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PERSPECTIVES

Emergence and spread of multi-drug resistant organisms: Think globally and act locally

Shu-Hui Tseng [a], Chun-Ming Lee [b], Tzou-Yien Lin [c], Shan-Chwen Chang [d], Feng-Yee Chang [a,e,*]

[a] *Centers for Disease Control, Department of Health, Taiwan, ROC*
[b] *Division of Infectious Diseases, Department of Internal Medicine, Mackay Memorial Hospital, Taiwan, ROC*
[c] *Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taiwan, ROC*
[d] *Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taiwan, ROC*
[e] *Department of Internal Medicine, National Defense Medical Center, Taiwan, ROC*

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Multi-drug-resistant organisms (MDROs) such as gram-negative Enterobacteriaceae with resistance to carbapenems conferred by New Delhi metallo-β-lactamase (NDM-1) are increasingly recognized as a global public health issue.[1—8] The World Health Organization (WHO) has chosen antimicrobial resistance as its theme for World Health Day—7 April 2011.[9] The organization strongly recommends that governments focus control and prevention efforts in four main areas including surveillance of antimicrobial resistance; rational antibiotic use, which includes educating health care workers and the public about the appropriate use of antibiotics; introducing or enforcing legislation related to stopping the selling of antibiotics without prescription; and strict adherence to infection prevention and control measures, including the use of hand-washing measures, particularly in health care facilities to limit the spread of multi-drug resistant strains and reduce the generation of antibiotic-resistant bacteria.[10—15]

Antimicrobial resistance and its global spread

A surveillance study published by the European Centre for Disease Prevention and Control in 2009[16] demonstrated that approximately 400,000 patients from 28 European countries suffered from infections because of strains of antibiotic-resistant bacteria, with *Escherichia coli* and *Klebsiella pneumoniae* being the most common causative pathogens.[17,18] The proportion of third-generation cephalosporin-resistant *E coli* increased significantly from 1.7% in 2002 to 8% in 2009, whereas the proportion of *E coli* isolates with resistance to four classes of antimicrobials increased more than 5-fold from 0.6% in 2002 to 3.4% in 2009.[16] The increase in antibiotic resistance among *K pneumoniae* is even more dire. The European Centre for Disease Prevention and Control reported that the rate of resistance of *K pneumoniae* to powerful and last-line antibiotics, namely carbapenems, increased from less than 1% to more than 25% in the European Union, 2009.[17]

* Corresponding author. Centers for Disease Control, Department of Health, 9F, No. 6, Linsen South Road, Zhongzheng District, Taipei City, Taiwan 10050, ROC.
E-mail address: fychang@cdc.gov.tw (F.-Y. Chang).

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The prevalence of MDROs in hospitals and medical centers in the USA has also increased steadily during the previous decade.[19–23] For example, the prevalence of imipenem-resistant *Acinetobacter baumannii* infection increased from 4.8% in 2000 to 21% in 2009, and the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) increased from 19% in 2000 to 51.5% in 2009. The rate of resistance of *E coli* to trimethoprim-sulfamethoxazole increased from 17.4% in 2000 to 23.9% in 2009, and that of *E coli* to fluoroquinolones rose from 3.3% in 2000 to 17.8% in 2009.[24] Furthermore, the prevalence of vancomycin-resistant enterococci (VRE) isolates has also increased markedly.[19,25] For example, VRE isolates accounted for 25% and 28.5% of all nosocomial infections in intensive care units (ICUs) in 1999 and 2003 respectively.[19,26,27]

Antimicrobial resistance is also a threat and challenge to the treatment of infectious diseases in Taiwan.[28,29] The Taiwan Nosocomial Infection Surveillance system, 2009, a nationwide surveillance study on the incidence and prevalence of antimicrobial resistance in Taiwan during the period 2003–2009, reported that the proportion of MRSA in ICUs in medical centers and regional hospitals decreased significantly ($p = 0.001$) from 89.3% in 2003 to 78.0% in 2009 (Fig. 1A); the proportion of VRE in ICUs increased significantly ($p = 0.001$) from 3.7% in 2003 to 19.1% in 2009 (Fig. 1B); and

