drugs in Foods.

- **Identify opportunities to link financial incentives to implementation of policies at the national or regional level**

  In the United States the most powerful strategy would be to make implementation of state policies to curb the misuse of antimicrobial drugs mandatory before states receive federal funds earmarked for public health. Similar opportunities should be explored in other countries.

- **Investigate methods for mandating technical or financial support from developed countries to developing countries**

  Fulfilment of legal duties often hinges on sufficient resources. In many developing countries, public health systems may be inadequate. Thus, financial and technical leadership is needed from national governments towards local authorities, and from international organizations towards developing countries. A precedent can be found in the proposed Convention on the Provision of Telecommunication Resources for Disaster Mitigation and Relief Operations, which obligates the parties, where possible, to lower or remove regulatory barriers for using telecommunication resources during disasters.

- **Investigate international law on personal control and data protection issues relating to antimicrobial resistance**

  At a time when antimicrobial resistance may have created a greater need for personal control measures for public health (e.g., with multidrug-resistant tuberculosis), the status of international law on the scope and nature of a government's power to undertake such measures should be reviewed. Lessons from international environmental efforts suggest that international law must play a major role in setting international standards for implementation at the national level, and creating the political, technical, and financial conditions necessary to integrate international and national law.

- **Build on experience in EU countries of legislation against use of antibiotics in growth promotion**

  The EU has passed legislation to eliminate antibiotics that are used in humans from being used as growth promoters in animal feeds. However, Denmark and Sweden have banned growth promoters entirely. If other governments are to follow that lead, they will need to be reassured that there are no adverse economic consequences. Therefore, data about the impact of legislation in Denmark and Sweden should be collected and publicized (see also Chapter V).

TABLE A. **SANITATION AND INFECTION CONTROL RECOMMENDATIONS FROM THE WHO REPORT "CONTAINING ANTIMICROBIAL RESISTANCE"(*50*) AND ENDORSEMENT BY EXPERT POLICY GROUP REPORTS**

Document	Cleanse hands after each patient contact to prevent the spread of infection	Movement of patients within and between hospitals is increasing and contributes to the spread of infection	Correct the lack of sterile supplies and poor sterilization	There are several proven methods for improving hand washing	Improve hand washing and/ or use of gloves and gowns to decrease infection rates	Additional issues raised by this document
(*5*) WHO 1995	Endorsed	Endorsed	Endorsed	Endorsed	Endorsed	
(*49*) WHO 2000	Endorsed	Endorsed; stresses international travel.	Endorsed	Endorsed	Endorsed	
(*21*) House of Lords (UK)	Endorsed	Endorsed	Endorsed	Endorsed	Endorsed	Yes
(*1*) USA DHHS		Endorsed	Endorsed			
(*6*) US Congress Office of Technology Assessment	Endorsed	Importance of coordinating infection control measures between acute hospitals and long-term care facilities.	Endorsed	Endorsed	Endorsed	
(*20*) Antimicrobial resistance	Endorsed	Endorsed. Emphasizes blurred boundaries between community and hospital and increased travel.	Endorsed			Yes
(*51*) Fidler		While microbes move freely around the world, unhindered by borders, human responses to infectious diseases are conditioned by jurisdictional boundaries.				
(*19*) UK Department of Health	These issues were outside the remit of this report. Nonetheless, there is strong endorsement of the critical role of infection control in the hospital and community in the containment of antibiotic resistance.					
(*13*) Shlaes, et al.						Yes
(*24*) USA General Accounting Office		Endorsed; stresses international travel.				

TABLE B. **SUGGESTED INFECTION CONTROL INTERVENTIONS FROM THE WHO REPORT "CONTAINING ANTIMICROBIAL RESISTANCE"(*50*) AND ENDORSEMENT BY EXPERT POLICY GROUP REPORTS**

		Key components of an Infection Control Committee				
Document	Establish an effective infection control programme	Surveillance of infection	Identification of outbreaks	Implementation of effective control measures (e.g., hand washing)	Sterilization and disinfection of equipment and supplies	Additional issues raised by this document
(*5*) WHO 1995	Endorsed	Endorsed	Endorsed	Endorsed	Endorsed	Yes
(*49*) WHO 2000	Endorsed					
(*21*) House of Lords (UK)	Endorsed	Endorsed	Endorsed	Endorsed	Endorsed	Yes
(*6*) US Congress Office of Technology Assessment						Yes
(*20*) Antimicrobial resistance	Endorsed			Endorsed		
(*7*) National Science and Technology Council (USA)						
(*13*) Shlaes, et al.	Endorsed	Endorsed	Endorsed	Endorsed	Endorsed	Yes
(*31*) Centers for Disease Control and Prevention (USA)						Yes

TABLE C. **SANITATION AND INFECTION CONTROL: ADDITIONAL INSIGHTS AND RECOMMENDATIONS BY EXPERT POLICY GROUP REPORTS**

Document	Additional issues raised
(*49*) WHO 2000	1. Emphasizes the importance of community sanitation for infection control in developing countries.
(*21*) House of Lords (UK)	2. Infection control beyond the hospital is an area of particular weakness (paragraphs 4.20–25). This is especially true of nursing and residential homes, which can act as reservoirs of MRSA and other resistant organisms, which are then carried back into hospitals.
(*20*) Antimicrobial resistance	3. Economic costs of infection control in the community (increased cost of hygienic production).
	4. Importance of sanitation in developing countries.
(*13*) Shlaes, et al.	5. Adopt CDC recommendations for isolation of patients colonized with resistant bacteria.

TABLE D. **SANITATION AND INFECTION CONTROL: ADDITIONAL SUGGESTED INTERVENTIONS BY EXPERT POLICY GROUP REPORTS**

Document	Additional issues raised
(*5*) WHO 1995	1. Link the prevention and control of antimicrobial-resistant organisms in hospitals to national and local quality assurance efforts. 2. Develop methods and standards for evaluating hospital infection and antimicrobial resistance control programmes, leading ultimately to a national accreditation system. 3. Develop educational programmes and hygienic standards for day care and extended-care facilities. 4. Promote standards of hygiene in the community, including safe water and food hygiene.
(*49*) WHO 2000	5. Promote other means of infection control (such as bednets in malaria endemic countries), education, and support for those living in developing countries.
(*21*) House of Lords (UK)	6. Purchasers and commissioning agencies for hospital services should put infection control and basic hygiene where they belong, at the heart of good hospital management and practice, and should redirect resources accordingly; such a policy will pay for itself quite quickly. NHS Executives should assure themselves that every NHS hospital is covered by a properly trained infection control team, as recommended in the Cooke Report (paragraph 11.26).
	7. The NHS should draw up national standards and guidelines for community infection control management, along the lines of the Cooke Report for hospitals. These should include a requirement that every district health authority should have at least one community infection control nurse (paragraph 11.28).
	8. Those responsible for the review of the Public Health (Control of Disease) Act 1984 should consider the shortcomings of the provisions for compulsory medical examination and detention in hospital, and the case for a more humane regime, and for extending the legislation to provide also for supervised treatment at home (paragraph 11.29).
(*6*) US Congress Office of Technology Assessment	9. Hospitals should consider instituting antibiotic-use subcommittees in the infection control committees.
(*13*) Shlaes, et al.	10. Make hospital administration accountable for the implementation and enforcement of policies adopted by hospital committees.
(*31*) Centers for Disease Control and Prevention (USA)	11. Top priority action item: Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote judicious drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied effectively on a routine basis, on a large scale, and cost-effectively.

TABLE E. **WHO SUGGESTED RECOMMENDATIONS FOR GOVERNMENT AND HEALTH SYSTEMS AND ENDORSEMENT BY EXPERT POLICY GROUP REPORTS**

	Items from "Containing Antimicrobial Resistance"(*50*)					
Document	**End poor communication and implementation of national policies**	**Institute effective regulatory mechanisms**	**Regulate sales, including informal sector sales**	**Establish Essential Drugs Lists**	**Establish national standard treatment guidelines**	**Additional issues raised by this document**
(*5*) WHO 1995	Endorsed	Endorsed	Endorsed		Endorsed	
(*49*) WHO 2000	Endorsed	Endorsed	Endorsed	Endorsed	Endorsed	
(*21*) House of Lords (UK)	Endorsed	Endorsed	Not a problem in the UK; condemned any OTC availability of antibiotics.	Endorsed WHO efforts in developing countries.	Endorsed need for national approach on implementing prudent use of antimicrobials.	Yes
(*1*) USA National Institutes of Health	Endorsed	Endorsed	Endorsed	Endorsed		
(*6*) US Congress Office of Technology Assessment					Endorsed	
(*20*) Antimicrobial resistance		Especially in developing countries.	Endorsed	Endorsed	Restricting access to a specific drug leads to excessive use of alternatives; policies need to address overall prescribing as well as use of specific drugs. Guidelines will not be effective unless they are evidence-based.	Yes
(*51*) Fidler		Endorsed	Endorsed			Yes
(*19*) UK Department of Health					Endorsed	
(*13*) Shlaes, et al.					Endorsed	
(*22*) Institute of Medicine (USA)				Endorsed		Yes
(*11*) American Society for Microbiology		Comments on developing countries only.				Comments on developing countries only.
(*39*) USAID	This document is a statement of intent rather than a review of the literature or set of recommendations. One of the statements of intent covers this current review and synthesis of information or recommendations.					

TABLE F. **WHO (*50*) ADDITIONAL SUGGESTED INTERVENTIONS FOR GOVERNMENT AND HEALTH SYSTEMS AND ENDORSEMENT BY EXPERT POLICY GROUP REPORTS. SEE ADDITIONAL ISSUES LISTED IN TABLES G AND H.**

Document	Identify and eliminate economic incentives (i.e., reimbursement practices) that encourage inappropriate antimicrobial use	Target advocacy for action towards relevant organizations (WTO, WB, IMF)	Adapt WHO model legal framework for license, sale, supply, distribution, promotion	Introduce legal requirements for collection of data on production, distribution, sales and consumption for human, veterinary and agricultural use	Introduce formal training and registration schemes for dispensing outlets	Additional issues raised by this document
(*5*) WHO 1995	This document covers the same issues, but sets them out as a series of general recommendations rather than specific suggestions for policy or implementation. For example it is suggested that countries should "develop information systems" but a legal requirement is not suggested. Regulation of promotion of antimicrobials is endorsed, but a legal requirement to monitor supply and distribution is not covered.					
(*50*) WHO 2000			Endorsed	Endorsed	Endorsed	
(*21*) House of Lords (UK)		Focus was on the UK, but endorsed UK support for WHO activities: "The Government's exemplary support for the WHO Division of Emerging Diseases should be maintained, and the United Kingdom Government's example should encourage other nations and agencies to contribute to this vital work."		Endorsed, particularly emphasizes the inadequate data about hospital or veterinary use.	Endorsed, supports more coordinated approach in the UK. Commends the work of the WHO in the developing world (paragraph 11.10).	Yes
(*6*) US Congress Office of Technology Assessment	Congress should review effects of Medicaid and Medicare reimbursement policies on antibiotic prescription patterns.					Yes
(*51*) Fidler		Endorsed (especially WTO)	Endorsed			Yes
(*7*) CISET (USA)		Endorsed (p7, p26)	Endorsed (p7, p26)	Endorsed (p7)		Yes
(*24*) USA General Accounting Office				Most countries do not have measures of total antibacterial use.		
(*22*) IOM (USA)		Endorsed	Endorsed (p64)			Yes
(*31*) CDC (USA)	Primarily concerned with surveillance, prevention and control of resistance in the US, where regulation of license and promotion already exists. However, does not deal with legislation compelling manufacturers to measure and report sales and consumption data.					

TABLE G. **GOVERNMENT AND HEALTH SYSTEMS: ADDITIONAL INSIGHTS AND RECOMMENDATIONS BY EXPERT POLICY GROUP REPORTS**

Document and levels of responsibility	Additional issues raised
(*49*) WHO 2000	
International Cooperation	Emphasizes the importance of making antibiotics available for treatment of infections in developing countries as a means of containing spread of infection in general and resistant strains in particular.
(*21*) House of Lords (UK)	
National and Local Governments	The evidence is clear (paragraphs 2.26–30) that prudent use is much harder to achieve if antimicrobials for internal use are available over the counter.
Hospitals	It is notoriously difficult to manage what cannot be measured; and we have heard much about the contrast between the excellent data on general practitioner prescribing, captured by both the Prescription Pricing Authorities and general practitioners themselves, and the lack of data on antimicrobial use in hospitals (paragraphs 10.4–7).
Doctors and Patients	We acknowledge the dilemma facing doctors and patients alike (paragraph 2.9), that what is prudent from the point-of-view of public health may be highly imprudent from the point-of-view of the individual patient, and vice versa.
Animal Health Regulators	The United Kingdom led the world in addressing the threat to human health posed by antibiotic use in farming practices with the Swann Report in 1969. Unfortunately, some of the recommendations of Swann were not acted upon and many believe that, had action been taken then, our present concerns would be much less than they are now, at least as regards the situation in the United Kingdom. The evidence that we have heard (paragraphs 3.7–13) strongly suggests that there is a continuing threat to human health from imprudent use of antibiotics in animals.
(*20*) Antibiotic Resistance	
National Government	Limit general access to new drugs (e.g., fluoroquinolones). Governments should make and provide materials to support intervention programmes (e.g., materials available from CDC). Grant licenses conditionally based on monitoring of resistance (especially in veterinary use).
Hospitals	Limit general access to new drugs (e.g., fluoroquinolones).
(*51*) Fidler	
International Cooperation	Private initiatives are building global information-sharing networks on various disease issues through the Internet and other information technologies; private companies are starting to monitor and test bacterial resistance globally; and some for-profit companies gather and sell epidemiologically useful information. These private efforts raise legal questions: privacy issues arise with the dissemination of epidemiologic data by private companies; this dissemination is treated differently in different countries; jurisdictional problems arise regarding legal regulation of information-sharing in cyberspace. The notion of personal control measures against drug-resistant malaria patients in Africa seems far-fetched, given the scale of the problem. Nevertheless, the importance of international human rights law to effective public health policies (as seen in the context of HIV/AIDS) demonstrates that complacency towards individual rights in any public health policy is dangerous legally and medically. International legal harmonization of principles for prudent antimicrobial drug use must include monitoring and enforcement, as well as financial, technical, and legal assistance provided by industrialized countries to developing countries. In the context of environmental protection, trade restrictions seeking to change a production process in another country, rather than to protect against health dangers from a particular product, have been ruled incompatible with international trade law. To avoid losing trade restrictions as part of a general strategy to combat antimicrobial misuse, legitimate trade restrictions against countries that systematically neglect recognized principles and practices for antimicrobial use might be considered; such a move would elevate the status of Codex's Code of Practice for Control of the Use of Veterinary Drugs and Guidelines for the Establishment of a Regulatory Program for Control of Veterinary Drug Residues in Foods, as the SPS Agreement has elevated the importance of Codex's Maximum Residue Levels for Veterinary Drugs in Foods. International law on intellectual property protection is a critical piece of the overall strategy against antimicrobial resistance.

TABLE G. **CONTINUED**

Document and levels of responsibility	Additional issues raised
National and Local Governments	Especially in federal systems, countries often divide authority for public health among various levels of government.
	Privatization of laboratory services by state legislatures may compromise national surveillance of emerging infectious diseases and investigation of outbreaks, because many surveillance systems rely on data from state laboratories.
	Increased surveillance for antimicrobial resistance may heighten privacy concerns with respect to other diseases, such as multidrug-resistant tuberculosis (MDRTB).
	In the United States, Congress could regulate use of antimicrobial drugs by monitoring interstate commerce in these products. Congress probably does not have the authority to regulate antimicrobial prescription practices directly; such authority rests with the states.
	Perhaps the most powerful US federal strategy would be to make implementation of state policies to curb the misuse of antimicrobial drugs mandatory before states receive federal funds earmarked for public health.
National Government	In countries where governments subsidize the purchase of antimicrobial drugs, legislative or regulatory changes in these subsidies could lead to a decline in the use of the drugs.
	Pharmaceutical companies that had developed antibiotics but never commercially exploited them might pursue more antimicrobial research and development if their earlier antibiotics (now without patent protection) were given extra legal protection, either under patent law or a legal regime like the Orphan Drug Act.
(*22*) Institute of Medicine (USA)	
National Government	Existing antibiotics may have activity against resistant pathogens but have not undergone clinical trials; advocates accept surrogate indicators of efficacy.
	Explore the value of extending patents as an incentive to prudent use.
Animal Health Regulators	Need to address ambiguities about registration of antibiotics in agricultural products and incorporate antibiotic resistance into discussions of food safety and the regulation of imports.

TABLE H. **GOVERNMENT AND HEALTH SYSTEMS: ADDITIONAL SUGGESTED INTERVENTIONS BY EXPERT POLICY GROUP REPORTS**

Document and levels of responsibility	Additional issues raised
(*5*) WHO 1995	
National and Local Governments	Support programmes to improve access to treatment and thus earlier detection and interruption of outbreaks of resistant bacteria.
National Government and Agricultural Industry	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.
	Define acceptable levels of antimicrobial agent residues in food from animal sources and ensure compliance with national standards.
(*49*) WHO 2000	
International Cooperation	Support countries in developing reliable supply systems.
International and National Governments	Make effective medicines accessible to the poor.
	Strengthen national and international capacity to ensure the quality of anti-infective drugs.
All Levels of Government and the Pharmaceutical Industry	Increase the availability of essential drugs.

TABLE H. **CONTINUED**

Document and levels of responsibility	**Additional issues raised**
(*21*) House of Lords (UK)	
International Cooperation	We commend the Government and the ABPI for their firm stand against over-the-counter antibiotics, and urge them not to give way. Since this is an area of EU responsibility, and the position in several other Member States appears to be different, we recommend that the Government should engage in active diplomacy to ensure that, should the issue be raised in the Council of Ministers, their position is understood and their allies are in place; and, in the long term, to induce those Member States which are currently more relaxed about over-the-counter antibiotics to introduce more controls.
National Government	The Government and the health authorities must do more to educate the public about the proper use of antimicrobials. In particular, we recommend a campaign targeted at mothers of young children. The Education Committee of the General Medical Council and the medical Royal Colleges should review the evidence that undergraduate curricula give insufficient emphasis to infectious diseases and antimicrobial therapy, and the Royal Colleges should increase the attention paid to antimicrobial therapy in their programmes of postgraduate education and vocational training (paragraph 11.6). The Medicines Control Agency should consider whether the drug licensing system could be used more effectively to encourage prudent use in the interest of public health (paragraph 11.9). The Government should respond positively to the EU proposal for an "orphan drug" regime, and should seek to ensure that the scheme gives the pharmaceutical industry a real incentive to work on novel treatments for problem diseases, particularly diseases of the world's poor, such as malaria (paragraph 11.40).
Local Government	The NHS Executive must work towards the goal of compatible and interconnected information technology for every general practitioner, every hospital ward and infection control team, and every clinical microbiology laboratory. They must accept the considerable cost involved; and they must give a strong lead from the centre to ensure compatibility (paragraph 11.51).
Hospitals	All hospitals should install computer systems for patient-specific prescribing information at ward level.
Doctors	We do not recommend that general practitioners should be required to establish antimicrobial susceptibility before prescribing (paragraph 2.22). This, we believe, would at present be impracticable, and would overload diagnostic services which are already stretched. But improved access to microbiological testing clearly reduces uncertainty in prescribing.
Veterinarians	The veterinary profession must address the use of potent agents important to human medicine (e.g., fluoroquinolones), by introducing rapidly a Code of Practice on when such compounds should be prescribed (e.g., when other agents have failed) and how (e.g., for no longer than necessary); we recommend self-regulation in preference to legislation.
(*1*) USA National Institutes of Health	
National Government	In countries with more restrictive legislation and more effective enforcement of antibiotics prescriptions, studies should be carried out on the effects of such legislation on requirements for training of health-care personnel and on economic and other consequences for patients and national health-care delivery systems. Legal restrictions on the use of antibacterial drugs may exert positive or negative effects on mortality and morbidity, especially among children.
National Government and Hospitals	Longitudinal studies must determine whether regulations and effective enforcement have any effect on the emergence of resistance.
National Government and Agricultural Industry	The public health consequences of restrictions on antibacterial use in food production and animal husbandry should be investigated.
(*6*) US Congress Office of Technology Assessment	
National Government	Congress can provide FDA with authority to negotiate extended market exclusivity to manufacturers that agree to restrictions on marketing of antibiotics. Congress could authorize FDA to extend market exclusivity for "off-patent" antibiotics that are effective against drug resistant bacteria. Congress could provide research support for a federal programme to conduct clinical trials of antibiotics to determine if they have uses against antibiotic resistant bacteria.

TABLE H. **CONTINUED**

Document and levels of responsibility	**Additional issues raised**
Veterinarians	The document is skeptical about the possibility of reaching consensus about veterinary use of antibiotics based on existing data, and about the value of additional studies.
(*20*) Antibiotic resistance	
National Government	Make assessment of resistance potential of new compounds part of their licensing.
(*51*) Fidler	
International Cooperation	The International Health Regulations mandate, for example, that Member States of the World Health Organization (WHO) report outbreaks of plague, cholera, and yellow fever to WHO.
	WHO has proposed including surveillance of antimicrobial resistance in the revision of the International Health Regulations and requiring drug resistance reporting.
	Creation of a legal duty does not ensure the success of a policy. WHO Member States have routinely ignored required outbreak reporting of plague, cholera, and yellow fever.
	Lessons from international environmental efforts suggest that international law must play a major role in setting international standards for implementation domestically and creating the political, technical, and financial conditions necessary to integrate international and national law.
	The importance of Codex food safety standards to international trade law was seen in the Beef Hormones Case, in which the WTO held that the EU violated the SPS Agreement for not providing scientific justification for a beef hormone regulation stricter than the relevant Codex standards.
National Government	Fulfilment of legal duties often hinges on sufficient resources. In many developing countries public health systems may be inadequate. Thus, financial and technical leadership is needed from national governments for local authorities, and from international organizations for developing countries.
	A precedent can be found in the proposed Convention on the Provision of Telecommunication Resources for Disaster Mitigation and Relief Operations, which obligates the parties, where possible, to lower or remove regulatory barriers for using telecommunication resources during disasters.
	The comprehensive statutory and regulatory system in the US that governs the acquisition, use, and transfer of biological agents that pose a threat to public health might serve as a model for legislation in other countries.
	At a time when antimicrobial resistance may have created a greater need for personal control measures for public health (e.g., with MDRTB), the status of US law on the scope and nature of the government's power to undertake such measures seems unsettled.
(*19*) UK Department of Health	
National Government	Licensing authorities should consider an antimicrobial agent's potential to select for resistance in addition to its safety and efficacy.
Pharmaceutical Industry	Consider finding ways, through pricing and other mechanisms, of ensuring that investment in the development of new antibiotics remains commercially viable.
(*7*) National Science and Technology Council (USA)	
National and International Governments	Introduce a global alert system requiring national governments to inform worldwide health authorities about outbreaks.
National Government	Establish a private sector subcommittee of the Interagency Task Force.
(*22*) Institute of Medicine (USA)	
International Cooperation	Explore International Conference on Harmonization (p59) as a forum for a global approach to rational antimicrobial use.
	Initiate dialogue, led by WHO with representation from WTO, EU and US Departments of State and Commerce, about regulation of antibiotics in agricultural products.

CHAPTER IV

Encourage research and product development

John F. Barrett

Abstract

The areas of research and development offer tremendous possibilities to have an impact on the antimicrobial resistance crisis worldwide. A historical review of support for antimicrobial resistance research and development, as a subset of infectious disease research including tuberculosis research, has determined a gross under-funding of this area, in academic, governmental and industrial laboratories over the past 10–15 years. There is a need to encourage federal, university, and private sector collaboration in basic and applied research.

Consensus points by governing bodies reviewing antimicrobial resistance over the past five years, consistent with current key-opinion-leader sentiment, show that the major needs include: basic research is needed to delineate the genetic and metabolic pathways, microbial physiology, and the causes of antimicrobial resistance; an increase in research for the identification and development of new drugs to fight antimicrobial resistance; and an increase in basic and applied research for new vaccines and other preventive measures.

In broader terms, research and development needs to cover a more global effort to provide compelling evidence for the prudent use of antibiotics, including the use in humans, animals and plants; provide incentives for the discovery and development of agents to combat antimicrobial resistance; facilitate innovative approaches to fight against resistance; and build worldwide alliances and partnerships to increase sensible access to antimicrobials (*1*,*5*,*6*,*7*,*8*,*11*,*19*,*20*,*21*,*22*,*39*,*49*,*50*,*53*).

Introduction

There is significant consensus among research professionals that the US Surgeon General, William Stewart, was wrong in 1969 when he was quoted as saying that we (the US population) could "…close the book on infectious diseases…" in addressing public concerns (from a health standpoint). All position-piece documents reviewed for this chapter make observations about the seriousness and deterioration of public welfare as infectious disease concerns continue to increase worldwide (*1*,*5*,*6*,*7*,*8*,*11*,*19*,*20*,*21*,*22*,*39*,*49*,*50*,*53*). In addition, many reports address antibiotic resistance in specific circumstances and microorganisms, and all identify antibiotic resistance as a growing problem (*54–69*).

The 1992 Institute for Medicine's (IOM) report on "Emerging Infections: Microbial Threats to Health" (*71*) indicates that "changes in technology and industry" are among those risk factors that have contributed to the inability to prevent or control microbial diseases. This IOM report (*70*) lists six general factors leading to the emergence of infectious diseases and antimicrobial resistance:

- environmental change and land use;
- breakdown of public interest health measures;
- international travel (transporting infectious diseases globally);
- changes in social behaviour;
- changes in technology and industry; and
- microbial adaptation and change (including resistance development).

The world is no longer simply a matter of geographical division of diseases, as the spread of infectious diseases continues to be demonstrated with the emergence of "developing nation diseases" in specific geographical centres in the industrialized world (e.g., tuberculosis, dysentery, etc.).

A practical way to look at emerging diseases is that a disease in one geographical area could easily be transmitted to the unaffected area, by simple delivery of the infectious disease by human carrier. Thus it is naive to believe that antimicrobial resistance in any part of the world is an "isolated problem".

The industrialized countries, by virtue of advanced technology and improved basic living standards, are privileged to not be subject to the massive outbreaks of infectious diseases that we see in the developing world. Basic sanitation, basic edu-

cation on maintaining good health, and widespread immunization against disease, provides a tremendous advantage to the occupants of the industrialized world. Short- and long-term gains are a matter of basic education and building a foundation so the next generation of developing countries' children have the same advantages as industrialized countries' children in sanitation and health care. However, research and development in the developing countries is virtually non-existent, and the short-term possibilities for changing this are remote.

This chapter reviews the expert reports (*1*,*5*,*6*,*7*, *8*,*11*,*19*,*20*,*21*,*22*,*39*,*49*,*50*,*53*,*54*) and other relevant literature from the viewpoint of research (basic and applied) and product development and attempts to summarize their recommendations.

Basic and applied research

Identification of research needs

All the expert reports reviewed made at least some mention of research and many had extensive sections devoted to research needs both to improve the understanding and management of antimicrobial resistance and to develop new drugs, vaccines and diagnostic tools. Recommendations from Wise and colleagues in the British Medical Journal's special (1998) issue on antimicrobial resistance include the need for increased understanding of antimicrobial resistance processes; and for encouragement to the pharmaceutical industry to increase its commitment to antimicrobial research (*71*,*72*). Huovinen and Cars (*73*) emphasize research [both basic and applied] as "…a cornerstone in the fight against bacterial resistance." From a better understanding of the microbiology and genetics of our endogenous flora, we may better understand the collateral damage of normal antibiotic usage in facilitating the evolution of resistance and the mechanism of transmissibility of resistant bacteria. More prudent use of antibiotics will be attained by the development of diagnostic technologies to enable rapid identification of bacterial versus viral pathogens.

A synthesis of the key research needs identified in the expert reports reviewed (*1*,*5*,*6*,*7*,*8*,*11*, *19*,*20*,*21*,*22*,*39*,*49*,*50*,*53*,*54*) follows:

Infrastructure and training

- Improvement in basic and applied research infrastructure (academic and industrial);
- Improvement in basic research training in academia to ensure a critical mass of researchers in the antimicrobial resistance field of research.

Infectious disease and microbial pathogenicity

- Improvement in understanding of how to prevent the infectious disease state and to treat new infectious diseases; basic research related to new and re-emerging pathogens/infections and better understanding of the infectious disease link to chronic diseases
- Basic research in molecular pathogenesis, including:
  - — the evolution of pathogenicity;
  - — the epidemiology and spread of pathogens and infectious disease transmission;
- Resources to enable the sequencing of the entire genome of additional microbial pathogens (including problem pathogens in developing countries).

Antimicrobial resistance

- Research into the source of antibiotic resistance genes; the mechanisms/frequency of 'reassortment' of these genes, the emergence and transfer of resistance genes among pathogens *in vivo* (in the host), and the distribution and dissemination of specific antimicrobial resistance genes over time, and factors affecting the loss of resistance determinants;
- Research on the correlations between resistance determinants in normal flora and the prevalence of resistant pathogens;
- A better understanding of the ability of genetic material to transfer in the bacterial ecosystem;
- Studies on the ability of bacteria to amplify genes and exchange genes leading to multiple drug resistance in bacteria;
- Mechanisms of antimicrobial resistance emergence, acquisition, spread, persistence, and decline of multidrug-resistant microorganisms;
- Research on factors that accelerate the development of drug resistance and methods to delay or reverse drug resistance;
- The need for more research examining ways to decrease resistance frequency.

New technologies

- Provide technologies to researchers to allow for the identification of quality, novel targets;
- Develop tools such as microbial genome sequence data, comparative genomics, DNA chip technology, and bioinformatics;
- Research in molecular genetics to identify novel targets.

New antimicrobials, vaccines, disease prevention and diagnostics

- Provide opportunities to translate basic research findings into applied, medically useful products/devices/technologies (i.e., drugs, diagnostics, vaccines, and other tools to inhibit antimicrobial resistance);
- Research the role of host factors and immunomodulation in clinical resistance and the human immune response to infectious diseases;
- Basic research towards the development of effective vaccines;
- Research of development of vector control interventions;
- Basic research on other disease preventative measures;
- Support of research and development and standardization of diagnostic tests;
- Research to discover/design/develop more reliable, rapid diagnostic techniques for identification of infections causing specific disease states;
- Increased research into methods to detect resistance to antimicrobial agents;
- Tools for the clinical/epidemiological researcher that can be used to more accurately and efficiently identify optimal therapeutic options for treatment of antibiotic resistant strains.

Research on antimicrobial use

- Links between prescribing and resistance at both the individual and population levels;
- Concepts concerning antibiotic use and their influence on delivery and compliance;
- Factors leading to inappropriate prescribing;
- An understanding of variation in antimicrobial use patterns that affect emergence and spread of resistance;
- Effect of preventative, therapeutic and growth-promoting agents used in the animal use field on the community microbiota.

Surveillance and information management

- Research to improve of surveillance tools, including computer programmes for data management and reporting;
- Research in methods for monitoring drug resistance;
- Development and assessment of computerized decision-support systems in hospitals;
- Encourage sharing of antimicrobial resistance data between industry, universities, and governmental authorities.

Additional research areas to consider

Understanding the costs of resistance

a) to the bacterium

One of the major research areas only minimally touched on in the reports reviewed was that of the cost of resistance to the bacterium (*1*,*74*). The understanding of the cost to the bacterium that receives or adapts to the resistant state is better understood in terms of the change in pathogenicity as the 'expense' of increased resistance. Where previously, resistance acquisition was viewed as a crippling event, it is now understood that it may actually confer a selective advantage to the pathogen (*74*).

b) costs to the health care system

A new field of marketing research and business management has arisen over the past years dealing with the pharmacoeconomics of health care (*75*), in which factors indirectly related to outcomes may be drawn into the value of one action over the other. For example, the 'cost' of antimicrobial resistance in the patient population may take into account loss of work time, allowing a quantitative assessment of the 'cost' of infection beyond the drug costs alone. If a treatment regimen gets the patient out of the hospital on oral medication, rather than continuation of therapy by intravenous administration, then the 'cost' of therapy overall, in terms of measuring the 'cost' of antimicrobial resistance, may factor in the absence of 2–5 additional hospital days (that may range from $1500–$2500 per day). Even the selection of the 'right' first-line antibiotic the

first time by the practicing physician, versus requiring a follow-up visit because the 'older' or generic antibiotic (with cost saving) did not work, has a 'cost' associated with the patient's return to the physician, as well as the cost to the physician. One of the criticisms of the for-profit-managed health care delivery systems may be that by providing an allotment of dollars per patient per year to the physician by contact regardless of the true cost, pushes the physician to cost-cutting methods (including the choice of an inappropriate antibiotic).

Areas where there is lack of consensus

There is no consensus as to the cause, effect, or solution to the worldwide antimicrobial resistance problem, nor as to the origin of antimicrobial resistance genes. However, it is clear that antimicrobial resistance stems from the use of antibiotics. While there is no high-level disagreement about the unmet medical need posed by antimicrobial resistance, there are differences in opinion vis-a-vis the scientific priorities.

Not surprisingly, there is no consensus as to the specific 'cause-and-effect' and assignment of 'blame' on the increase in antimicrobial resistance (*1,5,6,7, 8,11,19,20,21,22,39,49,50,53,54,60–69*); more basic and applied research is needed to answer this complex question definitively. However, it is clear to virtually all opinion leaders that antimicrobial resistance begins with the routine use of antibiotics for human health care, animal health, and agricultural purposes. There is most probably a link to the resistance emergence to the most frequently prescribed antibiotics and the alarming increase in resistant bacteria (*11*). For example, greater than 90% of *Staphylococcus aureus* were resistant to penicillin and other β-lactams as of 1994, and there is an notable increase in vancomycin resistance in enterococci. Likewise, but of unknown clinical relevance, there is an increase in the resistance to penicillins by *Streptococcus pneumoniae*.

Concerning resistance and selective pressure, there is not consensus among scientists as to whether removal of an antibiotic from the treatment regimen will: reduce the risk and/or expansion of resistance in the pathogen population; reverse the resistance frequency or prevalence in the bacterial population; or have no effect on the resistance frequency. In the House of Lords report (*21*) Reeves is quoted as stating "There is plenty of evidence, that if you remove the selection pressure, the organisms will slowly revert [to susceptible]….", whereas Davey provided evidence directly linking resistance to overall usage. In contrast to Reeves, Levin was quoted (*21*) that resistance is a one-way street, that if antibiotic use is cut back sharply, the proportion of resistant strains wanes slowly (if at all).

Effective efforts

The review of the expert reports seems to indicate the effectiveness of basic research in increasing our understanding of antibiotic resistance and the development of new drugs. Extensive research efforts in academia continue, albeit dwarfed by support to AIDS research, and have yielded excellent results from a better understanding of the molecular mechanisms responsible for antibacterial resistance, (*72, and references cited therein*) to new medicinal chemistry approaches to combat resistance in bacteria (*76, and references cited therein*). Historically, basic research has provided numerous advancements in understanding of microbes which has been applied to the engineering of drugs by pharmaceutical companies.

Ineffective efforts

Many of the US reports indicate funding (that is US-based) is woefully lacking for basic and applied research concerning antimicrobial resistance. As pathogens can vary greatly in industrialized versus developing countries (*77*), the priorities of 'medical need' are often misaligned. Priorities for funding have shifted away from bacteria-associated research to AIDS research over the past fifteen years. The lone exception appears to be the increase in TB research support (although this is still disproportionately small considering the worldwide morbidity and mortality due to TB).

Research and development efforts to provide compelling support for the 'prudent' use of antibiotics have failed to translate into prudent use; Reducing inappropriate use of antibiotics with supportive basic and applied research (*1,50,39,78,79*) has proved ineffective.

A critical role for new technologies

There is consensus (*1,5,6,7,8,11,19,20,21,22, 39,49,50,53,54*) that the molecular detection of genes that are associated with antimicrobial resistance is expected to be ascertained by the analyses of microbial genomes (*22*). The principles and

implications of mapping the prokaryotic genome(s) are to acquire the full sequence of microbial genes and to manage great volumes of sequence data through bioinformatics. It is hoped that once this 'raw' data is collected in analysable form (hence the 'informatics' in bioinformatics), this 'knowledge' (as opposed to raw data) will provide a foundation for the discovery and development of new antimicrobial agents, new vaccines, and new diagnostic tools for infectious diseases.

Consensus throughout the documents (*1,5,6,7, 8,11,19,20,21,22,39,49,50,53,54*) holds that comparative genomics (i.e., the ability to compare full length sequences of different bacterial, or even eukaryotic, genomes) may present the opportunity for the informatic-assignment of 'putative' essential function in microbes based on consistency of sequence similarity, but wet-biology proof is needed to confirm this informatics assignment. The best example of successful gene sequencing/bioinformatics may be The Institute for Genomic Research (TIGR), with the intention to sequence 50–100 microbial genomes within just a few years. But beyond the cataloging of raw sequences, TIGR and other groups are developing gene array technology that will allow for the simultaneous assessment of expression of all genes in a microbe under different environmental conditions (growth condition changes, stress, antibiotic insult, etc.). Among the data expected to be ascertained are: 1) the identification of genes involved in susceptibility or resistance to antimicrobial agents; 2) specific knowledge of gene function, including regulatory functions of different genes; 3) the identification of polymorphism shifts signaling the evolution of infectivity (virulence) and/or susceptibility/resistance to antimicrobials; and 4) the identification of potential antigens/proteins against which vaccines may be devised (*22*).

The genetic basis of resistance in bacteria may supersede the phenotypic (macro-) detection of resistances, frequently based on microbiological susceptibilities (minimal inhibitory concentrations, etc.). Undertaking the identification of the genotypic cause for changes in susceptibility may provide insight into the development of novel approaches to combat resistance. A shortcoming of genotypic characterization of resistance factors is that it provides but a 'snapshot' of genotypic character; it gives a single time point of 'data', but not necessarily a proven link to the resistance pattern, or an understanding of antimicrobial resistance. A match of both genotypic and phenotypic data is most probably the best approach and will most likely provide the greatest opportunities for advancements in the short-term. The expanded and coordinated use of resistance surveillance systems such as SENTRY or the Alexander Project (*80,81*) would provide 'live' tracking of antimicrobial resistance, allowing action to be taken as appropriate to contain antimicrobial resistance, as well as predict emerging deleterious trends or appearance of emerging pathogen susceptibility problems.

There is agreement (*1,5 ,6,7,8,11,19,20,21,22, 39,49,50,53,54*) that practical applications arising from genomic analyses and bioinformatic tallying/ annotation of sequence function of microbial genomes may be limited only by the imagination of the researcher. From these analyses a selection of high quality novel targets is expected to emerge, allowing the applied research groups to select any of the following subsets of data: 1) essential genes; 2) virulence/pathogenicity genes (non-essential genes); 3) broad spectrum genes (gram-positive and gram-negative); 4) narrow spectrum genes (gram-positive or gram-negative); and 5) targeted spectrum genes (i.e., Mycobacterium tuberculosis, Chlamydia pneumoniae). In addition, selectivity and specificity may be ascertained by comparative genomic analyses, such as comparison to eukaryotic sequences, to determine minimal sequence overlap as a surrogate "in silico" indication of selectivity for the microbial target (i.e. decrease in toxicity) (*22*).

Additionally, molecular technologies can and have been employed downstream to identify "in silico" essentiality of genes, and subsequently proven by so-called "knock-out" approaches in which the selective inhibition of expression of individual genes and monitoring of survival and/or growth of the knock-outs, is a surrogate of 'essential function' in vitro (albeit negative selection data-based). Alternatively, genomic footprinting methodologies and temperature-sensitive mutants also provide surrogate assays for 'essentiality' determination in bacteria.

Consensus throughout the documents (*1,5,6,7, 8,11,19,20,21,22,39,49,50,53,54,55*) holds that taking genomic sequence information to practical application of screen design has provided a variety of high-throughput screening assay formats including cell-free biochemical or genetic assays, assays based on phenotypic changes, binding assays, enzymatic assays, etc. Genetic technologies may ultimately allow multiplexing of prokaryotic targets, which in turn may increase the chances of

success and decrease overall research and development costs (*22*). Thus these new technologies are seen to play a critical role in future discovery efforts for new antimicrobials.

Funding for research

The estimate for infectious disease deaths throughout the world in 1998 was over 13 million (*54*) or almost a quarter of all deaths worldwide. Of these deaths, 3.5 million were due to pneumonia, 2.2 million to diarrhoeal disease, 1.5 million to *M. tuberculosis*, 2.3 million to AIDS, 1.1 million to malaria, and 1 million to measles (*54*). The first three of these diseases, totaling 7.2 million deaths, were the top infectious disease killers as well as the overall top three causes of deaths worldwide in 1900 (*54*), indicating little impact of research and development on reducing this infectious disease burden.The current estimate is that less than 2% of the total health research expenditures throughout the world is devoted to antimicrobial usage, delivery, and resistance (*49*). To quote from the WHO report (*49*): "Incentives are needed to encourage pharmaceutical companies to discover and develop new compounds, as well as intensify research into dosage regimens calculated to minimize the likelihood of selecting for resistance."

US funding of infectious disease, AIDS, and tuberculosis research

The priorities for research in the United States can be clearly identified in a review of funding amounts from 1993 through 2001 (estimated), in which over an 8-year period the total research budget doubled from $9.765 billion (1993) to $18,812 billion (2001, estimated). The AIDS research portion of this budget increased by 1.97-fold increase in funding support. Infectious disease research (other than AIDS and TB) received a 1.97-fold increase and TB research increased from $35 million (1993) to $86.8 million (2001, estimated), or a 2.48-fold increase in the research funding. Although the TB research budget represents a disproportionate increase in funding, it is in turn disproportionately less than that for AIDS research (*82,83*). From the 1995 CISET report (7), funding of work related to infectious diseases other than AIDS or TB was c.5% of total research funding; the Centers for Disease Control and Prevention (CDC) dedicated c.95% of its budget for prevention and control of infectious diseases to AIDS, TB, sexually transmitted diseases and vaccine-preventable diseases (*7*).

