

## Conference Summary

### Consequences of Bacterial Resistance to Antimicrobial Agents

In December 2002, a colloquium was organized by the Institut Pasteur and the Institut de Veille Sanitaire, Paris, France, to review what current knowledge exists on the impact of antimicrobial bacterial resistance and address the methodologic obstacles to its assessment.

Simply to state that a patient died of an infection caused by a resistant organism does not prove that the death was due to the resistance. To prove the statement as to cause of death, two approaches—"imputable death" and "attributable death"—are complementary and have been shown to provide comparable results. The estimation of "imputable death" requires analyzing the clinical history of a series of deaths that were caused by resistant strains of infection and to count by clinical judgment those related to the resistance. To estimate the "attributable" fraction of death or illness, the excessive risk for death or illness must be documented for patients who are infected with the resistant strains, in comparison with those who are infected with sensitive strains. The study design must control for confounders by matching the groups at inclusion or by adjustment. Among these confounders the most important are the severity of the underlying illness before onset of infection, which may be associated with both the risk for death and the risk of antibiotic resistance of the bacterium. The time at which death is evaluated is another key issue of the study design. An excessive rate of mortality may be observed during the first months of follow-up and not during a longer follow-up.

Multidrug- (isoniazid and rifampicin) resistant tuberculosis (MDRTB) is associated with a more than threefold increased death if an appropriate anti-TB regimen is not used early in the course of the infection. In western countries where the prevalence of MDRTB is low and second-line drugs are available, MDRTB only requires prompt detection and adequate management to limit the consequence of resistance. However, in developing countries where second-line treatments are not readily available, and where 95% of worldwide tuberculosis cases occur which are responsible for 26% of the potentially avoidable death, one can predict an increasing impact of MDRTB on death in the years to come. Several studies suggest that in acute otitis media caused by *Streptococcus pneumoniae*, the bacteriologic failure rate increases with penicillin G MICs. Although bacteriologic failure does not mean clinical failure, the risk for acute otitis media relapses and complications linked to resistance is poorly documented. Higher penicillin G MICs of *S. pneumoniae* strains observed in mastoiditis than those in otitis and sinusitis does not prove that the severe acute otitis media complications increase with *S. pneumoniae* resistance. Whether invasive infections with resistant *S. pneumoniae* strains are linked to excessive death rates remains controversial. Two studies suggest that death may be greater with higher levels of resistance to penicillin G, and several failures have been reported with macrolide or fluoroquinolone therapy. In countries with high levels of drug resistance and where multidrug resistance is frequent, such as southwestern Europe, the likelihood of treatment failure in meningitis or mastoiditis might be greater. Because widespread use of pneumococcal conjugate vaccine has been shown to reduce the risk for resistant infections, epidemiologic studies to evaluate potential benefits

of conjugate vaccine introduction are needed in countries most affected by resistance.

The quinolone resistance in bacterial diarrhea due to *Campylobacter jejuni* can lead to therapeutic failure associated with an increased duration of symptoms and an increased rate of hospitalization. For non-typhi *Salmonella*, resistance was associated with an increased rate and duration of hospitalization, a twofold increased risk of death during a 2-year period after the infection, and an increased rate of invasive infection (1). Antimicrobial use may cause a transient decrease in a person's resistance to colonization by noncommensal bacteria as well as infection upon exposure to a food-borne pathogen. The additional selective effect of antimicrobial resistance results in a greater than threefold increase in vulnerability to infection by an antimicrobial-resistant pathogen among persons receiving antimicrobial therapy for unrelated reasons. The net result, which has been demonstrated for salmonellae and campylobacters, is an excessive rate of illness caused by the interaction between resistance in these bacteria and unrelated use of antimicrobial agents in humans. This relationship may also explain why outbreaks of resistant food-borne agents which lead to an excess illness among immunocompromised persons or persons at risk, may be more common in hospitals than in communities. Studies of the clinical outcome of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in comparison to methicillin-sensitive *S. aureus* (MSSA) infections have produced conflicting results. A dozen studies compared MRSA and MSSA infections of the same infection site with adjustment for at least one recognized criterion of illness severity and included at least 30 patients. In studies of MRSA bacteremia in which the analyses took into account the presence of shock, the source of the

infection, underlying disease(s), the medical setting in which the infection occurred, the appropriateness of antibiotics prescribed, the age and sex of the patients, no increased death was associated with MRSA, although inappropriate therapy was associated with a poorer outcome. In contrast, for bone infections and mediastinitis, MRSA may increase the risk of death.