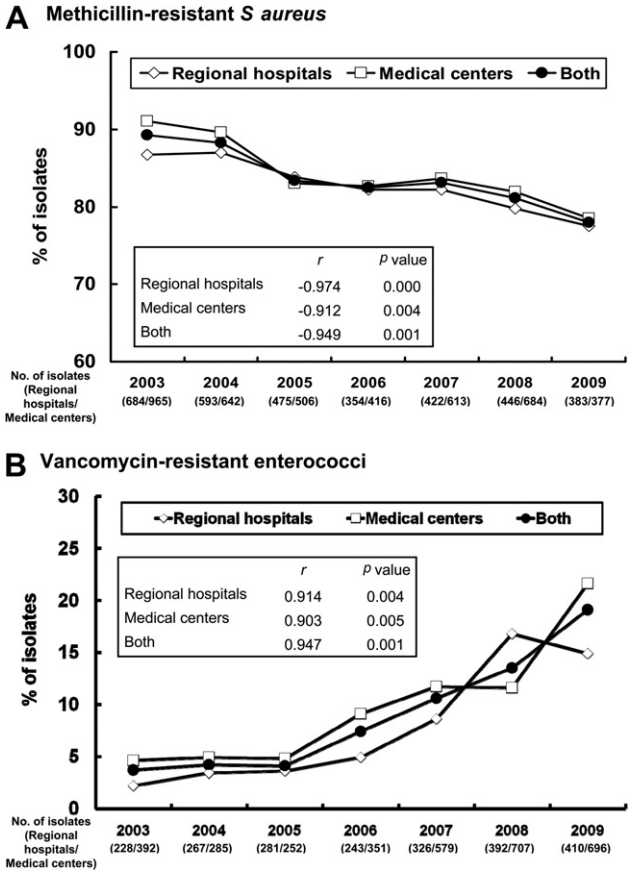

Figure 1. Annual trends in the rates of methicillin-resistant *Staphylococcus aureus* (A) and vancomycin-resistant enterococci (B) in intensive care units of medical centers and regional hospitals in Taiwan. Data from the Taiwan Nosocomial Infection Surveillance system, 2003–2009.

the proportion of *E coli* isolates resistant to carbapenems (imipenem or menorpenem or ertapenem) in ICUs in medical centers and regional hospitals increased ($p = 0.231$) from 0.5% in 2003 to 2.6% in 2009 (Fig. 2A). The study also showed that the proportion of *K pneumoniae* isolates resistant to carbapenems in ICUs in medical centers and regional hospitals increased significantly ($p = 0.001$) from 1.2% in 2003 to 6.0% in 2009 (Fig. 2B); that the proportion of Enterobacteriaceae isolates resistant to carbapenems (CRE) increased significantly ($p = 0.017$) from 1.4% in 2003 to 4.5% in 2009 (Fig. 2C); and that the proportion of *A baumannii* isolates resistant to imipenem or menorpenem in ICUs in medical centers and regional hospitals increased significantly ($p < 0.001$) from 18.0% in 2003 to 63.5% in 2009 (Fig. 2D). Furthermore, the study also found that the proportion of *Pseudomonas aeruginosa* isolates resistant to imipenem or menorpenem in ICUs in medical centers and regional hospitals remained stable (15%) during the study period.

Risk factors for antibiotics resistance

Several factors may lead to the increase in antimicrobial resistance, such as hospital stay before ICU admission, hospitalization period before ICU admission, length of ICU stay, surgical ICU stay, the type of operation, previous antibiotic use, inappropriate use of antimicrobial drugs,[19,30–35] and inadequate adherence to infection control practices.[19–48] In particular, some patients are more vulnerable to colonization and infections including those with severe disease, those with compromised host defenses because of underlying medical conditions, patients with recent surgery, and those with indwelling medical devices. Furthermore, hospitalized patients are likely to have more risk factors and higher infection rates than non-hospitalized patients, especially those who require treatment in the ICU.[32,49–52]

Akinci et al.[53] demonstrated that patients with infections because of imipenem-resistant (IR) gram-negative bacteria have longer lengths of stay in ICUs compared with patients infected with imipenem-susceptible isolates. Furthermore, they found that the risk of IR gram-negative bacteria infection was four times higher for patients who undergo surgery and 3-fold higher for patients on carbapenem therapy. According to Kim et al. in Korea, the presence of neutropenia and the prolonged use of cephalosporin (more than 7 days) were more common among patients with bacteremia caused by IR isolates than among patients with bacteremia caused by imipenem-susceptible isolates (odds ratio 3.03 and 3.82, respectively).[54] They also confirmed that neutropenia and prolonged cephalosporin use (more than 7 days) were independent risk factors for metallo-β-lactamase-producing *Acinetobacter* bacteremia (odds ratio 22.10 and 19.57, respectively).

