

PRIORITY RESEARCH TOPICS

Understanding all the issues associated with antimicrobial resistance is probably impossible, but it is clear that there are a number of key issues about which we need more information. Given the emerging clinical impact of antimicrobial resistance, urgent implementation of the Global Strategy for the Containment of Antimicrobial Resistance is required. However, at the same time, a clear research agenda highlighting the most important current knowledge gaps needs to be defined to guide the direction of future research efforts. In this manner, new data that are important to understanding and combating the problem can be channelled back to improve future containment initiatives. A summary of some important issues are described below:

1. Patients and the General Community

- Why are certain antimicrobials so popular; for example, injections rather than oral formulations; why some particular products rather than others (e.g. capsule rather than tablet; some colours rather than others)?
- What factors influence patients' expectations from antimicrobials, including marketing directed at the general public?
- What satisfies a patient in lieu of a prescription for an antimicrobial at every consultation?
- What is the impact of gender, age and other demographic factors on antimicrobial use?
- In what circumstances do large and small group campaigns designed to reduce antimicrobial use lead to behavioural change?
- Can health educators employ better marketing techniques?
- What patient educational materials and other supportive tools impact optimally on patient behaviour with respect to antimicrobial use?
- What is the effect of patient adherence to prescribed therapy on emergence of resistance?
- What is the impact of interventions that are designed to change antimicrobial use on patient outcome? For example: How do symptom scores and patient satisfaction compare when respiratory infections (e.g. purulent rhinitis/common

cold or cough/bronchitis) are treated with symptomatic therapy, antimicrobials or placebo? What is the impact of deferring antimicrobial therapy for acute otitis media? (since up to 80% of infections will resolve within 2-3 days without antimicrobial therapy). Do case management criteria for fever and rash in non-malarious areas (e.g. incorporated into guidelines for the integrated management of childhood illnesses) improve antimicrobial use?

- What is the extent of self medication (antibiotics accessed over the counter, drug sellers, "left over" from previous course) and what impact does it have on antimicrobial resistance?
- How reliable is syndromic self-diagnosis by an individual or parent in the community settings?
- What is the impact of antimicrobial use on levels of antimicrobial resistance in colonizing organisms as well as pathogens within a given community? In particular, what is the risk of resistance development with different intensity of use and how variable is this with different organisms and antimicrobial agents? What other community factors (e.g. water supply, cleaning practices, crowding, number of children in the home, etc.) promote transmission?
- Evaluate the effectiveness of self-treatment strategies for selected infections;
- If antimicrobial therapy is given for a specific infecting organism when the susceptibility is 20% or less, what is the impact on morbidity and mortality, including further antimicrobial resistance and the necessity for subsequent courses of therapy? This is most relevant for more minor infections.
- What is the epidemiology of resistance in daycare centres?
- Would the introduction of infection control principles reduce transmission of resistance in day care centres?
- Do antimicrobials present in the environment have an impact in promoting antimicrobial resistance in humans or animals?
- What is the attributable morbidity and mortality of antimicrobial resistance in different settings in both developed and developing countries?
- What is the natural history of antimicrobial resistance to a given antimicrobial agent if that antimicrobial agent is completely removed from use in the community?
- What are the determinants that lead to self medication?

2. Prescribers and Dispensers

- How can policies be translated into practice in a sustained manner to improve:
 - a) clinical diagnosis and disease management;
 - b) prescribing practices (antimicrobial use patterns);
 - c) patient care practices (handwashing, catheter insertion, etc.);
 - d) adverse effects monitoring and reduction.
- What are the most appropriate and cost-effective training strategies to achieve the above? Do these practices result in improved antimicrobial use and infection control and in reduction in the emergence and spread of antimicrobial resistance?
- What is the reliability and utility of point-of-use diagnostic strategies for common infectious diseases in clinical practice? Can more widespread use of these decrease antimicrobial use and resistance?
- What are the key interventions for a cost-effective outcome (reduced use, resistance etc)
 - a) Improved diagnosis
 - b) Practice/prudent use guidelines (use of evidence-based medicine to produce guidelines; how to communicate to prescribers; how to audit adherence, effect on antimicrobial use, resistance and health outcome)
 - c) Practice profiling and feedback
 - d) Education programs (small group, peer run, use of opinion leaders, different materials - printed, web based etc)
 - e) Use of decision support systems -(computer assisted stratified for patient risk and linked to prudent use guidelines)
 - f) Delayed prescriptions
- What role do dispensing physicians have on the inappropriate use of antimicrobials?
- Do counterfeit antibiotics/poor storage or low quality generics play a role in resistance selection?
- What role does incorrect dosing schedules (due to poverty/self medication/poor prescriber knowledge) have on resistance selection?
- Does the education of non-physician prescribers influence antimicrobial use?

3. Hospitals

- What are the links and interactions between antimicrobial resistance in hospitals, nursing homes and the community?
- What are the most cost-effective methods to limit transmission in hospitals with limited resources?
- What are the most efficient surveillance systems for identifying antimicrobial resistance either as a colonizer or causing infection, in different hospital settings in developed and developing countries?
- Is there a prevalence of antimicrobial resistance to a particular pathogen at which surveillance or infection control precautions to decrease spread are no longer warranted?
- In a facility which already has a high level of resistance in a particular organism, what are the benefits of intensification of infection control precautions in decreasing morbidity and mortality associated with the resistant organism?
- What infection control interventions provide the best cost benefit in facilities in developing countries?
- What is the most effective utilization of microbiology resources for diagnosis of infectious diseases in resource-poor countries and facilities?
- How can the role of clonal spread versus resistance selection be determined?
- What role do different prescribing strategies have, such as restricted use, class restriction, antibiotic cycling?
- Are hospital audit teams effective?
- What impact does the introduction of an antibiotic policy have on prescribing.