Product development—antibiotics, vaccines and diagnostics

Antibiotics

The UK Standing Medical Advisory Committee was commissioned to examine the issue of antimicrobial resistance in relation to clinical prescribing practices (*19*). Their mission was to examine all factors that may contribute to antimicrobial resistance, including the role of research. From this report, one very relevant observation is made: "The thrust of this report is focused on the conservation of present antimicrobial agents. However, it must be recognized that the way in which past resistance problems have been overcome (if only temporarily) has been by the development of new agents."

The "Report of the ASM Task Force on Antibiotic Resistance" (*8*), based on the workshop on "Antibiotic Resistance: Current Status and Future directions" held in 1994, drew consensus from a group of almost three dozen scientists from academia, government and industry. It states: "The relative utility of antibiotics is eroding, tipping the balance in favor of multidrug-resistant pathogens, and there appears to be few new drugs in the pipelines of the USA pharmaceutical companies. These developments amount to an incipient public health emergency, albeit one that is poorly appreciated or recognized" (*8*).

Also from the Task Force report (*8*), "…it should be realized that the research-intensive pharmaceutical industry is the source for most new drugs and that industries need to profit from their investments in order to pay for the research." As marketing projections are primarily based on historical usage, they may be misleading. Marketing and business specialists in industry should be involved in discussions on the problems of emerging antibiotic resistance (*8*). In addition, as cost can drive prescription use, the national and regional health care providers/payers should be involved in the consideration of use of antibiotics, balancing the use of antibiotics and risk of emergence of resistance against cost in the selection of appropriate type and use of antibiotics. In exchange for the rational market-support approach for selling products, industry should help support national efforts for the prudent use of antibiotics (*8*). In addition, the potential association of infectious diseases (including bacterial infection) with chronic diseases needs to be better understood (*82*), and this will require an

immense, long-term, research investment. Overall, research has been found to be 'cost effective' (*11*).

This section contains a synthesis of the many suggestions and recommendations for product development that came from the reports cited in the references. A summary is given at the end of the section.

Industry engagement

Industrial infectious disease research remains a puzzle. Clearly in the 1970s and 1980s major companies decreased support for their infectious disease efforts (*84,85*), especially antibacterials, with the understanding that the antibacterial needs were diminished, but the reality is that pharmaceutical companies have continued to support to some degree infectious disease, moving towards antiviral and in some cases antifungal research efforts, but not to the same extent as the increases in non-infectious disease research areas such as cardiovascular, CNS, lipid disorders, oncology, dermatology, etc. The success rate for antibacterial discovery and development, much diminished since the 'hey days' of the 1960s–1970s, continues to pose a "value risk" for industry (*21*). There is, however, no shortage of good ideas (*84,86,87*).

The UK Standing Medical Advisory Committee (SMAC) report (*19*) notes that: "It is also recognized that over recent years the pharmaceutical industry has developed vastly more efficient systems for seeking new antimicrobial agents. These strategies will, hopefully, yield new generations of antimicrobial agents by the end of the next decade." According to the report (*19*), development of a new antimicrobial agent costs about $500 million (£350 million), over an estimated 7–10 year period (within a 17–20 year window of patent life, depending on country of filing). The costs, together with an understanding that these agents will be used for a relatively short period of time in a therapeutic area subject to the development of resistance and high competition, it is easy to see why pharmaceutical companies may elect to invest in research in other therapeutic areas (*84,85*).

A survey of the public domain reports (see Table 1), databases and literature by this author indicates major efforts by large pharmaceutical companies, start-up biotechnology-based pharmaceutical companies, and many smaller start-up initiatives, directed towards antibacterial resistance problems. But with success being harder to come by and with very few new antimicrobial agents reaching the market, the perception of lack-of-effort is apparent.

TABLE 1

Company	Research area(s)
Abbott Labs	Antibacterials/genomics
Astra-Zeneca	Antibacterials/antifungals/genomics
Bristol-Myers Squibb	Antibacterials/antifungals/genomics
Cubist Pharmaceuticals	Antibacterials/genomics
Eli Lilly	Antibacterials/antifungals
Glaxo-Wellcome[1]	Antibacterials/antifungals/genomics
Johnson & Johnson	Antibacterials/antifungals
Merck	Antibacterials/antifungals
Microcide Pharmaceuticals	Antibacterials/antifungals/genomics
Pfizer Pharmaceuticals[2]	Antibacterials/antifungals/genomics
Schering-Plough	Antibacterials/antifungals/genomics
SmithKline-Beecham	Antibacterials/genomics

[1] Now one research unit.
[2] Through strategic external aliances

The decrease in industrial support may be revealed by the number of commercial Investigational New Drug (IND) submissions in infectious diseases from 1991 to 1999, dropping from 327 (1991) to 265 (1995) to 52 (1999) (*82,83*). At the equivalent interval of 9 years (but shifted backwards in real time due to unavailability of more current data), overall funding for research (all therapeutic areas) by industry increased at a rate more than 50% higher than that of government funding for research, with industry support rising from $6.19 billion (1986) to $18.65 billion (1995) (*82,83*). However, this increase does not reflect a commitment to infectious disease, but rather an increase in funding in the chronic disease areas, with an emphasis on non-infectious disease research.

As most INDs submitted for infectious diseases are not for individual, novel chemical entities, an examination of the serious downtrend in industrial support for infectious diseases can be seen in the comparison of New Molecular Entity (NME) submissions in the FDA Division of Anti-Infective Drug Products, indicating a decreasing trend in the deliverability of novel agents (*82,83*). The NME approvals in the years from 1991 to 1999 are summarized in Table 2. NMEs dropped from 4–6 per year in the early 1990s to just 1 per year in the late

TABLE 2

	1991	1992	1993	1994	1995	1996	1997	1998	1999
# NMEs	5	6	4	NR	2	8	1	NR	1
Average NME Approval Time	27.4 mo.	21.1 mo.	24.9 mo.	—	25.6 mo.	14.3 mo.	15.0 mo.	—	7.8 mo.

NR = none reported

1990s (although there was a single-year spurt of agents in 1996 with 8 NMEs). This may represent an under-reporting of agents in the late 1990s with the shifting of some approvals to the FDA Division of Special Pathogens and Investigational Drug Products, but even with these numbers factored in, the NMEs have dropped more than 2-fold in the 10-year period ending with the turn of the millennium (*82,83*).

Virtually all antibacterial agents over the past 18–20 years, up to the approval/launch of the first oxazolidinone in 1999 (Linezolid™, Pharmacia-Upjohn), have been against 'old' targets, i.e., targets subject to the emergence of resistance. Even Synercid™ (Rhone-Poulenc Rorer) is a new analogue of the virginiamycins used for many years in animal husbandry in the UK, with pre-existing resistance in the gene pool. Numerous problems have delayed or denied support, development, or approval of novel antibacterial agents, among them: toxicological problems with novel chemotypes; development of resistance, even among the quinolones; concern for restricted use of new antibacterial agents; and loss of gram-negative activity in the newer agents in development.

Development of new antimicrobials

Wise and colleagues (*71,72*) provide an overview of the development of new antimicrobial agents, categorizing research strategies into three groups:

1. improvement of existing agents;
2. vaccine developments; and
3. genomic approaches.

Existing classes (β-lactams, cephalosporins, and carbapenems) have been a rich source of agents in the past, but limited novelty opportunities and emerging resistance have diminished these agents' value. Older agents used solely in animal health, such as orthosomycins and avilamycins, may provide novel chemotypes for human drug development. Everninomycins, virginiamycins (streptogramins), oxazolidinones, t-RNA synthase inhibitors (Mupirocin™), magainin-like peptides, antisense agents, quorum-sensing agent inhibitors, and efflux pump inhibitors may provide novel approaches to combat resistance. These and others are summarized in Table 3.

TABLE 3. **SPECIFIC AREAS IDENTIFIED (*6*) WHICH MIGHT YIELD PROMISING PRODUCTS WITH ACTIVITY AGAINST ANTIBIOTIC RESISTANT BACTERIA INCLUDED:**

Streptogramins
Tetracycline analogues
Dual-action cephalosporins
Newer vancomycin analogues or vancomycin-like glycopeptides
Macrolides
Catalytic antibodies
Oligosaccharide-derived antibacterials
Antibiotic peptides
Bacterial/permeability increasing peptides
Magainins, cecropins, defensin-like molecules
Steroid antibiotics
Lactoferrin-based antibiotics
Anti-sense nucleotides

New strategies in antimicrobial development may afford unprecedented opportunities for new, novel antibacterial agents (*88*). The development of three major technologies have provided hope:

- the use of genomics to identify novel targets;
- the use of combinatorial chemistry, including parallel synthesis, providing a new level of high-throughput medicinal chemistry synthesis of compounds; and
- advancements in screening technologies have increased daily throughput by over 100-fold, which use much smaller amounts of compounds, and screen up to 20,000 compounds per day (*19*).

Partnerships and incentives for development of new antimicrobials

The Office of Technology Assessment (OTA) report (*6*), concerning research and development and its impact on antimicrobial resistance, suggested several options for encouraging the development of new antibiotics; among them was a common-theme found in many of the other reports i.e., the need for cooperative research among the government regulatory bodies, academia, and industry (*6*).

In the SMAC report (*19*), the following incentive recommendation is made to increase the pharmaceutical company support in a competitive and profit-limited 'competitive' market: "One possible way forward, balancing the need for continued innovation with that of drug conservation, lies in the trade-off between extended patent life and increased restriction."

Vaccines

"Vaccination is one of the safest and most cost-effective ways of preventing disease" (*19*).

Vaccines may represent the best chance for targeted coverage of a pathogen, although "resistance" to a vaccine may also be unavoidable if variants of the pathogen emerge which are not covered by the vaccine. McKeller et al. (*89*) suggest that the use of vaccines rather than prophylactic use of antibiotics should be the norm in infection management in animal health.

Vaccines may pose the most straightforward option for long-term solutions to the resistance problem e.g., for meningitis (pneumococcal, *Haemophilus influenzae* or *Neisseria*) (*6,21,90*). However, scientific feasibility, production capacity, delivery infrastructure, social compliance, political pressures, and cost constraints are not always easily managed in industrial countries, let alone developing countries (*6,21,90*).There are a number of important issues to deal with in developing a vaccine i.e.:

- Selection of disease states, microorganisms to target (geographical, patient population differences such as age, gender, culture);
- Risk versus benefit;
- Efficacy (different efficacies and length of protection);
- Antigenic variation of pathogens (that reduce the efficacy of the vaccine);
- Use of therapeutic vaccines;
- Choice in industrialized versus developing world vaccine targets;
- Delivery of a vaccination programme to developing world needs.

Also vaccination against a pathogen that is also a member of the normal commensal flora (e.g., *Escherichia coli*, enterococci, etc.) may be problematic or deleterious for the host.

Worldwide medical needs for bacterial vaccines are summarised in Table 4 (*6,21*).

TABLE 4

Bacteria	Infection
Neisseria meningitidis (serotype B)	Meningococcal infection
Mycobacterium tuberculosis	Tuberculosis
Streptococcus pneumoniae	Pneumonia for children under 12 years of age
MRSA	Systemic infections; endocarditis
Vancomycin-resistant enterococci	Systemic infections; endocarditis
Neisseria gonorrhoeae	STDs
Staphylococcus species	Skin and soft tissue infections; Upper respiratory, including sinusitus
Helicobacter pylori	GI diseases (ulcer)
Group A streptococci	Pharyngitis
Clostridium difficile	Colitis
Shigella flexneri	Gastrointestinal dysentery
Pseudomonas aeruginosa	Respiratory (cystis fibrosis); burn wounds
Chlamydia	STDs; coronary artery disease

The National Institute for Biological Standards and Controls cited in (*21*) suggested that much more needs to be done about vaccine research and development, especially aspects of research in immunology, microbial genetics, epidemiology, and pathogenesis. In addition, issues surrounding the formulation and delivery of vaccines are in need of major initiatives worldwide.

Diagnostics

The delay in the diagnosis of a specific pathogen in an infectious state may be the major reason for so-called "empirical use" of antibiotics and increases the risk of inappropriate use. As the typical anti-

microbial susceptibility testing takes ≥48 hours, the overall process from first contact with medical care to delivery of a specific diagnostic report (*21*) may be longer.

Among the new technology detection systems for rapid diagnosis of bacterial pathogens and resistance are (*6*):

- DNA probe assays.
- Target amplification methods.
- Enzymatic tests for specifically detecting resistance (i.e., β-lactamases).
- Tests based on indicator dyes or light-producing enzymes.
- DNA-based methods for testing antibiotic resistance.

Whereas rapid and reproducible bacterial identification in the clinic may become reality in the future, the estimates are minimally 5–10 years out, and most probably much longer when one considers the standardization issues, technology limitations, scale-up issues, cost constraints, politics, and legal issues (risk of putative action for making the wrong call). Genotypic testing, in which polymerase chain reaction (PCR) technology is used to amplify as little as a single bacterium's DNA (*in vitro*), may be technically feasible but the scale-up and application in the clinic will be a major undertaking. Most importantly, the identification of a microorganism by this technique in the patient may not always signal a causal relationship to the infection.

Novel interventions

Levy (*91*) encourages the prudent use of antibiotics and for us to stop trying "…to sterilize our environment." Levy argues that we need to review how antibiotics are used and where resistant strains reside, since resistance is mobile from country to country. We need to examine the "ecology" of the resistance, as this may tell us where the future resistance may occur from selective pressures. Lastly, the indiscriminate use of disinfectants designed to "…indiscriminately destroy bacteria…" rather than reserving the arsenal for a defensive approach, diminishes our capacity and capability to act when human health is threatened by multidrug-resistant pathogens (*91*).

A new approach to combating antimicrobial resistance has emerged in which relevant human host factors are identified and stimulated, especially at the first site of pathogen attack, the epithelial surface. Study of the intrinsic resistance of oral-nasal-pulmonary sites, gastrointestinal sites, and genitourinary sites may provide opportunities for host-facilitated resistance to microbial invaders. The link of pathogenesis and immunological response to microbial insult is a new field of study (beyond the many years of vaccine development), and may provide an "immunoprotective" approach to combating antimicrobial resistance (*22*).

Summary of recommendations for research and development

The generalized strategies from the USAID Report (*39*) with five key recommendations, the Epilogue from the Task Force on "Antimicrobial Use and Resistance Worldwide" (*1*) with eleven recommendations, and the 1999 WHO report (*50*) with eleven key recommendations, and the recommendations of other expert groups can be summarized and focused towards industrialized and developing countries as follows:

Industrialized countries

- Fund basic and applied research in academia, government and industry to better understand all relevant aspects of antimicrobial resistance (genetic, epidemiological, mechanisms, transfer of genetic material, etc.) and to ascertain short-term gains to combat the ongoing threat of antimicrobial resistance. Support surveillance of antimicrobial resistance as a research tool, and link the data from surveillance to action in response to the data (i.e., update old product labelling for pathogen/indication coverage for older antimicrobial agents that may be contributing to antimicrobial resistance by inappropriate use).
- Provide incentives to industry to address unmet medical needs and provide new antibacterials to combat antimicrobial resistance worldwide in the short term, while encouraging partnerships between industry, academia and government to better exploit existing and new technologies to combat antimicrobial resistance (drugs, vaccines, diagnostics). Remove 'anti-trust' risk of having industry collaborate on antimicrobial resistance. Provide intellectual property protection rights and enforcement to encourage industry to invest in antibiotic research and development in developing countries.

- Where industrial concerns elect to "pass" on infectious disease opportunities, provide a mechanism for a government or not-for-profit leadership/risk in development of an essential infectious disease therapy product (such as vaccine or drug or diagnostic test); in a reverse strategy of industry licensing-in from academia, rather establish the option for the reverse process (license from the industrial concerns) to occur.
- Ramp-up applied research, pairing pre-clinical and clinical research to better assess the correlation between *in vitro* antimicrobial resistance and clinical efficacy of drugs, and the links between the bacterial infectious state and chronic diseases.
- Provide sound experimental support for the rational and prudent use of antibiotics, in particular:
  - — Engage in clinical data-proven epidemiological outcomes research to determine methodology to decrease antimicrobial resistance by improvement in best practices for antibiotic use.
  - — Demonstrate proof of concept of using the most active (and safe) appropriate antibacterial regardless of cost, rather than the historical or least expensive agent;
  - — Explore clinical usage of 'resistance suppressive' agents (agents with decreased resistance development) such as the new quinolone antibacterial agents with the C8-methoxy substituent, and other chemotype antibacterials or anti-resistance agents if clinical data supports in-vitro data;
  - — Explore the use of adjunct therapy with "non-antibiotics", similar to β-lactamase inhibitors, to control or reverse antimicrobial resistance (e.g., efflux inhibitors);
  - — Stop using 'old' antibacterials with poor activity and efficacy and adopt more appropriate therapeutic agents (regardless of cost). This can be accomplished by the use of surveillance of antimicrobial resistance to guide appropriate therapeutic decisions;
  - — Examine pharmacokinetics, pharmacodynamics, and dosage regimens of antibiotics in relationship to resistance emergence probability;
  - — Recognize that the "prudent use of antibiotics" is not synonymous with "restriction of antibiotic use" in man.
  - — Address the use of antibiotics in agricultural and animal husbandry/feed (growth promoters) and act appropriately on the basis of definitive data/conclusions.
- Ramp-up basic research to provide for the exploitation of new technologies to capitalize on the genomic revolution. Exploit genomic information in its basic form to turn 'data' into 'knowledge' and extract information for new targets, new opportunities for vaccines, new opportunities for diagnostics, new insights into molecular mechanisms of antimicrobial resistance, and to identify up-and-coming antimicrobial resistance problems

Developing countries

- Identify and implement plans to identify solutions to major impact diseases in developing countries providing new therapeutic intervention options.
- Fund basic and applied research in academia, government and industry to better understand all relevant aspects of antimicrobial resistance in the developing world and provide research and development support for successful delivery of treatment regimens to developing countries that do not have the infrastructure to do so themselves by innovative approaches to treatment options.
- Invest in improving the quality of life and health overall, thus decreasing the risk of spreading infectious disease. Invest in local research and development to specifically address antimicrobial resistance problems and solutions.
- Invest in education about the appropriate treatment regimen (preventative measures, drug therapy, vaccines); provide support to invest in developing world diseases (even developments without industrial country 'value'); assist in implementation of preventive strategies through improving social infrastructure, sanitation, and water supply systems. Provide education about the relevance of surveillance that may be employed to implement appropriate antibiotic treatment regimens. Invest in education to provide a framework for future research and development in developing countries themselves.
- Help provide developing countries the same opportunity to build a quality infrastructure to address health needs in the long term, includ-

ing self-investment in research and development, through sharing of resources with developing countries.

- Invest in a vaccine strategy to combat antimicrobial resistance by preventing infectious diseases in man from vaccine-preventable diseases worldwide. Consider combining genetically-engineered vaccines and food stuffs as a delivery system for both food and vaccines (i.e., engineer specific antigens into the potato or rice plant).
- Remove governmental control/blockage from efforts to address antimicrobial resistance worldwide.

Conclusion

The need for basic and applied research and for new product development is recognized throughout the literature reviewed. The introduction of new technologies in drug discovery provide hope for the future but the lack of research support for non-AIDS infectious disease research, especially TB research and other unmet medical needs in the developing world, remains a serious limitation to global solutions of antimicrobial research. The refusal to recognize antimicrobial resistance in the clinic as a serious, relevant, real problem compromises world health.

CHAPTER V

Improve antibiotic use in animals

Scott A. McEwen

Abstract

Expert scientific panels from all over the world have reviewed the evidence for resistance selection in food animals and resultant human disease. Reports of several of the most recent expert deliberations are reviewed here, some of them devoted wholly to the subject of non-human antimicrobial use. While many uncertainties remain, recent studies have shown that agricultural uses of antimicrobials do have an impact. There is consensus among the documents reviewed that antimicrobial use in animals selects for resistance in zoonotic pathogens and commensal bacteria, and these resistant bacteria can be transmitted to humans through contact with animals or food, and that they can infect humans and cause disease which can be more severe or longer lasting than non-resistant infections. Furthermore, there is increasing concern about the reservoir of resistance that is building in enteric commensals of animals (e.g., *Escherichia coli*, *Enterococcus faecium*) which may be transferred to related, or even completely unrelated human commensals and pathogens through exchange of genetic material.

A number of strategies have been recommended to reduce human health impacts from non-human uses of antimicrobials, the most important being to increase surveillance of resistance and antimicrobial use, to implement good regulation to control antimicrobial use in animals in light of resistance concerns, and to take steps to ensure the prudent use of antimicrobials in animals, especially by reducing exposure of animals to low doses of antimicrobials for long periods of time (i.e., growth promoters and prophylactics) if such uses select for resistance to drugs used in human medicine. Other strategies include educational programmes for veterinarians, food animal producers, and dispensers of antimicrobials for non-human uses, reducing the need for antimicrobials through alternative treatments and infection control, and research.

Introduction

The human health impact of non-human uses of antimicrobials is an exceedingly controversial part of the overall resistance problem, and a part that is not very well understood. Antimicrobials have for years been used in food animals, pets, and farmed fish for treatment of disease and in some cases for growth promotion and disease prophylaxis; they have even been used to prevent bacterial infections in fruit. Humans do not live in a bubble; we share the environment with animals and plants. Bacteria that are around us and within us can move relatively freely throughout the ecosystem in food, water, air, and the soil. Most of the attention on non-human use has focused on animal agriculture because of the large volumes used there: as much as 50% of total antimicrobial production by weight.

Important findings from the literature review

Most of the documents reviewed made at least some reference to the public health problems of antimicrobial resistance from antimicrobial use in animals, plants, and aquaculture. A few documents (*9,18,24,25,92–95*) were wholly devoted to the subject. Some mentioned concerns about using resistance genes as markers in genetically-engineered plants. While there is uncertainty about the environmental impact of resistance marker genes, it is believed that the probability of their transfer to microorganisms leading to health problems is extremely low (*95*).

Antimicrobials are used therapeutically to treat food animals (cattle, sheep, poultry, fish, etc.) and pets for bacterial infections (*9,20,25,93*). Some animals are treated individually, although food animals may be treated in groups through medicated feed or water if individual animal administration is not feasible (e.g., poultry, fish) or is less efficient. Therapeutic doses are administered for varying periods of time, ranging from one to several days, depending upon the drug and approved application as indicated on product labels. In some cases,

veterinarians prescribe antimicrobials in an extra-label manner (e.g., increased dose or duration of treatment), either because labeled drugs are unavailable for the condition, or they are considered no longer effective.

Food animals, especially those raised intensively, may also be administered antimicrobials (usually, but not always under veterinary prescription) for prophylactic purposes during especially high-risk periods for infectious disease (e.g., after weaning or transport) or when one or more animals in the group are observed with clinical disease and more cases can be expected. Fruit may also be treated with antimicrobials (e.g., tetracycline and streptomycin) in some countries to prevent certain bacterial infections, for example, *Erwinia amylovora* (*19,21*).

Most controversially, food animals may also be administered antimicrobials for growth promotion or performance enhancement purposes (e.g., feed efficiency). In some cases, the distinction between prophylaxis and growth promotion is unclear because certain drugs may be approved for both purposes, and growth promoters may have disease prophylaxis benefits. Growth promoters are usually administered in relatively low concentrations, ranging from 2.5–5 mg/kg (ppm) depending on the drug and to some extent the species treated (*93*). Despite the fact that these drugs have been used extensively in agriculture for over three decades (*21*), scientists are not sure exactly how they improve growth efficiencies. It is believed, however, that in addition to dampening the effects of subclinical disease on growth, the drugs may suppress certain susceptible bacteria that compete for nutrients with the host animal. It has been pointed out that the benefits are greater under poor hygiene conditions, and their current efficacy is questioned because other means of controlling disease (e.g., biosecurity, vaccination) have been introduced more widely into intensive animal husbandry. It is believed that efficiencies of 1–11% can be realized (*21,93*). Another purported benefit of growth promoters is a reduction of total nitrogen and fecal output per animal marketed, which has environmental impact implications. One expert panel (*25*) went so far as to state that antimicrobials, in particular at sub-therapeutic doses (as in growth promotion and disease prophylaxis), had an important positive role in facilitating the intensification of food animal agriculture that is characteristic of many industrialized and some developing countries, thereby enabling the production of abundant quantities of food. Other reports contend that this intensification of food animal production is at least partially responsible for antimicrobial resistance problems in agriculture, by increasing the need for antimicrobial use. Aside from growth promoter use, which is more common under intensive animal rearing conditions than in extensive, or pasture-based husbandry, intensive rearing can increase the need for treatment by fostering the spread and clinical expression of infectious diseases of animals, and by enhancing the spread of resistant foodborne pathogens and other bacteria among animals.

Antimicrobial use data are sparse and most documents cite the difficulty in obtaining accurate, up-to-date consumption figures by species and intended use. It has, however, been estimated that as much as 50% of total antibiotic production (by weight) is used in animals and plants, with 50–80% used in some countries for growth promotion or disease prophylaxis and the rest used for therapeutic purposes (*9,20,21*). Usage patterns vary tremendously, but in some countries, a majority of food animals receive antibiotics at some point in their lives, and many for extended periods of time at subtherapeutic doses.

Many antimicrobials are administered to animals under veterinary prescription, but in some countries, they may also be available for veterinary use without a prescription. These drugs are frequently available over the counter in feed stores and pet shops and may be included in purchased feeds without veterinary prescription. Financial incentives exist for the production and distribution of veterinary drugs, just as they do for human antimicrobials. Pharmaceutical companies, importers, pharmacies and other retailers may all profit from the sale of antimicrobials to animal owners. Veterinarians may also profit from the sale of antimicrobials to food animal producers, and it has been reported that as much as 40% of their income can come from this source (*50*).

Most of the classes of drugs used in human medicine are also used in veterinary medicine, although there is considerable variability within and between countries in the range of drugs approved for use in various animal species. Some examples of antimicrobials approved (as of 1999) in the United States are presented in the Table.

Very little attention was given to antimicrobial use in pets in the documents reviewed, although this area will probably receive more attention in the future. Pets are frequently in close contact with their owners and when ill they are often treated

TABLE. **EXAMPLES OF ANTIMICROBIALS APPROVED FOR USE IN THE UNITED STATES** (ADAPTED FROM *25*)

	Antibiotics approved in the United States for various species			
Purpose	**Cattle**	**Swine**	**Poultry**	**Fish**
Treatment of various infections	Amoxicillin Cephapirin Erythromycin Gentamycin Novobiocin Penicillin Sulfonamides Tilmicosin Tylosin	Amoxicillin Ampicillin Chlortetracycline Erythromycin Gentamycin Lincomycin Sulfamethazine Tiamulin Tylosin	Erythromycin Fluoroquinolone Gentamycin Neomycin Penicillin Spectinomycin Tetracyclines Tylosin Virginiamycin	Ormetoprim Sulfadimethoxine Oxytetracycline
Growth and feed efficiency	Ampicillin Bacitracin Chlortetracylcine Lasalocid Monensin Oxytetracylcine	Arsenilic acid Bacitracin Bambermycin Chlortetracycline Penicillin Tiamulin Tylosin Virginiamycin	Bambermycin Bacitracin Chlortetracycline Penicillin Tylosin Virginiamycin	

with the same drugs used in human medicine.

Regulatory approval for use of antimicrobials in animals and plants, when it is accompanied by human health risk assessment by competent national regulatory authorities, may not include considerations of microbial safety (especially resistance). In fact, until recently only a small number of countries considered resistance at all in the veterinary drug approval process (*93*). Traditionally, human health safety determinations of veterinary antimicrobials focused on the effects of antimicrobial residues in foods of animal origin. The United States (*18*) required pharmaceutical companies to compile and report microbial safety data in their pre-approval submissions to regulatory authorities for drugs intended for long-term prophylactic or growth promotion use in feeds. Even in recent years when antimicrobial resistance issues have been in the forefront, some countries approved important drugs (e.g., fluoroquinolones) in light of epidemiological evidence from other countries of resistance emergence in foodborne pathogens (*19*). This suggests that antimicrobial resistance concerns were not addressed in the approvals, or any human health risks that were identified were insufficient to override other considerations.

There is consensus among the documents reviewed that treatment of animals and plants with antimicrobials leads to resistance in bacteria. The selection pressure of antimicrobial usage is thought to be greatest during low-dose, long-term exposure, which is characteristic of growth promoters and some disease prophylaxis. However, therapeutic treatments, administered at higher doses for shorter periods of time to individuals or groups of animals, can also select for resistance. Enteric bacteria of food animals are especially exposed to selection pressure because many drugs are administered in food or water but bacteria in other anatomic locations may also be exposed because many drugs are absorbed from the gut and others are administered parenterally. In addition, many drugs are excreted in active form in urine or faeces and peresist in the environment for prolonged periods of time, where they may exert selection pressure on environmental bacteria. In fish farming, for example, it has been estimated that as much as 70–80% of antimicrobials administered may end up in the sediment of the body of water (*96*). In general, the implications of this environmental exposure are poorly understood.

Antimicrobial resistance occurs in the target species of organisms (animal pathogens in the case of veterinary drugs) and in a variety of non-target species in the gut or in other sites. Resistance in the animal pathogens of most importance to animal health is often of little direct human health significance. While there are many bacterial infections of animals that can cause disease in humans (zoonoses), few of these (*Salmonella* is a notable exception) are important causes of clinical disease in food animals or pets. There are a variety of ways, however, that antimicrobial resistance arising in agriculture can have a negative impact on public health. The first two were most frequently mentioned in the reviewed documents:

1. Treatment of animals with antimicrobials important in human medicine, or drugs of the same family or class, can select for resistance to these drugs in zoonotic pathogens (e.g., *Salmonella, Campylobacter*). Resistant zoonotic pathogens can be transmitted from animals to humans through direct contact or indirectly through food or water, and cause illness which does not respond to treatment. Exposure of animals to drugs not used in humans (or no longer used in humans) can also select for resistance to drugs important in human medicine if the resistance determinants are genetically linked. For this reason, the linkage of two or more resistance genes on transmissible elements such as plasmids is of increasing concern. This phenomenon also makes the separation of antibiotics into "animal" and "human" use categories less tenable from a resistance point of view.

2. Genetic determinants of resistance in commensals of animals (e.g., *Escherichia coli*, enterococci) may be shared by exchanging plasmids, transposons or other transferable elements with related or even unrelated human pathogens during transient colonization of the gut of humans after ingestion of contaminated food or water.

Some of the documents drew attention to other potential human health impacts:

3. Extending the principle in (*2*) above, resistant bacteria from animals or plants are part of a larger antimicrobial resistance ecosystem, and their resistance genes could find their way through a variety of poorly understood, indirect pathways to human pathogens. These pathways could involve transfer of resistance genes through intermediary environmental organisms. Concern in some quarters has been expressed about inclusion of resistance markers in genetically-modified plants, however the documents reviewed do not consider this as an important issue (*93,21*).

4. As a consequence of taking an antimicrobial for some other reason (e.g., ear infection or pneumonia), people become more susceptible to disease when exposed through food or other source to a pathogen from animals that happens to be resistant to that drug (e.g., multi-resistant *Salmonella* spp.).

5. Resistance may be linked with other genetic determinants which render pathogens more capable of causing disease, and thereby increase their virulence. In this instance, resistant pathogens may cause more severe or longer-lasting disease in people than comparable susceptible pathogens.

6. Antimicrobial use in food animals may, in some cases, lead to an increase in the shedding of zoonotic pathogens (e.g., *Salmonella*) in animal faeces and thereby available for human exposure, whether or not the pathogen is resistant. This is a phenomenon called "pathogen load", and it could occur through a number of complex and poorly understood mechanisms whereby antimicrobial use in animals results, for example, in an increase in the duration of faecal shedding of foodborne pathogens, or an increase in the concentration of pathogens in faeces which may then contaminate food or water.

7. There is some concern that antibiotic residues eliminated in animal faeces and urine may exert resistance selective pressure on bacteria in soil and water. Treated animals and humans may excrete considerable quantities of active drug or metabolite and many of these residues are slow to degrade in the environment.

Most of the documents acknowledge that the public health impacts of antimicrobial use in animals and plants are complex and poorly understood. These issues have been the subject of considerable controversy and scientific debate for decades. There is consensus, however, that resistance does occur in zoonotic pathogens and commensals when animals are treated, that humans are occasionally exposed to these bacteria through contaminated food and water, and that illness, and sometimes treatment failure, does occur due to these resistant zoonotic infections. There is also consensus, however, that much uncertainty remains about the frequency with which these events occur, and the overall magnitude (numbers of people affected, severity of outcome, economic impact, etc.) of the public health impact of resistance arising in agriculture.

Some of the uncertainties were reconciled in recent years through a number of well-conducted epidemiological studies, carried out principally in Europe and the United States. The results of these studies are summarized later in the chapter. However, the reviewed documents were virtually unanimous in recommending more research and enhanced surveillance to better understand resistance in both medical and veterinary medicine. Surveillance of antimicrobial resistance among zoonotic pathogens and commensals in food animals, food

products, and foodborne infections of humans, as well as monitoring non-human uses of antimicrobials is thought to be the best way to identify and quantify the effects of non-human antimicrobial use on resistance throughout the food chain. "Only quantitative data, obtained through application of standardized laboratory methods, will allow for meaningful epidemiological analysis and evaluation" (*9*).

Antimicrobial resistance from agriculture is in many ways a food and water safety issue (*8*). Over the past couple of decades, food and waterborne diseases appear to have increased in incidence in a number of countries. A number of factors are probably responsible for this, including a greater burden of pathogens (resistant and susceptible) that is transmitted through the food chain from animal populations and plant products to humans. No doubt myriad factors are responsible for the emergence and dissemination of the wide range of these food and waterborne infections that are major public health problems for both industrialized and developing countries. These same factors may be important in promoting the spread of resistant zoonotic pathogens and commensals, as well as environmental bacteria, to humans. By the same token, steps that are being taken throughout the food chain to reduce the impact of food and waterborne infections in which resistance is not yet recognized to be a problem (e.g., *E. coli* O157:H7, *Salmonella enteritidis*) may also reduce the public health burden of resistance. Some of these steps include Hazard Analysis, Critical Control Point (HACCP) programmes, quality assurance programmes, irradiation and pasteurization (*19,92*).

The most important strategies that were recommended specifically to reduce the public health impact of antimicrobial use in agriculture fell into the following major categories (*9,25,50,53,92–95*): government regulation; education and prudent or judicious antimicrobial use guidelines; monitoring of antimicrobial use; surveillance of resistance; reducing the need for antimicrobials through alternative treatments and infection control; and research.

Effective and non-effective strategies

The human health impact of antimicrobial use in agriculture has been the subject of debate, discussion, analysis, expert panel deliberation, and qualitative risk assessment for decades. National and international expert panels and committees have produced a large number of documents; many of those are reviewed here. One of the most cited of these was the UK Swann Report of 1969 (*97*). This report is remembered as one of the first recommending that antimicrobial growth promoters and other drugs used without prescription in animal feeds should be restricted to antimicrobials that have little or no application as therapeutic agents in humans or animals, and will not impair the efficacy of a prescribed therapeutic drug through development of resistance. Secondly, the Swann Report recommended that therapeutic antimicrobials for animals should only be available under a veterinary prescription. These principles have been endorsed by most subsequent expert panels and task forces and lay a foundation for modern recommendations. The British government later implemented the Swann recommendations, and some credit was given to a reduction in antimicrobial-resistant *Salmonella* infections. Some have claimed, however, that the measures recommended by Swann were not effective because total antimicrobial consumption in UK agriculture did not decline, and further outbreaks of antimicrobial resistant salmonellosis eventually occurred. In reality, it is difficult to determine the effects on resistance and total use because there was no comprehensive surveillance system in place at the time. The US Food and Drug Administration (FDA) proposed in the 1970s to stop the sub-therapeutic (growth promotion and prophylactic) use of penicillin and tetracycline in animal feeds but was criticized because there was inadequate evidence of adverse human health effects and the proposal was unsuccessful (*6,24*).

In 1986, Sweden banned the use of growth promoters in animal production (*21*). Unfortunately, at the time the Swedish government did not have a resistance surveillance system in place with which to measure the effects of the ban on resistance in animals, foods, and humans. However, the quantities of antimicrobials sold for use in animals were monitored. Animal health statistics show that in the early stages after the rather abruptly introduced ban, increases in morbidity and mortality were observed (e.g., post-weaning diarrhoea in piglets and necrotic enteritis in chickens). To counteract this, antimicrobials used earlier for growth promotion were prescribed for prophylaxis during high-risk periods. Efforts were made to improve management, feed, and hygiene in order to adapt to non-routine use of antimicrobials. In the early 1990s, zinc oxide replaced antibiotics as prophylaxis for piglets. Since 1998, zinc oxide is only avail-

able in Sweden on prescription and use has declined to less than 10% of its maximum. Total sales of all antimicrobials for animals decreased fairly substantially (by approximately 60%) (*98*).

In the 1990s, public health surveillance in the UK and elsewhere in Europe identified some new resistance issues that once again heightened concerns about agricultural use of antimicrobials. Among these issues were the increase in *Salmonella typhimurium* DT104 infection in humans and animals, the appearance of fluoroquinolone-resistant *Campylobacter jejuni* infections in humans and poultry, and the occurrence of vancomycin-resistant enterococci (VRE) in pigs and poultry.

Salmonella typhimurium DT 104 was first identified in the UK but has since been found in many countries throughout the world where it is an important cause of disease in humans, cattle, pigs, poultry, and other animals. *Salmonella* strains appear to come and go in "waves" every few years (epidemics of DT29, DT204, DT193 and DT104 strains were observed in the UK (21) but DT104 was particularly concerning to public and animal health officials because of its pathogenicity and the fact that most isolates were resistant to at least five antimicrobials (pentaresistance). While the role of agricultural antimicrobial use in the genesis and spread of *Salmonella typhimurium* DT104 is unknown, there is good evidence that antimicrobial use in animals was associated with development of reduced susceptibility to fluoroquinolones among some isolates of this organism. This evidence rests mainly on the temporal relationship between approval of fluoroquinolones for use in food animals and identification of resistant (reduced susceptibility) strains. Shortly after fluoroquinolones were licensed as therapeutic agents for food animals in the UK, public health laboratories began to identify isolates with decreased susceptibility to quinolone drugs. This was particularly alarming because fluoroquinolones are very valuable drugs for treating humans for a variety of infections, including invasive salmonellosis.

Similarly, investigators in other European countries, (e.g., the Netherlands, Spain) where fluoroquinolones were approved for therapeutic treatment of poultry, identified substantial increases in the prevalence of fluoroquinolone resistance among poultry and human isolates of *Campylobacter jejuni*. This type of resistance was remarkable in the rapidity with which it appeared and increased in prevalence (*21,92*). Other countries have reported similar findings.

Avoparcin is a glycopeptide antimicrobial in the same family as vancomycin. It was approved for use in many European countries as a growth promoter. At the time since vancomycin was not widely used, there was little reason to be concerned about resistance problems in humans. Things changed, however, when vancomycin became critical in human medicine for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and other serious infections. Resistance to vancomycin, especially among enterococci (VRE) became an important public health problem in many countries. Researchers identified VRE in food animals exposed to avoparcin, where they were not found in animals in countries where avoparcin was not used as a growth promoter. Furthermore, the prevalence of VRE among non-hospitalized people in the community was much higher in countries that used avoparcin. There is evidence that VRE in food animals may have been a reservoir for resistance in humans, perhaps through exchange of genetic material between animal and human strains, or through transient colonization of the human gut by animal strains.

It is worth reiterating that prior to identification of the link between avoparcin use and VRE in food animals, the drug was thought to be an appropriate choice for a growth promoter. This is a good example of a major problem confronting the animal and pharmaceutical industries and those charged with drug regulation. Growth promoter drugs that are seemingly safe today because they are not used in people and do not select for resistance in people may not be in the same position tomorrow, if the same or related drugs become important in human medicine. Some older families of pharmaceuticals, previously not considered necessary or desirable for human medicine, are "retrieved" in order to combat new resistance problems (e.g., vancomycin for MRSA). More recently, the same sort of thing has happened with virginiamycin, which is a streptogramin antimicrobial that has been used for many years in agriculture, principally as a growth promoter in poultry and pigs but also in some cases for disease prophylaxis. There is now evidence that virginiamycin use selected for streptogramin resistance in enterococci and there is considerable concern that this could compromise the usefulness of related streptogramin drugs (e.g., pristinamycin and quinupristin-dalfopristin), which have been recently introduced for treatment of vancomycin-resistant enterococci and other bacterial infections in humans.

Growth promoters do not necessarily cause resistance problems in humans. For example, ionophores are a group of antimicrobials used widely in veterinary medicine for growth promotion in a variety of species, and for treatment and prevention of coccidiosis in poultry. Resistance has so far not been identified as a problem in animals and there are no indications that the family of drugs will become useful in humans, perhaps because of toxicity concerns.

It is important to point out that these examples of recent resistance concerns involve both growth promoters (avoparcin, virginiamycin) and therapeutic drugs (fluoroquinolones). Strategies to address these concerns are likely to be somewhat different; with the former, regulatory measures (i.e., decision to permit their use or not) are most important; with the latter, assurance of prudent use is very important in minimizing concerns.

Collectively, public health concerns arising from *Salmonella typhimurium* DT104, quinolone resistance in *Campylobacter jejuni* and *Salmonella*, and glycopeptide and streptogramin resistance in enterococci substantially raised the profile of antimicrobial resistance as a public health issue in the veterinary, agricultural and food industries. Some strategies have been implemented to reduce the public health impact, or to improve understanding of the type and magnitude of the impacts and these are discussed below.