Impact of antibiotic resistance

Antimicrobial-resistant pathogens that cause health care-associated infections (HAIs) are becoming increasingly common. Studies have shown an association between the development of multi-drug resistance and increases in mortality, lengths of hospital stay, and cost of health care.[19,55–60]

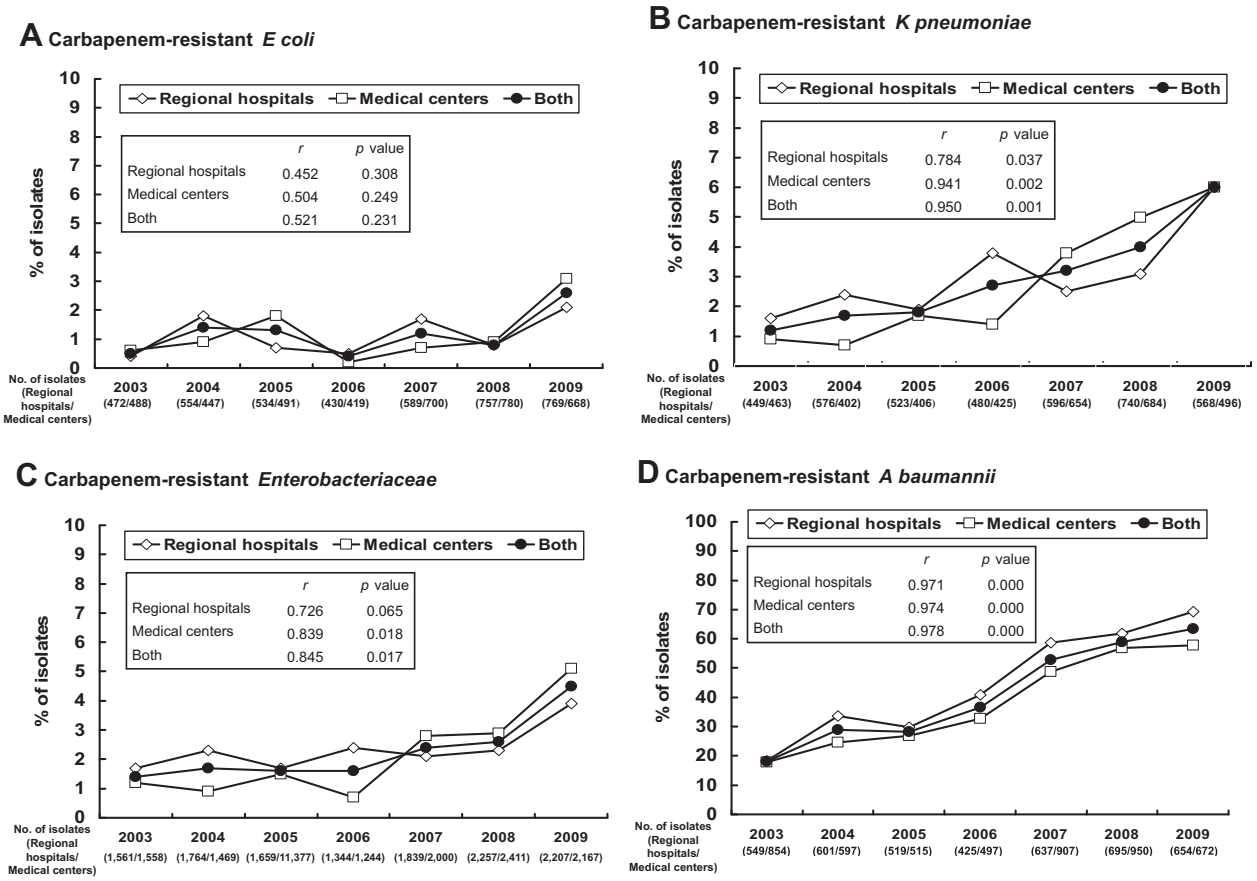

Figure 2. Annual trends in the rates of carbapenem-resistant *Escherichia coli* (A), carbapenem-resistant *Klebsiella pneumoniae* (B), carbapenem-resistant Enterobacteriaceae (C) and carbapenem-resistant *Acinetobacter baumannii* (D) in intensive care units of medical centers and regional hospitals in Taiwan. Data from the Taiwan Nosocomial Infection Surveillance system, 2003—2009.

