Building Communication Networks: International Network for the Study and Prevention of Emerging Antimicrobial Resistance

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The global nature of antimicrobial resistance and the failure to control the emergence of resistant organisms demand the implementation of a global surveillance program involving both developed and developing countries. Because of the urgent need for infection control interventions and for rapid distribution of information about emerging organisms, we initiated the International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR). Its main objectives are to serve as an early warning system for emerging antimicrobial drug-resistant pathogens, to facilitate rapid distribution of information about emerging multidrug-resistant pathogens to hospitals and public health authorities worldwide, and to serve as a model for the development and implementation of infection control interventions.

However, most data on antimicrobial-resistant pathogens were collected as part of studies sponsored by the pharmaceutical industry, and most of the studies were methodologically flawed; thus, the data were not useful for generalizations about antimicrobial resistance in hospitals. In addition, in many countries, a close interrelationship does not exist between the laboratory identifying multidrug-resistant pathogens and the infection control personnel responsible for the prevention and control of transmission of such isolates. Furthermore, many laboratory-based surveillance systems are designed for making patient treatment decisions; the data are not organized in a way that can be used to design and implement control and prevention interventions.

With the development of the Emerging Infections Plan at the Centers for Disease Control and Prevention (CDC) and the endorsement and adaptation of this plan by the World Health Organization (WHO), the emergence of antimicrobial resistance has become a public health priority (13,14). Public health authorities in the United States and Europe realize that the emergence of antimicrobial-drug resistance is a global problem; no country is spared, and resistant organisms emerging in one country are likely to spread to other countries. With increasing travel and patient movement throughout the world, the situation exists for transmission of multidrug-resistant pathogens from one country or continent to another (15-19).

Because of the urgent need for infection control interventions to prevent further emergence of antimicrobial drug-resistant strains and for a rapid distribution of information about emerging organisms, we initiated the International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR). The main objectives of INSPEAR are to serve as an early warning system for emerging resistant pathogens, to facilitate rapid distribution of information about emerging multidrug-resistant pathogens to hospitals and public health authorities worldwide, and to serve as a model for the development and implementation of infection control interventions.

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Centers, was designed to assess the methods used by participating in the program.

Proficiency testing to ensure quality testing in laboratories centers diagnose, conduct surveillance, and control infections.

Several activities essential to the implementation of the early warning system, such as the assessment of the way INSPEAR, were carried out.

Recent Activities

Since its initiation in 1998, INSPEAR has conducted several activities essential to the implementation of the early warning system, such as the assessment of the way INSPEAR centers diagnose, conduct surveillance, and control infections caused by multidrug-resistant pathogens, as well as proficiency testing to ensure quality testing in laboratories participating in the program.

An assessment of MRSA infections, performed in 90 centers, was designed to assess the methods used by bacteriology laboratories to identify S. aureus, to determine the susceptibility of S. aureus to antimicrobial drugs, and to assess the surveillance and infection control programs in INSPEAR centers. This study revealed many deficiencies:

- Isolation of vancomycin- and teicoplanin-resistant S. aureus was reported by three centers but was not confirmed, and public health authorities were not alerted. Of the laboratories surveyed, 11% used oxacillin disks with antimicrobial content different from that recommended by the National Committee for Clinical Laboratory Standards or the Comité de L’Antibiogramme de la Société Française de Microbiologie; 20% did not have an internal quality control program; 36% did not participate in external quality control programs; and 14% did not determine MRSA susceptibility to vancomycin. Of the health-care facilities surveyed, 77% reported surveillance activities; however, only 36.5% determined the incidence rate per admission, and only 23% determined the rate per patient-days; 40% of the facilities did not have an MRSA control program; and 54% did not monitor or control the use of antimicrobial drugs.

- These data clearly demonstrate the urgent need to strengthen the laboratory and epidemiologic capacities of INSPEAR centers.

A proficiency testing study was performed to investigate the ability of INSPEAR centers to detect clinically important resistance phenotypes, to assist centers in establishing reliable methods to detect particular resistances, to validate data from hospital laboratories participating in INSPEAR, and to ensure consistent quality testing in INSPEAR clinical laboratories.

Five strains were sent to the 116 participating laboratories: MRSA, hyper-beta-lactamase producing strain of S. aureus, glycopeptide-intermediate Staphylococcus epidermidis, and van A and van B Enterococcus faecalis.

Seventy-six laboratories responded. Most laboratories did well with both S. aureus challenges; however, 60 (79%) had difficulty detecting reduced susceptibility to glycopeptides in staphylococci. All laboratories testing van A E. faecalis identified it correctly as vancomycin resistant, but the results for van B E. faecalis varied. Thirty-nine (52%) of 75 laboratories reported susceptible results for vancomycin, but 19% misidentified van B E. faecalis as vancomycin resistant.

An assessment is being conducted to determine if participants have modified their testing methods based on the results of the proficiency testing and CDC recommendations.

Early Warning System

Another reason antimicrobial resistance is uncontrolled is that clinical microbiology laboratories and the medical community often are not aware of emerging resistance and therefore are not prepared. Preparedness implies that potentially emerging events be known, that laboratorians have the capacity to detect emerging resistance and screen rapidly for colonization, that risk factors for emergence be assessed, and that health-care facilities have access to microbiologic and epidemiologic assistance and have the capacities for efficient isolation precautions (e.g., private rooms with handwashing facilities, availability of gloves). Therefore, to coordinate the timely international scientific and public health response to emerging antimicrobial resistance, we designed an early warning system to monitor, analyze, control, and prevent important events in the emergence of antimicrobial resistance at both the global and regional or local levels. Overall, this early warning system should trigger early epidemiologic and microbiologic interventions to assess risk factors for emerging antimicrobial resistance, leading to more effective control.