Government regulation

Mention has already been made about the measures taken in UK after the Swann Report of 1969 (*97*) to restrict the use of growth promoters to drugs not used in human medicine, and about the suggestions in the literature that these measures were not effective in reducing total antimicrobial use in animals. There may, however, have been benefits in reducing incidence of resistant Salmonella. Although not discussed in the reports reviewed, it has been pointed out in the literature that any reduction in usage achieved through restrictions on growth promoters was compensated by increases in prescription drug use. This underscores the need in any overall strategy to carefully monitor all uses of antimicrobials and take appropriate control action if excesses are detected, and to reduce the need for antimicrobials by making improvements in animal management, hygiene, and health.

Many countries, most notably in Europe, have banned the use of avoparcin in animal feeds, and in some countries (e.g., Australia) the drug has been withdrawn voluntarily. Fortunately, some countries have monitored VRE prevalence in animals, food and humans and there are reports that the prevalence in food animals (initially in poultry) has decreased in Denmark and Germany since the withdrawal (*4*). Although immediate decreases were not seen in pigs in Denmark, recent data suggest that the prevalence of VRE in pigs is decreasing, and that levels may have been maintained, at least in part, by cross-resistance with macrolides (e.g., tylosin). Reduction in tylosin use has been accompanied by a decrease in VRE prevalence (*99*).

In 1999, four drugs (tylosin, virginiamycin, spiramicin, and bacitracin) were banned as growth promoters on the basis of the precautionary principle that they or related drugs are used in human medicine, or select for resistance to drugs used in human medicine. This action was also consistent with recommendations from the Swann Report and WHO. While this action was mentioned in the reviewed documents, the ban is so recent that there were no data available on its effects in terms of resistance trends among zoonotic or commensal bacteria, trends in antimicrobial usage in animals, or in terms of effects on the health of animals or indices of production (e.g., feed conversion, days to market, etc.). It is too early to tell what these effects will be; nevertheless, there are some recently published data from Denmark where reductions began a little sooner than in the rest of Europe (*99*). Danish farmers had actually decided voluntarily in 1998 to stop feeding growth promoters to food animals and phase out their use by 2000. The DANMAP 99 report (Danish Integrated Antimicrobial Resistance and Research Program) describes drug use patterns in the country in 1998, after the reductions were in place (*99*). The early stages of reduction in growth promoters were not accompanied by an increase in consumption of therapeutic drugs, but between 1998 and 1999 there was an increase in tetracycline use for treatment of enteric disease in swine.Time will tell whether additional positive or negative effects on therapeutic drug use will be seen in Denmark.

The effects of the European ban of 4 growth promoters on resistance in zoonotic bacteria and commensals are also largely unknown because the ban is so recent. DANMAP reported that sampling-related problems made the Danish *Salmonella* results from 1998 difficult to interpret, because many isolates from both animals and humans were linked epidemiologically. Resistance in *Campylo-*

bacter coli to erythromycin dropped by almost 50% in 1998, and this was attributed to withdrawal of tylosin (another macrolide) as a growth promoter. Among enterococci of pigs and poultry, reduction in resistance to vancomycin, virginiamycin, and erythromycin were observed after the ban. Among E. coli, the proportion of isolates resistant to one or more antimicrobials decreased over the same period, but changes in prevalence of resistance to specific banned growth promoters were not observed (*99*).

Another important regulatory development that has taken place in some, but not all countries, is the inclusion of antimicrobial resistance considerations in the drug approval process. In the United States, a great deal of attention has been given to the so-called "Framework Document" (Proposed Framework For Evaluating And Assuring The Human Safety Of The Microbial Effects Of Antimicrobial New Animal Drugs Intended For Use In Food-Producing Animals), developed within the Food and Drug Administration and published in 1998 (*24*). The Framework is "intended to provide a mechanism for evaluating and ensuring the human safety of antibiotics and other antimicrobials used in food animals, including those used for growth promotion" (*24*). The Framework is a conceptual risk-based process with the stated goal of preserving the effectiveness of drugs which are important in human medicine while enabling the safe use of antimicrobials in food animals. It provides for categorization of antimicrobials on the basis of an assessment of their importance to human medicine. Category I drugs (or members of a class of drugs) are essential for treatment of life-threatening diseases of humans, or are important for treatment of foodborne diseases of humans, or are members of a unique class of drugs used in humans. Examples include quinolones, vancomycin, and quinupristin-dalfopristin. Category II drugs are important for treatment of potentially serious human diseases, but for which suitable alternatives exist (e.g., ampicillin, erythromycin). Category III drugs have little or no use in human medicine or are not the drug of first choice for human infections.

Importantly, the Framework strategy would also categorize, into high, medium and low, the likelihood of human exposure of resistant human pathogens arising from the use of drugs in food animals. This is an attempt to use in the characterization of risk information on the ability of the drug to select for resistance in bacteria, the likelihood that resistant bacteria will be transmitted to humans through foods or other sources, and the likelihood that this transfer will result in the loss of treatment options. Categorization would include consideration of drug attributes (e.g., mechanism and rate of resistance or cross-resistance induction), the expected product use patterns (e.g., duration of treatment, species, number, and type of animals treated), and potential human contact (e.g., bacteria of concern, environmental and food contamination, food processing effects). Examples that were given include: a growth promoter used in multiple species and inducing resistance to an antimicrobial used in human medicine would be placed in the high potential human exposure category; a drug used for entire herd therapy during outbreaks of disease which occur in a small fraction of herds would be placed in the medium category; and a drug used for individual animal treatment of only occasional animals in herds, for a short duration, would be placed in the low category.

Another very important feature of the Framework in a regulatory sense is the notion of establishing safe resistance threshold levels for antimicrobials. Conceptually, the threshold level could be set at the level of resistance that carries with it insignificant likelihood of transfer to humans, if it were possible to accurately determine such a level. There is also provision for establishing levels for Category I drugs to be used in post-approval monitoring of resistance and which could serve as an early warning system indicating that resistance was reaching a level of concern. The document acknowledges that the usefulness of such thresholds depends upon the ability to demonstrate that they are sufficiently protective of public health, and that there is a capability of detecting when such levels are reached.

The Framework document also makes provision for requiring pharmaceutical companies to conduct pre-approval studies of drugs in order to characterize the type and rate of resistance development. Post-approval monitoring studies may also be required of certain drugs in order to identify emergence of resistance of sufficient concern to public health to trigger intervention and mitigation strategies. Finally, there is provision for requiring submission by pharmaceutical companies of detailed drug sales information by species, state, dosage form, year, and estimate of active units sold.

Another important initiative undertaken by FDA in 1999 was preparation and public presentation of a "Draft Risk Assessment on the Human

Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken". This effort could be a milestone in evidence-based regulatory decision-making in the area of antimicrobial resistance in agriculture. The risk assessment is a highly focused, structured assembly of scientific and public health information from a variety of relevant sources, including the scientific literature, public health surveillance databases, and expert opinion. The assessment is an attempt to estimate in quantitative terms the public health risk in one year from resistant foodborne pathogens due to the use of antimicrobials in food producing animals. Within the assessment, a mathematical model was developed which related the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens (a major source of *Campylobacter jejuni* infection in the United States). Fluoroquinolone resistance in *Campylobacter* was selected because campylobacteriosis is the most commonly reported bacterial foodborne disease in the United States, fluoroquinolones are important drugs in human medicine which are sometimes used to treat people sick with this disease, and fluoroquinolones are approved for use as therapeutic agents in poultry. As previously mentioned, fluoroquinolone resistance has been identified as a problem in *Campylobacter jejuni* in a variety of other countries where these drugs are used to treat poultry.

Using data from epidemiological studies and the FOODNET surveillance system in the United States, the model estimated the most likely and estimated range of cases of fluoroquinolone-resistant *Campylobacter jejuni* infections that occur in one year in the United States, and which are treated with fluoroquinolones by physicians. The risk assessment clearly describes the assumptions that are made in construction of the model and identifies the various uncertainties that arise from lack of knowledge or variability in data inputs. As an example of one outcome from this model, the estimated mean number of people with fluoroquinolone-resistant *Campylobacter* infection from chicken who received fluoroquinolone in 1998 was 5065 (with a 90% confidence interval of 2585, 8595).

This risk assessment is important for a number of reasons. Many stakeholders in the veterinary, animal production, and pharmaceutical sectors have for years been asking for a risk-based regulatory decision-making process on antimicrobials. Quantitative risk assessment is used in a number of fields to assist risk management decision-making when the magnitude of health impacts is clouded by complexity and uncertainty. This is certainly the case with estimating the human health impacts of antimicrobial use in agriculture. The FDA assessment is also a good example of the use of available surveillance data to estimate quantitatively the human health impact. Quantitative risk assessment is being used increasingly in other microbial food safety issues, and experience and confidence in the process are growing. An important next step for regulators is to identify the public health risks from resistance that are "acceptable" to society. A generally acceptable level of cancer risk from environmental chemicals is one per million in the population over a lifetime of exposure. It remains to be seen whether acceptable levels for microbial risks can be agreed upon internationally. If such levels (or "risk standards") can be agreed upon, quantitative risk assessment could be used to identify resistance thresholds, beyond which public health impacts become unacceptable. This will no doubt prove to be a difficult, but important task.

Education and prudent use of antimicrobials

None of the documents reviewed educational or prudent antimicrobial use strategies which have been shown to be effective in reducing resistance risks, nor was evidence presented that any have actually been implemented. There are anecdotal reports in the scientific literature that a number of national and international organizations (e.g., professional veterinary associations) have begun to develop prudent or judicious use guidelines for antimicrobials in animals, and in some cases, codes of antimicrobial prescription in veterinary practice. There are also some reports of attempts to draw attention to the issue in the minds of veterinarians and food animal producers, many of whom still believe that the only public health concerns that arise from antimicrobial use in food animals are residues of drugs in edible tissues.

Although not mentioned in the documents, Denmark has recently put significant limits on the ability of veterinarians to profit from the sale of antimicrobials in food animal production. The effects of this measure on antimicrobial sales and consumption are not yet known.

Monitoring of antimicrobial use

Some of the documents mentioned that some countries (notably in Scandinavia) have been assembling national antimicrobial consumption data, or have recently instituted the assembly of these data. Sweden was able to document the effects of their growth promoter ban on consumption of antimicrobials for prophylactic and therapeutic purposes because they had an antimicrobial use monitoring system in place. As described above, the United States has declared plans to require the submission of antimicrobial sales data to the FDA, which can be used to monitor trends in consumption, and in epidemiological and risk assessment studies addressing the associations between antimicrobial use and resistance in animals and humans. Although not specifically mentioned in the documents reviewed, Denmark has instituted an antimicrobial use monitoring system (DANMAP) to accompany its resistance monitoring.

Surveillance of resistance

Calls for resistance surveillance systems figure prominently in nearly all reviewed documents. It is generally hoped that these systems will provide descriptive data on resistance, which will enable the identification of temporal trends, emerging issues, and the extent of resistance in human and animal populations and food products.

Many countries have for some time had elements of national resistance surveillance in place. It was surveillance of resistance data assembled by the Public Health Laboratory Service in the UK which identified the emergence of decreased susceptibility to fluoroquinolones among *Salmonella typhimurium* DT104 isolates (*21*). Public health scientists in other countries have made similar contributions to our understanding of resistance issues.

Two comparatively new antimicrobial resistance surveillance programmes are the previously mentioned DANMAP in Denmark, and NARMS in the United States. DANMAP is run by the Danish Veterinary Laboratory (*22,99*). DANMAP reports are issued annually and describe antimicrobial consumption data in animals and humans, resistance in zoonotic bacteria (e.g., *Salmonella*, *Campylobacter*), resistance in indicator bacteria (e.g., *E. coli*, enterococci), and resistance in bacteria from diagnostic submissions from humans and animals. Summaries are included which include interpretation of observed trends, relationships between antimicrobial use patterns and resistance, and sources of potential bias. This programme is able to document the effectiveness of some of the strategies that have been used in Denmark to curtail resistance from food animals, most notably the ban on growth promoters.

In the United States, NARMS (National Antimicrobial Resistance Monitoring System) Enteric Bacteria Program tests antimicrobial resistance related to agriculture (*22,24*). It began in 1996 as a joint effort by the Centers for Disease Control and Prevention (CDC), FDA and US Department of Agriculture. Isolates (initially *Salmonella*, with addition of *Campylobacter* in 1997) are obtained from human clinical specimens, animal clinical specimens, normal animals, and carcasses at slaughter from across the United States. Data from NARMS were used in the FDA's quantitative risk assessment of fluoroquinolone-resistant *Campylobacter* from chicken (described above) and have been presented in a variety of scientific venues.

Alternative treatments and infection control

As mentioned above, Sweden reported that farmers eventually adapted to the ban on growth promoters by a number of means, including the implementing improved husbandry practices and increased use of zinc oxide (which has been criticized on environmental grounds (*21*), but now appears to be under control (*98*). While this is evidence that antimicrobial needs were reduced, there was no resistance monitoring in place that could measure the effect of management changes on resistance.

Barriers to action

There are many disincentives and barriers to the further implementation of resistance risk reduction strategies. These include a general lack of acceptance among veterinarians and food animal producers that a resistance problem exists in agriculture; a lack of scientific information on the extent and magnitude of public health risks; conflicting economic interests; the costs of implementing alternatives; lack of regulatory will and capability; lack of efficacious and economical alternatives to antimicrobials; and lack of resources to develop and implement strategies.

A major barrier is the lack of acceptance that agriculture and veterinary medicine are significant contributors to the human health impacts of resistance. Large numbers of veterinarians, other sci-

entists involved in agriculture, and food animal producers simply do not believe that antimicrobial use in food animals has substantial negative health effect on humans. This is not simply a lack of awareness due to inadequate or insufficient education or training, but has to do with the relative lack (until recently) of concrete examples clearly documenting the impacts. Unlike physicians, who see patients with disease caused by resistant bacteria, and who can see that resistance in hospital and community-derived pathogens is related to use of antimicrobials in those settings, veterinarians and producers do not see these cases. Until recently, few well-documented examples of human illness from resistant pathogens originating on the farm have been described, (e.g., the recently-described case of ceftriaxone resistant salmonellosis in a child apparently infected on a farm) (*100*). The tremendous complexity of the food production, processing, distribution and food service system in industrialized countries makes it extremely difficult to trace infections and resistance genes. If people do not believe that their practices and behaviours create public health risks, it is more difficult to get them to change these behaviours.

The lack of scientific information presents a further barrier to obtaining general agreement, even among people without a financial stake in the issue, when intervention strategies are warranted. Almost intuitively, many stakeholders in food animal industry and veterinary medicine call for a "science-based" or "risk-based" regulatory decision-making process on resistance issues. Many government agencies themselves call for more evidence before implementing interventions (*24*). There is a conflict between those who believe that enough evidence exists to warrant risk-reduction actions, and those who believe there is a need for more evidence of the nature and extent of the problem before attempting to fix it.

Balancing the risks of resistance against the benefits of antimicrobial use in agriculture is also a barrier to action. One of the reasons for this is that the risks and benefits are borne by different groups. The food animal producer might save the life of an animal (and therefore his investment) by treating it; he realizes directly the benefit of treatment. Any resistance risks arising from that treatment would most likely be realized by someone exposed to the resistant bacteria, far down the food chain. Conversely, if the producer reduces antibiotic use on his farm, he may not realize any direct benefit.

Just as there are some financial incentives for antibiotic use in humans, strong financial reasons exist for continued use of antibiotics in food-producing animals for food animal producers, veterinarians, and pharmaceutical companies.

If society as a whole is not prepared to accept some risk from the non-human use of antimicrobials then all uses would be banned from agriculture. Few people subscribe to this extreme view. This implies that some level of risk, however small, is acceptable in exchange for the perceived benefits of treating sick animals (alleviation of animal suffering) or reducing losses due to disease in animals. The difficulty comes in identifying the line of demarcation between acceptable and unacceptable risk. The general feeling among the veterinary and animal production communities is that the benefits of antimicrobial use in treating and preventing infectious disease in animals far outweigh the risks associated with their use in animals. As long as this feeling prevails, it will be a major barrier to implementing the strategies intended to reduce any risks that are indeed present.

There is a strong perception in some quarters that more drugs are needed in veterinary medicine so that food animal production can continue to be efficient and sick animals can be treated. The majority of bacterial infections of animals are not zoonotic and most veterinarians and producers feel that resistance among these pathogens is purely an animal health concern. Historically, the response to problems of resistance in veterinary medicine has been to reach into the cabinet for another new drug. Notably, an antimicrobial resistance crisis has not been perceived in veterinary medicine, as is the case in human medicine. Hence, some groups call for more regulatory approvals of new drug applications without acknowledging in any substantial way the need for stewardship of available antimicrobials in agriculture (*25*). There does not appear to be an appreciation of the animal health costs of antimicrobial resistance and that there are good animal health reasons to preserve the currently available drugs. Perhaps in the past, new drugs were so readily available that this was unnecessary, or pharmaceutical companies were sufficiently successful in marketing their new products that veterinarians and producers looked to new drugs rather than preserving the existing ones. In many ways, the effectiveness of drugs that have been available for therapy in veterinary medicine (e.g., penicillin, tetracycline) has in some countries been squandered by their excessive use as prophylactic agents or growth promoters.

Another barrier is the financial interest of various participants in food animal and plant production. These are not simply the interest in minimizing losses due to bacterial disease, or the financial interests of the pharmaceutical industries, which are essentially the same as those encountered in human medicine. Unlike physicians in most industrialized countries, antimicrobial sales are often an important source of income for veterinarians. Many include charges for other services (health management advice, for example) within the mark-up for drugs, and this source of income helps sustain rural veterinary practice, which can be difficult in many areas. Most professional organizations and individual veterinarians would recoil at the suggestion that profit was a motive for prescribing antimicrobials, and few if any data are available to support the contention. It would nevertheless be desirable to remove such financial incentives.

Many food animal producers operate on very narrow profit margins, and to stay in business they need to be as efficient and economical as possible. The costs of implementing animal husbandry or other management changes that could decrease resistance risks are a barrier. Many food animal industries have made major investments in control of infectious diseases for the simple reason that it was in their interest (and in their animals' interests) to eliminate or substantially reduce the impact of infectious diseases on their operations. Measures that reduce clinical disease in animals will decrease the need for antimicrobial treatment, which could reduce human health resistance risk. Some, perhaps many, of these changes (e.g., biosecurity measures) may also reduce transfer and dissemination of resistant zoonotic agents and commensals. However, few of the commonly used biosecurity measures or vaccination programmes are aimed specifically at foodborne zoonotic pathogens or commensals (with the exception of *Salmonella* programmes in some species), because they are normally not important causes of clinical disease in animals.

The lack of suitable, economically attractive, alternatives to antimicrobials is also a barrier to change. The experience of major changes instituted in some countries (e.g., Sweden, Denmark) is having an impact in other countries, but it would help greatly to have local examples of alternatives in place on typical farms in many or most countries, relevant to the agricultural systems of those countries.

From a regulatory standpoint (which is arguably more important to resistance containment for non-human than human uses of drugs) there are a number of barriers to implementation. There may be a lack of regulatory will in some countries because the subject is so controversial and rife with uncertainty, and effective political lobbying may be conducted by those in opposition to resistance control measures. Many countries lack the resources to conduct risk assessments to support regulatory change, and resources to implement surveillance programmes. There may also be reluctance or inability to regulate prescribing practices of veterinarians at the national level.

Recommended strategies

A recent WHO document (*94*) relevant to use of antimicrobials in animals has been produced which contains specific recommendations on a number of these strategies. This document is the most complete and recent set of recommendations pertaining to animal use and the interested reader should refer to the original in its entirety.

The document entitled "A Public Health Action Plan To Combat Antimicrobial Resistance" contains many action items for the implementation of strategies to address antimicrobial resistance within the United States (*53*). These are presented at a level of detail not found in most of the other documents making mention of non-human uses of antimicrobials and the interested reader should also to the original document for details.

Many of the documents reviewed mentioned that antimicrobial resistance is a global issue and steps are needed to control the international spread of resistance through movement of humans, animals and food products (*7*). One major document relating to the animal area was much more conservative than the others in its recommendations pertaining to resistance from agriculture (*25*). This document was prepared by a committee that was much more heavily representative of veterinary and pharmaceutical company interests than was the case with the other reviewed documents. It did not include in any of its major recommendations a call for the abolition or withdrawal of growth promoters of a similar class to drugs used in human medicine, or which select for resistance to these drugs. Nor did it recommend greater efforts to ensure the prudent use of antimicrobials. The other documents called for these actions.

The general strategies are presented below in abbreviated form from the original documents (*7,9,25,50, 53,92–95*), and in descending order of

priority. The main headings are given in order of priority (e.g., "surveillance of resistance" first), then specific strategies under each heading are prioritized by this author. In general, the most important strategies are to increase surveillance of resistance and antimicrobial use, to implement good regulation to control antimicrobial use in animals in light of resistance concerns, and to take steps to ensure the prudent use of antimicrobials in animals, especially by reducing exposure of animals to low doses of antimicrobials for long periods of time (i.e., growth promoters and prophylactics) if such uses select for resistance to drugs used in human medicine.

The top priority strategy is to improve surveillance of resistance arising in agriculture. Increased surveillance of resistance in foodborne pathogens, commensals of animals and humans, and monitoring of drug use is essential for the assembly of data that can be used to identify the important human (and animal) health impacts of resistance, and how these impacts relate to actual drug use in animals. This information is vital to good policy-making, and to convince people where the problems exist. To date, only a few countries have been able to construct reasonably comprehensive surveillance systems and none has a perfect programme in place. Other industrialized countries should be able to implement surveillance systems within 2–3 years. Developing countries in particular will have difficulties with this strategy, given the financial, human and other resource demands required for implementation. International cooperation is needed to disseminate the results of surveillance among all countries, so that even those without the infrastructure can use the results to conduct risk assessment, make policy, and manage risk.

Secondly, good regulation at the national level is urgently needed in all countries to control antimicrobial use. Since many countries have not even considered resistance issues when developing current policies, these need to be revised appropriately. Most countries will not have the resources to undertake elaborate risk assessments of all drugs used, however, examples of regulation and policy with supporting data should be made available through WHO to countries that can make use of it.

Third, encouraging prudent use of antimicrobials in all aspects of animal and plant production is essential. Veterinarians and animal owners in particular must be made aware of the facts of the impact of resistance on humans, and of the costs of resistance to themselves, their families and animals, and to the public. People need to have good reasons to modify their behaviour and these should be provided to them.

Surveillance of resistance

- Identify the components of a national post-approval resistance surveillance plan including organisms (zoonotic pathogens, enteric commensals from animals, food, humans), standards and methodologies, and core capacity (laboratory, etc);
- Undertake regular monitoring for resistant bacterial pathogens and commensals in food-producing animal populations and animal-based food products;
- Resistance monitoring in food animals should allow for correlation with similar data from humans;
- Data generated from surveillance of resistance and antimicrobial use should play a key role in the development of national policies;
- Closely monitor the use of antimicrobials in animal surveillance programmes. Post-approval surveillance is essential and should be able to detect resistance in time to take corrective measures;
- The threshold levels of resistance that are of public health concern must be defined; these levels should be low enough that any interventions they may trigger can still be efficacious;
- If resistance increases above levels of concern, then incremental interventions up to withdrawal of the drug from the market should be considered;
- Evaluate the usefulness of monitoring sentinel human populations (e.g., farm and abattoir workers) and people in the community for infection with resistant bacteria;
- Incorporate antimicrobial resistance explicitly in food safety monitoring of imported foods.

Monitoring of antimicrobial use

- Monitor closely the use of antimicrobials in animal surveillance programmes;
- Post-approval surveillance is essential and should be able to detect resistance in time to take corrective measures.

Government regulation

- Enforcement policies should be designed to ensure compliance with laws and regulations pertaining to the authorization, distribution, sale, and the use of antimicrobials in food-producing animals;
- Licensing of veterinary antimicrobial products should include consideration of safety issues related to the human health impact of resistance developing in food animals;
- Abolish the use of antimicrobials that are of a similar class to those used for treating humans as growth promoters in animals;
- A single, multidisciplinary government committee should oversee the regulation of antimicrobials in both human and non-human fields;
- Threshold levels of resistance for post-approval surveillance should be defined and provision should be made to modify or suspend the marketing of antimicrobials if thresholds are surpassed;
- Governments should assess the risks and benefits of antimicrobial use in agriculture; a risk-based evaluation of human health effects of all antimicrobials should be conducted, including currently registered products;
- Registration decisions should include consideration of the potential rate of resistance in the pre-approval evaluation.

Prudent or judicious use

- Encourage the prudent use of antimicrobials in animals, in accordance with similar strategies for humans; recommended dosages should be optimal for therapy and minimize the development of resistance;
- Develop and implement standards of practice to ensure that antimicrobials are not used as substitute for good farm hygiene;
- Ensure that animal producers employ production systems that promote animal health/welfare such that the use of antimicrobial agents is part of, not a replacement for, an integrated animal health programme;
- Prophylactic use of antimicrobials can only be justified when it can be shown that a particular disease is present or likely to occur, and such use should be regularly assessed for effectiveness and need;
- Establish codes of practice for veterinarians that reflect antimicrobial resistance concerns;
- Locally derived treatment guidelines should include a list of antimicrobials for conditions commonly presented in various species and offer a rational treatment choice based on scientific data;
- Treatment records should be kept and veterinarians should continuously evaluate their prescribing practices;
- Evaluate the impact of making all systemic veterinary antimicrobials available by prescription only;
- Support demonstration projects to evaluate programmes which use multiple interventions to promote judicious drug use and reduce infection rates;
- If sufficient evidence exists that profit from sales negatively impacts on prescribing, appropriate countermeasures should be taken;
- Advertising and promotion of animal health products should comply with national guidelines and codes of practice.

Education

- Conduct education programmes for veterinarians and farmers on the prudent use of antimicrobials (including the potential risks to human health of emerging resistance);
- Veterinary undergraduate, postgraduate and continuing education should be evaluated to ensure that prudent antimicrobial use and resistance are given high priority;
- Convey information to involved parties (e.g., veterinarians, farmers and dispensers) that facilitates understanding of the human health impacts of resistance;
- Expand the understanding of the ecology of antimicrobial resistance among involved parties;
- Support public health education campaigns on food safety and the merits of irradiation for reducing foodborne infections.

Research

- Evaluate the nature and magnitude of impacts of antimicrobial growth promoters and use the information to assist in risk-benefit assessments of each use;
- Seek alternatives (including vaccines) to antimicrobials for food animals;
- Conduct research to define the effects of antimicrobials in veterinary use and used in plants on the emergence of resistant bacteria;
- Evaluate the effect of current food processing and distribution methods on the emergence and spread of resistant organisms;
- Conduct research to better understand the molecular epidemiology and mechanisms of gene transfer, and the population biology and epidemiology of resistance;
- Assess the impact on household contacts of antimicrobial use in pets;
- Conduct pilot studies to assess the extent of environmental contamination by antimicrobial residues and resistant organisms that enter the soil or water from human and animal waste;
- Gather information on the relationship between antimicrobial pesticides and emergence of resistance.

Alternatives to antimicrobials

- Streamline the regulatory process for drugs and products that are not likely to cause antimicrobial resistance;
- Seek alternatives to antimicrobial growth promoters (vaccines, nutrition, etc).

Conclusion

Stuart B. Levy

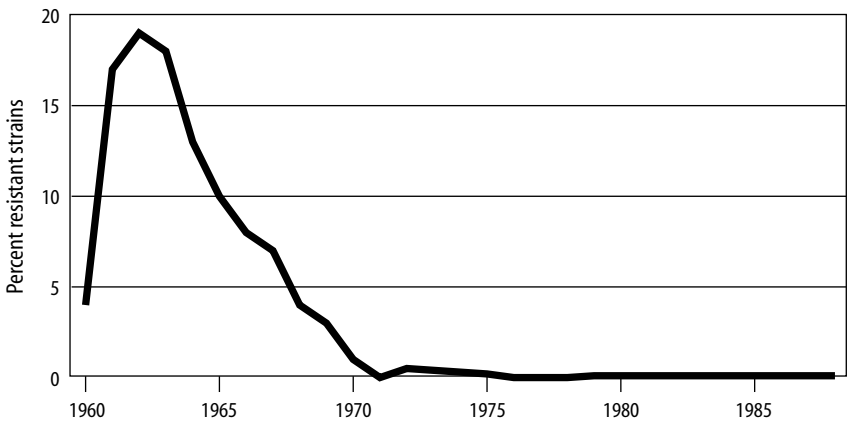
The year 2000 was a banner year for the recognition of antibiotic resistance as a priority public health problem around the world. The World Health Organization provided leadership in developing a global strategy for addressing antibiotic resistance (*26*). United States governmental organizations developed a detailed interagency plan with specific agency assignments (*53*). In addition, the United Kingdom, Sweden, Canada, and others began strong public awareness campaigns to improve antibiotic use. Even more remarkable is the commitment of countries with limited resources which have instituted national regulations to protect the potency of existing antimicrobial agents in their region. Of note, Chile, Panama and Costa Rica have recently established national regulations for the sale and prescription of antibiotics. To build on this momentum, a commitment from each country and institution is needed to roll back antibiotic resistance on a global basis.

Optimism for the future

Nations and local institutions must work together to preserve the power of antibiotics. Each country needs to act as a steward of antibiotics to pass them on to the next generation. Individual countries should maximize accessibility to appropriate antibiotics and minimize their misuse in order to extend their life in the country. The literature now documents that national and institutional initiatives can dramatically reduce the prevalence of antibiotic resistance (*14,20*). The strict enforcement of antibiotic use policies in hospitals has helped Denmark achieve a drastic reduction in the incidence of methicillin-resistant Staphylococcus aureus (see graph, *101*). Compliance with infection control procedures and the inclusion of clinical microbiologists in the prescribing process have also contributed to Denmark's success. By eliciting support from research scientists, health care providers, educators, and policy-makers, the resistance problem can be controlled in each country.

Because infectious disease seriously threatens the health and economy of each country, preserving the power of antibiotics should become a national priority. The WHO global strategy (*26*) provides an excellent framework for action by all country. Industrialized countries can take the lead in committing resources for more basic, clinical and applied research, and related interventions to curb antibiotic resistance. In all countries, government, non-governmental organizations, professional societies and clinical leaders at appropriate levels of jurisdiction must develop feasible approaches that are tailored to local conditions and available resources. In some instances, a simple hand washing or "antibiotic use improvement programme" will make an enormous difference (*20*). It is the combined efforts of these individual interventions that will become the global solution.

FREQUENCY OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) IN DENMARK



Source: V.T. Rosdahl, and A.M. Knudson (*101*). Reprinted with permission from SLACK, Inc.

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Some useful web sites

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  www.apua.org
- BUBL Catalog of Internet Resources—Infectious Diseases
  http://bubl.ac.uk/link/i/infectiousdiseases.htm
- Canadian Committee on Antibiotic Resistance
  http://www.ccar-ccra.org
- Center for Adaptation Genetics and Drug Resistance
  http://www.healthsci.tufts.edu/labs/Sblevy/home.html
- Center for Complex Infectious Diseases
  http://www.ccid.org/
- Centers for Disease Control and Prevention
  www.cdc.gov
- Eurosurveillance
  http://www.eurosurv.org/
- Global Polio Eradication Initiative
  http://www.polioeradication.org
- National Institute of Allergy and Infectious Diseases
  www.niaid.nih.gov/factsheets/antimicro.htm
- Infectious Disease News
  http://www.slackinc.com/general/idn/idnhome.htm
- Infectious Diseases Society of America
  www.journals.uchicago.edu/IDSA/guide/SE39_584.pdf
- International Society for Infectious Diseases
  http://www.isid.org
- Johns Hopkins University—Infectious Diseases
  http://www.hopkins-id.edu/index_id_links. html
- Karolinska Institut, Sweden
  http://micf.mic.ki.se/Diseases/
- National Foundation for Infectious Diseases, USA
  http://www.nfid.org/
- Project Icare: Intensive Care Antimicrobial Resistance Epidemiology
  http://www.sph.emory.edu/ICARE/
- Roll Back Malaria
  http://www.rbm.who.int/
- TDR (Special Programme for Tropical Disease and Research)
  http://www.who.int/tdr

- The Copenhagen Recommendations. http://www.sum.dk/publika/micro98
  These recommendations are a report from a conference on "The Microbial Threat," which promotes collection of data concerning the supply and sales of antimicrobials from individual nations to be shared internationally.
- The Epic Project: Developing National Evidence-Based Guidelines for Preventing Health-care-Associated Infection.
  http://www.epic.tvu.ac.uk/
- The Hot Zone: Emerging Infectious Diseases Reports and Web Sites
  http://www.qis.net/~edwardmc/eid.htm
- The HELICS project: (Hospitals in Europe Link for Infection Control Through Surveillance).
  http://helics.univ-lyon1.fr
- The MIKSTRA Programme
  http://www.stakes.fi/mikstra/e/
- The Scottish Intercollegiate Guideline Network (SIGN) Guideline on Antibiotic Prophylaxis in Surgery.
  http://www.show.scot.nhs.uk/sign/home.htm.

  This has national guidelines on antibiotic prophylaxis in surgery which addresses the benefits and risks involved in using antibiotics to prevent surgical site infections.
- The Swedish Strategic Program for the Rational Use of Antimicrobial Agents and Surveillance of Resistance
  http://www.strama.org
- UK Public Health Laboratory
  http://www.phls.co.uk/
- UK Public Health Laboratory Service's Management of Infection Guidance for Primary Care.
  http://www.phls.co.uk/advice/antibiotic/old/phls%20antibiotic%20guides%20refs% 2009.01.01.rtf

  The guidance template found on the website is designed so that the antibiotics and advice given may be changed to suit local circumstances, for example to reflect laboratory resistance data and cost.
- USA National Center for Infectious Diseases
  http://www.cdc.gov/ncidod
- Washington University Infectious Disease Division
  http://www.id.wustl.edu/
- World Health Organization
  http://www.who.int/
- WHO Antimicrobial Resistance InfoBank
  http://oms2.b3e.jussieu.fr/arinfobank/
- WHO Communicable Diseases home page
  http://www.who.int/health-topics/idindex.htm

APPENDIX A

Summaries of reports by expert policy groups (1987–2000)

(*1*) *Task Force Reports on Antibiotic Use and Resistance Worldwide (Fogarty Report)

Organization: National Institutes of Health, Fogarty Center

Year published: 1987

Selected key findings

- Antibiotic use varies greatly from country to country; surveillance data on antibiotic use, emergence of resistant strains, and availability to consumers were difficult or impossible to obtain.
- Practitioner knowledge, drug availability, and drug price are the three key factors that influence a prescriber's choice of antibiotics. Where antibiotics are available without a prescription, the same factors influence the choice of the consumer.
- The task force did not find enough evidence to prove that the implementation of firmer regulations regarding antibiotic use, or stricter enforcement of or better compliance with such regulations, slows the development or spread of resistance.
- Medical students in developing countries often receive inadequate training in basic bacteriology, infectious diseases diagnosis, and antimicrobial use. Theories of antimicrobial therapy are not always integrated with practical experience.
- There are almost no regulated requirements for health care providers to continue their education in pharmacological developments beyond their formal training. This lack is evident in both developing and industrialized countries.

Key recommendations

- Uniform data-collection systems at the national level.
- Support for and expansion of WHO's surveillance program for the global prevalence of antibacterial resistance.
- Studies on the mechanics of antibiotic resistance on the level of genetic elements, in order to devise plans on how to contain and reduce resistance.
- Research studies on antibacterial regulation that include the following:
  - Long-term, multicountry studies to determine whether or not regulation of antibiotic use and the enforcement of such rules have any effect on the development of antibiotic resistance.
  - Studies of the consequences of implementing restrictive regulations and enforcement, including the need to train health care personnel and possible economic impacts.
  - Studies that specifically examine the effects that regulations and enforcement have on children.
  - Investigation of the potential consequences to human health that would arise from restrictions on antibacterial use in food production and animal husbandry.
  - Studies that examine how national, regional, and institutional antibiotic use policies influence the training and education of physicians and other health care workers.
- Improved communications between the regulatory agencies that govern antibacterial use, and the people responsible for prescribing and using such agents.
- Research studies on antibacterial use in developing countries that include the following:
  - Studies that determine the efficacy of national formulary schemes, including drug costs, availability, as well as research and development of new agents.
  - Studies on the effects that having access to microbiology laboratory tests has on antibiotic prescription and use.
- Redesign of the curricula of medical schools in developing countries to provide more thorough

* The number in parenthesis refers to the citation listed in References.

education on diagnosing and managing infectious diseases.
- Creation of systems which will disseminate information on patterns of antibiotic use and development of antibiotic resistance to hospital staff.
- Research studies on the effects of education and information on determining antibiotic use, including: cultural and social reasons behind patient demand; the quality of physician education on the use of antibiotics, both during the course of study and after graduation; and the effects of pharmaceutical marketing campaigns on physicians' prescriptions of antibiotics.
- Evaluation of current policies on the use of antibiotics to determine what effects they have on the pharmaceutical industry's incentives to research, develop, and market new antibiotics.

Implementation suggestions
- To achieve standardized data on antibiotic use, institute "a standard index for measuring drug use in each country by using the same system of drug classification, the same unit of measurement (e.g., DDDs/1,000 population per day or grams/1,000 population per day), and the same point in the distribution channel in each country [and] by obtaining access to data of this type that are currently collected by private companies (i.e., International Medical Statistics) but are not made publicly available."
- WHO, USA Public Health Service, and ministries of health in other countries "should support research studies proposed by the task force, assist countries in establishing or improving their systems of drug regulation, facilitate collaborative research among investigators in different countries, and improve cooperation among regulatory agencies, physicians and other health workers, and drug companies."
- Regional and international centers for the study of antibiotic resistance should be established in Asia, Africa and Latin America by WHO, NIH, and CDC/USA Public Health Service/USA Department of Health and Human Services, in collaboration with ministries of health and other relevant agencies.
- "Establishment of field surveillance teams located in representative regions in developing nations. Such teams would gather information on actual antibiotic use, develop affordable strategies for preventing or curing infectious diseases, and determine the social, behavioral, and economic determinants of antibiotic usage for particular geographic areas and demographic groups."

Conclusions

"The importance of social and behavioral characteristics of individuals receiving antimicrobial therapy (as well as the supply and variety of antibiotics available) was noted in plenary discussions as influencing courses of antibiotic therapy. Studies of such variables are needed in order to answer questions related to under- or overutilization of antibiotics."

"There was the consensus that there is considerable suboptimal antibiotic use in the developing countries, where there is a tendency...for higher levels of microbial resistance... The developing nations have environmental conditions, infectious disease burdens, and associated needs and factors affecting antibiotic use and resistance patterns that differ from those in the developed nations. The participants in this project stressed the importance of recognizing and addressing these distinctions."

"Better data on utilization of antimicrobial agents in the developing world are needed. This would include information from studies on the magnitude of inadequate doses resulting in the failure to achieve bactericidal concentrations, on improper duration of therapy...and on the use of a single capsule or a limited number of capsules...for cultural, financial, or idiosyncratic reasons (associated with a transient sense of well-being)."

"Projects focusing on improving our understanding of the observed correlation between antibiotic use and subsequent resistance should be carried out... Multiple parameters should be assessed: microbiologic susceptibility patterns of the organisms principally involved; the kinds of diagnostic tests being performed; demographic patterns and associated social and behavioral characteristics; policies affecting antibiotic utilization; and the quantity and cost of antibiotics used. Such data assembled in one system have heretofore not been available."

"What is lacking, and of fundamental importance, is detailed information on the distribution over time of specific antimicrobial resistance genes and plasmids in the global bacterial ecosystem. Geographic information on individual components... is needed to trace and understand better the emerging patterns of such resistance."

"Some unified way to follow the incidence and prevalence of microbial resistance on a global scale

is required; however, it is not yet clear how best to proceed... It is, therefore, recommended that a workshop be convened to help elucidate the direction in which future surveillance studies should proceed, as well as to work out the details of a uniform methodology for collection and comparison of data."

"Fundamental studies at the cellular level concerning the cell's impressive capacity over time to defend itself against foreign agents should be supported and extended, particularly studies involving genetics and mechanisms for gene amplification and gene exchange leading to multidrug resistance."

"New diagnostic tools, simplified, appropriate, and more accurate and sensitive than tests currently available, are coming into use. The utilization of these newer techniques at the central surveillance level needs to be encouraged. These central surveillance systems, particularly those focusing on selected and important infectious disease in the developing nations...and on specific etiology agents ...should be expanded."

"Vaccine development and newer, more rapid diagnostic tests should provide additional means to combat the problem. Economic conditions and a climate favorable for the continued progress and expansion of medical therapeutics, as well as the widespread utilization of new antimicrobial agents, remain important factors in considering antibiotic use and antibiotic resistance worldwide."