Comparisons of mortality rate, length of stay in hospitals, and health care costs between patients with methicillin-susceptible *S aureus* (MSSA) bacteremia and those with MRSA bacteremia have shown that patients with MRSA bacteremia have a significantly higher rate of mortality, markedly longer lengths of hospital stay, and higher median hospital costs than patients with MSSA bacteremia.[61—63] Furthermore, surgical site infections caused by MRSA were shown to be associated with a 3.4-fold higher risk for death and a 2-fold increase in median hospital costs than surgical site infections caused by MSSA infections. According to Blot et al. in Belgium,[64] patients with MRSA bacteremia had a higher 30-day mortality rate than patients with MSSA bacteremia (53.2% *vs.* 18.4%, $p < 0.05$) and a higher in-hospital mortality rate (63.8% *vs.* 23.7%, $p < 0.05$).

Taiwan CDC strategies for confronting antimicrobial resistance

Prevention of antimicrobial resistance depends on appropriate clinical practices that should be incorporated into all routine patient care. The Taiwan Centers for Disease Control (Taiwan CDC) takes a multifaceted, evidence-based approach in accordance with WHO's strategies in four main areas.[41]

1. Surveillance of antimicrobial resistance[41]
   - 1.1 Establishment of the Taiwan nosocomial infection and antimicrobial resistance surveillance system (Fig. 3): This system focuses on the monitoring of HAI and antimicrobial resistance.
   - 1.2 To establish a national Communicable Disease Reporting System for laboratories in Taiwan. Multi-drug resistant bacteria including *S aureus* isolates with reduced susceptibility to vancomycin (vancomycin-intermediate or resistant *S aureus*) and carbapenem-resistant Enterobacteriaceae identified by the clinical laboratories will be confirmed by national reference laboratory affiliated in the Communicable Disease Reporting System.
   - 1.3 To conduct a project on "the status of multi-drug resistance, antimicrobial resistance mechanisms, and infection control measures of Enterobacteriaceae in Taiwan".
   - 1.4 To monitor the trend and spatial distribution of antimicrobial-resistant bacterial strains by implementing the National Collection and Confirmation of Antimicrobial Resistance program. The program will develop a database of antimicrobial-resistant bacteria including carbapenem-resistant Enterobacteriaceae, VRE isolates, and MRSA strains with vancomycin minimum inhibition concentration values ≥ 2 μg/mL.

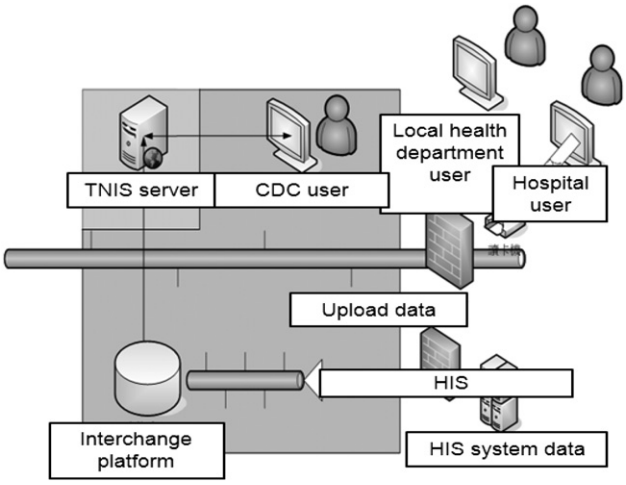

Figure 3. Taiwan Nosocomial Infection and Antimicrobial Resistance Surveillance System. CDC = Centers for Disease Control; HIS = Hospital Information System; TNIS = Taiwan Nosocomial Infection Surveillance.