Global Sentinel Events

The need to be aware of global sentinel events is leading to an important function of the program: the periodic publication of what INSPEAR members determine by consensus to be important types of antimicrobial resistance heretofore undescribed or of great public health importance (Table 1). Criteria used to arrive at this list included the overall ease of use of the list by most clinical and reference laboratories.

Table 1. Early warning system: global sentinel events

| Microorganism                      | Resistance                                                                 |
|------------------------------------|---------------------------------------------------------------------------|
| Streptococcus spp.                 | Penicillinase, gentamicin, glycopeptides, fluoroquinolones                 |
| S. pneumoniae                      | Vancomycin, third-generation cephalosporins, new fluoroquinolones (gemifloxacine, grepafloxacin, levofloxacin, trovafloxacin) |
| Staphylococcus spp.                | Glycopeptides (high level)                                                |
| Enterobacteriaceae                 | Carbenapenemase                                                           |
| Neisseria meningitidis             | Penicillinase, chloramphenicol, cephalosporins, fluoroquinolones           |
| Acinetobacter baumannii            | Carbenapenemase                                                           |
| Salmonella typhi                   | Third-generation cephalosporins, fluoroquinolones                          |
| Haemophilus influenzae             | Cephalosporins                                                            |
| Brucella spp.                      | Tetracycline, rifampin, streptomycin                                      |
| Clostridium difficile              | Glycopeptides                                                             |
| Clostridium perfringens            | Penicillinase                                                             |

Worldwide, and to serve as a model for the development and implementation of infection control interventions to prevent the emergence or transmission of antimicrobial drug-resistant pathogens in health-care facilities. Another important function of INSPEAR is to assist microbiologists and infection control personnel in hospitals and countries that lack the expertise needed to conduct microbiologic or epidemiologic studies.
laboratories and the actual and potential public health impact of resistance events based on factors such as pathogen virulence, frequency of infection caused by the pathogen, and absence of other licensed antimicrobial agents for treating infections caused by the pathogen. This list of events will be updated regularly and will be published and disseminated to national and international surveillance systems.

**Local and Regional Sentinel Events**

Local and regional sentinel events consist of the first observation of a clinically important form of resistance in a particular locality or region. Such resistant phenotypes may already be well described from other localities or regions of the world (Table 2). The new regional emergence of resistance in an INSPEAR facility may warrant a coordinated response from local or international INSPEAR members to prevent the resistant strains from becoming endemic.

**Table 2. Early warning system: local and regional sentinel events**

| Microorganism        | Resistance                                                                 |
|----------------------|-----------------------------------------------------------------------------|
| *Staphylococcus aureus* | Methicillin, intermediate susceptibility to glycopeptides                   |
| *Enterococcus spp.*   | Vancomycin                                                                  |
| *Enterobacteriaceae*  | Extended-spectrum beta-lactamase-mediated resistance, carbapenems, fluoroquinolones |
| *Acinetobacter baumannii* | Carbapenem                                                               |
| Any bacteria          | All antimicrobials available at the regional and local settings             |

**Functioning of the Early Warning System**

The early warning system should function according to subsidiarity, defined as the principle that a central authority should have a subsidiary function, performing only tasks that cannot be performed effectively at a more immediate or local level. When an emerging event is suspected at an INSPEAR center, the national or regional coordinator should be alerted and microbiologic confirmation performed at the local, national, or regional level when possible, or with additional INSPEAR resources (Figure). Once an event is confirmed, the INSPEAR coordinator will be informed and the public health authorities, WHO, and the INSPEAR centers will be notified.

At the same time, an epidemiologic investigation will search for additional cases and assess risk factors through cohort or case-control studies, and surveillance will be implemented. As with microbiologic support, epidemiologic investigation will be performed at the local, national, or regional level if possible; if necessary, INSPEAR resources will be provided. In addition, public health authorities, WHO, and INSPEAR centers will be notified so that measures may be immediately implemented if such an event occurs elsewhere.

**Responses to Emerging Resistance**

INSPEAR response may include immediate, specific responses, such as microbiologic support (e.g., confirmation of resistance, studying the mechanism of resistance, molecular typing to determine clonality) or on-site epidemiologic and infection control support (e.g., assistance with outbreak investigation, intervention studies, control measures) (Table 3). The level of response will be determined by local need, importance of the problem, and capacity of INSPEAR members to respond. In addition, the INSPEAR response to emerging resistance will include coordination of longer term studies to improve the methods for detection and control of resistance. Finally, the INSPEAR response will include the education and training of personnel at INSPEAR hospitals.

**Table 3. INSPEAR resources**

| Microbiology | Epidemiology |
|--------------|--------------|
| Bacterial identification | Surveillance system |
| Antimicrobial Resistance, testing, and characterization of mechanisms | Study design and conduct |
| Typing | Outbreak investigation |
| Quality control programs | Infection prevention interventions |
| Proficiency testing | Statistical analysis |
| Training | Statistical training |

**Conclusions**

INSPEAR is the first international program dedicated to the control of antimicrobial resistance that combines microbiologic and epidemiologic expertise provided by national reference laboratories and public health agencies. This program should facilitate control of novel antimicrobial-resistant pathogens at the time of their emergence and increase the likelihood of controlling and preventing those pathogens before they become endemic. However, as the results of our MRSA survey and proficiency testing indicate, the microbiologic and epidemiologic capacities of health-care facilities worldwide will need to be strengthened if our goal of detection and control of multidrug-resistant pathogens is to be achieved.

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