Authors: ***Task Force participants***: Stuart B. Levy (General Chairperson and Guest Editor), Jacques F. Acar, Gianni Acocella, Jerry Avorn, Ingebjorg Baksaas, Fernando Baquero, Gilles Bardelay, F. Ralph Batchelor, Karen Bell, Ulf Bergman, Enriquetta Bond, Kenneth Bridbord, James J. Burchall, John P. Burke (Guest Editor), Felipe C. Cabello, Charles C.J. Carpenter III, Georges Y. Causse, Leighton E. Cluff, Mitchell Cohen, Nananda F. Col, John V. Copeland, George Curlin, Joseph T. Curti, I. Damansjah, F. Daschner, Irving P. Delappe, M.N.G. Dukes, John M. Eisenberg, Tamara Erickson, Enrique Feffer, Susan E. Feinman, Peter I. Folb, Ernst Freese, Ryochi Fujii, Aleksander Goic, Julio Gonzales-Molina, Joseph E. Grady, Richard L. Guerrant, Richard Gustafson, Ken Harvey, Andrew Herxheimer, Scott D. Holmberg, M. Imdadul Huq, Hu Zhen, N. Islam, John E. Jefferis, Amir Jivani, Bengt Jönsson, William S. Jordan, Jr., Edward H. Kass, Dianne Kennedy, Thomas Kereselidze, H.H. Kleeberg, Dieter Koch-Weser, Goran Kronvall, Calvin M. Kunin, Yankel M. Kupersztoch, Louis Lasagna, Norman W. Lavy, Donald Le Blanc, David Lee, Philip R. Lee, Alan H. Linton, Helen Levens Lipton, Robert H. Liss, Hubert Loncin, Per Knut Lunde, Edgar J. Martin, R. Russel Martin, Ramiro Martines-Silva, Charles Medawar, Dianna Melrose, Arnold S. Monto, Stuart L. Nightingale, Richard Norton, Thomas F. O'Brien, Ronald W. O'Connor, Makoto Ohashi, Jorge Olarte, Nancy Olins, Peng Wen Wei, Maria Eugenia Pinto, Philip A. Pizzo, Richard J. Plumridge, Wayne Ray, J.P Revill, Ahmed Rhazaoui, Frederick C. Robbins, O.P.W. Robinson, Heonir Rocha, Vidal Rodriguez-Lemoine, Bernard Rowe, T. Donald Rucker, Theodore Sacks, Jay P. Sanford, William Schaffner, William E. Scheckler, Roy Shaffer, K.B. Sharma, Richard P. Silver, Harold J. Simon, Ewe Hui Sng, Stephen B. Soumerai, Visanu Thamlikitkul, John F. Timoney, A. Tognoni, Luiz R. Trabulsi, Themlma Tupasi, John R. Virts, V. Vymola, Craig K. Wallace (Guest Editor), Wang Fu, Bernd Wiedemann, Sidney Wolfe

Type of publication: Supplement to *Reviews of Infectious Diseases*; Volume 9, Supplement 3, May–June 1987

Pages: 89

Intended audience: International; policy-makers, government, health care providers

Study timeframe: The Task Forces met between fall of 1983 and spring of 1986.

Study process: Six task forces were assembled, comprised of representatives from different disciplines and countries. Each Task Force focused on a different aspect of antibiotic resistance; they developed their sections of the report over a year and a half of meetings and revisions.

Type of organization: Professional society

Languages (published in): English

Key contact

Ordering information: International Studies Branch, Fogarty International Center, Bethesda, MD 20892

Content: Stuart Levy, General Chairperson for the Task Force

(2) Healthy People 2000: National Health Promotion and Disease Prevention. Full report, with commentary

Organization: Public Health Service; USA Department of Health and Human Services

Year published: 1990

Selected key findings

- Patients in hospital Intensive Care Units account for about 15% of hospital admissions, but at least 50% of nosocomial infections (data from 1990).
- Approximately 40,000 people die each year from complications arising from pneumococcal disease.

Key recommendations

By the year 2000:

- "Reduce by at least 10 % the incidence of surgical wound infections and nosocomial infections in intensive care patients;
- Reduce acute middle ear infections among children aged 4 and younger, as measured by days of restricted activity or school absenteeism, to no more than 105 days per 100 children;
- Increase to at least 90 % the proportion of public health departments that provide adult immunization for influenza, pneumococcal disease, hepatitis B, tetanus, and diphtheria;
- Develop a set of health status indicators appropriate for Federal, State, and local health agencies and establish use of the set in at least 40 states."

Implementation suggestions

Reduction of nosocomial infections to be achieved through collaboration of hospital epidemiologists, infection control practitioners, the Association of Practitioners in Infection Control, Society of Hospital Epidemiologists of America, Surgical Infection Society, American Hospital Association, Joint Commission on the Accreditation of Health Care Organizations, and the Health Care Financing Administration.

Conclusions/Executive Summary

"In addition to application of specific measures, such as immunization and regulation of food, water, and sewage disposal, there is a need for continued public education about basic hygienic practices, in home, school, and occupational settings; for continued education of health care students and workers about the epidemiology and prevention of these diseases; and for research to improve immunizations, diagnostic methods, and therapeutic modalities."

Authors: ***Principal staff/editors***: James A. Herrell, Lynn M. Artz, Ashley Files, David Baker. ***Project Coordination and Development***: Barbara Anderson, John Bailar, Amber Barnato, Sandra Buesking, Mary Jo Deering, Christopher DeGraw, Olga Emgushov, Martha G. Grazier, Toni M. Goodwin, Linda M. Harris, Douglas B. Kamero, Thomas Kim, Loretta M. Logan, Patricia Lynch, Caroline McNeil, Linda D. Meyers, Diane Rittenhouse, Marilyn K. Schulenberg, Sara L. White, Jennifer Woods, Christina Wypijewski, Michael Yao, Daniel Yarano

Type of publication: Report

Pages: 692

Intended audience: United States; citizens, policymakers

Study timeframe: N/A

Study process: The report is the result of a collaboration of 22 expert working groups, a consortium including almost 300 national organizations and all state health departments, and the Institute of Medicine of the National Academy of Sciences. The IOM and the USA Public Health Service held regional and national hearings and gathered testimony from over 750 individuals and organizations. More than 10,000 people participated in the public review, after which the objectives were revised and refined.

Type of organization: United States Federal Government

Languages (published in): English

Key contact

Ordering Information: Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325; tel.: (202) 783-3238; fax: (202)275-0019.

(3) Emerging Infections: Microbial Threats to Health in the United States

Organization: Institute of Medicine

Year published: 1992

Selected key findings

The Committee focused on factors that contribute to the emergence and re-emergence of infectious diseases, including:

- *Human demographics and behavior*. Contributing factors are movement of the ever-growing global population into urban areas, with corresponding crowded conditions, poor hygiene and sanitation, and lack of clean water supplies; increasing numbers of people with suppressed immune systems, including the elderly and people infected with HIV; and the transmission of disease through sexual activity and substance abuse.
- *Technology and industry*. Hospitals are increasingly implicated as sources of infection; many nosocomial infections have developed resistance to antibiotics thanks to the combination of a population very susceptible to infection, and the widespread therapeutic and prophylactic use of antibiotics.
- *Microbial adaptation and change*. The evolutionary mechanisms of microbial pathogens allow them to adapt to new host cells or host species, produce "new" toxins, bypass or suppress inflammatory and immune responses, and develop resistance to drugs and antibodies.
- *Breakdown of public health measures*. Inadequate sanitation, complacency on the part of medical officials, physicians, researchers and other public health workers, war, economic hardship, and natural disasters may all undermine any progress made by advances in science and technology.

Key recommendations

- "The committee recommends the development and implementation of strategies that would strengthen state and federal efforts in USA surveillance. Strategy development could be a function of the Centers for Disease Control (CDC). Alternatively, the strategy development and coordination functions could be assigned to a federal coordinating body (e.g., a subcommittee of the Federal Coordinating Council for Science, Engineering, and Technology's Committee on Life Sciences and Health), specifically constituted to address this issue."
- "The committee recommends that additional resources be allocated to the to the Centers for Disease Control to enhance the National Nosocomial Infections Surveillance System in the following ways:
  - — Include data on antiviral drug resistance.
  - — Include information on morbidity and mortality from nosocomial infections.
  - — Increase the number of NNISS member hospitals.
  - — Strive to make NNISS member hospitals more representative of all USA hospitals.
  - — Evaluate the sensitivity and specificity of nosocomial infection surveillance activities performed in NNISS member hospitals.
  - — Determine the reliability of antimicrobial susceptibility testing performed in NNISS member hospitals."
- "The committee recommends that the USA Public Health Service develop a comprehensive, computerized infectious disease database."
- "The committee recommends that international infectious disease surveillance activities of USA government agencies be coordinated by the Centers for Disease Control (CDC). Alternatively, a federal coordinating body could be assigned the coordinating function. Implementation of surveillance activities, however, should remain with the appropriate federal agencies (e.g., the CDC, Department of Defense, National Institutions of Health, USA Department of Agriculture)."
- "The committee recommends that the United States take the lead in promoting the development and implementation of a comprehensive global infectious disease surveillance system. Such an effort could be undertaken through the USA representatives to the World Health Assembly."
- "The committee recommends the expansion and coordination of National Institutes of Health-supported research on the agent, host, vector, and environmental factors that lead to emergence of infectious diseases. Such research should include studies on the agents and their biology, pathogenesis, and evolution; vectors and their control; vaccines; and antimicrobial drugs. One approach might be to issue a request for proposals (RFP) to address specific factors related to infectious disease emergence."
- "The committee recommends increased research on surveillance methods and applied control strategies; on the costs and benefits of prevention, control, and treatment of infectious disease; and on the development and evaluation of diagnostic tests for infectious diseases. Reinstating and expanding (both in size and scope) the extramural grant program at the Centers for Disease Control, which ceased in 1973, would be one important step in this direction. Similarly, the Food and Drug Administration's (FDA) extramural grant program should be expanded to place greater emphasis on the development

of improved laboratory tests for detecting emerging pathogens in food."

- "The committee recommends the domestic and global expansion of the CDC's Epidemic Intelligence Service program and continued support for Centers for Disease Control's (CDC) role in the Field Epidemiology Training Program."
- "The committee recommends continued support, at a minimum at their current level of funding, of Department of Defense overseas infectious disease laboratories."
- "The committee recommends that Congress consider legislation to fund a program, modeled on the National Health Service Corps, for training in public health and related disciplines, such as epidemiology, infectious diseases, and medical entomology."
- "The committee recommends that clinicians, the research and development community, and the USA government introduce measures to ensure the availability and usefulness of antimicrobials and to prevent the emergence of resistance. These measures should include the education of health care personnel, veterinarians, and users in the agricultural sector regarding the importance of rational use of antimicrobials (to preclude their unwarranted use), a peer review process to monitor the use of antimicrobials, and surveillance of newly resistant organisms. Where required, there should be a commitment to publicly financed rapid development and expedited approval of new antimicrobials."
- "The committee recommends that the National Institutes of Health give increased priority to research on personal and community health practices relevant to disease transmission. Attention should also be focused on developing more effective ways to use education to enhance the health-promoting behavior of diverse target groups."

Implementation suggestions

Responsibilities delegated to various government agencies and departments of the United States, primarily CDC and NIH.

Conclusions/Executive Summary

"The key to recognizing new or emerging infectious diseases, and to tracking the prevalence of more established ones, is surveillance. A well-designed, well-implemented surveillance program can detect unusual clusters of disease, document the geographic and demographic spread of an outbreak, and estimate the magnitude of the problem. It can also help to describe the natural history of a disease, identify factors responsible for emergence, facilitate laboratory and epidemiological research, and assess the success of specific intervention efforts. The importance of surveillance to the detection and control of emerging microbial threats cannot be overemphasized. Effective intervention against [emerging] diseases necessitates coordinated efforts by a variety of individuals, government agencies, and private organizations. The committee believes that the current USA capability for responding to microbial threats to health lacks organization and resources. Vaccines and antimicrobial drugs have led to significant improvements in public health in the United States and in many other nations during the latter half of this century. Despite this encouraging history, the committee is concerned that many of the vaccines and drugs available today are the same ones that have been used for decades. It believes that there is a need to review the present vaccine and drug armamentaria with a view toward improving availability and capacity, as well as safety and efficacy."

Authors: ***Edited by***: Joshua Lederberg, Robert E. Shope, and Barry R. Bloom. ***Task Force Members***: Robert L. Buchanan, John R. David, Ciro A. De Quadros, Patricia N. Fultz, John J. Holland, Dean T. Jamison, Edwin D. Kilbourne, Adel A.F. Mahmoud, Gerald L. Mandell, Stephen S. Morse, June E. Osborn, William C. Reeves, Philip K. Russell, Alexis Shelokov, P. Frederick Sparling, Andrew Spielman. ***Project Staff***: Ruth Ellen Bulger, Polly F. Harrison, Stanley C. Oaks, Jr., Elizabeth E. Meyer, Nancy Diener, Greg W. Pearson.

Type of publication: Report

Pages: 294

Intended audience: Primarily the United States; policymakers, lay public, government, scientists, physicians

Study timeframe: February 1991 to July 1992

Study process: 19-member multidisciplinary committee convened to identify significant emerging infectious diseases, develop plans on how to deal with them, and make recommendations on how to approach similar threats in the future. The full committee met four times during the 18-month study. Four task forces and subcommittees also formed according to specialties, and met to address more specific topics.

Type of organization: Non-profit public health and advisory organization; advisor to Federal Government on issues of public health

Languages (published in): English

Key contact

Ordering information: National Academy Press, www.nap.edu
Content: Joshua Lederberg and Robert E. Shope, Committee Co-chairs

(4) Addressing Emerging Infectious Disease Threats.A Prevention Strategy for the United States

Organization: Centers for Disease Control and Prevention; National Center for Infectious Diseases

Year published: 1994

Selected key findings

Surveillance is the key to tracking the development and spread of infectious diseases, reservoirs of disease, and antimicrobial drug resistance.

One weakness in the United States' strategy to control infectious diseases is the lack of multidisciplinary approaches. The USA needs stronger connections between laboratory science and public health practices, as well as economic analyses of the impacts of both infectious diseases and the interventions proposed to stop them.

Most federal government funds dedicated to surveillance of infectious diseases at the state level go towards only four categories of disease: tuberculosis, HIV/AIDS, sexually transmitted diseases, and certain vaccine-preventable diseases. This leaves a large number of other emerging infectious diseases under-funded and under-observed.

The current approach to public health in the United States (i.e., the focus on treatment rather than prevention; reactive rather than proactive policies; and general complacency) leads to the emergence and spread of infectious diseases that ought to be preventable.

Key recommendations

- "Expand and coordinate surveillance systems for the early detection, tracking, and evaluation of emerging infections in the United States;
- Develop more effective international surveillance networks for the anticipation, recognition, control, and prevention of emerging infectious diseases;
- Improve surveillance and rapid laboratory identification to ensure early detection of antimicrobial resistance;
- Strengthen and integrate programs to monitor and prevent emerging infections associated with food/water, new technology, and environmental forces;
- Strengthen and integrate programs to monitor, control, and prevent emerging vector-borne and zoonotic diseases;
- Expand epidemiologic and prevention effectiveness research;
- Improve laboratory and epidemiologic techniques for the rapid identification of new pathogens and syndromes;
- Ensure timely development, appropriate use, and availability of diagnostic tests and reagents;
- Use diverse communication methods for wider and more effective delivery of critical public health messages;
- Establish the mechanisms and partnerships needed to ensure the rapid and effective development and implementation of prevention measures;
- Ensure the ready availability of the professional expertise and support personnel needed to better understand, monitor, and control emerging infections;
- Make available state-of-the-art physical resources (laboratory space, training facilities, equipment) needed to safely and effectively support the preceding goals and objectives."

Implementation suggestions

"Between 1994 and 1996, CDC intended to implement its recommendations by establishing priority goals in the four areas of Surveillance, Applied Research, Prevention and Control, and Infrastructure. They include the following:

- Strengthen notifiable disease surveillance at the state and local levels;
- Establish two physician-based Sentinel Surveillance Networks to detect and monitor emerging diseases;
- Establish four population-based Emerging Infections Epidemiology and Prevention Centers to conduct focused epidemiology/prevention projects emphasizing foodborne and waterborne infectious diseases and potentially vaccine preventable diseases;
- Strengthen and link four existing sites for a global consortium to promote the detection, monitoring, and investigation of infections emerging internationally that could affect the health of Americans;

- Reestablish an extramural program to support emerging infectious disease prevention and control activities, such as evaluating the role of prescribing practices in the development of antimicrobial drug-resistant pathogens;
- Initiate prevention effectiveness studies to assess the impact of food preparation guidelines on the incidence of foodborne infections such as *E. coli* O157:H7 and *Salmonella enteritidis*;
- Develop additional means to deliver laboratory and public health information informing health professionals about emerging infections and antimicrobial drug resistance;
- Develop and implement guidelines for the prevention of opportunistic infections in immunosuppressed persons;
- Provide state-of-the-art training in diagnostic evaluation and testing for medical laboratory personnel to ensure the diagnosis and surveillance of emerging infection;
- Establish a public health laboratory fellowship in infectious diseases that will train medical microbiologists in public health approaches to diagnosis and molecular epidemiology."

Conclusions

"As the United States moves towards comprehensive health care reform, it is crucial that emerging infectious disease threats be addressed and that the basic tenets of prevention-oriented public health policy form an internal component of plans for health care reform.

Strengthened efforts in the prevention and control of emerging infectious diseases will complement and improve the effectiveness of current efforts in HIV/AIDS, TB, STDs, and immunizations as well as other important infectious diseases. To provide the vigilance and rapid response required to effectively address emerging infectious diseases, significant improvements in public health policy, program design, and infrastructure are needed. A far-reaching and comprehensive strategy, carefully integrated with broader plans for health care reform is required.

Effective public health policy results from interaction, cooperation, and coordination among a wide range of public and private organizations and individuals. Particularly critical to this process are CDC's partnerships with state and territorial health departments; other federal agencies; professional organizations; academic institutions; private health care providers; health maintenance organizations and health alliances; local community organizations; private industry; and international partners, including WHO and international service organizations and foundations. Each of these partners will play an integral role in the cooperative efforts required to safeguard the public's health from emerging infectious disease threats."

Authors: Emerging Infections Working Group: Ralph T. Bryan, M.D., Robert W. Pinner, M.D., Robert P. Gaynes, M.D., C.J. Peters, M.D., Meredith A. Hickson, M.P.H., Judith R. Aguilar

Type of publication: Report

Pages: 46

Study timeframe: The Advisory Committee considered scientific literature from 1976 to 1993.

Study process: The plan was developed by the CDC in partnership with representatives from state and local public health organizations, other federal agencies, health care professionals, members of medical and public health professional associations, infectious disease experts, and public service organizations. Committee members met several times to discuss the plan and gather additional input between December 1992 and June 1993.

Type of organization: Federal Government

Intended audience: United States; physicians and other health care providers, policy-makers

Languages (published in): English

Key contact

Ordering Information: Centers for Disease Control and Prevention, National Center for Infectious Diseases, Office of Program Resources EP, Mailstop C-14, 1600 Clifton Road, Atlanta, GA 30333

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

Organization: World Health Organization, Division of Bacterial, Viral Diseases and Immunology.

Year published: 1994

Selected key findings

- There is a lack of data on the economic consequences of antibiotic resistance and of community-acquired infections.
- It may be useful to reconsider older alternatives to antibiotics, including bacterial interference, serum therapy, and bacteriophages.

- The approach of the pharmaceutical industry to the development and spread of antimicrobial resistance includes: continued chemical modification of existing agent classes; interference with resistance mechanisms to increase target access; and searching for agents with novel mechanisms of action.

Key recommendations

Recommendations for WHO:

- "Communicate the importance of the problem of antimicrobial resistance to developed and developing countries and other international health agencies;
- Improve systems for surveillance of antimicrobial resistance;
- Develop recommendations to improve clinical use of antimicrobial agents and decrease selection of resistant bacteria;
- Develop strategies to decrease the selection and transmission of resistant microorganisms in medical centers;
- Develop strategies to decrease transmission of resistant microorganisms in the community and plans for responding to outbreaks of bacterial pathogens;
- Develop strategies to decrease the emergence and dissemination of resistant organisms in veterinary medicine and the environment;
- Support the development and evaluation of new preventive and curative modalities."

Implementation suggestions

- Communication would be improved through distribution of newsletters and bulletins (i.e., *Weekly Epidemiological Record*, *WHO Drug Information Bulletin);* facilitation of interaction among government agencies, academic institutions and the pharmaceutical industry; and data sharing and surveillance system linkage.
- Improvement of surveillance systems would be achieved by helping national laboratories to determine their current status and needs to successfully identify bacterial pathogens and test them for susceptibility; distribute and help to install WHONET software in laboratories; help laboratories to develop quality control and assurance programs.
- Reduction of antibacterial resistance in medical centers would be achieved by developing educational programs and hygienic standards in daycare centers and long-term care facilities; infection control training programs for hospital personnel; and linkage between hospital infection control programs to quality assurance efforts at the national and local levels.
- Transmission of resistant organisms in the community would be decreased through promotion of community hygiene standards for safe water and food and support of programs for improved access to treatment.
- The emergence and spread of resistant organisms in veterinary medicine and the environment would be decreased by ensuring that only qualified veterinary personnel be permitted to prescribe antimicrobial agents for the treatment of infections in animals; prohibiting the use of antimicrobial agents for growth promotion that are also used in human medicine; and by discouraging "the unnecessary use of therapeutic antimicrobials for prophylaxis in food animals."

Conclusions/Executive Summary

"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. 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. 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. 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 behavioral sciences."

Authors: ***Participants***: Dr. Y.Z. Abou, Dr. J.F. Acar, Dr. G.A.J. Ayliffe, Dr. N. Citri, Dr. B. Cookson, Dr. Wang Fu, Dr. D.A. Goldmann, Dr. D. Grossklaus, Dr. M. Guzman, Dr. R.E.W. Hancock, Dr. R. Helmuth, Dr. P. Huovinen, Dr. J.M. Hughes, Dr. W. Johnson, Dr. E.L. Kaplan, Dr. T.S. Kereselidze, Dr. P. Kriz, Dr. G. Kronvall, Dr. A. Kucers, Dr. M.K. Lalitha, Dr. R. Leclercq, Dr. B. Levin, Dr. I. Lind, Dr. A. Marton, Dr. A. Medeiros, Dr. G.H. Miller, Dr. T.F. O'Brien, Dr. G. Orefici, Dr. K. Rahal, Dr. B. Tasmussen, Dr. B. Rowe, Dr. R. Bradley Sack, Dr. J. Schindler, Dr. N.A. Semina, Dr. J. Stelling, Dr. F. Tenover, Dr. A. Tomasz. ***Observers***: Dr. R. Bax, Dr. D.H. Bouanchaud, Dr. E. Bozkurg, Dr. I. Carugo, Dr. R. Charnas, Ms. M. Cone, Dr. H. Dekoning-Gans, Dr. R. Kessler, Dr. C. Krasemann, Dr. H. Locher, Dr. J.S. Mantell, Dr. O. Morin, Dr. G. Mosely, Dr. D. Pontani, Dr. A. Roos, Dr. C.D. Rothermel. WHO ***Secretariat***: Dr. M. Couper, Dr. D. Cohn, Dr. Svein-Erik Ekeid, Dr. M.M. El-Nageh, Mrs. K. Esteves, Dr. E. Griffiths, Dr. C.-C. Heuck, Dr. J.W. LeDuc, Dr. L.J. Martinex, Dr. N. Pearce, Dr. A. Pio, Dr. J. Perriens, Dr. M. Raviglione, Dr. K.B. Sharma, Dr. Hulian Sima, Dr. A. Sow, Dr. K. Tankari, Dr. E. Tikhomirov, Dr. G. Torrigiani, Dr. P.I. Trigg

Type of publication: Meeting report

Pages: 33

Intended audience: Global; policy-makers, pharmaceutical industry, health care providers

Study timeframe: The working group met from November 29 to December 2, 1994.

Study process: The working group, comprised of professionals from the fields of clinical medicine, research and public health, met to review the current status of the nature and consequences of antimicrobial resistance, and to make recommendations on alleviating the problem.

Type of organization: International, non-governmental, public health agency

Languages (published in): English

Key contact

Ordering Information: Communicable Disease Surveillance and Response Documents, World Health Organization, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4198, attention CSR Documents; email: csr@who.ch, attention Documents.

(6) Impacts of Antibiotic-Resistant Bacteria

Organization: Office of Technology Assessment; Congress of the United States

Year published: 1995

Selected key findings

- Inappropriate antibiotic use contributes to the increase of selection pressure for the selection and spread of antibiotic resistance. It is possible that as much as 50% of antibiotic use is inappropriate.
- Although only one-third to one-half of the 24.5 million otitis media cases that occur each year benefit from antibiotics, physicians often prescribe them. Parental pressure and time constraints that keep physicians from testing for viral sources of the disease are common reasons for resorting to potentially ineffective antibiotic prescriptions.
- At any given time, 25% to 35% of all hospitalized patients are receiving antibiotic treatment, whether therapeutic or prophylactic. The result of such heavy use among a very vulnerable population often leads to the emergence and spread of antibiotic-resistant bacteria.

Key recommendations

(The Advisory Board presents options, rather than direct recommendations)

Surveillance

- "Congress could support the establishment of a national surveillance system, including providing funding. The features of current, limited systems can be incorporated and combined to produce a system of desired size, complexity, and cost. Any system must have a strong advisory group that includes diagnostic laboratory and computer experts, clinicians, hospital administrators, pharmaceutical company researchers, academic scientists, and federal and state regulatory and health officials."

Infection control

- "Congress could encourage all states to adopt guidelines for the coordination of infection control measures between acute care and long-term care facilities and to extend guidelines to include all antibiotic-resistant bacteria."

Research funding

- "Congress can make money available for studies of the development, transfer, and persistence of

antibiotic resistance [and] for research into the basic biology of bacteria;
- Congress can make resources available for the study of appropriate use of devices that present infection risks to hospitalized patients."

Controlling antibiotic use
- "Review Medicare and Medicaid reimbursement policies for their unanticipated effects on antibiotic prescription patterns."

Antibiotics in animal husbandry
- "Collect information about associations between animal husbandry uses of antibiotics and antibiotic-resistant bacteria in humans;
- Design a study to determine the sources of antibiotic-resistant bacteria in the human diet;
- Study the benefits of antibiotic use in animal husbandry. An analysis of written information could probably determine the costs of the antibiotics in feeds."

Negotiated marketing agreements for antibiotics:
- "Congress can provide FDA with authority to negotiate extended market exclusivity to manufacturers that agree to restrictions on marketing of antibiotics."

Development of off-patent compounds as antibiotics
- "Congress could authorize FDA to extend market exclusivity for off-patent antibiotics that are shown to be effective against antibiotic-resistant bacteria;
- Congress could establish a federal program to conduct clinical trials of antibiotics to determine if they have uses against antibiotic-resistant bacteria."

Implementation suggestions

The Advisory Panel suggested delegation of responsibilities to various government agencies and departments of the United States. Increased funding for the creation of surveillance systems and infection control guidelines, and for research and development would come from Congress. FDA would be responsible for facilitating the development of new antibiotics, and for helping to determine the future uses of antibiotics in food animals and plants. Internal hospital surveillance systems should continue, and should be linked to other hospitals within a geographical area, with the eventual goal of a nation-wide system overseen by CDC.

Conclusions/Executive Summary

"The problems caused by antibiotic-resistant bacteria can be ameliorated through two major routes: 1) prolonging the effectiveness of currently available antibiotics through infection control and optimal use of existing antibiotics and 2) developing new antibiotics to treat resistant bacteria."

"Although all persons are susceptible to illnesses related to antibiotic-resistant bacteria, some are more than others. The poor, people without adequate health care, the incarcerated, the homeless, military personnel, children in daycare facilities, the elderly, and the immuno-suppressed are more susceptible to these illnesses than the general population. However, because most of the general public comes in contact with members of these vulnerable populations daily, the general public is at risk because the diseases or illnesses can spread from person to person... Therefore, it is crucial that the scientific and medical communities, the pharmaceutical industry, and the general public cooperate to find solutions that will slow the pace of antibiotic resistance and lessen the impact of illness on public health."

Authors: ***Advisory Panel***: Gail Cassell, PhD; Anne Bolmstrom; Robert J. Bywater, PhD; Barry Eisenstein, MD; Prabhavathi B. Fernandes, PhD; Winston Frederick, MD; Joshua Lederberg, PhD; Stephen Lerner, MD; Stuart Levy, MD; Robert C. Moellering, Jr., MD; Barbara Murray, MD; Tom O'Brien, MD; Lone Simonsen, PhD; Harry Taber, PhD; Alexander Tomasz, PhD; Richard Wenzel, MD, MSc; Craig Townsend, PhD; Michael Zasloff, MD, PhD

Type of publication: Report

Pages: 183

Intended audience: United States; policy-makers, health care providers

Study timeframe: The Advisory Panel reviewed the scientific literature from 1961 to 1995, with a few references from the late 1930s and 1940s.

Study process: The Advisory panel reviewed scientific literature, explored biological mechanisms behind antibiotic resistance, and researched new antibiotics.

Type of organization: Federal Government

Languages (published in): English

Key contact

Ordering information: USA Government Printing Office, Superintendent of Documents, Mail Stop: SSOP, Washington, DC 20402-9328

(7) Infectious Disease: A Global Health Threat

Organization: National Science and Technology Council; Committee on International Science, Engineering, and Technology Policy (CISET)

Year published: 1995

Selected key findings

- The re-emergence of infectious diseases may be linked to human behavior (increased travel and trade across borders, shifts in population demographics, the poor quality of public health infrastructures) and ecological changes (climate and weather changes, evolution of microorganisms, disruption of ecosystems due to human use patterns).
- The cost of treating antibiotic-resistant bacterial infections in the United States was $4 billion in 1994, and projected to increase.
- The USA response to reports of outbreaks of infectious disease is often informal, loosely coordinated among government agencies, and hampered by a lack of funding to conduct a complete investigation.

Key recommendations

Work in partnership with other countries, with WHO, and with other international organizations to improve worldwide disease surveillance, reporting, and response by:

- Establishing regional disease surveillance and response networks linking national health ministries, WHO regional offices, USA Government laboratories and field stations abroad, foreign laboratories and medical centers, and WHO collaborating centers;
- Ensuring that reliable lines of communication exist between local and national medical centers and between national and regional or international reference facilities, especially in parts of the world where modern communications are lacking;
- Developing a global alert system whereby national governments can inform appropriate worldwide health authorities of outbreaks of infectious disease in a timely manner.

Strengthen the USA capacity to combat emerging infectious diseases by:

- Enhancing collaborations among USA agencies to ensure maximum use of existing resources for domestic and international surveillance and response activities;
- Rebuilding the USA infectious disease surveillance public health infrastructure at the local, state, and federal levels;
- Working with the private and public sectors to improve USA capacity for the emergency production of diagnostic tests, drugs, and vaccines;
- Strengthening technical training programs in disciplines related to infectious disease surveillance and response;
- Establishing an Interagency Task Force to coordinate the implementation of these recommendations;
- Establishing a private sector subcommittee of the Interagency Task Force that includes representatives of the USA pharmaceutical industry, medical practitioners and educators, and biomedical scientists.

Implementation suggestions

The committee recommends giving greater authority to certain government agencies and departments to monitor and respond to disease outbreaks. To this end, it recommends the convening of an Interagency Task Force, consisting of Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health, the Department of State, Department of Defense, and USA Agency for International Development, and others as necessary.

Conclusions

The elements of a global network for disease surveillance already exist but need to be strengthened, linked, and coordinated. For instance, many USA Government department and agencies maintain or support field stations and laboratories in Africa, Asia, and the Americas that may be electronically linked to provide an initial framework for a network for global infectious disease reporting. In partnership with other countries and with WHO, this skeletal surveillance network could be expanded over time to include many international resources, including national health ministries, WHO Collaborating Centers, hospitals, and laboratories operated by other nations, and American and foreign private voluntary organizations.

Authors: Report generated by members of CISET and its working group comprised of members from 28 government agencies and departments

Type of publication: Report

Pages: 56

Intended audience: United States; policy-makers

Study timeframe: Working group convened December 14, 1994

Study process: Various government agencies and departments contributed input on the role of the United States in detecting, reporting, and responding to outbreaks of new and re-emerging infectious diseases.

Type of organization: Government

Languages (published in): English

Key contact

Centers for Disease Control and Prevention, Office of the Director, National Center for Infectious Diseases: (404) 639-2603

(*8*) Report of the ASM Task Force on Antibiotic Resistance

Organization: American Society for Microbiology

Year published: 1995

Selected key findings

- Broad spectrum antibiotic use for otitis media is selecting for resistance against other more dangerous pathogens.
- Physicians contribute to the resistance problem by inadequately diagnosing ailments before prescribing antibiotics, prescribing antibiotics to treat viral illnesses, inappropriately prescribing broad spectrum antibiotics, and acquiescing to patient demand for antibiotic prescriptions when their use would be ineffective.
- Nearly one half of antibiotics used in the USA are used in farm animals (according to 1988 report by the National Academy of Sciences).
- The estimated yearly cost of treating infections in humans that are related to antibiotic-resistant organisms in the United States is over $4 billion.

Key recommendations

- Establish a national surveillance system to do the following:
  - — "Focus on the most prevalent bacterial and fungal pathogens (not viral) that concern human health. This will assess isolates from clinical disease cases and routine isolates so that no bias from one center testing only the "problem" isolate or more resistant isolates compromises the results. Attention will be given to the trend in upward "creep" of MICs [Minimal Inhibitory Concentration]. There is also a need to monitor food sources such as animal products at the supermarket level as well as imported fruits, vegetables, and other products that may carry colonizing, drug-resistant bacteria and colonizing fecal flora in some patient populations. *Salmonella* and *Shigella* both should be monitored. *Salmonella* gives the best window into the impact of uses of antibiotics in the animal world, and the fraction of *Shigella* that is imported gives us an excellent view of the impact of antibiotic uses in the developing world. Monitoring of soil waste in farms should also be considered;
  - — Establish a baseline of antimicrobial *in vitro* efficacy to which the following can be compared: earlier data from similar surveillance studies found in medical literature reviews, especially if these studies utilized comparable methodologies and surveillance techniques; subsequent surveillance data resulting from the establishment of a national surveillance system analyzed in a longitudinal manner; non-USA data to assess the international risks of resistance;
  - — Accumulate concurrent demographic profile information to assess the relationships between organisms emerging in hospitals of various sizes or disease therapy focuses and pathogens prevalent among ambulatory patients in the community and animals housed in various environments. The role of drug use in these environments shall be addressed;
  - — Establish a mechanism whereby organisms possessing certain phenotypic and genotypic resistance patterns will be referred to adequately funded laboratories for detailed study. Various molecular typing and investigative procedures can lead to earlier understanding of developing resistance mechanisms and spread of epidemic clones;
  - — Allow for the future assessment of the encountered resistant pathogens' effect on patient outcomes, general community health, and the costs of health care delivery. Surveillance will target areas for specific intensive interventions for prevention (like vaccine campaigns and antimicrobial use reduction programs). Surveillance will also identify areas where epidemiologic investigations are needed to improve understanding of spread of drug-resistant strains and to

identify ways to interfere with spread;
— Maximize the possibility that data will lead to significant forms of professional health care intervention to reduce the probability that resistance to the drug will be spread widely and have an adverse impact on the national quality of health care outcomes. Interventions ideally should be focused at the local level but regional and national interventions could also provide great benefits;
— Provide expert federal agencies and societies the information to modify recommendations regarding therapy or prophylaxis of disease or regarding testing procedures. These can be implemented at various levels related to patient or institutional demographics or by geography (local, regional, national);
— Provide a compatible system in which subsets of participants could be grouped for common benefits. Examples include federal hospitals (Veterans Administration [VA], military, etc.), animal care facilities (university-based, USA Department of Agriculture [USDA], etc.), recognized HMO-like programs, and academic institutions such as university teaching hospitals;
— Provide the accumulated data to pharmaceutical manufacturers, thus providing the validations of contemporary drug spectrums. This will be valuable in establishing meaningful organism coverage indications in antimicrobial agent package inserts;
— Provide a system that can be modified to address any discovered area of concern related to the effective therapy of infectious organisms. This could allow expansion to cover fungi, viruses, cell-associated organisms, and some parasites."
— Monitor bacterial pathogens considered important in human and animal infections. Testing schedules of various strains and species will vary according to the recommendations of the surveillance oversight panel. A significant number of organisms should be tested, with medical statisticians contributing input to the final list.
— Conduct a broad sampling of geographically dispersed laboratory isolates, with a focus on human pathogens. Criteria for selection of laboratories will be based on state population density and diversity of demographic populations.
— Monitor demographic profiles of participating hospitals and laboratories with yearly updates.
— Establish testing methods that are of reference quality and closely follow the documents published by the NCCLS. Where possible, conduct initial screening using the disk diffusion method (MCCLS M2-A5) for those pathogen-antimicrobial combinations that can be accurately tested."

- Strengthen professional and public education in the area of infectious diseases and antibiotics to reduce inappropriate usage of antibiotics.
  — "An urgent need exists for more appropriate selection and use of antimicrobial drugs. The curriculum of health professional (medical, dental, nursing, and veterinary) schools and postgraduate educational programs should be strengthened in the areas of sterilization, disinfection, hazards of inappropriate antimicrobial drug use, appropriate diagnosis and treatment of infectious diseases, and antibiotic resistance. These efforts should result in reduction of spread of infectious agents and more prudent use of antibiotics;
  — Better guidelines should be established and enforced to reduce the spread of infectious agents and antibiotic resistance in the hospital environment, nursing homes, daycare facilities, and food production industries;
  — Educational materials should be developed and widely distributed to patients and food producers. The need for partnerships in improving antimicrobial use of cost-effective treatment of infections and to preserve the effectiveness of antimicrobial drugs for the future should be emphasized."
- "There is an urgent need for more basic research directed toward development of new antimicrobial compounds, effective vaccines, and other prevention measures.
  — In FY 1994 allocations to the National Institute of Allergy and Infectious Diseases of the NIH for funding of non-AIDS infectious disease research were reduced by $20 million. Increased appropriations are urgently needed to fund areas of research directly related to new and re-emerging infections and antibiotic resistance;
  — More basic research is needed to delineate the genetic and metabolic pathways, including essential regulatory factors, that determine virulence as well as antibiotic susceptibility

or resistance in pathogens of human and veterinary importance...;
— More resources should be devoted to the sequencing of the entire genome of microbial pathogens, particularly in closed populations (i.e., hospitals, child care facilities, and food production facilities);
— More basic research is needed to better understand the genetics of microorganisms and the development of antibiotic resistance, particularly in fungi and newly described pathogens;
— Research is needed for development of rapid, reliable diagnostic techniques for identifying specific infectious causes of illness…;
— More basic research is needed to facilitate development of effective vaccines and other prevention measures."

Implementation suggestions

Implementation of the task force's recommendations would be conducted by the National Center for Infectious Diseases of the CDC. Establishment of priorities and implementation of policies would be carried out by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH), the USA Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration.

Conclusions/Executive Summary

"There is an urgent need for effective domestic and global surveillance of antibiotic resistance in animals and humans. There is also an urgent need for more prudent use of antibiotics in both human and veterinary medicine, particularly as it relates to food production. Of equal urgency is the need for better hospital infection control and implementation of guidelines to reduce spread of infection and antibiotic-resistant pathogens in the hospital environment. There is a great need for strengthening the curriculum of human and veterinary health care professionals in the areas of sterilization and disinfection, mechanisms of antibiotic resistance, and factors contributing to its spread, including inappropriate antibiotic usage. There is also a need for patient education regarding appropriate uses of antibiotics. More basic research is needed to more clearly delineate mechanisms of antibiotic resistance and to identify new antimicrobial targets. Lastly, greater emphasis must be placed upon research related to rapid, reliable diagnostic tests and vaccines for prevention and control of infectious diseases."

Authors: ***Task force***: Gail H. Cassell, Ph.D., Gordon L. Archer, M.D., Thomas R. Bear, M.D., Mary J. Gilchrist, Ph.D., Donald Goldmann, M.D., David C. Hooper, M.D., Ronald N. Jones, M.D., Stanley H. Kleven, D.V.M., Ph.D., Joshua Lederberg, Ph.D., Stuart B. Levy, M.D., Donald H. Lein, D.V.M., Ph.D., Robert C. Moellering, M.D., Thomas F. O'Brien, M.D., Bennie Osburn, D.V.M., Ph.D., Michael Osterholm, Ph.D., David M. Shlaes, M.D., Ph.D., Martin Terry, D.V.M., Sue A. Tolin, Ph.D., Alexander Tomasz, Ph.D. ***Government Liasions***: Robert F. Breiman, M.D., Jean Cooper, Ph.D., James M. Hughes, M.D., John La Motagne, Ph.D., Edward McSweegan, Ph.D., Albert T. Sheldon, Ph.D., Fred Tenover, Ph.D. ***Industrial Liasions***: Jerry Boscia, M.D., Carl J. Craft, M.D., Susan Froshauer, Ph.D., Michael McCabe, D.V.M., Catherine Reese, Ph.D., Ray Testa, Ph.D. ***Office of Technology Assessment***: Sean Tunis, M.D., Justin Latus, M.P.P.

Type of publication: Report

Pages: 23

Intended audience: United States; microbiologists

Study timeframe: N/A

Study process: Task Force members participated in a workshop conducted July 6, 1994, and reviewed relevant scientific literature.

Type of organization: Non-profit, life science society

Languages (published in): English

Key contact

ASM Headquarters, 202-737-3600.
Available on the web at: http://www.asmusa.org/pasrc/pdfs/antibiot.pdf

(9) The Medical Impact of the Use of Antimicrobials in Food Animals. Report of a WHO Meeting.

Organization: World Health Organization, Division of Emerging and Other Communicable Diseases Surveillance and Control.

Year published: 1997

Selected key findings

- At the time of the report, *Salmonella* serotypes showing reduced susceptibility to fluoroquinolones in humans had been observed in France, Germany, Ireland, the Netherlands, Russia, Spain and the United Kingdom.
- There is a lack of quantifiable data on the preva-

lence and spread of resistance in zoonotic bacteria or indicator agents, including *Escherichia coli, Entereococcus faecium* and *Enterococcus faecalis*.
- Prior to the use of fluoroquinolones in poultry production, there has been a dramatic rise in the incidence of fluoroquinolone-resistant *Campylobacter jejuni* in live poultry, poultry meat and from infected humans.