2. Rational antibiotic use, including educating health care workers and the public about the appropriate use of antibiotics[41,65,66]
   - 2.1 To establish regulations for antibiotic usage. This will be accomplished through hospital accreditation and infection control inspection mechanisms to help hospitals develop and effectively implement control strategies for antibiotics.
   - 2.2 To establish guidance through collaboration with experts, academic organizations, and societies.
     - 2.2.1 Regulation of national health insurance payment such as declaring "Directions for Drug-Restricted Benefits for National Health Insurance" will be set and updated through collaboration with medical institutions, research institutions, drug supplements, and experts.
     - 2.2.2 Antimicrobial usage for upper respiratory tract infections has been restricted since 2001. The costs of antimicrobial agents used in the treatment of ambulatory patients with acute upper respiratory tract infections without evidence of bacterial involvement are not reimbursed.
     - 2.2.3 Regulations for the use of prophylactic antibiotics, which focus on reducing overuse of prophylactic antibiotics during clean and clean-contaminated procedures, were implemented beginning in 2001. Observance of these regulations is included in hospital accreditation and infection control inspection criteria.
     - 2.2.4 Continue working with related institutions and academic groups and societies and updating the guidelines of "appropriate use of antibiotics" and "special antibiotic use". Antibiotic-prescribing guidelines for physicians will be developed.
   - 2.3 To enhance education of appropriate antibiotic use and antimicrobial resistance for medical students and medical staff
     - 2.3.1 To implement relevant online learning and training of prudent use of antibiotics for health care workers.
     - 2.3.2 Infection control will be included in a mandatory 40-hour general medicine training programs after graduation.
     - 2.3.3 All physicians will be subject to a certain level of continuing education, including courses on infection control, every 6 years.
     - 2.3.4 Implementation of "infection control, proper use of antibiotics, and implementation of education and monitoring mechanisms" will be added to the infection control course to improve the quality of medical care. Furthermore, promotional materials will be distributed to enhance education and training for basic medical and non-medical staff.
   - 2.4 To enhance knowledge of antibiotics, antimicrobial resistance, and sensitivity tests among staff in microbiological laboratories. The National Health Research Institutes will conduct related workshops each year to discuss current use of antibiotics, evolution of drug resistance, hospital and community transmission, and drug-resistant strains.
   - 2.5 To enhance the understanding of antibiotics among the general population, and promote the "5 basic principles" concept: do not listen, do not trust, do not purchase, do not take, and do not recommend.
3. Introducing or enforcing legislation related to stopping the selling of antibiotics without prescription[67]
   - 3.1 Local health authorities will supervise pharmacies that sell antibiotics with a prescription.
   - 3.2 Drug investigations and pharmaceutical-related regulations will be included to enrich and strengthen the knowledge and investigative ability of health officers when conducting national pharmaceutical seminars.
   - 3.3 Notify all pharmacies to maintain self-discipline and not to sell antibiotic agents to the public without prescription.
   - 3.4 Continue to promote medicine-pharmacy separation, and strengthen professional service of community pharmacies such as providing the public with correct medication advice.
   - 3.5 Production, marketing and stocks will be listed as check points when follow and investigate domestic antibiotic factories.
   - 3.6 To counsel and strengthen medical related industries and increase the knowledge of drug use among the public.
4. Strict adherence to infection prevention and control measures, including the use of hand hygiene measures, particularly in health care facilities[41,65,66]
   Reinforce infection control capacity in hospital/medical institutions: continue to make improvements in hand hygiene measures, environmental cleaning, contact protection, standard operating procedures related to the handling of invasive equipment and other infection control measures.

4.1 Continue to promote the WHO "hand hygiene" campaign. Enforce hand hygiene by promoting hand hygiene as an integral part of patient safety, and by evaluating performance indicators regularly to encourage hospitals to improve continually. The three strategies of implementation include intervention, financial incentives, and performance. Promotion of hand hygiene among health care workers will comprise dividing hospitals into different groups according to the hospital level; rewarding participating hospitals for installing hand hygiene facilities; and encouraging hospitals to undertake system changes in hand hygiene measures and establishing demonstration centers for hand hygiene. Our goals are: (1) to promote the use of alcohol-based handrubs, increase the accessibility of hand hygiene facilities, and establish hand hygiene facilities at each point of care; (2) to raise health care workers' recognition in five moments for hand hygiene approach. This approach recommends health care workers to clean their hands before touching a patient, before clean/aseptic procedures, after body fluid exposure/risk, after touching a patient, and after touching patient surroundings; and (3) to diminish the rate of HAI and reduce costs for health care resources.