The complete results of standard antimicrobial susceptibility tests are not generally available to the prescriber before at least 48–72 hours. The initial regimen prescribed may be not adequate during the first 2 to 3 days of treatment. This may impact death or illness attributable to multi-resistant bacteria. Shortening this interval, rapid diagnosis techniques based on molecular identification of resistance mechanisms could improve outcome. For example, methicillin resistance in *S. aureus* colony is detectable within 6 hours. Studies on clinical specimens showed that resistance-detection techniques, coupled with DNA identification of the bacterium, gave an excellent concordance to discriminate MRSA and MSSA and for MDRTB. Advances in the field of DNA microchips might soon improve the clinical impact of these techniques.

With more clinical failures, more expensive alternative regimens, the cost-effectiveness ratio of the treatment of antimicrobial bacterial resistant infections will inevitably rise. However, very few studies have addressed this issue; it requires precise and documented scenarios based on close collaboration between clinicians, microbiologists, epidemiologists and economists. Proposing prospective scenarios and foreseeing all the public health consequences of antimicrobial bacterial resistance is difficult. Although the impact on life expectancy should remain relatively limited in western nations, this will not be the case in developing countries where alternative regimens are

usually either not available or too costly.

Quantifying the consequences of antimicrobial bacterial resistance is a key element for allocating resources for public health programs. Some evidence exists of such consequences on illness and death, most of which appear to be associated with inappropriate or delayed therapy. Nevertheless, more studies which take into account the specific methodologic difficulties mentioned above are needed to better convince policy makers.

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**Reference**

1. Helms M, Vastrup P, Gerner-Smidt P, Molbak K. Excess mortality associated with antimicrobial drug-resistant *Salmonella typhimurium*. *Emerg Infect Dis* 2002; 8:490-5

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## Vets, Meds, and Zoonotic Threats

The fourth international conference on emerging zoonoses (September 18–21, Ames, Iowa, USA) brought together 180 scientists and healthcare specialists from 18 countries working to control diseases transmitted from animals to humans. The meeting took place under the auspices of the Center of Food Security and Public Health, USA, and the Institute for International Cooperation in Animal Biologics (a collaborating center of the World Animal Health Organisation [OIE]).

A multidisciplinary and global approach shed new light on both old and new zoonoses. For example, brucellosis topics covered a wide range of material, from economic aspects of control in Mongolia to characterization of *Brucella* isolates from feral swine in coastal South Carolina. Another presentation concerned the increasingly appreciated role of wildlife in the dynamic epidemiology of other zoonotic infections, such as tuberculosis. Scientists also explored the intricate routes prions follow between wildlife and domestic animals; between sheep, cattle, and humans; and between the tongue and brain of infected animals.

Since most agents of bioterrorism potential are zoonotic, a full session was dedicated to bioterrorism and biodefense. It included a global view, a report on national preparedness by Israeli hospitals, and examples of research that may eventually help experts coping with bioterrorism but would also unfortunately be accessible to persons with malicious intent.

Innovative methods for preventing spread of foodborne pathogens were presented, including the use of fluorescence spectroscopy to detect fecal contamination on animal carcasses or the use of vaccination to reduce transmission of zoonotic pathogens and drug-resistant nonpathogens through the food chain to humans. In the field of xenotransplantation, key components of a source-animal production facility were described. The feasibility of breeding pigs free of designated pathogens offers hope for wide use of xenotransplantation in the near future.

Participants also discussed current trends and challenges of protozoan parasitic zoonoses, including cryptosporidiosis, toxoplasmosis, African and Latin American trypanosomiasis, and leishmaniasis. Controversial zoonotic viruses were given an important place in the conference. These included hepatitis E virus, with similar strains causing liver disease in