Key recommendations
- Adherence to the recommendation made by the WHO advisory group of 1994, specifically: "The use of any antimicrobial agent for growth promotion in animals should be terminated if it is: used in human therapeutics; or known to select for cross-resistance to antimicrobials used in human medicine."
- "National authorities should define threshold levels of resistance in bacteria and circumstances where mitigation procedures should be instigated and, if such procedures are unsuccessful, when approval should be withdrawn;
- No antimicrobial should be administered to a food animal unless it has been evaluated and authorized by competent national authorities. This evaluation should include a thorough risk assessment which includes the development of resistance that may impact public health; and post-market monitoring program to detect emergence of resistance of public health significance. If such emergence is detected, appropriate action should be taken, which may include the withdrawal of the antimicrobial in question;
- Increased concerns regarding risks to public health resulting from the use of antimicrobial growth promoters indicated that it is essential to have a systematic approach towards replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives;
- Request the Codex Alimentarius Commission to include issues of antimicrobial resistance among the terms of reference of the Codex committee on Residues of Veterinary Drugs in Foods;
- National authorities should maintain records of export/import figures of bulk chemicals with potential antimicrobial use, as such information is vital for quantitative assessments of the medical risks related to the use of antimicrobials in livestock production;
- WHO should continue to support ongoing efforts to harmonize residue standards internationally;
- Countries should ascertain and monitor the prevalence of resistant bacteria in food-producing animal populations and animal-based food products;
- Classes or organisms to be included in national monitoring programs should be the important zoonotic foodborne bacteria (with *Salmonella* as the primary group of organisms) and key indicator bacteria… If feasible, programs should include *E. coli* and *Campylobacter*. In addition, other potential veterinary and human pathogens (e.g., *Enterococcus*) should be considered, based on an individual country's requirements;
- National practices of antimicrobial use in animals would be reviewed, and antimicrobial use policies be developed to reduce the risks of selection and dissemination of antimicrobial resistance."

Implementation suggestions
- WHO's Program on Antimicrobial Resistance Monitoring would be responsible for coordinating international efforts to conduct surveillance of resistant bacteria in food animals and food from animal sources, and for training personnel in the medical and veterinary sectors on antimicrobial resistance testing and national policy framework development activities.
- An expanded version of the WHONET software would be used to monitor data on bacteria collected from food animals and food of animal origin.
- Collaborations among the medical, veterinary and agricultural sectors would be responsible for coordinating surveillance efforts at the local, regional, or national level.
- WHO and the Food and Agricultural Association of the United Nations would convene experts to develop international guidelines for prudent use of antimicrobials in food animal production.

Conclusions/Executive Summary

"Microbiological and clinical evidence is mounting that resistant bacteria or resistance determinants might be passed from animals to humans, resulting in infections that are more difficult to treat. With an increase in the prevalence and distribution of antimicrobial-resistant infections in hospitals and the community, the question has been raised as to how this escalation of resistance could have been influenced by the use of antimicrobials in livestock production. Timely public health action is needed to control or mitigate any medical

problem that might be related to the widespread application of antimicrobials outside the medical sphere. The most desirable action is the limitation, or more prudent use, of antimicrobials, particularly where alternatives are available. In situations where there is evidence of a link to medical problems, appropriate control action is needed. In light of shrinking public resources and the increasing need to conduct scientifically-substantiated risk assessments for prioritizing public health action, national policies on the use of antimicrobials in animals must balance the possible benefits to livestock production against the medical risk and public health consequences deriving from their use."

Authors: ***Participants***: Professor J. Acar, Dr. F. Angulo, Dr. D. Bell, Professor T. Blaha, Dr. J. Boisseau, Dr. J. Borvendég, Dr. Anne Brisabois, Dr. R. Buchanan, Dr. Celia Carlos, Dr. Paula Fedorka-Cray, Professor A. Franklin, Professor C. Friis, Professor H. Goossens, Professor J. Gropp, Dr. R. Helmuth, Dr.A. Hoszowski, Professor S. Jin, Dr. I.A. Kroetz, Dr. Hilde Kruse, Dr. J.-P. Lafont, Professor R. LeClerq, Dr. S. Levy, Dr. J. MacKinnon, Dr. J.L. Martel, Dr. G. Martin, Dr. S. McEwen, Dr. S. McOrist, Dr. M.N. Mohd Nordin, Professor A. Panin, Dr. Laura Piddock, Professor M. Pugh, Dr. A. Rattan, Professor L. Songkram, Dr. S. Sundlof, Dr. W. Thiel, Dr. Linda Tollefson, Dr. H. Trolldenier, Dr. J. Turnidge, Dr. P. Wall, Dr. U. C. Warsa, Dr. H. Wegener, Professor B. Wiedemann, Professor M. Wierup, Professor W. Witte, Dr. C. Wray, Dr. M. Zervos, Dr. Dorothée André, Dr. J. Blancou, Dr. J. Paakkanen, Dr. J. Perez-Lanzac, Professor P. Peters, Dr. Barbara Röstel, Dr. M. Rutter ***Observers***: Dr. P.P. Bosman, Dr. S. Brown, Dr. R. Bywater, Dr. R. Carnevale, Dr. R. Froyman, Dr. T. Gomez, Dr. S. Lens, Dr. M. Lütoz, Dr. Margaret Miller, Dr. K. Morita, Dr. S. Pitlik, Dr. Andrea Sanwidi, Dr. T. Shyrock, Dr. P. Sundberg, Dr. T. Tselentis, Dr. C. Verschueren, Dr. L. Vogel ***WHO Secretariat***: Dr. R. Crom, Mr. G. Hartl, Dr. Sudarshan Kumari, Dr. N. Moran, Dr. A. Reilly, Dr. K. Stöhr, Dr. Rosamund Williams.

Type of publication: Meeting Report

Pages: 24

Intended audience: Global; policy-makers, agricultural industry

Study timeframe: The meeting was held from the 13th to the 17th of October, 1997.

Study process: During the four weeks prior to the meeting, 522 experts received 39 presentations prepared by those who would be participating in or observing the meeting. The experts discussed and commented on the material. Presentations were given and discussed during the first three days of the meeting. On the last two days, working groups drafted reports on medical impacts of antimicrobial use in livestock production, surveillance and risk management. The reports were discussed and adopted during the meeting's final session.

Type of organization: International, non-governmental, public health agency

Languages (published in): English

Key contact

Ordering Information: Communicable Disease Surveillance and Response Documents, World Health Organization, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4198, attention CSR Documents; email: csr@who.ch, attention Documents.

Available on the web at: http://www.who.int/emc-documents/zoonoses/whoemczoo974c.html

(*10*) America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests

Organization: Institute of Medicine

Year published: 1997

Selected key findings

- The United States lacks a coordinated, national plan for conducting basic health research and development and applying it towards the improvement of global health.
- Prevention is the most cost-effective approach to infectious disease, with millions of dollars saved globally each year once a major disease is eradicated.

Key recommendations

"The USA government should:

- act to facilitate the development of an effective global network for surveillance of infectious diseases, using the full potential of the information and communications revolution and fostering the capacity of developing countries in both biomedical surveillance and communications;
- further develop and extend the network to pro-

vide an early warning system for possible biological or chemical attacks;
- take an active role in global efforts to share information between countries on the most effective means of financing and delivering health care in order to maximize efficiency and equity;
- increase its investment in research and development in biomedical science related to major global health problems through expanded partnerships and cost-sharing with other governments and international donors;
- continue federal support for the education and training of health researchers and practitioners from other countries as an international public good toward health leadership that benefits both our own nation and others;
- form an Interagency Task Force on Global Health within the government to anticipate and address global health needs and to take advantage of opportunities in a coordinated and strategic fashion."

Implementation suggestions

The Task Force designates the USA Department of Health and Human Services as the organization most capable of carrying out the recommendations in the report, including setting of priorities and coordinating the efforts of other health agencies around the world.

Greater financial support of the United Nations by the United States would help to implement more effective strategies for achieving better global health, and give the USA more leverage to enact the kinds of global policies that it considers to be necessary.

Conclusions/Executive Summary

"For the United States to engage successfully in global health, coordination among the multiple USA agencies with statutory responsibilities in the area will be needed, as well as the formation of partnerships with the USA industrial and academic sectors and nongovernmental organizations, other nations, and international organizations. Without active USA engagement and coordination, in concert with the complementary efforts of other nations, the struggle to ensure health around the globe threatens to fragment or falter, with the likely outcome that our own national health, economic viability, and security will suffer. This report outlines the compelling case for America's active engagement in global health and offers recommendations on how this may best be achieved."

Authors: Barry R. Bloom, Harvey V. Fineberg, Jacquelyn Campbell, Richard G. A. Feachem, Julio Frenk, Dean Jamison, Eileen T. Kennedy, Arthur Kleinman, William E. Paul, Allan Rosenfield, Patricia L. Rosenfield, Thomas J. Ryan, Susan C. M. Scrimshaw, June E. Osborn, John H. Bryant, William H. Foege, David P. Rall

Type of publication: Report

Pages: 62

Intended audience: United States; policy-makers

Study timeframe: The report considers information from 1985 to 1997.

Study process: Committee members conducted a workshop in November of 1995, and solicited input from national and international public health and government organizations.

Type of organization: Non-profit public health and advisory organization; advisor to Federal Government on issues of public health

Languages (published in): English

Key contact

Ordering information: National Academy Press, www.nap.edu
Content: Barry R. Bloom and Harvey V. Fineberg, Co-Chairs of the IOM Board on International Health

(*11*) New and Re-emerging Infectious Diseases: A Global Crisis and Immediate Threat to the Nation's Health; the Role of Research

Organization: American Society for Microbiology

Year published: 1997

Selected key findings

- Antibiotic-resistant bacterial infections in the United States cost approximately $4 billion in medical costs annually.
- Infectious diseases were the third leading cause of death in the United States in 1996.
- From 1980 to 1996, the death rate from infectious diseases in the United States has increased more than 50 percent.

Key recommendations

- Encourage investment in research in the fields of microbiology, immunology and infectious diseases.

- Focus research on molecular genetics and the biochemistry of bacteria, viruses, and fungi.

Implementation suggestions

Implementation of recommendations can be achieved by increasing funding to USA government agencies, including the National Institute of Allergy and Infectious Diseases and the National Institutes of Health.

Conclusions/Executive Summary

"Increased research funding is critical to address the current threats from new and re-emerging infectious diseases through the development of better diagnostic tests, new drugs, and vaccines. In addition, increased funding would provide new opportunities for making major advances to define the potential role of infectious agents in chronic diseases, such as cancer, that currently have no known causes."

Authors: Not specified

Type of publication: Booklet

Pages: 13

Intended audience: United States; scientists, policymakers

Study timeframe: Report considers scientific literature from 1992 to 1996

Study process: Analysis of documents on emerging infectious diseases

Type of organization: Non-profit, Life Sciences Society

Languages (published in): English

Key contact

American Society for Microbiology, Public Affairs Office, 202-942-9209

Available on the web at: http://www.asmusa.org/pasrc/pdfs/newandre.pdf

(*12*) Resistant Organisms: Global Impact on Continuum of Care

Organization: Royal Society of Medicine

Year published: 1997

Selected key findings

- Attitudes of patients and physicians are key factors that contribute to the inappropriate prescribing and use of antibiotics (Levy; Plotnick).
- Resistance is a local problem, dependent on patterns of use within a hospital and on each hospital's infection control programs (Levy).
- Resistance is an ecological problem; overuse of antibiotics has removed susceptible organisms and seen their replacement with resistant ones. It is possible to reverse the problem through the reduction of antibiotic use (Levy).
- Factors such as sterility and type of instruments, wound preparation, wound closure, etc. contribute to the likelihood of infection during surgical procedures (Henderson).

Key recommendations

- More accurate diagnosis before prescribing any medication (Levy; Plotnick).
- Resuscitate efforts to identify and monitor the emergence and spread of infectious diseases (Plotnick).
- Evaluate different methods of antibiotic use, including shorter or cyclical courses.
- Improve staff to patient ratios in hospitals, to allow for better diagnosis and prescribing (Lee).
- Modify prescribing practices to eliminate excessive antibiotic prophylaxis before surgery (Henderson).

Implementation suggestions

Rear Admiral Plotnick and Laura Lee both recommended strategies developed by the CDC (in cooperation with a variety of regional, national, and international public and private organizations) which act on issues of surveillance, research, prevention, control, and institutional management.

Conclusions/Executive Summary

The abatement of the problem of antibiotic resistance can only be achieved through cooperation of prescribers, patients, government, pharmaceutical and agricultural industries. Surveillance, infection control, and improved prescribing practices are all important components of any collaborative effort.

Authors: Jean Davis, Professor S. Michael Emmerson, David K. Henderson, MD (co-editor), Laura Lee, Stuart B. Levy, MD (co-editor), Rear Admiral Julia R. Plotnick

Type of publication: Conference proceedings

Pages: 70

Intended audience: United States, United Kingdom; health care providers

Study timeframe: Conference held September 27, 1996

Study process: Varies with each presentation

Type of organization: Independent professional organization

Languages (published in): English

Key contact

Ordering information: Royal Society of Medicine Press, Lmt., +44 (0) 20 7290 3945; email: kirsty.orriss@roysocmed.ac.uk

(*13*) Guidelines for the Prevention of Antimicrobial Resistance in Hospitals (SHEA Position Paper)

Organization: Society for Healthcare Epidemiology of America; Infectious Diseases Society of America

Year published: 1997

Selected key findings

- The authors contend that, contrary to many studies, antibiotic-resistant bacteria are not necessarily less virulent than their susceptible parents, and that even in cases where the second generation bacteria are less virulent, they are no less dangerous to vulnerable hospital populations.
- Making a definite connection between antimicrobial use and antimicrobial resistance in hospitals is often confounded by lack of consistency from hospital to hospital in defining resistance, methodologies used in susceptibility testing, and other variables.

Key recommendations

Recommendations for hospitals

- "Establish a system for monitoring bacterial resistance and antibiotic usage;
- Establish practice guidelines and other institutional policies to control the use of antibiotics, and respond to data from the monitoring system;
- Adopt the recommendations of the Centers for Disease Control and Prevention's (CDC) Guidelines for Isolation Precautions in Hospitals, as concerns the isolation of patients colonized or infected with resistant microorganisms."

Recommendations for prevention & reduction of antimicrobial resistance in hospitals

- "It is recommended that hospitals have a system for monitoring antimicrobial resistance of both community and nosocomial isolate on a monthly basis or at a frequency appropriate to the volume of isolates.
- It is recommended that hospitals monitor the relationship between antimicrobial use and resistance, and assign responsibility through practice guidelines or other institutional policies.
- It is recommended that hospitals apply Contact Precautions to specified patients known or suspected to be colonized or infected with epidemiologically important microorganisms that can be transmitted by direct or indirect contact."

Recommendations for future studies

- "It is recommended that research to define the mechanism of transfer of bacteria and their resistance determinants among patient populations and to determine methods to prevent emergence and transfer of resistance, including control of antibiotic usage, be supported with increases in targeted research funding.
- The development and testing of protocols for measuring the effect of a variety of antimicrobial usage controls is recommended for use in multiple hospitals to determine the most effective ways to prevent and reduce antimicrobial resistance in specific species to specific antimicrobials.
- It is recommended that educational methods, including those that are interactive and computer-based, be developed to improve the appropriateness of antimicrobial prescribing.
- The efficacy of various levels of infection control precautions should be documented by controlled trials.
- Controlled studies of behavior modification, including novel approaches, to permit the efficient application of recommended guidelines within hospitals are recommended.
- The efficacy of quality improvement approaches to control of resistance should be studied."

Implementation suggestions

Guidelines developed by the CDC and the National Committee for Clinical Laboratory Standards are suggested as ways for microbiologists and physicians to monitor antibiotic prescribing and use.

Conclusions/Executive Summary

"There is convincing evidence that we share a

single ecosystem globally in terms of resistance. The selection of resistance in one organism in one part of the world, even within an animal population, may have long-term, important implications for human health globally. Therefore, management of the problem of antimicrobial resistance within hospitals is a community responsibility, both within and outside of the hospital…Good stewardship of antibiotic usage combined with strong infection control will be required. To achieve this, all levels of personnel within the hospital must be involved, from top administration down to individuals performing services and providing patient care."

Authors: David M. Shlaes, MD, PhD; Dale N. Gerding, MD; Joseph F. John, Jr., MD; William A. Craig, MD; Donald L. Bornstein, MD; Robert A. Duncan, MD; Mark R. Eckman, MD; William E. Farrer, MD; William H. Greene, MD; Victor Lorian, MD; Stuart Levy, MD; John E. McGowan, Jr., MD; Sindy M. Paul, MD; Joel Ruskin, MD; Fred C. Tenover, MD; Chatrchai Watanakunakorn, MD

Type of publication: Position paper

Pages: 17

Intended audience: United States; scientific community

Study timeframe: The authors reviewed scientific literature dating from 1977 to 1996.

Study process: The authors analyzed existing scientific literature on antibiotic resistance mechanisms and spread.

Type of organization: Non-profit public health organization

Languages (published in): English

Key contact

Reprint requests: David M. Shlaes, MD, Wyeth-Ayerst Research, 401 N. Middletown Rd., Pearl River, NY 10965

(*14*) Symposium on Antibiotic Resistance: Origins, Evolution, Selection and Spread

Organization: Ciba Foundation

Year published: 1997

Selected key findings

- Antibiotic resistance is an ecological problem, in that the balance between susceptible and resistant bacteria has been disrupted.
- In order to determine the extent of antibiotic resistance in hospitals, it is necessary to take into account each hospital's pattern of antibiotic use.
- A report on the monitoring of antibiotic use in a hospital in Greece proved the efficacy of a rigorous program of prescription control. The combination of prescription monitoring, improved hygiene, educational programs and the limitation of certain antibiotics resulted in (for example) ceftazidime-resistant *P. aeruginosa* levels decreasing from 45% to 8% after three years. (Giamerellou & Antoniadou)

Key recommendations

- Increase development of novel antibiotic agents.
- Increase emphasis on infection control and hygienic practices.
- Enact multidisciplinary approaches to reducing hospital resistance rates, including cooperation between pharmacies and diagnostic laboratories, and between infectious disease physicians and clinicians.

Implementation suggestions

Not given

Conclusions/Executive Summary

"This meeting has put these issues [antibiotic use and mechanisms of resistance] aside in order to focus on a larger view of the problem, and to define the potential for return to a healthier state vis-à-vis susceptible flora. There is a need for new guidelines on more rational utilization of future novel antimicrobials within the context of ecology. There is also a cost to discover and develop these. Thus, we shall want to keep them from succumbing to a similar fate, i.e., encountering resistance. In this effort, consumers can join physicians and the pharmaceutical industry in maintaining this efficacy. Whether antibiotics are available over-the-counter in developing countries or demanded and stockpiled in the developed countries, they are too often in the hands of consumers who use them incorrectly."

Authors: S.B. Levy, J.E. Davies, P. Huovinen, H. Seppälä, J. Kataja, T. Klaukka, R. Gaynes, D. Monnet, W. Witte, H. Giamarellou, A. Antoniadou, F. Baquero, M.C. Negri, M.I. Morosini, J. Blazquez, M. Lipsitch, B.R. Levin, R.E. Lenski, K. Bush, R.A. Skurray, N. Firth, R.M. Hall, M.C. Roberts, M.L. Cohen

Type of publication: Report

Pages: 250

Intended audience: Global; scientists

Study timeframe: 3-day symposium in July of 1996.

Study process: Participating scientists discussed a variety of pre-submitted articles on antibiotic resistance.

Type of organization: International scientific and educational non-profit

Languages (published in): English

Key contact

Ordering: John Wiley & Sons, Ltd., cs-books@wiley.co.uk; telephone: +44 1243 779777
Content: Stuart B. Levy, MD, Symposium Chairman 1996

(*15*) The Current Status of Antimicrobial Resistance Surveillance in Europe: Report of a WHO Workshop held in Collaboration with the Italian Associazione Culturale Microbiologia Medica

Organization: World Health Organization, Division of Emerging and Other Communicable Diseases Surveillance and Control

Year published: 1998

Selected key findings

- There is not enough communication between antimicrobial resistance surveillance networks and the decision makers at the regional and national levels in Europe.
- Quality assurance standards that evaluate the validity of surveillance data vary throughout Europe, making it difficult to make accurate comparisons.
- A coordinated effort by the various European surveillance systems is necessary to effectively address the emergence and spread of antimicrobial resistance.

Key recommendations

- "The communication chain between antimicrobial resistance surveillance networks and national and regional decision makers must be strengthened and used."
- "There is a need to harmonize quality assurance standards throughout Europe."
- "Adequate support for microbiology and epidemiology training programs, for laboratory infrastructure, and for data analysis and communication, is required."
- "Further discussions are necessary, to develop collaboration between existing antimicrobial resistance surveillance programmes."

Implementation suggestions

According to participants' responses to a questionnaire circulated before the workshop, implementation of any recommendations or improvements depends on adequate funding, standardized methodologies of susceptibility testing, improved government support, a greater number of trained professionals to carry out surveillance efforts, and increased awareness of the resistance problem by health care providers.

Conclusions/Executive Summary

"The emergence and spread of antimicrobial resistance is a significant problem to all people in all countries, both developed and developing. It impacts both patients with infections and clinicians facing growing limitations on their efficacious use of antimicrobials. It influences a health care system's ability to implement rational drug use policies and efficiently allocate resources. Because the emergence of antimicrobial resistance is a global problem that affects us all, national and international efforts are needed to address the problem. Information and experience, must be shared so that all can learn and benefit."

"At present, many groups are attempting to harmonize local, national and international antimicrobial resistance surveillance methodologies. These attempts are not necessarily coordinated with one another, however, and there is a growing perception, reinforced by discussions held during this workshop, that a positive role could be played by a pan-European coordinating group. Such a group could reflect the various national and European-wide interests in antimicrobial resistance surveillance. It could be initiated as a study group of the European Society of Clinical Microbiology and Infectious Diseases and focus on actively promoting the performance of good-quality local studies which generate internationally comparable data. Such data could, in turn, be used to facilitate the accurate interpretation of results between studies and generate information on the extent of antimicrobial resistance in Europe. An essential component of any group's success, of course, will be adequate funding." (I. Phillips)

Authors: ***Participants***: Professor Jacques F. Acar, Professor Fernando Baquero, Dr. Andre Bryskier, Dr. Otto

Cars, Dr. Giuseppe Cornaglia, Dr. Patrice Courvalin, Dr. Roberta Fontana, Dr. Herman Goossens, Dr. Marija Gubina, Dr. Waleria Hryniewicz, Dr. Pentti Huovinen, Dr. Vincent Jarlier, Dr. Mark E. Jones, Professor Smilja Kalenic, Professor Conor T. Keane, Dr. Marianne Konkoly, Dr. Karl G. Kristinsson, Professor Herminia de Lencastre, Dr. David Livermore, Professor Enrico Magliano, Dr. Boyka Markova, Dr. Anna Marton, Dr. Jolanta Miciuleviciene, Dr. Helmut Mittermayer, Dr. Kathrin Muelemann, Professor Carl Erik Nord, Professor Alvaro Pascual, Professor Ian Phillips, Professor Arne C. Rodloff, Professor Jirí Schindler, Dr. Ivonna Selga, Dr. Anatoly Shapiro, Dr. Thomas Lund Sørensen, Dr. Marc Sprenger, Dr. Martin Steinbakk, Professor Leonid Stratchounsky, Professor Marc Struelens, Dr. Alkiviadis C. Vatapoulos, Professor Jan Verhoef, Professor Richard Wise. ***WHO Secretariat***: Dr. Ana Estrela, Dr. Colette Roure, Dr. John Stelling, Dr. Rosamund Williams, Dr. Clara Witt.

Type of publication: Meeting report

Pages: 80

Intended audience: Europe; policy-makers, microbiologists, those who are responsible for surveillance networks

Study timeframe: The workshop was held on December 12, 1997.

Study process: The participants met to present and discuss the variety of antimicrobial resistance systems in operation throughout Europe, to highlight the features of successful programs, and to discuss how those features may be incorporated into other systems.

Type of organization: International, non-governmental, public health agency

Languages (published in): English

Key contact

Ordering Information: Communicable Disease Surveillance and Response Documents, World Health Organization, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4198, attention CSR Documents; email: csr@who.ch, attention Documents.

Available on the web at: http://www.who.int/emc-documents/antimicrobial_resistance/whoemcbac981c.html

(*16*) Papers presented at the International Conference on Emerging Infectious Diseases in Atlanta, GA, March 1998. Compiled in *Emerging Infectious Diseases* 4(3): 353–515

Organization: Centers for Disease Control and Prevention, National Center for Infectious Diseases

Year published: 1998

Selected key findings

- The National Institute of Allergy and Infectious Disease (NIAID) dedicates about 21% of its non-AIDS infectious disease budget to emerging infectious diseases. NIAID's total emerging diseases budget increased from $39.3 million in 1993 to a projected $85 million in 1999. (Fauci)
- Nosocomial infections were estimated to be responsible for 88,000 deaths and $4.5 billion in treatment costs in 1995. Approximately one-third of such diseases are preventable. (Weinstein)

Key recommendations

Surveillance

One author recommends "...dramatically strengthened local surveillance, including both laboratory and epidemiologic capacity; commitment on the part of local governments; and a strong collaborative international research and response system." (Broome)

Research

The NIH recommends expanding research on the ecologic and environmental aspects of disease emergence and transmission; expanding research on the microbial mechanics of disease emergence; supporting the development of vaccines and other preventive therapies, especially for diseases that are threatening to emerge or reemerge; and "strengthening the current USA research and training infrastructure for detection and responding to outbreaks of infectious diseases." (Fauci)

Nosocomial infections

Improve national surveillance of nosocomial infections that occur in the hospital and in home healthcare settings; improve the design of devices that are associated with nosocomial infections; institute aggressive antibiotic control programs, perhaps making them mandatory for hospitals that receive federal reimbursements; and develop new and microbiologic methods for detecting and investigating outbreaks of multidrug-resistant pathogens.

Implementation suggestions

- Continuation and strengthening of Field Epidemiology Training Programs that respond to reports of emerging infections. Use of the Internet and other communication technologies to gather and share surveillance information. (Broome)
- Continued collaboration between the public and private sectors. (Fauci)
- Hospital personnel would be responsible for implementing infection control policies, especially those concerning basic hygiene. (Weinstein)

Conclusions

- "We are better able in 1998 to address the threats of emerging infections, but we are by no means fully prepared. We must have the capacity to identify new or reemerging threats and to respond successfully. We need to be creative and efficient in identifying necessary resources… Eradication activities also contribute to health capacity development, and the laboratory and surveillance capacities created for polio eradication should also be useful in detection of and response to emerging infectious diseases. Many other creative approaches and collaborations are needed for an effective global response to whatever our microbial adversaries may produce." (Broome)
- "The importance of basic research to the control of emerging and reemerging diseases cannot be overemphasized. Emerging diseases research encompasses many disciplines, and research advances that fall under the rubric of emerging diseases will be relevant not only to specific diseases being studied but to a broad range of disciplines such as vaccinology, immunology, and drug development." (Fauci)
- "Several enduring truths characterize the field of infection control. Hospitals will become more like ICUs, and more routine care will be delivered on an outpatient basis. Given the choice of improving technology or improving human behavior, technology is the better choice. The major advances in overall control of infectious diseases have resulted from immunization and improved hygiene, particularly hand washing. We must work with hospital personnel on better implementation of existing infection control technologies so that we will not need to rely solely on technologic advances." (Weinstein)

Authors: Stephen A. Morse, Donna E. Shalala, Claire Broome, James Hughes, David Heymann, Guenael Rodier, Joshua Lederberg, D. Peter Drotman, Anthony Fauci, Karen Hein, David Relman, Sir John Pattison, Bradley Perkins, Thomas Nchinda, Alison Mawle, Martin Cetron, Jay Keystone, David Shilm, Robert Steffen, Kenneth Castro, Mary E. Chamberland, Jay Epstein, Roger Y.Dodd, David Persing, Robert G.Will, Alfred DeMaria, Jr., Jean C. Emmanuel, Beatrice Pierce, Rima Khabbaz, William Foege, Donald Hopkins, Robert Weinstein, Jonathan Kaplan, Gary Roselle, Kent Sepkowitz, Janet McNicholl, Susan Cookson, Ronald Waldman, Brian Gushulak, Douglas MacPherson, Frederick Burkle, Jr., Christophe Paquet, Erich Kliewer, Patricia Walker, Frederick Murphy, Robert G. Webster, Duane Gubler, R Colwell, P. Epstein, M. Hall, P. Reiter, J. Shukla, W. Sprigg, E. Takafuji, J. Trtanj, James Childs, Robert E. Shope, Durland Fish, Francois X. Meslin, Clarence J. Peters, Karl Johnson, Emilio Debess, David Dennis, Suzanne Jenkins, Robert Tauxe, Samantha Yang, Deborah Deppe, James LeDuc, Robert Pinner, Bradford Kay, Ralph J. Timperi, Stephen S. Morse, David Forslund, Julie J. McGowan, Tom OíBrien, Lela Folkers, Maria Teresa Cerqueira, Robert E. Quick, James Kanu, Gauden Galea, EliasAbrutyn, Ann Marie Kimball, Carrie Horwitch, Patrick OíCarroll, Sumarjati Arjoso, Chaiyos Kunanusont, Ya-Shin Lin, Clifford Meyer, Laura Schubert, Phillip Dunham, David Bell, Gail Cassell, D. A. Henderson, Joseph McDade, David Franz, Stanley Falkow, George Alleyne, May C. Chu, Alexandra Levitt, Karl Western

Type of publication: Peer-reviewed journal

Pages: 164

Intended audience: United States; policy-makers, government agencies, hospital personnel

Study timeframe: Varies

Study process: Varies

Type of organization: Federal Government

Languages (published in): English

Key contact

Ordering information: EID Editor, CDC/NCID/MS C12, 1600 Clifton Road, NE, Atlanta, GA 30333

Available on the web at: http://www.cdc.gov/ncidod/eid/vol4no3/contents.htm

(17) Preventing Emerging Infectious Diseases: A Strategy for the 21st Century

Organization: Centers for Disease Control and Prevention, National Center for Infectious Diseases

Year published: 1998

Selected key findings

- New developments since 1994 that necessitated an update of *Preventing Emerging Infectious Diseases* include: new emerging threats; advanced scientific findings; new methods of discovering, tracking, and communicating outbreaks; changes in health care delivery; and increased public awareness and government response.
- Implementation of CDC guidelines on group B streptococcal disease helped to reduce its incidence by over 40% between 1993 and 1995 in the communities that followed the guidelines.
- A combination of improved practices in the food industry, surveillance, and public education decreased the incidence of invasive listeriosis by 44% between 1989 and 1993; the reduction was maintained through 1996, the last date cited in the report.

Key recommendations

Surveillance

- "Strengthen infectious disease surveillance and response;
- Improve methods for gathering and evaluating surveillance data;
- Ensure the use of surveillance data to improve public health practice and medical treatment;
- Strengthen global capacity to monitor and respond to emerging infectious diseases."

Applied research

- "Develop, evaluate, and disseminate tools for identifying and understanding emerging infectious diseases;
- Identify the behaviors, environments, and host factors that put people at increased risk for infectious diseases and their sequelae.
- Enhance epidemiologic and laboratory capacity;
- Improve CDC's ability to communicate electronically with state and local health departments, USA quarantine stations, health care professionals, and others;
- Enhance the nation's capacity to respond to complex infectious disease threats in the United States and internationally, including outbreaks that may result from bioterrorism;
- Provide training opportunities in infectious disease epidemiology and diagnosis in the United States and throughout the world."

Prevention and control

- "Implement, support, and evaluate programs for the prevention and control of emerging infectious diseases;
- Develop, evaluate, and promote strategies to help health care providers and other individuals change behaviors that facilitate disease transmission;
- Support and promote disease control and prevention internationally."

Implementation suggestions

Surveillance

- "Extend the ELC [Epidemiology and Laboratory Capacity] program to all state, territorial, and large local health departments;
- Strengthen the EIP [Emerging Infections Program] network by increasing its demographic and geographic representativeness and enhancing its laboratory and epidemiologic capacity;
- Use the existing provider-based sentinel networks to monitor syndromes and diseases, and establish at least one additional network;
- Integrate public health information and surveillance systems;
- Use surveillance data to analyze questions of public health importance;
- Facilitate access to surveillance data that can be used in clinical practice;
- Assist global surveillance and response efforts through increased support of CDC-based WHO Collaborating Centers;
- Help monitor conditions that favor the emergence or spread of infectious diseases."

Applied research

- "Develop, evaluate, and disseminate testing methods for infectious agents;
- Identify factors that influence the risk of developing infectious diseases;
- Assess the role of infectious agents in causing or exacerbating chronic diseases and syndromes for which the causative agents are unknown;
- In collaboration with other organizations, support research to develop and evaluate new antimicrobial drugs and prophylactic agents, as well as methods to control disease vectors and reservoirs;
- Support research to develop new methods of disinfection;

- Support social science and behavioral research to develop better prevention programs."

Infrastructure and training

- "Define core public health functions and capacities needed for monitoring the spread of microbes and responding to infectious disease outbreaks, and provide personnel in state and large local health departments with essential equipment and training;
- Strengthen CDC's capacity to serve as the national and international reference laboratory for diagnosis of infectious diseases and for drug-resistance testing;
- Promote the development and production of diagnostic and reference reagents for use by public health laboratories;
- Work with state health departments to standardize new diagnostic techniques and facilitate their use throughout the United States;
- Assist other USA agencies, international organizations, and other nations in building global capacity for disease surveillance and response;
- Enhance national surge capacity for responding to outbreaks of unusual size, duration, and severity;
- Ensure the continued training of epidemiologists in problems related to emerging infectious diseases;
- Increase the number of laboratory scientists trained in infectious diseases through the Emerging Infectious Diseases (EID) Laboratory Fellowship Program and add a track for international students;
- Expand CDC's efforts to train counterparts in developing countries in the use of epidemiologic and laboratory methods for combating emerging infectious diseases."

Prevention and control

- "Expand existing community-based programs;
- Develop and support new community-based demonstration programs in the target areas.
- Evaluate the impact and cost-effectiveness of alternative approaches to reducing infectious diseases;
- Increase the use of vaccines to prevent and control emerging infectious diseases;
- Work with health care providers, hospitals, managed care organizations, and others to improve patient outcomes related to infectious diseases;
- Work with private industry, government agencies, and others to develop systems that promote prompt identification of infectious disease problems and rapid implementation of control measures;
- Develop, implement, and evaluate disease prevention guidelines that can be used by the public, health care providers, and health care systems;
- Work with foreign governments, WHO, the USA-European Union Task Force on Communicable Disease, other international partners, and the CISET Emerging Infectious Disease Task Force to promote global programs for the prevention and control of infectious diseases;
- Provide technical assistance and transfer cost-effective technologies to other countries, using governmental and nongovernmental channels;
- Participate in bilateral and multilateral initiatives to improve global infectious disease prevention and control;
- Work with WHO and other partners to complete the revision of International Health Regulations;
- Work with developing countries to sustain health care improvements and surveillance efforts after outbreaks."

Conclusions/Executive Summary

"Achievement of the objectives described in this plan will improve our ability to understand, detect, control, and prevent infectious diseases. The outcome will be a stronger, more flexible USA public health infrastructure well-prepared to respond to well-known disease problems and to address the unexpected, whether it is an influenza pandemic, a disease caused by an unknown organism, or a bioterrorist attack."

Authors: Sue Binder, M.D., Alexandra M. Levitt, Ph.D., Judith R. Aguilar, David M. Bell, M.D., Martin S. Cetron, M.D., Mary E. Chamberland, M.D., Mark L. Eberhard, Ph.D., Duane J. Gubler, Sc.D., Meredith A. Hickson, M.P.H., Jonathan E. Kaplan, M.D., Rima F. Khabbaz, M.D., James W. LeDuc, M.D., Susan A. Maloney, M.D., William J. Martin, Ph.D., Alison C. Mawle, Ph.D., Patrick McConnon, M.P.H., Martin I. Meltzer, Ph.D., Siobhan O'Connor, M.D., Alan J. Parkinson, Ph.D., Anne Schuchat, M.D., Steven L. Solomon, M.D., Robert V. Tauxe, M.D., Fred C. Tenover, Ph.D., Theodore F. Tsai, M.D., Robert B. Wainwright, M.D., Helene D. Gayle, M.D., Walter A. Orenstein, M.D., Barbara R. Holloway, M.P.H., James S. Marks, M.D., M.P.H., Edward J. Sondik, Ph.D., Linda Rosenstock, M.D., M.P.H., Walter W. Williams, M.D., M.P.H., Stephen B. Blount, M.D., M.P.H., Karen K. Steinberg, Ph.D., Edward L. Baker, M.D., M.P.H.

Type of publication: Report

Pages: 75

Intended audience: United States; physicians and other health care providers; policy-makers

Study timeframe: The Steering Committee reviewed scientific literature from 1982 to 1998, with the bulk of material from the mid- to late-1990s.

Study process: The Committee evaluated and updated CDC's plan from 1994, *Preventing Emerging Infectious Diseases*.

Type of organization: Federal Government

Languages (published in): English

Key contact
Ordering information: Office of Health Communication, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Mailstop C-14, 1600 Clifton Road, Atlanta, GA 30333. Available online at http://www.cdc.gov/ncidod/emergplan

(*18*) Human Health Safety Criteria. Guideline 18.

Organization: Food and Drug Administration, Center for Veterinary Medicine; USA Department of Health and Human Services

Year published: Updated on July 28, 2000.

Selected key findings
No findings are presented.

Key recommendations
Antibacterial drugs that are used in the treatment of animals and have not been found to transfer resistance to antibacterial drugs that are used in human clinical medicine must undertake the following studies:

- Controlled studies to determine whether or not the antibacterial drug, given at subtherapeutic levels, causes "an increase in the relative quantity or prevalence of *Salmonella* in animals or the duration of shedding of these *Salmonella* as compared to controls; and/or an increase in the proportion of resistant *Salmonella*, the degree of resistance, and the resistance spectrum;"
- Controlled studies to determine whether or not antibacterial drugs administered to animals increase the number of coliforms that are resistant to antibacterial drugs that are used in human clinical medicine and may transfer that resistance to human intestinal tracts;
- Controlled studies "to determine whether the consumption of food produced by animals receiving antibacterial drugs will result in: a. An increase in the intestinal flora of the prevalence of pathogenic bacteria; b. An increase in the degree and spectrum of resistance of the intestinal flora to drugs used in human clinical medicine."

The guideline also recommends the conducting of a literature survey, "to determine the incidence of reports of hypersensitivity resulting from antibacterial drugs in food."

Implementation suggestions
The criteria are guidelines for implementing the policies and complying with the regulations mandated by Congress and FDA.

Conclusions/Executive Summary
"The...criteria must be satisfied in order to establish that the use of low and/or intermediate levels of an antibacterial drug in animal feeds is a safe practice from the aspect of human health. In general terms, such drug use should not result in: (1) a significant adverse effect in the relative quantity, prevalence and shedding of *Salmonella* organisms in animals, (2) a significant increase of *Salmonella* organisms resistant to drugs used in human clinical medicine in the animal, (3) a significant increase in the resistance of coliforms to antibacterial drugs used in human clinical medicine provided this resistance is transferable to bacteria in man, (4) enhancement of pathogenicity of bacteria, or (5) adverse effect to humans due to ingestion of residues of the antibacterial drug, metabolites, or degradation products."

Authors: Not identified

Type of publication: One of 98 guidance documents created by the Center for Veterinary Medicine to clarify the laws made by Congress or the Food and Drug Administration that affect regulated industries. They include guidance on testing procedures, manufacturing processes and scientific protocols.

Pages: 3

Intended audience: United States; regulated animal health/food production industries, FDA employees responsible for enforcement

Study timeframe: N/A

Study process: N/A

Type of organization: Federal Government

Languages (published in): English

Key contact

Ordering information: Food and Drug Administration, Center for Veterinary Medicine, Communications Staff, 7500 Standish Place, HFV-12, Rockville, Maryland 20855; Telephone: (301) 594-1755

Available on the web at: http://www.fda.gov/cvm/fda/TOCs/guideline18.html

Comments and questions to: Policy and Regulations, Team (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD, 20855

(*19*) The Path of Least Resistance

Organization: United Kingdom Department of Health, Standing Medical Advisory Committee, Sub-Group on Antimicrobial Resistance

Year published: 1998

Selected key findings

- Although only 20% of prescriptions of antimicrobials for human use in the UK are for hospital use, they are the site of the greatest resistance problems.
- Of the 50 million antibiotic prescriptions written each year in the UK, about 50% are for respiratory tract infections; about 15% are for urinary tract infections.
- Incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) increased dramatically between 1989 and 1997: 1.5% of the organisms were resistant in 1989, compared to 31.7% in 1997.
- There is every reason to anticipate the further spread of resistance to currently susceptible organisms. The most likely of these would be vancomycin-intermediate MRSA, quinolone resistant *E. coli*, and the resistance of gram-negative bacteria to carbapenems. The emergence of penicillin resistant *Neisseria meningitidis* and *Streptococcus pyogenes* are also possible.
- The pressures of time and volume of patients in hospital emergency wards often increases the likelihood of inappropriate antibiotic prescriptions.
- A lack of clinical trials on antibiotic use in long-term care facilities, combined with the vulnerable nature of the population and inadequate diagnostic capabilities, have hampered efforts to control antibiotic resistance in such facilities in the UK and the USA.