4.2 To conduct a project entitled "the integrated bundle to lower catheter-related bloodstream infections".

4.3 To establish infection control guidelines for monitoring, allocating, and isolating multi-drug resistant strains as well as caring for patients with infections because of MDROs by reviewing relevant studies in the medical literature, and by consulting the advisory committee and infectious disease control experts. The Department of Health needs to consider various views from medical practice units and institutions. After reviewing various points, infection control guidelines will be announced in each health care setting for reference and modification of standard procedures.

4.4 To establish a national infection control network (Fig. 4). The Taiwan CDC divides Taiwan into six regions. Every region has a command center to help prevent and control infectious diseases in each region. The Taiwan CDC has also established a robust infection control framework in health care settings: this includes the supervision of establishing a hospital infection control committee and the assignment of physicians and nurses responsible for implementing and promoting infection control.

NDM-1 Enterobacteriaceae in Taiwan

According to the Communicable Disease Control Act and to require medical institutes and personnel to report such cases and offer a basis for implementing control measures for public health issues, the Taiwan CDC decided to include NDM-1 Enterobacteriaceae infection as a Category IV Notifiable Infectious Disease on September 9, 2010.[68]

Although no confirmed cases of NDM-1 Enterobacteriaceae infection had been identified in Taiwan at that time, clinicians were, nonetheless, required to report NDM-1 Enterobacteriaceae infection within 24 hours of diagnosis to the Taiwan CDC Notifiable Infectious Disease Reporting System (Fig. 5) to prevent subsequent spread. The Taiwan CDC Notifiable Infectious Disease Reporting System comprises specimen delivery, collection, diagnosis,

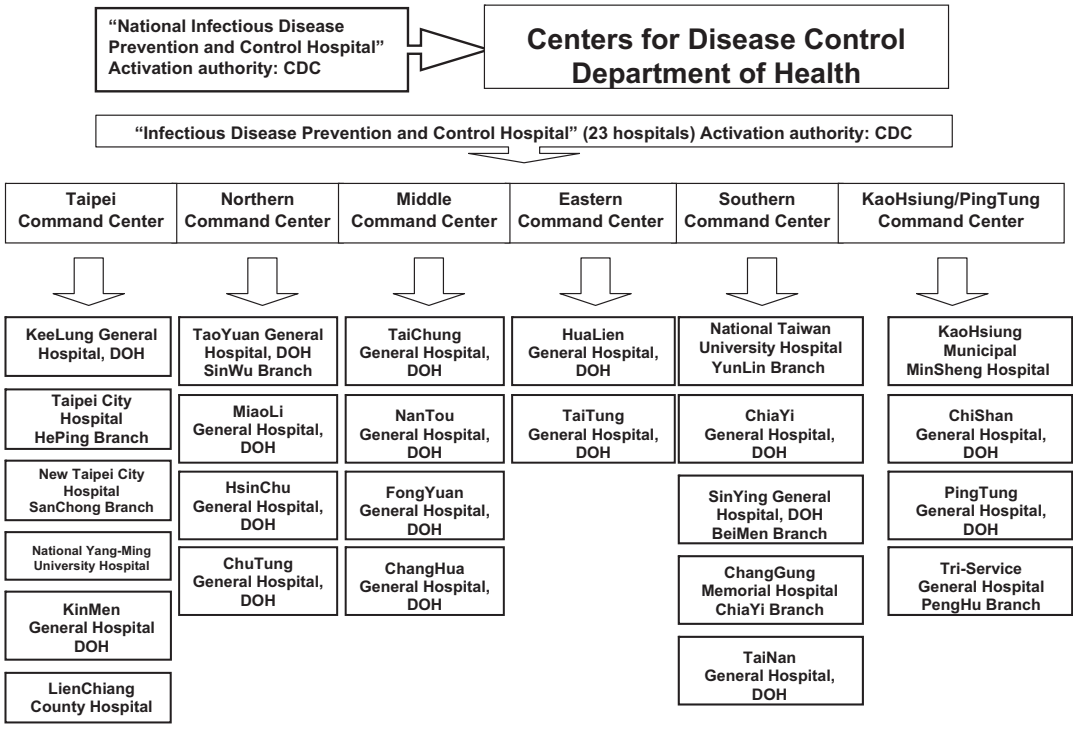

Figure 4. National Infectious Disease Prevention and Control Network in Taiwan. DOH = Department of Health.