4. Use of antimicrobials in food-producing animals

- Clinical trials to optimise dose, dose interval and duration of antimicrobial treatment in animals to improve prescription use of antimicrobials;
- What are the best means to prevent and control foodborne and zoonotic diseases at the animal production level to reduce the risk of transmission of resistant bacteria to humans;
- Non-antimicrobial alternatives for the control of infectious diseases and syndromes in animals, particularly multifactorial diseases in young animals;
- Development of more rapid diagnostic methods for bacterial infections to reduce need for empirical treatment;

- To what degree is there interspecies transfer of antimicrobial resistance (i.e. between plants, animals, humans and environmental organisms);
- What is the rate of development of medically important bacterial resistance in food-producing animals, in relation to duration of exposure to and concentration of antimicrobial (especially concentrations below the minimum inhibitory concentration) and including the resistance selection potential of antimicrobials at permitted minimum residue levels;
- Effect of cessation of use of specific antimicrobials on the prevalence and persistence of resistant bacterial in food-producing animals and their immediate environment;
- Information on the stability of important antimicrobials and their metabolites in the environment;
- Impact of the use of antimicrobials in domestic pets and birds on the development and persistence of resistance bacteria in the farm environment;
- Alternative approaches for growth promotion that do not require antimicrobials;
- Risks from the presence of resistance genes in bacteria used as probiotics;
- Appropriate risk assessment models and data needed to allow the models to be implemented;
- Appropriate post-approval monitoring schemes to complement pre-approval risk assessment models.

5. National Governments and Health Systems

- What would be the impact on antimicrobial resistance of enforcement of existing laws and regulations?
- What are the effects of health sector reform and health care policy with respect to antimicrobial use and antimicrobial resistance?
- Do economic and regulatory strategies have an impact on changing prescribers' behaviour?
- Does the prospect of litigation lead to defensive over-prescription of antimicrobials and thus increase occurrence and spread of resistance?
- What are the effects of reimbursement, patient charges, and health insurance on antimicrobial resistance? For example:
 - a) Do these have an impact on inappropriate antimicrobial use?

b) To what extent does a patient's economic situation lead to misuse of antimicrobials?

c) Do cost control policies have an impact on inappropriate antimicrobial prescribing?

- Are the effects of rigid formularies, antimicrobial use approval systems and treatment guidelines positive or negative with respect to antimicrobial resistance?
- What are the essential quality assurance procedures required to ensure meaningful antimicrobial resistance data?
- What is the role and cost-effectiveness of laboratory diagnostic results, including culture and antimicrobial susceptibility testing, in specific patient care circumstances, including managed care settings?
- Can rapid diagnostic methods, applicable to international surveillance systems, be developed to identify resistant bacteria?
- What incentives are needed for companies to expand research into improved rapid diagnostics for infections, including simple, affordable, field-adapted diagnostics?
- What are the key surveillance networks for combating antimicrobial resistance?
- What is the minimum effective surveillance, including data elements and case finding for antimicrobial resistance at a national level, to support a national strategy for antimicrobial resistance?

6. Drug & Vaccine Development

- What incentives are needed for pharmaceutical companies to expand research in discovery of new molecular entities and new modalities of preventing and managing infection (such as vaccines and immune modulators) that will provide new, affordable treatments in the future?
- What criteria/data can be used to predict, at an early stage of drug development, the dosage regimens that should be explored in major clinical trials to minimize the risk of selecting resistance while achieving favourable outcome?
- Can clinical trial protocols be designed so that the role of resistance in determining clinical and microbiological outcome can be assessed?
- How can clinical trials be developed and funded to promote preservation of current antimicrobial agents, rather than promoting development and use of new agents?

7. Pharmaceutical promotion

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

8. Microbiology of Resistance

- What are the most appropriate pharmacokinetic and pharmacodynamic factors which determine the maximum efficacy and minimum emergence of resistance for an antimicrobial?
- What is the natural history of antimicrobial resistance in colonizing organisms if further antimicrobial therapy is not given?
- What is the dose and duration of therapy that maximizes efficacy and minimizes emergence of resistance?
- What is the impact of oral versus injectable therapy on resistance?
- What are the effects of combination antimicrobial therapy on resistance and on efficacy?
- What is the biological price, in terms of reduced fitness, that microorganisms pay for antimicrobial resistance?
- Why do some antimicrobials have a greater tendency to select for resistance than others (both within and between antimicrobial classes)?
- What are the clinical implications of resistance detected in vitro?
- What are the effects of antimicrobials with long half-lives on the development of resistance both in pathogens and in the normal flora?
- What is the impact of vaccines on the problem of antimicrobial resistance in general and on the carriage of resistant strains (including specific stereotypes)?
- How should breakpoints for susceptibility be derived to minimise selection of resistance?
- Can mathematical modelling be used to establish threshold resistance rates to prompt intervention?
- What are the roles of non-antibiotic factors in resistance selection, e.g. heavy metals?

- What adaptive mechanisms do organisms have to allow persistence of resistance, e.g. increased colonisation proficiency, acquisition or mutation to of virulence genes etc?
- What potentiates the loss of resistance genes?
- Does the reversal of resistance, which can occur upon termination of antibiotic use, relate to the loss of the resistance determinants or the replacement of resistant bacteria with susceptible bacteria of the same species in the environment?