Key recommendations

The Sub-Group recommends:

- The implementation of a two-tiered national campaign to improve community prescribing of antibiotics: a Campaign on Antibiotic Treatment for general practitioners, and a National Advice to the Public campaign for patients and consumers;
- "That further support for appropriate prescribing in primary care be provided by developing and promulgating evidence-based national guidelines for the management of certain infections, under the aegis of the National Institute for Clinical Excellence [and] that such national guidelines are adapted for local use during the development of Health Improvement Plans;
- That [guidelines] should be integrated within computerized decision-support systems as soon as possible. These guidelines should also be promulgated widely through the medical literature;
- That studies be undertaken in selected hospitals to develop and test one or more prototype decision-supported systems. To be fully effective, these computer-based advisory systems should include information from local antimicrobial sensitivity profiles. These in turn should feed into regional and national surveillance databases;
- That local prescribing information should, whenever possible, be harmonized with that in the British National Formulary (BNF) and other formularies. Guidelines and formularies should also take account of the proposed national evidence-based guidelines to be produced under the aegis of the National Institute of Clinical Excellence all such local guidelines should include, as a minimum, certain standard items of information on the drug, dosage and duration of therapy;"
- That greater emphasis be placed on the teaching of guidelines for antimicrobial prescribing to medical, dental, pharmaceutical, nursing and veterinary students;
- "That a strategic system for resistance surveillance of antimicrobial resistance should be developed as swiftly as possible, and that this should cover the whole of the UK;
- That research into antimicrobial resistance should become a high priority for all funding bodies concerned with health care and biomedical research;"
- That existing guidelines for hospital infection control be more closely adhered to, and that

guidelines for infection control in the community be developed;
- "That the use of antibiotics in animals should be guided by the same principles as those for prescribing in humans—namely, they should be used only for those clinical conditions where their use is likely to provide a genuine health benefit;
- That alternative means of animal husbandry be developed so that the use of antibiotics as growth promoters can be discontinued;
- That consideration be given by the appropriate bodies to finding ways through pricing and other mechanisms of ensuring that investment in the development of new antibiotics remains commercially viable for the industry;
- That industry should be encouraged to undertake studies of optimum prescribing regimens for new antimicrobial agents, for each indication and in adults and children as appropriate;
- That every effort is made by the Government to raise the profile of antimicrobial resistance as a major public halt issue meriting priority action from all Member States of the European Union."

Implementation suggestions

The committee recommends the establishment of a National Steering Group to institute the first phase of the national strategy to counter the development of antibiotic resistance. The NSG's mandate is to form sub-groups consisting of experts who can focus on particular aspects of the problem, and then to report to the Chief Medical Officer within a year. The CMO in turn may request that the Standing Medical Advisory Committee reconvene the Antimicrobial Resistance Sub-Group in order to develop the strategy's next phase.

Conclusions/Executive Summary

"The recommendations in this Report are directed towards ensuring that best practice in antimicrobial prescribing becomes routine practice. This will require a willingness, on the part of health care professionals and the public alike, to treat antimicrobial agents as a valuable and non-renewable resource, to be treasured and protected in their own, and everyone else's interest."

Authors: ***Sub-Group Members***: Dr. Diana Walford, A. Close, Dr. A. Dearmun, Professor T. Duckworth, A. Ewing, Dr. J. Gilley, Dr. R. Horne, Professor A. Johnson, Professor C. Peckham, Dr. S. Willatts, Dr. G. Youngs, Dr. A.M. Johnston, Professor P. Littlejohns, C. Murphy, Dr. G. Patou, Dr. M. Powell, Dr. P. Wilkie, Professor R. Wise, Dr. P. Clappison, I. Cooper, Professor B.I. Duerden, R. Fenner, Dr. J. Leese, Dr. K. Ridge, Dr. W. Smith, M. Hart, Dr. D.M. Livermore, Dr. J.R. Weinberg

Type of publication: Report

Pages: 152

Intended audience: Primarily United Kingdom, but also implications for global audience; policy-makers, prescribers, consumers and patients

Study timeframe: The Sub-Group reviewed literature dating from 1969 to 1997, with a few references from the 1930s and 40s.

Study process: Review of case-studies, review of the basis and impact of resistance, commission of an independent review of evidence

Type of organization: Government

Languages (published in): English

Key contact: Available on the web at http://www.doh.gov.uk/smac1.htm

and from: Publications Unit, PHLS, Headquarters Office, 61 Colindale Avenue, London NW9 5DF; tel: 0181 200 1295

(*20*) Antimicrobial Resistance: A special edition of the British Medical Journal

Organization: British Medical Journal

Year published: 1998

Selected key findings

- Butler, et al., assessed the attitudes of physicians and patients in South Wales when prescribing or withholding antibiotics for sore throats. Patient expectations for antibiotics were found to be a compelling factor for prescription, even though the drugs are largely ineffective for the condition.
- Ferranti, et al., demonstrated that amoxycillin and folate inhibitors are just as effective as newer, more expensive broad-spectrum antibiotics in the treatment of uncomplicated acute sinusitis.

Key recommendations

- Increase patient and prescriber education, surveillance, and research.
- For developing countries: improve prescription regulation, access to diagnostic tools, surveillance, and education of the public, doctors and veterinarians.

- For international organizations: achieve international consensus standards for resistance surveillance, and create a global repository of information on resistance in key pathogens.
- For hospitals: encourage multidisciplinary cooperation in policy implementation, timely detection and reporting of antibiotic resistant strains, and aggressive control of the transmission of epidemic resistant bacteria.

Implementation suggestions

Developing countries: Not specified.

International organizations: Adoption of resolution on antimicrobial resistance that was presented at 1998 World Health Assembly.

Hospitals: Needs and resources vary from hospital to hospital; programs for infection control or the development of policies should be tailored with those differences in mind.

Conclusions/Executive Summary

"The increasing resistance problems of recent years are probably related to the use of increasingly broad spectrum agents (cephalosporins and fluoroquinolones) and crowding of the most vulnerable members of society in daycare centers and nursing homes. These problems are compounded by the worldwide phenomena of pressure on health care systems for greater efficiency, with higher bed occupancies and stretched nursing and medical care. Added to this are pressures to allow over-the-counter use of antibiotics in western countries so as to reduce health care costs. To effect change much will be required by the medical profession, politicians, the pharmaceutical industry, and not least patients."

Authors: Richard Wise, Tony Hart, Otto Cars, Reinen Helmuth, Pentti Huovinen, Q. A. McKellar, David M. Livermore, Alasdair P. Macgowan, Martin C. J. Wale, Stef L. A. M. Bronzwaer, Richard Coker, Bjorn-Erik Kristiansen, Yngvar Tveten, Andrew Jenkins, David Wilkinson, S. B. Squire, Paul Garner, Alan P. Johnson, Marina Warner, Neil Woodford, David C. E. Speller, Valerie Schwoebel, Benedicte Decludt, Anne-Claire de Benoist, Sylvie Haeghebaert, Gabriela Torrea, Veronique Vincent, Jacques Grosset, Sarah D. de Ferranti, John P. A. Ioannidis, Joseph Lau, William V. Anninger, Michael Barza, Christopher C. Butler, Stephen Rollnick, Roisin Pill, Frances Maggs-Rapport, Nigel Stott, John Turnidge, C. A. Hart, S. Kariuki, R. J. Williams, M. J. Ryan, Marc J. Struelens, Herman Goossens, Marc J. W. Sprenger, Peter M. Hawkey, Deenan Pillay, Maria Zambon, Claude Carbon, Richard P. Bax, A. M. Johnston, Christopher C. Butler, Edward A. Belongia, Benjamin Schwartz, Paul Farmer, Jim Yong Kim

Type of publication: Peer-reviewed journal

Pages: 90

Intended audience: Global; physicians, other health care providers

Study timeframe: varies

Study process: varies

Type of organization: Private company

Languages (published in): English, and local editions in Belgium, Brazil, China, Greece, Hungary, Latin America, Middle East, Netherlands, Pakistan, Poland, Portugal, Romania, Scandinavia, South Africa, South East Asia, Turkey and West Africa

Key contact

Editor, Richard Smith: editor@bmj.com;
Telephone: +44 (0) 171 387 4499

(21) Select Committee on Science and Technology: Resistance to Antibiotics and Other Antimicrobial Agents

Organization: House of Lords

Year published: 1998

Selected key findings

- Drug formularies and policies vary widely throughout the United Kingdom's hospital system; they are often created without input from junior staff, and new staff are not well informed of existing policies.
- Increased hospital infections may be linked to a decline in hygiene, staffing shortages, and a National Health Service policy of maximum occupancy for beds.
- Reporting of resistance to the Public Health Laboratory Service is voluntary and informal. The PHLS favors mandatory reporting of certain resistances and of any unusual or unexpected resistance markers in any microorganisms.

Key recommendations

- "The Royal Colleges should increase the attention paid to antimicrobial therapy in their programs of postgraduate education and vocational training.
- Health authorities should step up their efforts in the areas of prescribing audits, feedback and

educational outreach (including communication skills).
- The pharmaceutical industry and grant-giving bodies should give priority to work on rapid affordable systems for diagnosis and susceptibility testing.
- The Medicines Control Agency should consider whether the drug licensing system could be used more effectively to encourage prudent use in the interest of public health.
- Antibiotic growth promoters, such as virginiamycin, which belong to classes of antimicrobial agent used (or proposed to be used) in man and are therefore most likely to contribute to resistance in human medicine, should be phased out, preferably by voluntary agreement between the professions and industries concerned, but by legislation if necessary.
- The UK National Health Service should set itself targets for controlling MRSA in hospitals, and publish its achievements. The NHS should also draw up national standards and guidelines for community infection control management."

Implementation suggestions

Responsibilities were delegated to various government agencies and departments of the United Kingdom.

Conclusions/Executive Summary

"This enquiry has been an alarming experience, which leaves us convinced that resistance to antibiotics and other anti-infective agents constitutes a major threat to public health and ought to be recognized as such more widely than it is at present. We commend the current trend towards local antibiotic formularies and evidence-based clinical guidelines, giving professionals agreed definitions of prudent practice in particular situations. But the issuing of documents is not enough to turn policy into practice; it must be followed through in professional education, and continuing professional development. We do not recommend that GPs should be required to establish antimicrobial susceptibility before prescribing. This, we believe, would at present be impracticable, and would overload diagnostic series which are already stretched. But improved access to microbiological testing clearly reduces uncertainty in prescribing. Potent agents important to human medicine, such as the fluoroquinolones, deserve extreme economy of use in veterinary practice. There is still much that needs to be done to increase understanding of the mechanisms of resistance and the action of antimicrobials and, in the clinical sphere, methods of using agents to best advantage."

Authors: ***Sub-Committee members***: Lord Dixon-Smith, Lord Gregson, Lord Jenkin of Roding, Baroness McFarlane of Llandaff, Baroness Masham of Ilton, Lord Perry of Walton, Baroness Platt of Writtle, Lord Porter of Luddenham, Lord Rea, Lord Soulsby of Swaffham Prior, Lord Walton of Detchant, Lord Winston; ***with Specialist Advisors*** Professor Harold Lambert and Professor Richard Wise

Type of publication: Report

Pages: 108

Intended audience: United Kingdom; policy-makers, general public

Study timeframe: July 1997 to March 1998

Study process: Sub-Committee members conducted interviews at the Headquarters of the Public Health Laboratory Service, King's College Hospital, and with individual experts in the United States and United Kingdom. Members also gathered evidence from the agricultural and pharmaceutical industries, international and regional health organizations, and professional medical and scientific societies.

Type of organization: Government

Languages (published in): English

Key contact

The Publications Centre: PO Box 276, London SW8 5Dt; Tel. +44 0345 58 54 63; fax +44 0170 873 8200; Web site: http://www.hmso.gov.uk/

(22) Antimicrobial Resistance: Issues and Options. Workshop Report from the Forum on Emerging Infections

Organization: Institute of Medicine

Year published: 1998

Selected key findings

- The global effort to control antibiotic resistance lacks adequate surveillance mechanisms and comprehensive databases.
- There is a lack of research on the greater impacts of antibiotic use in animals, including the transfer of resistance.
- There has been insufficient analysis of the reservoir of antimicrobial drug-resistant genes.

Key recommendations

Surveillance:

- "Funding, implementation, assumption, or assignment of leadership, and formation of partnerships for implementing the 1995 American Society of Microbiology's detailed recommendations for a comprehensive resistance surveillance program;
- Improving data gathering and analysis, perhaps through national systems that would continuously monitor antimicrobial usage in hospitals, community and farm environments;
- Including information about the effects of resistance on the outcome of infections in data collection systems;
- Selecting and strengthening the laboratories in a set of sentinel hospitals as bases for global assessment of the prevalence and transmission of the most critical antibiotic-resistant genes, including training laboratory personnel in sentinel hospitals in standardized methodologies;
- Designing categories and pathways for reducing data sets into comprehensive packages for use by clinicians and researchers;
- Expanding distribution of NCCLS Guidelines and perhaps increasing the frequency with which they are updated."

The use of antibiotics in food production

- "Collaborative access to data from veterinary reference laboratories;
- Systematic, collaborative development, by the United States Department of Agriculture, the American Veterinary Medical Association, the Food and Drug Administration and producer organizations, of strategies and educational materials toward expanding ecological understanding;
- Developing cost-benefit and cost-effectiveness models of different on-farm antibiotic usages to enhance the public health community's understanding of farmer perspectives."

Prolonging antibiotic effectiveness

- "Implementing a joint project involving all pertinent professional societies in developing unitary guidelines (including checklists for providers to use in clinical settings) for antimicrobial use, implementing their extensive dissemination, and, very importantly, updating them periodically based on annual data from longitudinal studies;
- Quantifying the risks of injudicious antimicrobial use and developing descriptive and predictive models of the differences that judicious use would make, to help in policy development, advocacy, and action;
- Designing and implementing research on clinical outcomes from shorter courses of therapy and different dosing regimens, as the basis for updating practice guidelines and revising labeling."

Developing new products

- "Conduct studies of gene flow in order to understand the diversity and prevalence of resistant gene families and to discern the origins of resistant genes and how they spread from one organism to another."

Legal and regulatory approaches

- "Exploring whether increased resistance and rapid diminution of effectiveness of existing antibiotics might justify awarding greater authority to the CDC to monitor and enforce legal duties regarding resistance, and consideration of the means by which this might be accomplished;
- Developing alternative ways to define efficacy-for example, surrogate markers, *in vitro* technologies, and animal models-to address the lack of well-defined populations for clinical trials."

Implementation suggestions

Existing projects of various government agencies and departments of the United States are cited as foundations for implementing the above recommendations, including: a surveillance project being conducted by CDC, USDA and FDA; the USDA's reports on food safety and antibiotic resistance; and the EPA's considerations of the use of antibiotic pesticides. The food-production industry is also cited as a potential source of funding, research, and the development of guidelines for prudent antibiotic use in food-producing animals.

Conclusions/Executive Summary

"The evidence and opinions presented at this workshop suggest…that the transition from a historically generous armamentarium to one at least temporarily much less lavish could be mitigated by wiser policies, both to conserve what remains and to plan for what is to come; policies for the most cost-effective use of antibiotics; evidence-based regulation, with transparent balancing of risks and benefits; and as already exemplified in genome projects, social investment in the underlying science needed to develop new antimicrobial agents. Also, because antimicrobial drug resistance is increasingly known to be a global problem, it can be

addressed only with international cooperation, at a minimum in the acquisition and sharing of information. Whatever frictions might ensue from shaping and implementing such policies would be more than offset by the savings in medical and hospital costs and, most importantly, by the deaths and disability avoided."

Authors: ***Editors***: Polly F. Harrison and Joshua Lederberg. ***Forum Participants***: Joshua Lederberg, Vincent I. Ahonkhai, Steven J. Brickner, Gail H. Cassell, Gordon H. Defriese, Nancy Carter Foster, Renu Gupta, Margaret A. Hamburg, Dieter Hinzen, James M. Hughes, J. Stanley Hull, Samuel L. Katz, Kenneth W. Kizer, William Kohlbrenner, John R. LaMontagne, Carlos Lopez, Stephen S. Morse, Solomon Mowshowitz, Stuart L. Nightingale, Michael T. Osterholm, David M. Shlaes, John D. Siegfried, P. Frederick Sparling. ***Forum Liaisons***: Barry R. Bloom, Enriqueta C. Bond, Gary Christopherson, Michael Hughes, Stephanie James, C. Michelle Limoli, Stephen M. Ostroff, Gary Roselle, Fred Tenover. ***Study Staff***: Jonathan R. Davis, Polly F. Harrison, Gretchen G. Kidder, Christina Thacker

Type of publication: Workshop Report

Pages: 115

Intended audience: United States; policy-makers, government

Study timeframe: Workshop conducted in July of 1997

Study process: Workshop discussion, with participants from government, industry and academia

Type of organization: Non-profit public health and advisory organization; advisor to Federal Government on issues of public health

Languages (published in): English

Key contact

Ordering information: National Academy Press, http://www.nap.edu

Content: Joshua Lederberg, Chair, Forum on Emerging Infections

(*23*) Protecting the Crown Jewels of Medicine: A Strategic Plan to Preserve the Effectiveness of Antibiotics

Organization: Center for Science in the Public Interest

Year published: 1998

Selected key findings

No original key findings; report cites findings from original sources of research.

Key recommendations

- Congress should allocate funding for an antibiotic use initiative (including public and professional education, national surveillance, research and development, etc.).
- The Department of Health and Human Services should include goals for decreasing inappropriate use of antibiotics and antibiotic resistance in its *Healthy People 2010* initiative.
- The FDA should change its policies on antibiotic advertising to curtail inappropriate antibiotic use.
- The FDA should ban all subtherapeutic uses of antimicrobial agents that are used in human medicine or might select for cross resistance to antimicrobials used in human medicine.

Implementation suggestions

- Increased funding from Congress to implement national education programs and surveillance.
- Government health care facilities should serve as models for the prudent use of antibiotics.

Conclusions/Executive Summary

"Despite antibiotics' extraordinary value, the overuse of those miracle drugs in medicine and agriculture endangers their continued effectiveness. The more antibiotics are used, the more likely it is that bacteria will develop mechanisms to evade them. The development of new antibiotics has not kept up with the development of antibiotic resistance. The time has come when public and private institutions, as well as the general public, must change their policies and practices to prevent further increases in antibiotic resistance. Rather than believing that new drugs continually can be developed to treat antibiotic-resistant infections, public-health prevention measures should be adopted."

Authors: Patricia B. Lieberman, Ph.D., Margo G. Wootan, D.Sc.

Type of publication: Booklet

Pages: 27

Intended audience: United States; general public

Study timeframe: Works cited incorporate research findings from 1972 to 1998.

Study process: Compilation of statistics and information from other sources (USDHHS, CDC, American Society for Microbiology, scientific journal articles, etc.).

Type of organization: Non-profit, public health organization

Languages (published in): English

Key contact
Center for Science in the Public Interest, 202-332-9110

(*24*) The Agricultural Use of Antibiotics and Its Implications for Human Health

Organization: United States General Accounting Office

Year published: 1999

Selected key findings
Experts from the Department of Health and Human Services, CDC and FDA "believe that resistant strains of three specific organisms that cause illness or disease in humans—*Salmonella, Campylobacter*, and *E. coli*—are linked to the use of antibiotics in animals."

There is only one federal program that specifically tests for antimicrobial resistance related to agriculture: the National Antimicrobial Resistance Monitoring System's Enteric Bacteria program. The program tests samples of *Campylobacter* and *Salmonella* from humans and animals for susceptibility to 17 antibiotics.

"About 95 percent of *Salmonella* DT-104 strains are resistant to five antimicrobials—ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline."

Between two and four million people each year contract *Campylobacter* infections; out of every 1,000 reported cases, one will develop into Guillain-Barré Syndrome, which may result in paralysis.

Key recommendation
Development and implementation of a plan by the Secretaries of Agriculture and of Health and Human Services that creates a framework for evaluating the risks and benefits of the current and future uses of antibiotics in agriculture.

Implementation suggestions
The Departments of Agriculture and Health and Human Services would create the plan, devising the goals and timeframes, and identifying the resources necessary to determine the safest uses of antibiotics in agriculture. The Departments will also see to the filling of the existing gaps in data and research.

Conclusions/Executive Summary
"Although research has linked the use of antibiotics in agriculture to antibiotic-resistant strains of specific foodborne pathogens that affect humans, agricultural use is only one factor in the emergence of antibiotic resistance in non-foodborne pathogens. Debate exists over whether the role of agricultural use in the overall burden of antibiotic-resistant infections of humans warrants further regulation or restriction. CDC believes the potential human health risks call for action to restrict antibiotics for growth promotion in animals. We first raised concerns in 1977 about the potential human health risks of this practice. Today, more than two decades later, federal agencies have not reached agreement on the safe use of antibiotics in agriculture. In developing a federal response, both human health concerns and the impact on the agriculture industry are factors to consider."

Authors: ***Major Contributors***: Robert E. Robertson, Erin Lansburgh, Stuart Ryba, Natalie Herzog, Jerry Seigler, Shannon Bondi.

Type of publication: Report to Senator Tom Harkin, Ranking Minority Member, Committee on Agriculture, Nutrition, and Forestry.

Pages: 33

Intended audience: United States

Study timeframe: The review was conducted between May 1998 and April 1999. It covered material from 1969 through 1999.

Study process: The authors conducted interviews with representatives from USA government agencies, the agricultural industry, and agricultural associations. They also reviewed existing research on the subject and consulted with experts and officials from CDC, FDA, USDA, and others to get their opinions on the material.

Type of organization: Federal Government

Languages (published in): English

Key contact

Ordering information: USA General Accounting Office, P.O. Box 30750, Washington, D.C., 20013; tel.: (202) 512-6000; fax: (202) 512-6061

Available on the web at: http://www.gao.gov/

(*25*) The Use of Drugs in Food Animals: Benefits and Risks. Report by the Committee on Drug Use in Food Animals and the Panel on Animal Health, Food Safety, and Public Health

Organization: National Research Council

Year published: 1999

Selected key findings

- "Use of antibiotics increases the risk of emergence of microorganisms that are resistant to specific, and perhaps other, antibiotics. Development of this kind of resistance is not restricted to antibiotic use in food animals; it is far more prevalent because of misuses in human medicine;
- A link can be demonstrated between the use of antibiotics in food animals, the development of resistant microorganisms in those animals, and the zoonotic spread of pathogens to humans. The incidence of the spread of human disease in that way is historically very low, but data are seriously inadequate to ascertain whether the incidence is changing;
- A major impediment to determining the effect of antibiotic use in food animals on human health risk is the complexity of food animal drug treatment and subsequent food-processing and handling interactions. Post-farm good processing, storage and improper handling and cooking are major contributors to the chain of events that allows the pathogen to contaminate the product, proliferate on or in the food, and attain the large numbers that cause disease;
- Substantial information gaps contribute to the difficulty of assessing the effect of antibiotic use in food animals on human health."

Key recommendations

- "The Center for Veterinary Medicine should continue procedural reform to expedite the drug approval review process and broaden its perspective on efficacy and risk assessment to encompass review of data on products already approved and used elsewhere in the world;
- To improve drug availability, worldwide harmonization of requirements for drug development and review should be considered and further enhanced among the federal agencies that are responsible for ensuring the safety of the food supply;
- The Center for Veterinary Medicine should base drug use guidelines on maximal safe dosage regimens for specific food animals, consider greater emphasis on the pharmacokinetics of drug elimination from tissues that are consumed in large quantity, and set drug withdrawal times accordingly;
- Increased funding for basic research that explores and discovers new or novel antibiotics and mechanisms of their action, including the development of more rapid and wide-screen diagnostics to improve the tracking of emerging antibiotic resistance and zoonotic disease;
- Establishment of integrated national databases to support a rational, visible, science-driven decision-making process and policy development for regulatory approval and use of antibiotics in food animals, which would ensure the effectiveness of these drugs and the safety of foods of animal origin;
- The committee recommends that further development and use of antibiotics in both human medicine and food animal practices have oversight by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy, the animal production industry, research, epidemiology, and the regulatory agencies;
- Increased public- and private-sector research on the effect of nutrition and management practices on immune function and disease resistance in all species of food animals;
- Increased public- and private-sector research on strategies for the development of new vaccination techniques, on a better understanding of the biochemical basis of antibody production, and on genetic selection and molecular genetic engineering for disease resistance."

Implementation suggestions

Issues concerning antibiotic use in food animals and humans should be coordinated with regard to use patterns, resistance trends, surveillance data, and

recommendations for use in a partnership of regulatory agencies, pharmaceutical companies, the food animal industry, and animal and human health care professionals.

Conclusions/Executive Summary

"The committee concludes that the use of drugs in the food animal production industry is not without some problems and concerns, but it does not appear to constitute an immediate public health concern; additional data might alter this conclusion. The greatest concern is associated with the use of antibiotics in food animals in such a way that there is a potential for antibiotic resistance to develop in or be transferred to pathogens that can cause disease in humans. This report acknowledges that there is a link between the use of antibiotics in food animals, the development of bacterial resistance to these drugs, and human disease—although the incidence of such disease is very low. A substantial change in the human health risk posed by antibiotic use would affect not only how animal drugs are reviewed, approved, and used, but also how food animals are produced. It should be noted that antibiotics are still effective for their intended purposes at the recommended dosages. New antibiotic drugs are needed to combat emerging animal diseases that do not respond to traditional drugs and so threaten public confidence in animal agriculture and human medicine. Professionals in human health care should be concerned that they do not have enough specialty antibiotics to treat resistant and emerging infections in humans, as should veterinarians. The question is, should newly discovered medications be held in reserve for human or animal use only? Antibiotics should be available to treat specific human and animal disease with proper accountability and oversight of the drugs used."

Authors: ***Committee on Drug Use in Food Animals***: James R. Coffman, George W. Beran, Harvey R. Colten, Connie Greig, Jean Halloran, Dermont Hayes, John B. Kaneene, Kristin McNutt, David Meeker, Stephen C. Nickerson, Thomas Seay, R. Gregory Stewart. ***Panel on Animal Health, Food Safety, and Public Health***: John A. Shadduck, Kenneth Berns, Michael P. Doyle, Hollis N. Erb, John Ferry, Jere E. Goyan, Werner Heuschele, Helen H. Jensen, Franklin M. Loew, Joy A. Mench, Harley Moon, Wilson G. Pond, R. Gregory Stewart. ***Board on Agriculture***: Dale E. Bauman, John M. Antle, Sandra S. Batie, May R. Berenbaum, Leonard S. Bull, William B. Delauder, Anthony S. Earl, Essex E. Finney, Jr., Cornelia Flora, George R. Hallberg, Richard R. Harwood, t. Kent Kirk, Harley W. Moon, William L. Ogren, George E. Seidel, John W. Suttie, James J. Zuiches. ***Food and Nutrition Board***: Cuthberto Garza, John W. Erdman, Lindsay H. Allen, Benjamin Caballero, Fergus M. Clydesdale, Robert J. cousins, Michael P. Doyle, Johanna T. Dwyer, Scott M. Grundy, Charles H. Hennekens, Janet C. King, Sanford A. Miller, Ross L. Prentice, A. Catharine Ross, Robert E. Smith, Virginia A. Stallings, Vernon R. Young.

Type of publication: Report

Pages: 253

Intended audience: United States; food-production industry, policy-makers, veterinarians

Study timeframe: The report considers information from 1968 to 1998.

Study process: The Committee reviewed the major classes of drugs used in food animals; reviewed scientific literature; heard testimony on animal-drug-related issues; reviewed federal regulations that provide guidelines and list mandatory practices for drug use, monitoring capabilities for drugs and residues in foods, veterinary oversight in prescription drug use, rates of violations, and instances of documented health problems.

Type of organization: Non-profit organization, the working arm of the National Academy of Sciences and the National Academy of Engineering

Languages (published in): English

Key contact

Ordering information: National Academy Press, http://www.nap.edu

Content: James R. Coffman, Chair, committee on Drug Use in Food Animals

APPENDIX B
Local action around the world

APUA Latin American Initiative

Report prepared by APUA

The mission of APUA is to promote the prudent use of antibiotics in order to preserve their power for future generations. The establishment of foreign-affiliated chapters to conduct research and education activities tailored to local needs is an important vehicle for achieving this goal. APUA's Latin America Initiative was developed to strengthen and expand existing APUA country activities to curb the development of antibiotic resistance and to coordinate these activities with related activities in the region. Through the Initiative, APUA's regional network of chapters has grown from five to ten, with eight additional countries in the process of developing chapters. This regional initiative has been funded largely by the United States Agency for International Development (USAID) and the Pan American Health Organization (PAHO) and is being implemented in collaboration with PAHO's IMCI (Integrated Management of Childhood Illness) Unit.

A key feature of the Initiative is the network of APUA country chapters. With a strong foundation in microbiology and infectious disease, chapter members work at the grassroots level to tailor interventions to local situations and to provide a link between data and action within their countries. Through the Initiative, APUA is collaborating with PAHO and its Member States to develop interventions to curb antibiotic resistance. PAHO, with APUA and other partners, has been involved in developing a strategic plan for the surveillance of antibiotic resistance as well as laboratory training activities to support a regional surveillance network. APUA has also been working with the IMCI Unit of PAHO to develop and implement projects to curb antibiotic resistance within the context of IMCI. APUA will continue to expand its network of chapters in Latin America and support existing chapters as they work more aggressively towards documenting, understanding, and containing antibiotic resistance.

Activities of the APUA Latin American Initiative

The Latin America Initiative increases the impact and reach of chapter work by providing a mechanism to link countries and share resources, information, and expertise. Activities supported through the initiative include country-specific projects as well as efforts to develop regional communications and region-wide research and educational activities. These activities are coordinated to build on PAHO activities at the country and regional levels. This section includes a list of activities in the region supported by APUA or conducted in collaboration with WHO, PAHO, ministries of health, and other institutions and organizations.

Chapter development activities

The Latin America Initiative has grown from the initial group of five country chapters to include the following countries: Argentina, Chile, Colombia, Cuba, Dominican Republic, Ecuador, Guatemala, Mexico, Venezuela and Uruguay. Efforts are currently underway to establish APUA chapters in the following countries:Bolivia, Brazil, Costa Rica, El Salvador, Honduras, Nicaragua, Paraguay and Peru.

Research activities

- A study conducted by our Uruguay chapter in 1999 compared the rate at which antibiotics were prescribed for children with pharyngitis to the actual need for antibiotics, based on the percentage who tested positive for *Streptococcus pyogenes*. The study showed that while 75% of the 212 children who presented with pharnygitis at an outpatient clinic were prescribed antibiotics, only 15% tested positive for Group A *Streptococcus pyogenes* (GAS). By demonstrating the overuse of antibiotics for children with pharyngitis, the study aims to persuade pediatricians to modify their prescribing habits. The study was funded by the Ministry of Health, PAHO, and APUA.

- In 2000, APUA funded a study by its Guatemalan chapter titled "Study of the Risk Factors for Antibiotic Resistance of *S. pneumoniae* among Guatemalan Children from Different Socio-Economic Strata and Health Care Delivery Systems", to be completed in 2001.
- APUA, in collaboration with PAHO, is conducting a regional survey of physician's knowledge, attitudes, and practices (KAP) regarding antibiotic resistance and use. The survey, developed by APUA and pilot-tested in Argentina, will initially be conducted in 9 countries, and will inform the development of appropriate treatment guidelines and provider educational materials.
- APUA provides technical assistance to chapters in the region, including help with meeting and conference planning, providing speakers, supporting the south-to-south exchange of expertise, and proposal development for grants from APUA and other funding sources.
- Five chapters were awarded grants from the 2000 Joint Initiative to conduct research on antibiotic use. APUA provided technical support during proposal development.
- APUA chapters contributed to the IMCI News bulletin produced by PAHO.
- The new APUA chapter in Colombia has plans to develop a surveillance and reporting network for antibiotic resistance in tertiary hospitals throughout the country using WHONET software. The plan includes the dissemination of regular reports on resistance to hospitals and national health authorities, including a formal annual report from the network.

Training and educational activities

- APUA conducted a Continuing Medical Education session on "Improving Antibiotic Use in the Management of Childhood Illnesses" held in June 2000 at the Global Health Council annual meeting in Washington, DC. This session, attended by clinicians, public health professionals and policy makers, featured background information on the antimicrobial resistance problem, specifically as it relates to children's health in Latin America. It also described the APUA-PAHO/ IMCI partnership as a model for collaborative work to contain resistance and other related projects sponsored by the two organizations, such as surveillance, capacity-building, and provider trainings.
- APUA provided assistance in the design of a comprehensive one-week training course in testing organisms for susceptibility to antibiotics and resistance surveillance, which was conducted by the Ministry of Health in Argentina, in collaboration with PAHO and the APUA-Argentina chapter. APUA plans to adapt the course for use in other countries in the region, in collaboration with PAHO.
- In collaboration with PAHO, APUA produced a Spanish version of the APUA patient education brochure and health care provider wall poster for distribution via PAHO and APUA chapters throughout Latin America.
- APUA supported the development or translation of articles in Spanish on otitis media and the prevention and treatment of pneumococcal infections, that were published on the APUA Web site and in the monthly bulletin of PAHO's IMCI programme.
- A week-long Latin America regional training course on laboratory surveillance methods for detecting antimicrobial resistance, was held in April 2000 in Buenos Aires, Argentina. The course was organized and designed by the Argentine Ministry of Health and founding members of APUA-Argentina, with assistance from PAHO and APUA. One hundred microbiologists from Argentina, as well as 20 participants from other Latin American countries, attended this hands-on training to improve and update their skills and knowledge in susceptibility testing techniques, specific organisms, interpreting test results, quality control, and the management of susceptibility data. Participants will take these newly-acquired skills and knowledge back to their colleagues. APUA and PAHO plan to sponsor similar trainings in other Latin American countries, after adapting the course to address challenges faced by less developed countries in the area. The refined curriculum will also serve as a model for other countries with limited resources outside of the region.

Conference and networking activities

- APUA, in collaboration with PAHO and the Pan American Association for Infectious Diseases, organized a symposium on "Prudent Use of Antibiotics in the Developing World" during the

International Congress on Infectious Diseases (ICID) in Buenos Aires in April 2000. The symposium covered partnerships to address antibiotic resistance, the application of community research results to clinical practice, effective strategies for provider education, and the process of designing clinical guidelines for antibiotic use.

- APUA has established a Spanish-language listserve for the Latin America region. The listserve, moderated by APUA's Latin America Project Director, allows Latin American health professionals to regularly exchange information on research related to antibiotic resistance and use, offer or seek technical assistance from other participants, and post announcements of upcoming meetings and funding opportunities.

Moldova: Nongovernmental organizations and antibiotic programmes

Report prepared by Natalia Cebotarenco, Ph.D., Director of the Association Drugs, President APUA Moldova, "natalie"@drugs.mldnet.com or natalie@drugs.moldova.su

Antibiotics have revolutionized the treatment of common bacterial infections and have a vital role in reducing child mortality. Since antibiotics were first introduced, their consumption has increased dramatically in most parts of the world. Resistant bacterial strains have emerged and spread throughout the world because of the remarkable genetic plasticity of the microorganisms, heavy selective pressures of antibiotic use, and the mobility of the world's population.

The problem of resistance to antimicrobial drugs is particularly troublesome in a country like the Republic of Moldova that also has economic and societal problems. After the collapse of the Soviet system, Moldova instituted an economic reform that tried to establish a market economy. The economic changes led to increasing numbers of private pharmacies. Moldova has 4.35 million citizens and 1500 registered pharmacies. More than 85% of the pharmacies are private. This situation brought a flood of medicines on the market in Moldova and created a situation of uncontrolled dispensing of medicines.

Increasing the availability of antibiotics and enhancing their appropriate use are two interrelated aims. With the increasing quantity and variety of pharmaceuticals available today in Moldova, the potential inappropriate use of antibiotics is a growing concern. The sale of medicines by prescription, including antibiotics, has almost ceased in Moldova. Officially, antibiotics are prescription-only drugs in Moldova. In practice, they are widely available in many pharmacies and even on the streets. The doctors' recommendations are often ignored as patients are lured by drug store offers. On the other hand, doctors are extremely underpaid in Moldova and can gain some money by selling or prescribing antibiotics. Thus it is often hard to discuss the concept of a rational choice of an antibiotic with health care providers and the general public.

The situation in Moldova shows several problems associated with the use of antibiotics including widespread inappropriate antibiotic use, young children frequently medicated with antibiotics for too short a course, and a vast majority of self-medicated treatment regimes. Only one-sixth or one-seventh of the antibiotics are recommended by a doctor and resistant respiratory pathogens are widespread among the children.

A non-governmental medical organization is formed to provide drug information

With new political possibilities in 1995, a medical non-government organization, Association DRUGS, was established in Moldova. The Association DRUGS provides unbiased, up-to-date information on the safety and efficacy of drugs to interested health professionals, consumers and government institutions such as the Ministry of Health, the National Institute of Pharmacy, the Moldavian Medical and Pharmacy University "N.Testemitanu".

The first project by the Association DRUGS in 1995 was the establishment of the Information Centre with the goal of promoting rational drug use and the Essential Drugs concept in Moldova.

Since its beginning, the Association DRUGS has provided 47 seminars and training sessions on various aspects of rational drug use at the hospitals in Chisinau (capital of Moldova) and in regions of Moldova, as well as the Postgraduate Faculty of the Medical and Pharmacy University of the Republic. More than 2,700 physicians and pharmacists took part in its educational programmes. Since January 1996, 34 issues of the independent Drug Bulletin were published with 1,500 samples distributed free-of charge for physicians and pharmacists. Through the activity of Association DRUGS, a network was created for rational drug use in Moldova, which

included authorities from the Ministry of Health, the National Institute of Pharmacy, Medical and Pharmaceutical University of Moldova, pharmacists, physicians, journalists and non-governmental organizations.

From the beginning of the activity in 1995, the Association DRUGS analysed 1500 records from the children's hospital "V. Ignatenco" in Chisinau (the capital of Moldova), focusing on physicians' antibiotic prescriptions. The most common pediatricians' problems were inappropriate antibiotics prescriptions that included polytherapy and the overprescribing of antibiotics:

- Acute respiratory infections were treated with 1–2 antimicrobials
- Acute pneumonia was treated with 2–3 antimicrobials, occasionally 4 antimicrobials
- Predominance of antibiotic injections
- Duration of treatment too short (fewer than 3 days) or too long (more than 15 days)
- Overuse and too high a dose of antimicrobials
- Inappropriate choice of antibiotic group
- Predominance of gentamicin and cefalosporins of the second or third generation
- Non-consideration of microbiology control before or during treatment course by antibiotic
- Non-consideration of the problem of antibiotic resistance in daily work.

The survey showed that there was no professional awareness of the problem of antibiotic resistance. Antibiotic resistance problems have not been and are not identified as national priorities of the health care system.

Was education of pediatricians carried out continually? Were guidelines for treatment developed?

Given the chronic state of deficient funding that covers only 5–7% of the hospitals' needs, the antibiotic resistance problem must be approached by changing the educational system for physicians. However, the education programmes in the medical school and University of Moldova do not include the themes "Formulary system in the hospital", "Analyzing the cost-effectiveness of treatment", "Essential Drugs Lists development", "Rational drug use" and other items in the update.

In Moldova, the guidelines for the treatment of the most common infectious diseases were developed and distributed without general discussion or follow-up; a few scientific seminars were formalized but were not necessarily interactive. Practically speaking, the treatment guidelines are not available to many physicians. Many Moldavian pediatricians' English knowledge is not good enough to allow them to get information or enable them to follow international recommendations and guidelines. For these reasons the guidelines do not work in Moldova yet.

Considering that the incorrect prescribing of antibiotics by physicians is one of the factors that stimulates the development of antimicrobial resistance, it is necessary to create an appropriate educational strategy.

How can the behaviour of pediatricians be changed?

As poor prescription practices were originally attributed to a lack of appropriate prescribing information, the main strategy focused on providing up-to-date information regarding appropriate prescriptions of antibiotics and the antimicrobial resistance problem. Education on the proper use of antibiotics has a limited effect if the existing drug distribution patterns and information sources are not rationalized. Health workers who try to change patterns of antibiotic use realize more and more that what is rational depends very much on what people think is rational, what their living conditions are and what drugs and diagnostic tools are available in the health care context.

In order to improve the situation with inappropriate antibiotic prescriptions, a training programme has been developed with the support of the APUA and United States Pharmacopoeia in collaboration with the Association DRUGS in Moldova. The health training programme was created in 1998-1999 to help middle and lower level health workers, especially pediatricians, learn to use antibiotics more wisely and to help prevent antibiotic resistance.

A pilot training programme was conducted at the Moldavian Medical and Pharmacy University to explore the practicalities, acceptance and educational value of the postgraduate department's pediatricians. During a needs assessment period, meetings were held with authorities from the Ministry of Health, pediatricians from the different levels of the health system, and pharmacists to help identify barriers to rational antibiotic use. In addition, teachers from academic institutions became involved. These groups see the need to change the medical curriculum to include the antibiotic resistance problem and to monitor prescribing practices

in different health care facilities. Concerns expressed included the high number of prescriptions, inadequate information about antibiotic use, and problems with the poor quality of donated antibiotics.

The educational programme had five components:

1. Questionnaire assessment of Knowledge, Attitude and Practice Survey (KAPS) of middle and lower level pediatricians.
2. "Improving Antibiotics Use" Training.
3. Distribution of the manual, "Antibacterial Therapy", in Russian to the participants of the training issued by the United States Pharmacopoeia.
4. Distribution of the APUA Newsletter among pediatricians and publishing the result of the KAPS-survey in the informational bulletin of the Association DRUGS.
5. Using mass media to attract the public's attention to the topics of antibiotic rational use and antibiotic resistance.

The session of the training "Improving Antibiotics Use"consisted of:

- How to choose the most cost-effective antibiotics for essential drug list and formulary
- Control the rise of antibiotic resistance
- Limit antibiotic over-prescribing
- Limit over-prescribing due to patient pressure
- Guidelines for drug donations
- Risks of using antibiotics for the treatment of acute respiratory infections.