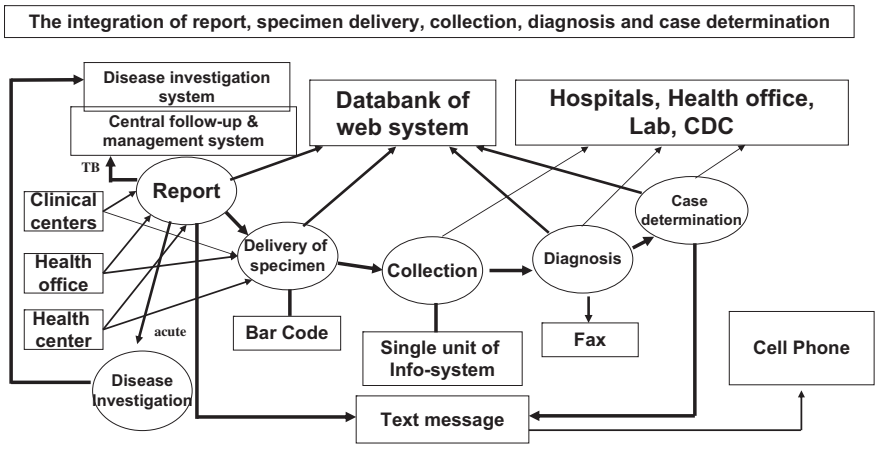

Figure 5. Taiwan CDC notifiable infectious disease reporting system. CDC = Centers for Disease Control.

and case determination. The definition of the following cases should be used to report confirmed cases of NDM-1 Enterobacteriaceae:

1. Clinical characteristics (an illness that has one of the following characteristics):
   1.1 Presence of infection, especially in patients who have had medical treatment, including invasive and surgical procedures.
   1.2 Suspected cases of NDM-1 Enterobacteriaceae.
2. Epidemiological characteristics (an illness that has any one of the following characteristics):
   2.1 Patients who had traveled abroad during the past 6 months, especially those with medical history.
   2.2 Patients who have not had hospital treatment overseas, but have had contact with suspected cases of NDM-1 Enterobacteriaceae when receiving hospital treatment.
3. Laboratory characteristics: Detection of CRE isolates recovered from the patient's specimen.
4. Case definition: A case that meets the abovementioned clinical, epidemiological and laboratory characteristics.
5. Clinicians must file a report on the cases that meet the aforementioned characteristics within 24 hours of diagnosis. Specimens from the patients must also be collected and submitted to the Taiwan CDC for final identification. Clinicians are also welcome to report cases that meet only the clinical and epidemiological characteristics but that could not be verified for drug resistance to the health authorities.

The Taiwan CDC confirmed the first case of NDM-1 Enterobacteriaceae infection in Taiwan on January 14, 2011.[69] The isolate was confirmed to be NDM-1 *Klebsiella oxytoca*. In accordance with the Communicable Disease Control Act, the hospital reported the case to the health authority on January 10, 2011. The hospital has been implementing all relevant infection control measures according to standard operating procedures of the Taiwan CDC for reporting NDM-1 Enterobacteriaceae infection (Fig. 6). The abovementioned case has been receiving medical treatment in a single room since his admission to the hospital. During the period October to December, 2010, this was the only case among 81 isolates of CRE that tested positive for NDM-1 in the hospital. So far, there is no evidence of nosocomial infection involving NDM-1 Enterobacteriaceae in that hospital. In Taiwan, the CDC, major medical centers, and research institutes have collected a total of 1,000 CRE strains and none of them were NDM-1-positive Enterobacteriaceae. Consequently, the case is suspected to be an imported case but more information will be collected and studied to confirm that hypothesis.

To combat antimicrobial resistance and its global spread, the Taiwan CDC continuously works on control measures based on WHO's recommendations such as coordinating the implementation of hospital accreditation associated infection control inspection programs, boosting the quality of the infection control inspection programs, and giving advice or sharing experience on infection control practices through on-site audits to improve the performance of infection control programs in health care settings. The CDC has also established the Taiwan Nosocomial Infection and Antimicrobial Resistance Surveillance system for gathering and documenting surveillance data on the occurrence of HAIs and the status of antimicrobial resistance nationwide. To date, the system is used by 100% of medical centers and over 90% of the regional hospitals in Taiwan.

In addition to the four-point framework for planning and implementing relative approaches, the Taiwan CDC will also promote the implementation of hospital infection control measures at a reasonable operating cost. Together with the medical payment system, these measures will leverage hospitals' motives. Effective infection control can prevent at least 20% of HAIs. Hence, medical resources can be saved if the occurrence of HAIs is prevented. However, some determinants may influence the effectiveness of infection control measures such as allocation and training of clinical human resources; the availability of equipment, supplies, and hospital hardware; ward allocation of infected patients; management support, and investment. The above determinants are related to funding allocation. To reduce the problem caused by antimicrobial resistance, the medical payment system needs to be combined. This includes the rationalization and enhancement of the national health insurance system. The performance and assessment of health care settings' infection control will be

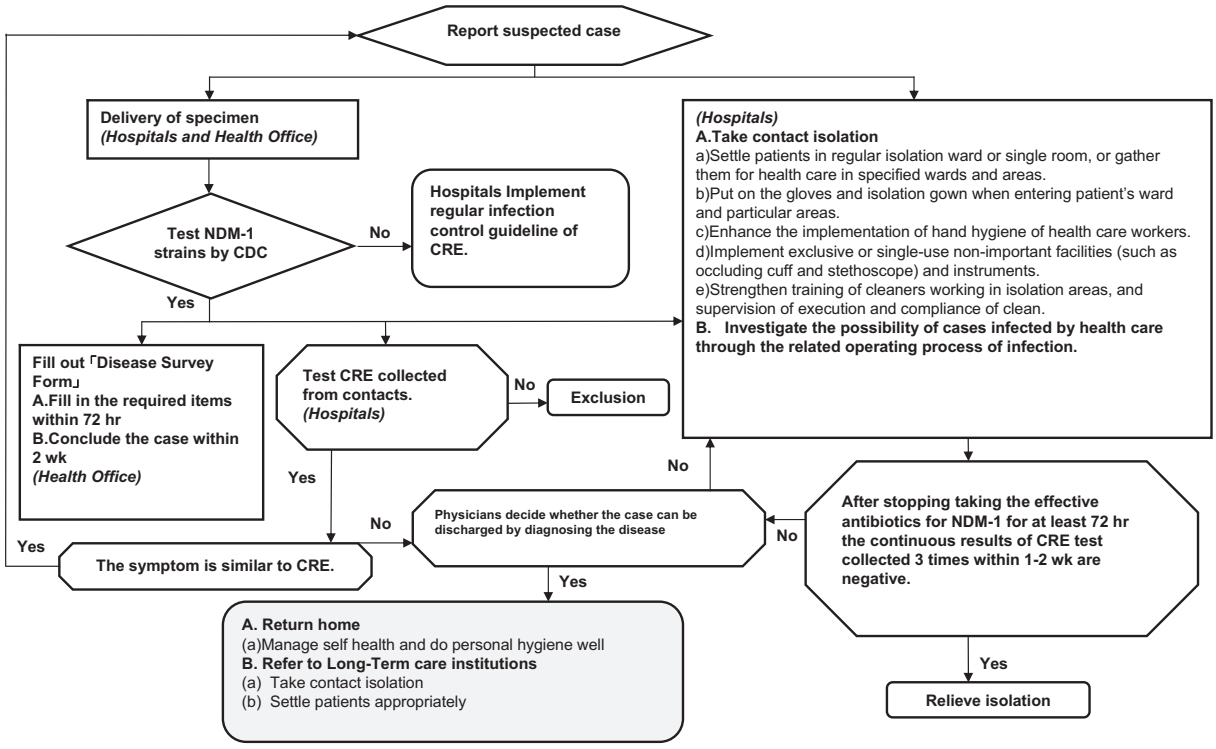

Figure 6. Standard operating procedure for reporting NDM-1 Enterobacteriaceae infection in Taiwan. CRE = carbapenem-resistant Enterobacteriaceae; NDM-1 = New Delhi metallo-β-lactamase.

based on peer ratings. As a result, this might provide appropriate care to those affected by microbes and protect patients' rights. Multi-drug resistant bacteria are not new and will continue to appear. Therefore, the Taiwan CDC will make every effort to combat antimicrobial resistance by targeting consumers, prescribers and dispensers, veterinarians, managers of hospitals and diagnostic laboratories, patients and visitors to health care facilities, as well as national governments, the pharmaceutical industry, professional societies, and international agencies.

Acknowledgments

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