The effectiveness of the training in increasing the students' knowledge of rational antibiotic use and antibiotic resistance problems was measured by a pre-test and post-test multiple choice examination. Evaluations showed that the course increased the knowledge and understanding of pediatricians, helped them develop more positive attitudes, and demonstrated the importance of multiprofessional teamwork and communication among the physicians' different specialities. Participating pediatricians believed that postgraduate courses should include early and regular opportunities for shared learning.

The key principle underpinning this framework is that a range of educational transactions may need to occur for learning to be effective.

The development of training programmes in hospitals is still largely at a rudimentary level in Moldova. Appropriate training experiences in managed care organizations may be a valuable strategy to address the current disconnect between the traditional hospital-based education of pediatricians and the expanded competencies necessary to practice in intensively managed, integrated and accountable health systems. A main assumption is that a new learning strategy will either fit into existing patterns or trigger changes in the way that teachers/trainers and learners talk together.

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Nepal: Developing a national antibiotic policy

Report prepared by Mr. Shyam P. Lohani, M. Pharm., Programme Coordinator, United Hands to Nepal, Chapter Coordinator, APUA Nepal. Contact: uhn@mos.com.np

Background

The Drug Act was promulgated in Nepal in 1978 to 1) control the production, distribution, sale, export and import of drugs and 2) to ensure the availability of safe, quality and efficacious drugs to the general public. Its first amendment was added in 1988. To prevent misuse and abuse of drugs, all of the available drugs are classified into three categories according to their composition, efficacy and use as per the provision of the Drug Act. The three categories are:

1. Group 'Ka'—Narcotic, psychotropic drugs and potent active therapeutic agents.
2. Group 'Kha'—Antibiotics, hormones and general therapeutic agents.
3. Group 'Ga'—Other common drugs which are safer.

Drugs in groups 'Ka' and 'Kha' are prescriptive drugs while those in group 'Ga' are over the counter drugs. According to the Drug Act, drugs placed in the 'Ka' and 'Kha' categories are to be prescribed by practitioners registered with the Nepal Medical Council.

His Majesty's Government (HMG) of Nepal published a National Essential Drug List in 1986, which was revised in 1992 and again in 1997. To promote appropriate use of anti-infective drugs, the National Essential Drug List categorized the drugs according to the different levels of health care.

- **Sub-health posts** (the most peripheral health care facilities, which are a part of each Village Development Committee): amoxicillin, cotrimoxazole and tetracycline.
- **Health posts** (775 health care facilities): amoxicillin, procaine benzyl penicillin, chloramphenicol, cotrimoxazole, and tetracycline.
- **District level** (75 public health offices and 50 district hospitals): amoxicillin, benzathin penicillin, benzyl penicillin, cloxacillin, procaine benzyl penicillin, chloramphenicol, ciprofloxacin, erythromycin, gentamicin, metronidazole, tetracycline, rifampicin, streptomycin, ethambutol, sulfaacetamide, doxycycline and nitrofurantoin.
- **National List**: The national list includes all the drugs from the district level plus Cefotaxime.

In addition to the antibiotics in the national list, other antibiotics available in the private sector retail shops need to be registered with the Department of Drug Administration (DDA), Nepal. A new molecule, including an antibiotic, is not registered in Nepal until it is included in the recognized pharmacopoeia as per the convention adopted by the Drug Advisory Committee.

Antibiotic use pattern in Nepal

Several research studies examined the prevalence of antibiotic prescriptions:

- In 1994, in collaboration with the WHO, the DDA studied the prescribing habits of private practitioners; this study showed that antibiotics were prescribed in 49.85% of all cases.
- In 1997, in collaboration with PHCP/GTZ, another DDA study (the Rapid Assessment of Pharmaceutical Management and Utilization) showed that antibiotics were prescribed in 59% of all encounters in health facilities.
- In 1998, PHON conducted a study on Priority and Misused Drugs in health facilities and private sector practitioners which showed that antibacterials were prescribed in 50.7% of all encounters.

Research on dispensing practices showed recommendations of antibiotics for diarrhoeal diseases, fevers and viral infections.

Large amounts of antibiotics are used in animals not only as curative agents, but also as prophylactic agents and as growth promoters. The total amount of antibiotics used in food animals and in feed in Nepal is not known. However, restricting attention to the human use of antibiotics is not enough to curb bacterial resistance.

The participants of a regional drug information workshop at Nepalgunj and Pokhara on January 9–14, 1999, advocated for the need for a separate policy for antibiotics. It was felt that a policy should be developed for prescribing of antibiotics and raising the general public's awareness of bacterial resistance to antibiotics.

In response to this, the APUA-Nepal chapter, on the request of the Department of Drug Administration and the Ministry of Health, prepared a draft of a National Antibiotic Policy developed by a committee of experts from the health, veterinary, agriculture and other fields. The initial draft of the National Antibiotic Policy was presented in a workshop on May 18–20, 2000, at Dhulikhel, Nepal. The participants presented their comments and suggestions on the draft. These comments were used to prepare a final draft which is pending at the Ministry of Health for approval.

Details of the proposed national antibiotic policy (2000)

The draft policy has nine sections: the preamble, definition, main policy, objectives, strategic guidelines, national antibiotic control committee, research and development, technical cooperation and monitoring and supervision. The draft recommends:

- Classifying antibiotics into three categories: reserved, restricted, and semi-restricted.
- Dispensing antibiotics only with a prescription or within a nationally approved protocol.
- Establishing interagency cooperation among governmental, non-governmental and private institutions to promote the prudent use of antibiotics by health care professionals and the gen-

eral public, with the assistance of His Majesty's Government (HMG) of Nepal.

- Creating a National Antibiotic Control Committee comprised of concerned experts from human and animal health, agriculture, professional organizations, and organizations involved in consumer rights and awareness under the auspices of HMG.
- Establishing a national antibiotic surveillance system.
- Developing curricula for training and education on the prudent use of antibiotics, and incorporating them at all levels of prescribers' and dispensers' education.
- Promoting prudent use of antibiotics by implementing periodic training of health care workers who are eligible to prescribe drugs.
- Creating and regulating a National Antibiotic Therapeutic Advisory Committee (NATAC) comprised of concerned experts from relevant sectors, under the auspices of HMG.
- Facilitating research on prescribing, dispensing, and use of antibiotics as well as antibiotic resistance.
- Encouraging the involvement of national and international agencies in technical training, education, and research related to the prudent use of antibiotics.
- Creating subcommittees of the National Antibiotic Control Committee to be responsible for effective implementation of the antibiotic policy as well as for monitoring and supervising its implementation.
- Requiring that antibiotics used for therapeutic purpose in humans and animals not be used as growth promoters or prophylactic agents in animal feed.
- Developing national antibiotic guidelines, which will assist individual health and veterinary institutions to formulate local antibiotic guidelines.
- Developing facilities for antimicrobial resistance testing and detection of antibiotic residue in livestock products in health and veterinary institutions, with the help of HMG.

■ Viet Nam: Hospital case study and national antibiotic policy

Report prepared by Dr. Hoang Thuy Long, Director of National Institute for Hygiene and Epidemiology, Vietnam. Chapter Head, APUA Vietnam.
Contact: daihocyhn@hn.vnn.vn

Policy of the Ministry of Health on the rational, safe, and effective use of drugs

In 1997–1998, the Vietnamese Ministry of Health enacted a set of regulations to ensure the rational, safe, effective and economic use of drugs. These regulations:

- Established a Drug and Therapeutic Committee (DTC) in each hospital whose function was to oversee correct drug provision, management, and use.
- Strengthened the policy of rational, safe and economic use of drugs in the clinic and polyclinic institutions.

The Drug and Therapeutic Committee's tasks are:

- To implement the national policy of using drugs in hospitals.
- To set up basic regulations concerning the supply, management, and use of drugs in hospitals and then submit the regulations to the hospital's director for approval.
- To set up the lists of drugs used in hospitals and submit the lists to the hospital's director for approval.
- To set up the drugs' distribution procedure, submit the procedure to the hospital's director for approval and help the director to implement the procedure.
- To help the hospital's director carry out the following activities:
  - — Supervise rational prescription of drugs:
  - — Set a rational prescription standard.
  - — Check the contents of case histories that refer to the drug use process.
  - — Supervise adverse drug reactions in the hospital.
  - — Organize drug information.
  - — Organize scientific research and training on current knowledge of drugs.
  - — Set up a cooperative relationship between the pharmacist and the physicians and nurses for drug use in patients.

Prior enactment, these Instructions were tested for a year in four city or provincial hospitals in North Vietnam. In 1999, the Ministry of Health organized a conference to evaluate the impact of the Drug and Therapeutic Committees after two years of operation.

The results of this evaluation showed:

- Active participation by the Drug and Therapeutic Committee in the drug regulation in the hospitals.
- Enhanced supervision of adverse drug reactions.
- The Pharmacy Departments supplied a sufficient quantity of drugs of good quality.
- In some hospitals:
  - — The Pharmacy Department was able to advise and provide drug information.
  - — A good working relationship was established between physicians, pharmacists and nurses to consult about drug use in patients.
- In many hospitals the Drug and Therapeutic Committee had just been established and is not yet a fully functioning entity.

Lessons learned from this experience

- Instruction and management by the Ministry of Health of the activities of the Drug and Therapeutic Committee
- Instructional activities of the Drug and Therapeutic Committees and of the provincial health service

■ Utilization and management of antibiotic use in Hospital Gynecology-Obstetric Hanoi (1995–1999)

Bui Suong, MD, Hospital Gynecology-Obstetric Hanoi and Nguyen Thi Vinh PhD, Medical College Hanoi, Viet Nam

This article is from the report of the workshop "Rational, safety use of antibiotics" held on February 28–29, 2000 in Hanoi.

Bacterial infection remains one of several factors leading to high mortality rates. Antimicrobial agents play a decisive role in reducing the mortality and the incidence of bacterial infections. Today antibiotics are widely and inappropriately used. Anybody can buy antibiotics without a prescription. Hundreds of different brands of antibiotic products are on the market and lack of information favours their misuse, such as unnecessary use, incorrect choice, incorrect dose, incorrect administration, or poor drug quality. This misuse is the reason for increasing bacterial resistance, leading to prolonged treatments in hospitals and increased expenses for drugs and services.

In March 1996, as one of the four pilot projects, the Ministry of Health established the Drug and Therapeutic Committee (DTC) at the Hospital Gynecology-Obstetric Hanoi (HGOH). The HGOH is a top-ranked hospital in Gynecology and Obstetrics in Hanoi City. The HGOH treats gynecological diseases and pathologic pregnancies, provides sterility treatment, family planning and obstetric services. The registered capacity of the hospital is 200 beds, but it is always working at overcapacity with both out- and in-patients. The hospital is a reliable institution for women in Hanoi and surroundings.

After being established, the HGOH Drug and Therapeutic Committee organized regular meetings to encourage appropriate prescribing models and drug choice for each patient. As time went on, models were reviewed and improved as needed. The appropriate choice of antibiotic:

- Was specific for the pathogen germ.
- Was quickly and well absorbed at the infection site.
- Was appropriate to the treatment goal: gynecological, obstetric, post- obstetric, newborn, inpatient, or outpatient.
- Was appropriate to the treatment subject, i.e, pregnant, newborn.
- Minimized adverse drug reactions.
- Was of reasonable cost and acceptable to patients.

The HGOH's Drug and Therapeutic Committee has observed changes in antibiotic use since the Committee was implemented.

1. The proportion of patients using antibiotics in the hospital

About 90% of patients used antibiotics. The remaining 10% included pregnant patients planning to nurse their newborns and some doubtful cases of ex-uterine pregnancies; antibiotics were not used in these cases.

TABLE 1. **OUT- AND IN-PATIENTS AT HOSPITAL GYNECOLOGY-OBSTETRIC HANOI**

	1995	1996	1997	1998	1999
1. Total number of patients examined	46,030	52,147	60,868	74,974	75,068
Total number of examinations	68,902	78,061	90,746	105,886	105,021
Total number of abortions	4,931	5,417	6,150	7,099	7,619
2. Total number of inpatients	10,487	12,007	12,342	13,061	14,600
Total number of deliveries	5,778	6,139	6,924	7,204	7,682
* Difficult	2,419	2,893	2,992	3,207	3,057
* Normal	3,359	3,246	3,932	3,997	4,625
Total number of operations	1,943	2,393	2,540	2,979	3,100
* Gynecological	593	784	976	1,193	1,142
* Obstetric	1,353	1,609	1,549	1,777	1,958
3. Average duration of therapy (days)	6.7	6.3	6.0	6.4	5.8

TABLE 2. **ANTIBIOTIC USE BY PATIENTS**

	1995	1996	1997	1998	1999
Number of patients using antibiotics	9,616	10,926	11,207	11,820	11,753
Total number of patients	10,487	12,007	12,342	13,061	14,600
%	91.7%	91%	90.8%	90.5%	80.5%

- Generally, only one antibiotic was used for prophylaxis after abortion or delivery with episiotomy.
- When necessary, antibiotic combination therapy was used as follows:
  - — β-lactam (ampicillin) + aminoglycoside (gentamicin) were the main combination used
  - — β-lactam (cephalosporine) + metronidazole
  - — β-lactam + aminoglycoside + metronidazole
  - — Quinolone + aminoglycoside (few/gynecologic)
  - — Antibiotic + antifungi
- Antibiotic combination therapy was reduced in 1999 because antibiotic prophylaxis was introduced in surgery in 1996 and was implemented hospital-wide in 1998.
- Antibiotic use was greatly reduced in 1999 (19.5%) because antibiotic use was removed for all cases of normal delivery with tidy amniotic fluid, entire placenta, no episiotomy.

TABLE 3. **PROPORTION OF PATIENTS USING ANTIBIOTIC COMBINATION THERAPY**

	1995	1996	1997	1998	1999
Percent of patients using antibiotics	91.7%	91%	90.8%	90.5%	80.5%
Percent of patients using one antibiotic	50.8%	57.4%	71.4%	74.6%	68.6%
Percent of patients using two antibiotics	30.3%	25%	15.3%	12.3%	10.5%
Percent of patients using ≥ 3 antibiotics	10.6%	80.6%	4.1%	3.6%	1.4%

TABLE 4. **PROPORTION OF EXPENDITURE FOR ANTIBIOTICS**

	1995	1996	1997	1998	1999
Expenditure for antibiotics (thousands Vndong)	322,127	646,867	905,159	1,010,433	1,043,799
% of total drugs expenditure	45.8%	45.6%	44.3%	43.8%	43.5%

- The expenditure for antibiotics is appropriate for a top-ranked hospital for Gynecology and Obstetric Surgery in Hanoi City.
- The proportion of antibiotic expenses was gradually reduced from 1995 to 1999.

Today about twenty antibiotics are being used, with ten in common use. The Drug and Therapeutic Committee considers every sort of antibiotic. To be chosen, the antibiotic must be therapeutically effective, have few adverse drug reactions, and be manufactured by a reliable firm. Only one brand product of every antibiotic is used, making supervision and management easier. While the kinds of antibiotics may be increased or decreased, the quantity of expensive antibiotics was reduced from 1995 to 1999.

2. Antimicrobial prophylaxis

From 1996 the hospital has used cefuroxime 0.75g x 03 (or 04) ports/case to test for prophylaxis in surgery (gynecological and obstetric) due to the short duration. Hygienic measures, sterilization and disinfection methods reduced the post-operative infection rate considerably (from 19.8% to 11.7% in the period studied). Because of its success, this is now the standard order for antimicrobial prophylaxis in the hospital. The post-operative infection rate is 5% (fever 38.5–39 °C, inflammation at incision site) with no cases of serious post-operative infection.

Today, antimicrobial prophylaxis achieves good results, reducing pain for patients, shortening antibiotic duration, avoiding drug complications, reducing the effect on the mother's milk (childbirth operation). In addition, good economic results were achieved, reducing medical service and reducing total expense for treatment in comparison to long-term therapy with antibiotics. The antimicrobial prophylaxis regimen could help to reduce the rise and spread of antibiotics resistant pathogens also.

3. Managing measures for rational, safe use of antibiotics by the Drug and Therapeutic Committee

In 1998, the HGOH's Drug and Therapeutic Committee became a full-fledged, independent entity in the hospital. The Committee has eight members, with the director as the chairman and the head of Pharmacy Department as the permanent secretary. Since its establishment, the Committee has been advising the director on the rational, safe and effective use of drugs, including antibiotics. All leaders of the hospital understand the necessity of the rational, safe and effective use of drugs for therapy, as promoted by the Ministry of Health.

The Drug and Therapeutic Committee guidelines for the Pharmacy Department and the Planning Department are:

Drug providing

- The Pharmacy Department provides sufficient drugs on time and at high quality. Drugs are generally obtained from state pharmaceutical firms.
- Only one of several products under the same generic name is used; this product must be of good quality and meet the therapeutic demand to facilitate the management and supervision of antibiotic use in the hospital.

Prescribing

- On a yearly basis, experts are invited to give lectures on special topics in clinical pharmacy, such as antibiotics, vitamins, drug interactions, adverse drug reactions. The audience is made up of physicians, pharmacists and nurses from the whole hospital.
- One pharmacist and two physicians (special first level) revise, advise and help the physicians to prescribe rational, safe, effective antibiotics.
- A clinic pharmacist helps physicians choose appropriate drugs for treatment of patients.
- At the weekly general meeting of the hospital, the Pharmacy Department reports the case histories of inappropriate drug use in order to correct future problems.
- Monthly, if a sudden change in the quantity of drug use is recognized, the Pharmacy Department reviews the case histories to find a reason for the change. It reports to the Drug and Therapeutic Committee and makes suggestions for solving the problem to gradually improve the quality of treatment.

Drug use

- The Pharmacy Department regularly makes guidelines and supervises the nurses and midwives in using drugs according to prescription. The Pharmacy Department cooperates with the

clinical departments to watch the effectiveness of drug use and report any decrease in effectiveness to the Drug and Therapeutic Committee. The Pharmacy Department monitors any adverse drug reactions in time to recover. In four years, fifty cases of adverse drug reaction were found, in which 38 cases were caused by antibiotics. All cases were treated in time with no complication.

- The physicians prescribe according to the guidelines and the list of drugs, which are rewritten by the Drug and Therapeutic Committee each year, so that the use of antibiotics in the hospital is becoming more rational, safe and effective. The post-operative infection rate is being reduced. Therefore, although the number of inpatients is increasing, the average duration of treatment is decreasing (from 6.7 days in 1995 to 5.8 days in 1999).

Conclusion

Enacting the policies of the Ministry of Health with the determination of the director of the board and under the leadership of the Drug and Therapeutic Committee, all physicians adhere strictly to the prescribing regulations and therapeutic guideline. Antimicrobial prophylaxis and the rational, safe use of antibiotics showed a high degree of effectiveness.

To improve results, we will promote the effectiveness of the Drug and Therapeutic Committee activity by:

- Strengthening science research activities in the hospital.
- Encouraging and providing conditions for personnel to improve their professional knowledge.
- Re-educating physicians on prescribing regulations, principles of drug use in general and of antibiotic use in particular.
- Regularly providing to physicians, pharmacists and nurses sufficient and up-to-date information about drugs in the drug list and their administration.
- Reinforcing surveillance on therapeutical effectiveness of drugs being used in the hospital, finding out about drugs with bad activity and/or adverse drug reactions in order to eliminate that drug from the drug list.
- Strengthening supervision on rational, safe use of drugs in the whole hospital (including in- and out-patients) from the examination phase through prescribing and realization of medical orders to the final result. There could be punishment for infringed cases.

Greece: Hospital case study of an antibiotic policy

Report prepared by Helen Giamarellou, MD, PhD, Professor of Internal Medicine, Athens University School of Medicine, Sismanoglio General Hospital, Athens, Greece; President, APUA Greece; Anastasia Antoniadou, MD, Nearchos Galanakis, MD, George Petrikkos, MD, Erasmia Sarmi, Pharmacist. Contact Dr. Helen Giamarellou at: hgiama@ath.forthnet.gr

This is a report on the encouraging results of our implementation of an antibiotic resistance policy in Laiko General Hospital during the period 1992–1998.

In Greece, as in other settings, high antibiotic resistance rates run in parallel with huge antibiotic consumption in hospitals and in the community. We implemented a antibiotic restriction policy in a 500 bed University teaching hospital. In this hospital, antibiotic consumption before 1990 ranged between 62–78% with the highest rates in the General Surgery and Urology Departments (75–100%). The main overuse involved long-term surgical prophylaxis, while one-third to one-half of antibiotic consumption involved the unjustified use of third generation cephalosporins, carbapenems, newer quinolones and vancomycin. Resistance rates among Gram-negative isolates were already high (Table 1) and the threat of losing all new active compounds because of their unjustified overuse was a reality.

Since 1991, an antibiotic restriction programme proposed by Professor Giamarellou and her team was implemented by the Infection Control Committee of the Laiko General Hospital. According to the programme, all new antimicrobials (third and forth generation cephalosporins, aztreonam, imipenem and later meropenem, vancomycin and later teicoplanin and all newer quinolones) were ordered to the hospital pharmacy only after physicians had completed a restricted antibiotic form, which had to be inspected and signed by the hospital infectious diseases clinicians (Laiko Hospital had 3 of them) or by physicians with a proven interest in infectious diseases. The programme was also supplemented by enforcement of the rules of

TABLE 1. **RESISTANCE RATES TO SEVERAL ANTIMICROBIAL AGENTS OF 5454 GRAM-NEGATIVE ISOLATES FROM 55 GREEK HOSPITALS DURING A 3-MONTH PERIOD (SPRING 1989)**

Antimicrobial agent	*Pseudomonas aeruginosa*	*Acinetobacter* spp	*Enterobacter* spp	*Klebsiella pneumoniae*
Cephalothin	—	—	95%	63%
Cefotaxime	—	—	77%	51%
Ceftazidime	31%	92%	67%	46%
Imipenem	14%	1.1%	4.2%	0.5%
Ciprofloxacin	26%	59.6%	13%	10%
Amikacin	44%	91%	51%	45%
Gentamicin	45%	83%	43%	36%
Netilmicin	61%	90%	66%	45%

hygiene (particularly of hand washing and appropriate use of gloves), educational programmes for small groups of physicians belonging to different clinics, "consensus agreements" regarding mainly surgical prophylaxis, febrile neutropenia and nosocomial pneumonia (often in the form of clinical protocols) and limited susceptibility reporting from the hospital's Central Diagnostic Laboratory. The results were immediate and restricted antibiotic consumption was dramatically diminished (Table 2).

In order to improve further the quality of prescribing, an Antibiotic Team was formed in 1992, composed of an infectious diseases physician, a clinical microbiologist and a pharmacist, who undertook the mission to apply an audit programme in close cooperation with the pharmacy, as an extension to the already active restriction policy. Three times a week, an infectious diseases physician (who rotated monthly) audited the antibiotic restriction forms, before the pharmacy had delivered the required antibiotics (the pharmacy delivered drugs to departments three times a week). Whenever an order form was incomplete or the justification for requiring any restricted antibiotic seemed irrational, the infectious diseases physician visited the clinics and discussed the case with the resident doctors. Every justified order form was valid for five days, after which a new complete and justified order form

TABLE 2. **THE INITIAL EFFECT OF A RESTRICTED ANTIBIOTIC POLICIES PROGRAMME ON RESTRICTED ANTIBIOTIC CONSUMPTION**

	Number of patients on restricted antibiotics				
Restricted antibiotic	**January 1988[a]**	**September 1989**	**January 1990**	**March 1990**	**June 1990**
Vancomycin	118	32	15	16	15
Imipenem	102	28	22	32	13
Ceftazidime	150	60	43	54	26
TOTAL	370	120	80	102	54

[a] control = consumption without restriction

TABLE 3. **CONSUMPTION OF RESTRICTED ANTIMICROBIALS IN DIFFERENT CLINICS AFTER THE IMPLEMENTATION OF AN AUDIT PROGRAMME**

	Percentage of patients on restricted antibiotics				
Clinic	**November 1991 (without audit)**	**November 1992 (with audit)**	**November 1993 (with audit)**	**February 1994 (with audit)**	**February 1995 (with audit)**
TOTAL	9.6%*	6.5%	6.2%	6.6%	5.8%
General surgery	12.2%	35	0.9%	1.4%	0.7%
Orthopedics	8.4%	1.9%	3.3%	1.8%	2.5%
Urology	2.7%	0.3%	0.9%	0.8%	1%
Transplant Unit	19%	18%	7%	12%	7.7%
Internal Medicine (neutropenics)	11.6% (14%)	12.8% (29%)	11.4% (25%)	11.4% (41%)	11.2% (43%)

* before 1991 consumption exceeded 30%

needed to be sent to the pharmacy if the treatment was further prolonged.

In addition, every two months the Antibiotic Team organized scientific meetings with the staff and the residents of each clinic to discuss irrational order forms, case studies, and treatment guidelines. Such meetings provoked large-scale discussion and were considered to be the most effective educational programme on antibiotic use. At the same time surveillance of resistance and in-hospital antibiotic consumption was performed every 3 months and the results were released to physicians and discussed during the above-mentioned meetings.

After the introduction of the audit programme a further significant reduction in restricted antibiotics was observed (Table 3). The reduction was mainly attributed to the implementation of correct prophylaxis guidelines in the surgery departments (single dose of a second-generation cephalosporin perioperatively in clean-contaminated operations and three doses of vancomycin in orthopedic and vascular surgery with the use of prosthetic material). It is of interest that despite the fear that restriction of advanced antibiotics might increase the consumption of non-restricted antibiotics, the overall antibiotics use was reduced by more than 50%, ranging between 32% and 38.5% (= patients receiving antibiotics/patients hospitalized x 100) (Table 4).

After three years of applying the audit programme, there was a significant reduction in the resistance rates of several classes of antibiotics (Table 5). In particular, for *P. aeruginosa*, a major nosocomial threat, resistance to ceftazidime was reduced from 45% before 1990 to 8% in 1995, while for imipenem it remained low, at the same levels as when the antibiotic was introduced into the Greek market (5–10%). Interestingly, although aminoglycosides as a group were not officially restricted, their prescription in the hospital was self-limited due to the introduction of the newer β-lactams and the fear of nephrotoxicity and were confined only to septic or profoundly neutropenic patients. As a result of this minimal use, mean resistance rates for amikacin and gentamicin decreased from 55% and 85% respectively before 1990 to 12% and 19%. However, it should be pointed out that resistance to quinolones was not influenced by the antibiotic policy programme, but showed a steady increase, with levels of 35% and 30% for *P. aeruginosa*, and Enterobacteriaceae, respectively, observed in the spring of 1995. Consequently, the Infection Control Committee and the

TABLE 4. **TOTAL CONSUMPTION OF RESTRICTED AND NON RESTRICTED ANTIBIOTICS**

Year	Restricted antibiotics	Non restricted antibiotics
1991	12.5%	32%
1992	7.5%	36.5%
1993	7.3%	38.6%
1994	7.9%	34.7%

TABLE 5. **INDICATIVE DECREASING RESISTANCE RATES**

Antibiotic	Indicative Resistance Rates (%)			
	P. aeruginosa		*Enterobacteriacea*	
	1991	1994	1991	1994
Ceftazidime	45	8	—	—
Imipenem	7	7.5	0	0
Ciprofloxacin	20	35	2	8
Gentamicin	61	28	18	10

Antibiotic Team decided that the quinolones should be totally restricted in the hospital, prescribed only in cases where a pathogen was exclusively susceptible to this class of antimicrobials and after consultation with an infectious diseases physician and the approval of the Head of the Infectious Diseases Department. As a result, consumption of quinolones decreased abruptly (by 80%) during the first trimester, but it took two years of continuous application of the restriction policy to observe a marked decrease in quinolone resistance among the Gram-negative nosocomial pathogens (Table 6).

The above-mentioned policy has been success-

TABLE 6. **RESULTS AND IMPACT OF A TOTAL RESTRICTION PROGRAMME OF QUINOLONES ON RESISTANCE RATES**

	1st trimester 1995	4th trimester 1996
Patients hospitalized	5181	5215
Number of patients taking quinolones (%)	140 (2.7%)	30 (0.5%)
Defined Daily Dose (DDD)	1167	250
Sensitivity to Ciprofloxacin		
E. coli	92%	95%
P. aeruginosa	66%	82%
P. mirabilis	70%	84%
K. pneumoniae	74%	94%
Acinetobacter baumannii	15%	50%

ful in decreasing resistance rates in the closed system within a university hospital, because:

- Although restriction and audit were the main parameters of the policy, as an entity it was a multidisciplinary programme including surveillance, education, treatment guidelines, limited reporting sensitivity testing, consultation, and implementation of hygiene measures;
- The audit was effective because infectious diseases physicians had the cooperation of the microbiology laboratory and the pharmacy;
- The team that tried to apply it consisted mainly of infectious diseases physicians who worked with enthusiasm and belief, despite initial difficulties with their fellow doctors' attitude;
- Respected opinion leaders in the field of infectious diseases guided the programme, a fact that made the work of the Antibiotic Team easier.

The lessons we learned from this experience, especially the fact that controlling and limiting antibiotic use can reverse increased microbial resistance, can be applied to hospitals and the community. We are trying now to implement such a policy in hospitals on a national scale. Of course a prerequisite is the presence of an infectious diseases physician in every hospital who will be responsible for the implementation of the policy.

■ Russia: Hospital Case Studies of Antibiotic Policies

Report prepared by Leonid S. Stratchounski, MD, PhD, Director, Institute of Antimicrobial Chemotherapy (IAC), Russian Federation, Smolensk; President, APUA Russia; Roman S. Kozlov, MD, MSc, PhD, Deputy Director of Science, Institute of Antimicrobial Chemotherapy (IAC), Russian Federation, Smolensk; Coordinator, APUA Russia; Alla S. Andreeva, MD, Clinical Pharmacologist, Smolensk Regional Hospital, Russian Federation, Smolensk; and Oleg L. Rozenson, MD, PhD, Assistant Professor, Department of Clinical Pharmacology & Antimicrobial Chemotherapy, Smolensk State Medical Academy, Russian Federation, Smolensk.Contact Dr. Roman Kozlov: roman@cliph.keytown.com

Antibiotic Policy: Introduction of an antibiotic policy into a large regional hospital

This is a report of the implementation of an antibiotic policy in the Smolensk Regional Hospital (SRH): 1,320 beds, 30 wards.

Background

The introduction of an antibiotic policy into hospitals has previously been shown to be an effective tool in the curbing of antimicrobial resistance. Such policies have not been used extensively in Russia previously for a variety of reasons, including:

- Isolation of practicing doctors from modern international trends in antimicrobial chemotherapy.
- The results of microbiological investigations (including susceptibility testing) have little influence on clinical practice.
- Presence of a 'gap' between microbiologists and clinicians.

Description of the antibiotic policy

- Clinicians were taught about rational antimicrobial chemotherapy on a regular basis via seminars, case discussions, distribution of literature, participation in symposia and postgraduate courses.
- Clinical pharmacologists were appointed to the SRH and provided regular consultation with physicians on the choice of antimicrobials.
- A Formulary Committee was established with the introduction of a formulary and its regular update.
- Microbiological services were improved by means of:
  - — Continuous education of personnel in the microbiological laboratory (including the principles of selective reporting of susceptibility testing results);
  - — After-hours coverage;
  - — Implementation of internationally recognized guidelines (National Committee for Clinical and Laboratory Standards (NCCLS)) for susceptibility testing within the microbiological laboratory;
  - — Establishment of resistance monitoring programmes and data management (using WHONET and other software).

The main areas addressed in the antibiotic policy

- The analysis of antimicrobials use within the SRH and by different wards (using the recommended WHO ATC/DDD methodology).

- Education of both microbiologists and clinicians on clinical pharmacology of antimicrobials and current issues on antimicrobial resistance.
- Development and implementation of antimicrobial drug formularies.
- Policy to restrict the prescription of III-IV generation of cephalosporins, carbapenems, amikacin, vancomycin, and so on.
- Improvements in the microbiological service provided.

Level of policy enacted

This was a regional level policy that could be used as an example for other hospitals wishing to implement a similar strategy.

Interim results of the antibiotic policy

In 1999, a total of 33 antimicrobials were used in the SRH and 4 antibiotics were not given in comparison with 1997.

Over the same time period, hospital expenses on antimicrobials decreased by 40%.

Interim analysis of intensive care unit (ICU) data from 1997 was compared with data from 1997 (before and after implementing the above policy).

In general, the consumption of antimicrobials decreased 1.3-fold in 1999 compared with 1997 (from 214.43 DDDs to 162.95 per 100 beds/days, respectively). This was mainly due to a 1.2-fold decrease in the use of penicillins (from 118.6 to 98.23 DDDs per 100 beds/days in 1997 and 1999, respectively), a 1.8 times decrease in the use of all cephalosporins (from 20.4 to 11.4 DDDs per 100 beds/days in 1997 and 1999, respectively) and a 1.4-fold decrease in the use of aminoglycosides, especially gentamicin (from 48.9 to 34.0 DDDs per 100 beds/days). There was also a decrease in the consumption of imipenem and ciprofloxacin.

There was a decrease in resistance amongst nosocomial gram-negative bacteria: the resistance of P. aeruginosa to gentamicin decreased from 75.0% to 31.2% in 1997 and 1999, respectively and to amikacin from 7.0% to 1.8%.

At the same time, no changes were noted in resistance profiles of *E. coli*, *Klebsiella* spp., *Enterobacter* spp. and *Acinetobacter* spp.

In conclusion, the interim analysis showed that the establishment of an antibiotic policy in the SRH (by means of education of health care providers, antimicrobial resistance surveillance, and a formulary system) had financial advantages (a total 2.2-fold decrease in hospital spending on antimicrobials) and led to improvement in the resistance profiles of the most prevalent pathogen in the ICU (P. aeruginosa). An analysis of the influence of the antibiotic policy on the development of antimicrobial resistance in other hospital wards is currently under investigation.

Lessons learned from the above policy applicable to other countries

Education of health care providers, implementation of antimicrobial formulary and establishment of close connections between microbiologists and clinicians have proved to be the most crucial issues. Such approaches could be successfully used in both industrialized and developing countries.

Antibiotic Prophylaxis Policy: Optimization of antibiotic prophylaxis in surgical wards of Smolensk Regional Hospital (SRH)

Background

Antibiotic prophylaxis in surgery is an area where the consumption of antimicrobials remains very high. The analysis of indications, regimens and duration of antibiotic prophylaxis in the hospital indicated that optimization in this area is required, due to:

- Non-evidence-based administration of antibiotic prophylaxis.
- Irrational selection of antimicrobials for prophylaxis.
- Long duration of antibiotic prophylaxis.

All the above have led to the establishment of the main objective of the study: to evaluate the practice of antibiotic prophylaxis, conduct economic analysis of antibiotic prophylaxis in abdominal surgery in the SRH, and to evaluate the impact of educational and administrative activities on antibiotic prophylaxis.

Description of the antibiotic prophylaxis policy

- Targeted teaching of surgeons about the modern concept of antibiotic prophylaxis. Special attention was given to heads of departments.
- In collaboration with SRH authorities, the development and distribution of official recommendations on antibiotic prophylaxis within the surgical wards of SRH.

The main areas addressed in the antibiotic prophylaxis policy

- The education of surgeons on rational antibiotic prophylaxis and the principles of evidence-based medicine.
- The development and implementation of practical recommendations on antibiotic prophylaxis within the surgical wards of the SRH.
- Involvement of the authorities of the SRH in the implementation of antibiotic prophylaxis.

Level of policy enacted

This was a regional level policy, which could be used as an example for other hospitals wishing to implement a similar strategy.

Results of the antibiotic prophylaxis policy impact

Analysis was based on patient data, gathered retrospectively in 1993 and 1998. Three hundred and twenty-seven patients who underwent open cholecystectomy (OCE), appendectomy (AE) and hernia repair (HR) were included in the analysis. Antibiotic prophylaxis frequency and quality (selection of antimicrobials, dosage regimens, route of administration, post-operative duration) were assessed. In 1993, none of the patients received preoperative antibiotic prophylaxis, however, many patients received antimicrobial treatment after their operation for 5 to 8 days. In 1998, the following preoperative antibiotic prophylaxis frequency was registered: OCE–78%, AE–0%, HR–46%. In 1993, antibacterial administration without evidence of postoperative infection was registered for OCE in 82% cases compared to 31% cases in 1998.

Lessons learned from the antibiotic prophylaxis policy applicable to other countries

- Educational and administrative activities have a positive impact on antibiotic prophylaxis practice in surgery.
- The monitoring of antibiotic prophylaxis practice and feedback to surgeons needs to be implemented in hospitals for the optimization of antibiotic prophylaxis.

In our opinion, this policy can also be used in developing countries.

■ Bulgaria: Hospital Case Studies and National Antibiotic Policy

Emma E. Keuleyan, PhD, Assistant Professor, Department of Microbiology, Head Antimicrobial Resistance Laboratory, Medical University, Sofia, Bulgaria; Coordinator APUA Bulgaria Chapter.
Contact: keuleyan@medfac.acad.bg

In Bulgaria, as in other countries, the emergence and dissemination of antimicrobial resistance has been recognized as a major obstacle in antimicrobial chemotherapy, as well as an event with wide biologic significance. Several years after R - plasmids have been discovered by Okhiai and Akiba in Japan, the scientists started investigations on the genetic mechanisms of resistance and its epidemiology.

Some publications from the 1960s are cited below:

- Tyagunenko Y and Z Kyolean. 1967. Transmission of Multiple Antimicrobial Resistance in Strains of Fam. Enterobacteriaceae. Epidemiol Microbiol Infect Dis (Sofia). 4, 1, 26–31
- Tyagunenko Y and Z Kiolean. 1968. Studies on some characteristics in the transmission and manifestations of an episome with 5 R–markers. Proceedings of the Postgraduate Medical Institute ISUL. 15, 1, 35–41 (English).

With time, new aspects, new methods, and new approaches got more people interested in the antibiotic problem. The Department of Microbiology at Medical University,Sofia and the National Centre of Infectious and Parasitic Diseases have played the leading role in this evolution of knowledge, research, and activities.

As shown by experience, antibiotic resistance continues to increase and spread globally. Bulgaria has had some success in decreasing the antibiotic resistance problem, illustrated by the following examples.

A. Institutional level

Some hospitals, primarily at universities, have initiated programmes for resistance surveillance and control of infections, and established therapeutic committees to optimize antibiotic use.

1. Alexander's Hospital—Medical University, Sofia (1, 2)

While third generation cephalosporins, tetracyclines and aminopenicillins were widely used in 1993–

TABLE 1. **ALEXANDER'S HOSPITAL**

Antimicrobial resistance rate

Microorganism	Resistance in %	
	1997	3/1993–3/1994
Penicillin – R *S. pneumoniae*	33	32
MRSA	23	31
HLGenR Enterococcus	21–46	42
Ampicillin – R E. coli	75	65
ESBLs Enterobacteriaceae	5–16	2–5
P. aeruginosa – R to Ciprofloxacin	55	22
R to Ceftazidime	28	17
R to Amikacin	45	9
A. baumannii – R to Ciprofloxacin	50	20
R to Ceftazidime		51

Emerging in 1997: VRE <5%, R to Imipenem in *P. aeruginosa* – 30%; in *A. baumanni* – 5%

Antibiotic consumption (grams x 1000)

	1996	1997	(DDD/100/day) 3/1993–3/1994
Aminopenicillins	10	17.5	3.2
Aminopenicillins/inhib Bla	11	9.5	0.3
Cephalosporins 1st gen	21.5	68.0	2.0
Cephalosporins 2nd gen	27.5	26.5	2.7–3.4
Cephalosporins 3rd gen	19.5	7.5	1.4–3.5
Aminoglycosides	7.0	8.5	0.7–2.5
Tetracyclines	2.1	4.0	3.3
Quinolones	10.45	4.5	3.3
Trimethoprim/ Sulfamethoxazole	6.8	10.3	0.8

1994, the comparative analysis of 1997–1996 shows some improvement (decrease in third generation cephalosporins, tetracyclines, which need further restriction, and aminopenicillins for Gram-negative infections).

Comment: The reported success in antibiotic usage could be explained by: 1) introducing the WHONET programme in 1993; 2) establishing a Therapeutic Committee; 3) introducing the practice of a visiting microbiologist; 4) restricting some broad-spectrum antibiotics; 5) cycling of antibiotics for empiric therapy; 6) and the personality of the head of laboratory.

2. Military Medical Academy

Antimicrobial resistance monitoring was performed for a 20 year period. (3; and E. Savov–DSci thesis "Contemporary approaches to study problematic microorganisms for hospital pathology", 1999)

Significant resistance to gentamicin was developed around the middle of the 1970s. Amikacin was introduced in 1979. Like earlier experience in the world, the decision was made to restrict gentamicin and use amikacin as a first line aminoglycoside.

TABLE 2. **MILITARY MEDICAL ACADEMY**

Resistance towards aminoglycosides in %

Microorganism	First Period				Second Period					
	Gentamicin		Amikacin		Gentamicin			Amikacin		
	1975	94	75	94	1994	95	96	1994	95	96
E. coli	5	15	4	2	15	5	3	2	0	0
K.pneumoniae	13	60	3	8	60	63	25	8	12	5
E. cloacae	27	60	5	8	27	26	21	8	6	9
S. marcescens	13	55	9	11	55	30	22	11	4	3
P. aeruginosa	27	57	12	17	57	73	60 (data from thesis)			

As a result, by the end of the second period, a 2 to 3-fold decrease in resistance to gentamicin was achieved in enterobacteria, without significant dynamics in resistance to amikacin. There was also some decrease in gentamicin resistance among Gram-positive bacteria (*S. aureus, S. epidermidis, E. faecalis*). Data from the Hospital Pharmacy about antibiotic consumption showed that antibiotics prescriptions had decreased in 1997 by 30% from 1996 and by 56% from 1995. The author's opinion is that personal contact between microbiologists and clinicians was more effective than written guidelines and programmes.

3. Queen Ioanna Hospital–Medical University, Sofia

In 1993, a Therapeutic Committee was proposed and a Hospital Antibiotic Policy was established after wide discussions. This document suggests antibiotic prescribing to be at three levels: antibiotics for common use (prescribed by every physician); restricted antibiotics (to be discussed with the chief of the unit, e.g., 3rd generation cephalosporins); reserved antibiotics (for particularly resistant microorganisms, severe infections, or emergency; they need permission from the department and repre-

sentative of the Therapeutic Committee, e.g., imipenem, vancomycin). Because of the higher resistance rate to gentamicin, it was restricted and amikacin suggested to be the first line amino-glycoside.

TABLE 3. **QUEEN IOANNA HOSPITAL–MEDICAL UNIVERSITY, SOFIA**

Resistance to aminoglycosides in %

Microorganism	Gentamicin			Amikacin		
	1993	1995	1999	1993	1995	1999
E. coli	9	6	8	3	3	6
Klebsiella spp	41	34	26	7	5	17
Enterobacter spp	34	30	22	11	13	19
Serratia spp	62	53	24	9	35	22
Proteus spp	25	18	16	5	8	19
P. aeruginosa	24	60	59	5	37	50
Acnetobacter spp	51	77	66	36	70	69

A decrease in resistance rates to gentamicin was achieved in Enterobacteriaceae, the most significant decrease occurring in *Serratia*. However, this hospital had an increase of resistance to amikacin. This may be due to the strains with ESBLs (genes located on the same transposon).

Comment: It may be time to restrict amikacin.

The data cited above are from "Queen Ioanna Hospital Antibiotic Policy", 1993 and from "Annual Analysis of Antibiotic Resistance Rate and Antibiotic Use in QIUH", 1994, 1995, 1996, 1997, 1998, 1999", N. Hadjieva; N. Hadjieva and D. Ivanova. They have been presented at national and international congresses.

B. National level of the efforts to fight antimicrobial resistance

In her PhD thesis "Pharmacotherapeutic and pharmacoeconomic aspects of treatment with antimicrobial drugs in Bulgaria", 1997, M. Popova evaluated the approaches for antibacterial treatment of respiratory tract and urinary tract infections and antibiotic prophylaxis in surgery. She conducted the studies at two university hospitals, one general hospital in Sofia, one general district hospital, one specialized hospital, and several polyclinics. She also analysed the national antibiotic consumption during the period from 1979 to 1994 by implementing DDD/1000/ day methodology.

Her results show that the most common errors in prescribing practice were:

- Antibiotics given without objective data about bacterial infection
- Antibiotic prescribing not taking into account the results from the Microbiology Laboratory
- Lack of strategy about the empirical choice of antibiotic (misuse of broad-spectrum antibiotics)
- Frequent use of tetracyclin, tetracycline–oleandomycin and chloramphenicol
- Frequent use of ampicillin p.o. and subdosing of azlocillin
- Late initiation and long lasting antimicrobial prophylaxis in surgery
- Use of expensive and reserved antibiotics when other possibilities are available
- Occasional long therapies for pneumonia and pyelonephritis.

A survey about national antibiotic consumption showed that the most frequently prescribed antibiotics were:

1. Tetracyclines
2. Broad-spectrum penicillins (ampicillin and amoxicillin)
3. Sulfamethoxazole–Trimethoprim
4. Aminoglycosides (gentamicin)
5. Chloramphenicol
6. Narrow spectrum penicillins, macrolides, cephalosporins, lincozamides, and quinolones.

This list, while similar to those from other Central and Eastern European countries (*4, 5*) does not reflect contemporary principles of antibiotic usage. The author explains this non-prudent antibiotic policy by:

- Lack of systematic data about the dynamics of resistant strains
- Lack of a regular drug supply and insufficient budget
- Lack of basic, independent drug information
- Lack of an official strategy at most hospitals
- Lack of "sensitivity" in the society towards the problems of antibiotic use
- Lack of a pharmacoeconomic approach.

To overcome these problems she suggested:

- Optimizing the contacts between clinicians and microbiologists
- Establishing a hospital Therapeutic Committee
- Publishing guides for antimicrobial treatment and prophylaxis
- Establishing a Society for rational antibiotic use with wide participation of antibiotic prescribers, consumers, and providers.

This measure, according to M. Popova, would be able to curb self-medication, irrational prescribing, free sales, and the unethical promotion of antibiotics.

Comment: It is also necessary to establish a National Antibiotic Policy for both the hospital and ambulatory settings with strong legal and financial support of the Ministry of Healthcare, Government, and Parliament.

Recent data about approaches in antimicrobial treatment indicate significant improvement (*6–9*). While some past examples of antibiotic prophylaxis in surgery sound anecdotal, today most institutions use antibiotic prophylaxis consistent with international standards. Similarly, recent data about national antibiotic consumption show some improvement (Bulgarian Drug Agency, M. Popova; data have been sent to EURO DRUG):

Antibiotics	DDD/1000/Day		
	1994	1995	1999
Tetracyclines J01A	7.38	7.09	4.24
Amphenicols J01B	0.29	0.20	0.18
Penicillins J01C	7.23	7.76	7.64
Broad-spectrum Penicillins J01CA	5.15	6.22	5.96
Comb.Penicillins/Bla inhibitor J01CR	0.54	0.14	0.27
Cephalosporins J01D1	1.21	1.95	1.37
Carbapenems J01DH			0.004
Sulfonamides & Trimetoprim J01E	1.35	1.03	1.08
Macrolides & Lincosamides J01F	0.85	0.61	0.42
Aminoglycosides J01G	2.42	1.70	0.87
Quinolones J01M	0.09	0.27	0.034
Glycopeptides J01XA			0.001
Imidazoles J01XD			0.41
Urinary antiseptics G04A			0.67

As it can be seen from the table, in 1999 pencillins and broad-spectrum penicillins were the most commonly used antibiotics. From 1994 to 1999, use of aminoglycosides decreased nearly three-fold and use of tetracyclines decreased nearly two-fold.

Many factors have contributed to a better understanding of the consequences of antimicrobial resistance and the necessity of prudent antibiotic use. Among them, special attention has to be given to:

- The impact of scientists in research and education
- Political changes
- International collaboration and support.

Impact of scientists in research and education

Different aspects of epidemiology and mechanisms of resistance in Bulgaria, and methods for their detection have been studied (*3, 10–42*). A total of seventeen fellowships on the problems of antibiotic policies, methods for detection of mechanisms and epidemiology of antimicrobial resistance, and susceptibility testing were performed in leading world centres during the last 15 years. Eight research projects received grants from Bulgarian (Ministry of Education and Sciences, Medical University–Sofia) and international (APUA) organizations. These issues have been the focus of 8 theses. Pharmacodynamics, pharmacokinetics, and pharmacoeconomics studies were performed and several clinical trials were carried out.

Educational activities have been addressed to practitioners, providers, and consumers of antibiotics. More working hours for studying antimicrobial chemotherapy and antimicrobial resistance have been included in the education of students in medicine, dentistry and pharmacy. Written materials on principles of rational antibiotic therapy have become available for junior doctors. Post-graduate education courses on strategies of antimicrobial chemotherapy for different audiences (microbiologists, physicians, nurses) have been organized on a regular basis by the Medical University of Sofia and NCIPD. Popular articles were published in mass media and television discussions took place for the education of antibiotic consumers.

Political changes

Since 1989, when democratic changes started in Bulgaria, new criteria and new standards of drug

use were developed. State laws about drugs and pharmacies in human medicine were published and updated. Significant changes were made in drug regulation. As new antibiotics are licensed, each is given a complete description of dosage regimen and indications for all forms. The Ministry of Healthcare, National Drug Institute and Medical University's Pharmacy Faculty elaborated "Indicators to Follow up the National Drug Policy in Bulgaria" (1994–1996)—P. Uzunov, T Benisheva, G Petrova, Y Uzumov. A health care reform started on July 1, 2000, whose aim is to change the previously centralized state health care system to an insurance-based practice.

International cooperation and support

The progress during the last few years would not have been possible without the support of different international organizations. The World Health Organization (WHO) supported many different projects and activities. Professor Thomas O'Brien came personally to Bulgaria to speak on antimicrobial resistance and to introduce his WHONET programme for resistance surveillance. This programme now performs most resistance monitoring in Bulgaria. APUA supported the establishment of the APUA Bulgaria Chapter in 1998. The APUA has funded the current research project: "Survey of Antimicrobial Resistance in Bulgaria—first step in understanding the necessity of rational antibiotic policy" (E. Keuleyan and E. Savov) and recently supported another project: "Attempt to improve antibiotic use in Bulgarian hospitals" (E. Keuleyan and T. Sokolov). The European Community has several programmes to support education (Tempus), research, and other activities (PHARE). Due to a PHARE project, many international journals became available to Bulgarian scientists. PHARE supported the edition, "Bulgarian Therapeutic School", in 1995.

The Open Society Foundation has supported activities for Bulgarian scientists, including training courses, fellowships, participation at congresses, and organizing of symposia. During 1998 it supported a conference in Sofia on anaerobic infections with participation of the American Society for Microbiology. Bulgarian scientists participate in different international programmes, projects and organizations: WHO (Essential Drugs, EURO DRUG, Emergency Diseases); APUA; National Committee for Clinical and Laboratory Standards (NCCLS); WHO/CDC External Quality Assurance Programme; European Study Group on Antibiotic Policy; European Study Group for Antimicrobial Resistance Surveillance; European Study Group of Nosocomial Infections; European Society for Clinical Microbiology and Infectious Diseases (ESCMID); European Antimicrobial Resistance Surveillance System (EARSS); etc. All these forms of international collaboration are playing a substantial role in developing different activities to overcome the antimicrobial resistance problem.

Numerous additional organizations are taking part in the improvement of antibiotic use in Bulgaria; they can not all be cited and acknowledged in this brief review. It is also difficult to assess the particular impact of all factors, events, activities, and works that are dealing with developments in this area. The author's opinion is that fellowships in the prestigious world centres play a very important role for the development of future leaders in science, clinical work, and education. Among the activities that have not been mentioned, some that deserve to be noted are:

- In 1994 a National Society of Chemotherapy was created, which became a member of the International Society of Chemotherapy (ISC), the European Society of Chemotherapy (FESCI) and the Mediterranean Society of Chemotherapy. The First National Conference on Chemotherapy took place in Sofia in 1995.
- In 1998, the First National Conference on Pharmacoeconomics was organized in Sofia.
- Materials about antibiotic resistance are being discussed at the meetings of the National Societies of Clinical Microbiology and Medical Microbiology,.
- Efforts have begun for standardization and quality assessment in Clinical Microbiology (*43*). A specialized laboratory for these purposes was established at the National Center of Infectious and Parasitic Diseases. In April 2000, a Conference on Standardization and Quality Control was organized by Becton Dickinson—Bulgaria and NCIPD in Borovetz.
- An Expert Committee on Antibiotic Policy working with the Ministry of Healthcare was created in August 2000, to work on developing and establishing a national programme for a rational antibiotic strategy.

In conclusion, these are some examples of what has been done in recent years in Bulgaria to curb

antimicrobial resistance. This experience is on a small scale. Many more people need to be engaged to accomplish the goal. Many more people need to be educated and convinced of the problem. The perfection of antimicrobial chemotherapy will not come with the efforts of a small group of people or with fleeting interest. World experience shows that this is a difficult and long process. Curbing antimicrobial resistance will take more knowledge, work, education and funds.

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■ Sweden: National Antibiotic Use and Surveillance Projects

Major change in the use of antibiotics following a national programme: Swedish Strategic Program for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA). Sigvard Molstad, Otto Cars. *Scand J Infect Dis* 31:191–5, 1999. Report prepared by Otto Cars, Swedish Institute of Infectious Disease Control, Solna, Sweden; Chairman, STRAMA, Leader, APUA Sweden, otto.cars@smi.ki.se

STRAMA

The increase in bacterial resistance in Europe, the increasing sales of antibiotics in Sweden and the spread of penicillin-resistant *S. pneumoniae* (PRSP) in southern Sweden have alarmed both the medical profession and national health authorities. Therefore a national project named STRAMA,

Swedish Strategic Program for the Rational Use of Antimicrobial Agents and Surveillance of Resistance, was initiated in 1994.

National STRAMA-group

A national STRAMA group (www.strama.org) was appointed which was composed of specialists in infectious diseases, microbiology, general practice, ear, nose and throat (ENT), and pediatrics, from the Swedish Reference Group for Antibiotics. In addition, the national STRAMA-group included members from the Swedish Institute for Infectious Disease Control, the Swedish Medical Products Agency, the National Board on Health and Welfare, the National Corporation of Pharmacies, the Swedish Veterinary Agency, the Society of County Medical Officers for Communicable Diseases, and the Swedish Network for Pharmacoepidemiology (NEPI). The primary goal of the National STRAMA-group was to stimulate the formation of STRAMA-groups in each county. Together with these regional groups, the national STRAMA-group mission was to increase knowledge and understanding of the relationship between antibiotic consumption and bacterial resistance by both the medical profession and the public at large. The main objectives were to minimize the development and spread of resistance, both in outpatients and in hospitals, by a reduction of inappropriate antibiotic use, especially of broad-spectrum antibiotics, and to further develop and support resistance surveillance programmes.

Regional STRAMA-groups

In each county at least one STRAMA-group has been formed. The County Medical Officers for Communicable Diseases are chairing these regional groups, which include specialists from different medical fields, e.g., infectious diseases, ENT, pediatrics, microbiology, general practice and pharmacy. Some of the groups also include primary care nurses. The groups' main objective is to evaluate the use of antibiotics in the area and the pattern of resistance. After identifying problems in the area, the group uses its knowledge to influence health care workers to improve diagnostic procedures and the prescribing pattern of antibiotics. In some counties with tertiary care hospitals, special groups are formed to influence the use of antibiotics in hospitals. Since the immediate threat was the increasing incidence of PRSP, in most counties the initial work concentrated on the treatment of respiratory tract infections and antibiotic usage in pre-school children.

Antibiotic sales statistics

Apoteket AB (Corporation of Swedish pharmacies) keeps records of sales of medicinal products from the wholesalers to the pharmacies. From these databases, raw data on sales of antibiotics are extracted. The Anatomical Therapeutic Chemical classification system (ATC) is used for classification of drugs. The unit of measurement is defined daily doses (DDD) for human medicine and for veterinary medicine mostly in Kg of active substance. Dispensing of antinbiotics is monitored by all pharmacies. This implies that data are broken down according to hospital or community use. Prescriptions statistics are available for outpatients as DDD as well as number of prescribed items/ 1000 inhabitants/ day. From 1980 to 1995 this has been based on a sample of 1 out of 25 prescriptions, after 1996 all prescriptions served have been registered. The statistics are produced at national, county and since 1998 also at community level. It can be broken down to individual drugs, sex and age groups.

The Swedish Reference Group for Antibiotics (SRGA) and the Swedish Institute for Infectious Disease Control have developed a national recommendation for standardized antimicrobial susceptibility testing (www.srga.org). All 30 Swedish microbiological laboratories use the SRGA standardized disc diffusion method. The species related MIC and zone-diameter breakpoints from SRGA have been uniformly adopted as well as SRGA recommendations for external and internal quality assessment programmes. SRGA and the Swedish Institute for Infectious Disease Control perform yearly surveys of approximately 3000 strains (100 per laboratory) of each of *S. pyogenes, H. influenzae, S. pneumoniae* and every second year of *E. coli, Klebsiella* spp., *Enterobacter* spp, against a specified number of commonly used antibiotics. Special surveys have been directed towards antibiotic resistance in Gram-negative hospital isolates, UTI pathogens from primary care isolates and pathogens isolated from patients at Intensive Care Units. Findings of methicillin-resistant pneumococci (MIC>0.5 mg/l) and vancomycin-resistant enterococci (VRE) has been made notifiable.

In 2001, an Antibiotic Resistance Steering Group was formed at the Swedish Institute for

Infectious Disease Control. The aim of this group is to coordinate an extended national surveillance of resistance built on existing networks of clinical laboratories.

Activities and results

Between 1993 and 1997 the total antibiotic use was reduced by 22%; the reduction was especially evident for macrolides and broad-spectrum antibiotics. The reduction of antibiotic consumption has been more prominent in Sweden than in the other Nordic countries. Recommendations have been produced for the use of macrolides, vancomycin, fluoroquinolones and on the treatment of urinary tract infections, chronic bronchitis and skin and wound infections. A folder with information on respiratory tract infections, antibiotics and resistance has been distributed to all Swedish medical health care centres. Three symposia have been arranged for the regional groups. Media interest for the project has further increased the knowledge and understanding of the problem in the general population. During the last year Sweden has been engaged in several European Union (EU) projects concerning antibiotic resistance. The national STRAMA-group will continue to regularly follow the use of antibiotics and the incidence of resistance, coordinate necessary surveillance programmes and other activities in the counties and, if needed, make recommendations on identified problem areas.

The South Swedish Pneumococcal Intervention Project

Role of communicable disease control measures in affecting the spread of resistant pneumococci: the Swedish model. Karl Ekdahl, Otto Cars. *Clin Microbiol Infect* 1999; 5: 4S48-4S54.

During the last 20 years, the spread of penicillin resistant and multiresistant *Streptococcus pneumoniae* has become an increasing international problem. In the early years of the 1990s, the incidence figures in Malmöhus County in southern Sweden increased to 8–15%, while the corresponding figures for the rest of Sweden have remained at lower levels. Recommendations from a national expert committee were issued in 1995, outlining possible intervention measures against the spread of penicillin-resistant pneumococci (PRP) with minimal inhibitory concentration (MIC) for penicillin G (PcG) ≥0.5 mg/L among small children. The first large-scale attempt to implement these recommendations was started in Malmöhus County, in March 1995. The project is still running and has been followed by similar initiatives in most other Swedish counties.

Since March 1995, all PRP with MIC for PcG ≥0.5 mg/L have been directly reported from the three microbiology laboratories in the county to the Regional Center of Communicable Disease Control (RCCDC) in Malmö. Comprehensive retrospective data are available from January 1995.

Whenever an individual with an infection due to PRP is identified ("index case"), the RCCDC contacts the local health care centre of that patient. The local physician is then responsible for securing nasopharyngeal specimens from family members and other close contacts (e.g., day care group) of the index case, in order to identify carriers in the surrounding area ("contact cases"). All carriers (index cases as well as contact cases) are followed with weekly nasopharyngeal cultures, until two consecutive negative specimens have been obtained ("PRP negative"). All control cultures, and other health care contacts due to the project, are free of charge for the individual patient. If an identified carrier is a child participating in any form of child day care, nasopharyngeal specimens are also obtained from the staff and other children in that day care group. If more carriers are found, the screening procedures can be extended to the whole day care centre. Repeated cultures are then obtained every 1–2 weeks from the children and staff, until no more carriers are identified. Pre-school children who are identified as carriers stay away from group day care until they are PRP negative. The parents of these children are able to stay at home with full reimbursement from the social security system, if the day care cannot be arranged in any other way.

During the period from January 1, 1995 to June 30, 1998, 1545 PRP carriers (1492 individuals) were identified in Malmöhus County. Of the 1545 episodes, 642 (41%) were in index cases and 903 (59%) in contact cases. The pattern of carriage has shown a pronounced seasonal pattern, with most cases occurring during the winter months. Altogether 170 of approximately 600 day care centres in the county have been screened for PRP during the period. The number of PRP carriers in each day care centre has varied within great intervals (median 2, interval 1–23), and in half of the day care centres no further PRP carrier was identified. Screening cultures were, on average, obtained twice in each day care centre, before the day care centre could be declared "PRP-free".

The "Swedish intervention model" has applied traditional communicable disease actions (contact tracing and isolation) to a new phenomenon (antibiotic resistance). The measures are under continuing evaluation and the final conclusions have not yet been drawn.

Audit project

Medical audit changes physicians' prescribing of antibiotics for respiratory tract infections. Eva Melander et al. *Scand J Prim Health Care* 1999; 17:180–84.

In Sweden a prescription is needed to receive an antibiotic, and 60% of all antibiotics are prescribed for respiratory tract infections (RTIs). Several guidelines have been issued on a national level, giving rather strict criteria for antibiotic prescribing for RTIs. However, the actual sales of antibiotics do not show compliance with given recommendations in guidelines. Different methods have been tried to change the prescribing of antibiotics for RTIs, but the habits of physicians seem difficult to change. A group studied the diagnostic procedure and prescribing of antibiotics in clinical practice by applying the special Audit Project Odense model (APO) for quality development. The APO model has been applied in Denmark and Sweden for some years, and the method is based on a registration of consultations in a diagnostic area (e.g., hypertension, diabetes), where each participating physician during a limited period of time should be able to register a considerable amount of consultations. Participating physicians choose the registration parameters before the registration. Statistics are collected from the registered parameters. Each participating physician receives his own personal result, making a comparison between his own prescribing and the general group possible. The aggregated data of all consultations reflects clinical practice, which in turn can be compared with guidelines, national recommendations or other studies in the same field. The same registration shall be performed after approximately one year. Most importantly, between the two registrations a discussion should take place and an educational programme based on the result of the first registration be formulated.

The APO method was asked for in Orup, a medical district in Malmöhus County, to see if a change in the antibiotic prescribing habits of participating physicians could be obtained. Consultations for RTIs during the same periods among 25 doctors from a neighboring area who had not taken part in any intervention or follow-up discussion served as a control. The first registration took place during 4 weeks in January–February and the second during 4 weeks in November–December. The physicians registered diagnosis, diagnostic methods, C-reactive protein, bacterial culture, X-ray, ultrasound, antibiotic prescribing (penicillin V, ampicillins, macrolides, tetracyclines, cephalosporins, "other antibiotics" and "no antibiotic").

In Orup, 33 physicians participated in the first registration, 25 in the second. Twenty GPs who participated in both registrations were included in the study and registered 1124 consultations for RTIs during the first period and 926 during the second. In the control group the 25 GPs registered 1313 consultations for RTIs during the first period and 1309 during the second.

The proportion of patients not prescribed any antibiotic increased in both groups—in the intervention group from 45 to 55% and in the control group from 36 to 40%.

The APO model is a method for internal revision of medical practice. The method is based on knowledge of recorded aspects of work and, through discussion, the participants agree on what is better and what is worse general practice and change their care accordingly. The registrations are anonymous and the individual physician's result is known only to himself. The APO model has been used on several occasions in Sweden but has not previously been evaluated.

■ United Kingdom: Tackling antibiotic resistance in the UK and Europe

A Personal Perspective by Ian M. Gould, Consultant Microbiologist, Department of Medical Microbiology, Aberdeen Royal Infirmary, Aberdeen Royal Hospital, Aberdeen, Scotland. Contact: i.m.gould@abdn.ac.uk

In 1988, the British Society for Antimicrobial Chemotherapy (BSAC) formed a working party (WP), having been stimulated into action by the Infectious Diseases Society of America (IDSA) Task Force Reports. Up until then, there had been no national initiatives concerning antibiotic prescribing, which historically was probably at a lower level than in the United States.

In addition, because of the National Health Service, with free care for all, there was less of an issue in the costs of antibiotics which, at least in hospitals, amounted to less than 20% of hospital drug use.

With a nationwide survey the BSAC WP established which control measures were then operational in UK hospitals, amounts of consumption in general practice, and educational practices for medical students. Serious deficiencies were noted in antibiotic policies and other control measures. Recommendations were made for minimum control measures to be implemented in hospitals. Educational activities were established as sub-optimal and levels of consumption in general practice were noted to be rising at 2–3% per year (past numbers). However, as measured by DDDs, consumption levels seemed moderate by comparison to many other European countries (20 DDD/ 1000 patient days).

These working party reports were published in 1993–4. In subsequent years little seems to have happened except for local initiatives complicated by reforms of the National Health Service and introduction of the purchase-provider split which may have been counter-productive by reducing the use of laboratory services by general practitioners who then had to pay for these services. The same cost-conscious reforms in hospitals led to a marked reduction in bed numbers with consequent overcrowding, bed shortages, and boarding possibly leading to an upsurge in nosocomial spread of multidrug-resistant bacterial clones. There was also pressure to increase the emphasis on broad-spectrum empiric therapy and reduce the use of timely laboratory investigations to discharge patients early.

At this time an increase in hospital cases of *C. difficile* colitis was attributed to over-zealous interpretation of the British Thoracic Society guidelines for hospital treatment of community-acquired pneumonia which recommended third generation cephalosporin therapy for severe pneumonia but which were commonly re-interpreted as recommending this treatment for any case of pneumonia requiring hospital admission.

At the time of the House of Lords enquiry into the problem (1997), which may have been initiated by the personal experiences of one or two of their Lordships after they or their relatives acquired a methicillin resistant *Staphylococcus aureus* (MRSA) infection in a hospital, there had already been some activity at a European level with the Commission starting to give grants for Pan-European surveillance of resistance. Learned societies like the European Society for Biomodulation and Chemotherapy (ESBIC) and The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) formed study groups to study resistance surveillance, nosocomial infection, and antibiotic policies such as ESGAP (www.escmid.org). Community action groups such as SWAB (Holland) and STRAMA (Sweden) were formed to educate both the public and prescribers; the European Medicines Evaluation Agency (EMEA) and the Office International des Epizooties (OIE) formed working groups to address resistance and surveillance issues; and the Copenhagen meeting brought all the European Union (EU) countries together to address the issues in 1998.

The most notable result of this meeting was the ban on the use of antibiotic growth promoters in 1999, which is currently implemented but is being debated in the courts by two pharmaceutical manufacturers. Nevertheless, it seems to have had a major impact on the animal consumption of antibiotics in all European Union countries, if official figures are to be believed. No doubt there is a large black market which we know little about.

In light of the House of Lords Report (1998), the UK government was stimulated into action with its own expert Standing Medical Advisory Committee Report and its separate response to the House of Lords Report (1999). The first result of this was a public education campaign advising patients not to pressure their doctors to give them antibiotics for colds and flu and recommending 3 days treatment for simple UTIs. There is some evidence now, from this and similar local campaigns, of reduced expectations by patients, but no sudden downturn in community prescribing of antibiotics-there has been a slow (3%) annual downturn since the mid 1990s.

Meanwhile, the Public Health Laboratory Service in England and Wales (PHLS), WMA (Welsh Microbiological Association), SMA (Scottish Microbiology Association) and a local Northern Ireland initiative have been using computerized laboratory facilities to organize national surveillance systems both for nosocomial infection and antibiotic resistance, although all are still in their pilot phases. The Scottish Government produced two documents underlining the importance of infection control and nosocomial infection surveillance and the PHLS published results of a large survey on nosocomial infection. Combined with a report from the National Audit Office (NAO) and others, criticizing the levels of nosocomial infection and poor standards of hospital cleanliness, the UK government (1999) (and latterly the Scottish Government) have formed multi-disciplinary expert advisory groups on antibiotic resistance surveillance and nosocomial infection.

It is also the intention to monitor antibiotic consumption and quality of prescribing and there is a commitment to computerized prescribing in hospitals by 2005 and computer links between laboratories and general practitioners by 2001. All general practitioners should have had computerized prescribing facilities and links to the Internet by the end of 2000. At the moment, all prescriptions in general practice are monitored but there is little data available on the indications for prescribing. Approximately 80% of antibiotic consumption takes place in the community. At the moment there is no formal measurement of prescribing in hospitals but the little data in the public domain suggests a continued annual increase in cost and DDD, although, as a percentage of hospital drug budgets, it probably remains stable at 20%.

The little available comparative data suggests the UK hospital antibiotic consumption compares quite well with most European countries (40DDD per 100 Patient Days). This area is also a priority for the EU.

It is hoped that the latest round of reforms of the National Health Service, with its drive to improve quality and ensure better education of and performance by doctors, will improve antibiotic prescribing. This includes the introduction of Clinical Governance which intends to make doctors responsible for the quality of their antibiotic prescribing and empower their employers to ensure that this quality is achieved. At the moment, accreditation of doctors (and hospitals) is in its infancy but developing rapidly, and it is hoped that CPD will have a large part devoted to antibiotic resistance although legislatively. The matter of how much can be done legislatively to force the issues of Antibiotic Resistance and Nosocomial Infection with hospitals is another matter.

The newly formed Clinical Standards Board (Scotland) and Commission for Health Improvement (England, Wales & Northern Ireland) should have the teeth to deal with this and consideration is being given to benchmarking hospitals of similar types for infection and antibiotic resistance rates. There are encouraging signs from the government that they intend hospitals to carry the issue of antibiotic resistance forward as a Strategic Goal.

The drive towards evidence-based guidelines and policies is slowly progressing with separate government, PHLS, BSAC, Royal College of Physicians, and other institutions' initiatives, and the PHLS have published evidence-based guidance for primary care doctors on the Internet (www.phls.co.uk) The BSAC has also reformed its Education Working Party and the National Prescribing Centre in Liverpool has developed a computer self education and assessment programme for changing doctors' practices, which looks specifically at antibiotic prescribing.

With the merger of many pharmaceutical companies, consequent movement out of the UK, and the development of European Registration of new antibiotics, there is a great concern in the UK at the loss of a research base from which to develop new antibiotics, so new initiatives in this field are likely. While there are always counter rumors, there does seem to be a genuine, continued desire both at a UK and a European level to continue with these initiatives, not withstanding the politics!

It is too early yet to evaluate the success of any of this activity. With devolution and the establishment of the Scottish Parliament and the Welsh and Northern Ireland General Assemblies there is even more danger of duplication of activities than there would have been otherwise, so one of the main concerns will be to ensure coordination. To this end there are a relatively small number of core opinion-leaders who seem to serve on most of the UK central and devolved advisory committees and working parties and it is hoped that they will ensure as little duplication as possible.

At a European level the commission in Luxembourg has an interest in many aspects of the issues and has recently issued a draft resolution calling for a publicity campaign with an annual Antibiotic Free Day. They are also interested in as much harmonization of antibiotic use and control measures between member states as is possible and there is some possibility of legislative control on measurement of antibiotic consumption, both in animals and humans. On the issue of antibiotic resistance surveillance, Pan-European initiatives are proving expensive and there is a move to improving the quality of routinely generated data from diagnostic laboratories so that it can be used for European surveillance purposes.

Unfortunately there are several systems of susceptibility testing in common use in Europe in addition to National Committee for Clinical and Laboratory Standards (NCCLS). These include Swedish, French (CA-SFM), German (DIN) and UK (British Society for Antimicrobial Chemotherapy, BSAC) methods, all with different interpretative criteria. There have been calls for a European system, perhaps adopting NCCLS in all countries, but we are nowhere near reaching agree-

ment. Many people consider the diversity of susceptibility testing methods a strength, especially when discovering new resistance mechanisms, and they suggest that establishing comparability between different systems will be a satisfactory compromise. They have, though, been saying this for 30 years and we don't seem to be any further forward. Scotland, which does not have a PHLS, has decided to adopt NCCLS and also the NISS system for nosocomial infection surveillance and Wales and Northern Ireland may well do the same. England (through the PHLS) looks as though it will adopt the BSAC methodology for susceptibility testing and the NINS (Nosocomial Infection National Surveillance) system for nosocomial infection surveillance. This latter system uses a different set of risk factors than NISS (Nosocomial Infection Surveillance System)

■ Scotland: Antimicrobial Resistance Strategy and Action Plan 2001

Ian M.Gould, Consultant Microbiologist, Department of Medical Microbiology, Royal Infirmary, Aberdeen Royal Hospital, Aberdeen, Scotland.
Contact: i.m.gould@abdn.ac.uk

The main causes of antibiotic resistance bacteria in diseases of humans in the UK at present are:

1. Excess antibiotic use in primary care
2. Excess use in hospitals exacerbated by epidemics of antibiotic resistant bacteria in our hospitals.

The underlying reasons are prescriber ignorance and lack of ownership of the problem.

Audits repeatedly show poor quality, often completely unnecessary antibiotic prescribing, poor cleaning standards in hospitals, and poor compliance with infection control procedures. The action plan concentrates on recommendations to address these areas with detail on implementation.

In hospitals, audits repeatedly show unnecessary antibiotic use in the absence of positive microbiology and in patients with no sepsis parameters. Often unnecessary, expensive, broad spectrum, toxic agents are administered by the IV route for too long, in often inappropriate doses. There is both inappropriate and under-utilization of laboratories. There is a lack of understanding of how the laboratories can help in therapeutic decision-making, such as deciding the need for empiric therapy, the choice of antibiotic, or how to streamline or stop the therapy. Finally, there is poor compliance with antibiotic policies.

Poor compliance with policies for hospital cleaning, hand washing, standard precautions, barrier nursing, and isolation of colonized or infected patients also occurs due to ignorance, bad practice, overcrowding, or lack of facilities.

The solutions are:

1. Via education, persuade all doctors, health administration and managers to accept ownership of the problem.
2. Use incentives, penalties, or extensive, aggressive education to get doctors to change their ways of practice (known to be very difficult). Implementation and audit should become priorities for health boards, hospital trusts, etc.
3. Increase resources to allow better patient isolation, improved laboratory facilities, (including access to them and communication by them), improved hospital cleanliness, increased staff-patient ratios and reduced overcrowding/boarding of patients.

Animals and horticulture, surveillance and research are all important (but side) issues. We know there is a major problem, albeit much greater in most other countries than in the UK, and we understand enough about the causes to address them now.

APPENDIX C

About the authors

Alliance for the Prudent Use of Antibiotics (APUA)

75 Kneeland Street
Boston, MA 02111-1901
Phone: 617-636-0966
Fax: 617-636-3999
E-mail: apua@opal.tufts.edu

Jerry L. Avorn, M.D.

Director, Program for the Analysis of Clinical Strategies
Brigham and Women's Hospital
Suite 341
221 Longwood Avenue
Boston, MA 02115-5822
Phone: 617-278-0930
E-mail: javorn@partners.org

Associate Professor of Medicine at Harvard Medical School and Chief of the Division of Pharmaco-Epidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, geriatrician, and pharmaco-epidemiologist, his research centres on medication use, with particular reference to elderly patients and chronic disease. Topics of particular interest include: scientific, policy, and social determinants of physician prescribing practices; efficacy and effectiveness of specific medications; compliance by patients with prescribed regimens; methods to improve the appropriateness of drug prescribing and drug taking; quantification of risks and benefits of drugs; and pharmaceutical cost-effectiveness analysis. Dr. Avorn is also director of the Program for the Analysis of Clinical Strategies, a research unit with faculty and staff representing the disciplines of epidemiology, internal medicine, health services research, psychiatry, and biostatistics. He attended Columbia College and Harvard Medical School, and completed a residency in internal medicine at the Beth Israel Hospital in Boston. Dr. Avorn serves on several national and international panels as an expert on the determinants and outcomes of medication use, and until August of 1998 was President of the International Society of Pharmaco-Epidemiology. Dr. Avorn is the author of over 150 papers in the medical literature on medication use and its outcomes.

John F. Barrett, Ph.D.

Executive Director, Microbiology Department
Bristol-Myers Squibb Company
Pharmaceutical Research Institute
5 Research Parkway
Wallingford, CT 06492-7660
Phone: 203-677-6499
Fax: 203-677-6771
E-mail: john.barrett@bms.com

Currently Executive Director of Anti-Infectives Research at Bristol-Myers Squibb, Wallingford, CT. With 16 years experience in the pharmaceutical industry, he has experience in a wide breadth of antibacterial and antifungal discovery and development efforts at Pfizer and Johnson & Johnson's RW Johnson Pharmaceutical Research Institute. Dr. Barrett received his B.S. in Biochemistry from Temple University in Philadelphia, PA, and his doctorate in Microbiology and Microbial Physiology from Temple University School of Medicine, with the late Gerry Shockman, Ph.D. He completed a postdoctoral fellowship in genetic engineering with Roy Curtiss III, Ph.D. (UAB and Washington University), and joined Pfizer in 1985, RWJPRI in 1989, and BMS in 1997. His research efforts have included β-lactams, penams, penems, β-lactamase inhibitors, quinolones, novel gyrase inhibitors, HIV gp120/CD4 antagonists, cephems, signal transduction inhibitors, virulence factors, and mammalian topoisomerase II inhibitors. Dr. Barrett is a member of numerous editorial boards and author of over 160 publications, as well as the 1999–2000 Division A Chair of the American Society of Microbiology. He became a Fellow in the American Academy of Microbiology in 2000. He leads a group of research scientists seeking the identification and development of novel antimicrobials and

antifungals through a combination of classical discovery strategies and techniques and a proprietary genomics effort. Dr. Barrett has been involved with the development of several antibacterials currently on the market including ofloxacin, levofloxacin, and gatifloxacin, and is currently working on the development of a novel MRSA-cephem (BMS-247243) and the des-quinolone (BMS-284756/T-3811) at Bristol-Myers Squibb.

Peter G. Davey, M.D.

Professor of Clinical Pharmacology
University of Dundee
Nethergate, Dundee DD1 4HN
Scotland, UK
Phone: +44 (0)1382 660111
E-mail: peter@memo.dundee.ac.uk

Has expertise in clinical pharmacology, infectious diseases, and health economics. He has served as a Professor of Pharmacoeconomics, Clinical Pharmacology and Infectious Diseases at the University of Dundee, Scotland. Among his many teaching activities, he has developed new curricula focusing on antimicrobials for a number of courses for medical and dental students. He has extensive research experience, including clinical trials and evaluations of antimicrobials, assessments of antimicrobial action *in vitro* and in experimental animals; clinical pharmacokinetic studies of antimicrobials, and studies of gentamicin treatment. Since 1996, Dr. Davey has served as Head of Pharmacoeconomics for the Medicines Monitoring Unit (MEMO), where he focuses on economic evaluation and outcomes research of drug treatment, and on antibiotic policies and their influence on the development of drug resistance in hospitals and the community. He has helped develop treatment guidelines and national policies on antibiotic use in Scotland, served as an advisor to the House of Lords Commission on Antimicrobial Resistance, and has spoken extensively on antimicrobial use at international symposia, conferences, and meetings.

Stuart B. Levy, M.D.

President, Alliance for the Prudent Use of Antibiotics
Room 704, South Cove
Tufts University School of Medicine
136 Harrison Avenue
Boston, MA 02111-1817
Phone: 617-636-6765
Fax: 617-636-0458
E-mail: stuart.levy@tufts.edu

President and founder of the Alliance for the Prudent Use of Antibiotics, and immediate past president of the American Society for Microbiology. A microbiologist and physician, Dr. Levy discovered the mechanism for tetracycline resistance (efflux) and was among the first to document the transfer of drug resistance among animals and humans. Dr. Levy is the author of one of the most important books on the subject, *The Antibiotic Paradox: How Miracle Drugs are Destroying the Miracle*, which has been widely cited in both the lay and scientific media. He has also written more than 200 scientific and medical papers and special journal editions on the topic. A world-renowned leader in the field of antibiotic use and resistance, he has chaired and served on numerous national and international advisory boards and committees, including: the NIH Fogarty Center's study on The Use of Antibiotics Worldwide (as Chairman); the advisory panel for the USA Office of Technology Assessment report on the Impacts of Antibiotic Resistant Bacteria; the EPA Subcommittees on Health and Antibiotic Resistance; and the WHO Scientific Advisory Group on Antimicrobial Resistance. Dr. Levy has also served as a consultant for the World Health Organization, the USA FDA, the National Institutes of Health, and other national and international organizations. He is currently Professor of Medicine and of Molecular Biology/Microbiology, the Director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine, and a Staff Physician at the New England Medical Center.

Scott A. McEwen, D.V.M.

Professor, Department of Population Medicine
University of Guelph
Guelph, Ontario N1G 2W1
Canada
Phone: 519-824-4120, ext. 4751
E-mail: smcewen@uoguelph.ca

Professor in the Department of Population Medicine, Ontario Veterinary College, University of Guelph. He is a veterinarian whose research focuses on the epidemiology of food-borne infections in food animal populations, particularly *Salmonella, E. coli* and antibiotic resistant organisms. He has

conducted extensive research on human health impacts of antimicrobial use in animals, including studies of antibiotic and chemical residues in milk and meat, and the association between resistance and antibiotic use on farms, and has published more than 80 papers in peer review journals. Dr. McEwen has served as a consultant for WHO on the human health impact of antimicrobials in food animals, and as panel member for the U.S. FDA on antimicrobial resistance risk assessment. He also chaired the Health Canada Advisory Committee on Animal Uses of Antimicrobials and their Impact on Resistance and Human Health. Dr. McEwen teaches food safety to veterinary students and graduate students at the University of Guelph.

Thomas F. O'Brien, M.D.

Medical Director, Microbiology Lab
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115-6110
Phone: 617-732-6803
E-mail: tobrien@rics.bwh.harvard.edu

Vice President of APUA, is a leading authority on antibiotic resistance and AMR surveillance. An infectious disease specialist and microbiologist, Dr. O'Brien helped develop the WHONET surveillance program. He also set up the WHO Collaborating Center for Surveillance of Resistance to Antimicrobial Agents at Brigham and Women's Hospital in Boston in 1985, which has established an international network of microbiology laboratories dealing with antimicrobial resistance surveillance. Dr. O'Brien has served as an advisor on numerous national and international committees dealing with antimicrobial resistance, including the NIH Task Force on Antibiotic Resistance, which he chaired from 1984 to 1986; the WHO Scientific Working Group on AMR (1981); the FDA's Veterinary Medicine Advisory Committee (since 1994); the Office of Technology Assessment Advisory Panel on Impacts of Antibiotic-Resistant Bacteria; the Inter-Agency (FDA, CDC, USDA) Working Group on Antimicrobial Resistance; and the CDC Working Group on Drug Resistant *Streptococcus pneumoniae*. He has also served as a consultant on antimicrobial resistance to WHO (in Geneva and Manila), PAHO, the British House of Lords, and the National Health Research Institute of Taiwan, among others. Medical Director of the Microbiology Laboratory at Brigham and Women's Hospital for the past 20 years, Dr. O'Brien is a pioneering researcher in the area of antimicrobial resistance, having conducted microbiological studies on resistance since the mid-1960s.