

## ORIGINAL ARTICLE

# Controlling a Multicenter Outbreak Involving the New York/Japan Methicillin-Resistant *Staphylococcus aureus* Clone

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**OBJECTIVE.** To describe the control of an outbreak of infection and colonization with the New York/Japan methicillin-resistant *Staphylococcus aureus* (MRSA) clone in multiple healthcare facilities, and to demonstrate the importance of making an MRSA management policy involving molecular typing of MRSA into a statewide public health responsibility.

**SETTING.** A range of healthcare facilities, including 2 metropolitan teaching hospitals and a regional hospital, as well as several community hospitals and long-term care facilities in a nonmetropolitan healthcare region.

**INTERVENTIONS.** A comprehensive, statewide MRSA epidemiological investigation and management policy.

**RESULTS.** In May 2005, there were 3 isolates referred to the Western Australian Gram-Positive Bacteria Typing and Research Unit that were identified as the New York/Japan MRSA clone, a pandemic MRSA clone with the ability to spread and replace existing clones in a region. Subsequent investigation identified 28 additional cases of infection and/or colonization dating from 2002 onward, including 1 involving a colonized healthcare worker (HCW) who had previously been hospitalized overseas. Of the 31 isolates detected, 25 were linked epidemiologically and via molecular typing to the isolate recovered from the colonized HCW. Four isolates appeared to have been introduced separately from overseas. Although the isolate from the single remaining case patient was genetically indistinct from the isolates that spread within Western Australia, no specific epidemiological link could be established. The application of standard outbreak management strategies reduced further spread.

**CONCLUSIONS.** The elimination of the New York/Japan MRSA clone in a healthcare region demonstrates the importance of incorporating MRSA management policy into statewide public health programs. The mainstays of such programs should include a comprehensive and effective outbreak identification and management policy (including pre-employment screening of HCWs, where applicable) and MRSA clone identification by multilocus sequence typing.

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In the mid-1990s, the New York/Japan methicillin-resistant *Staphylococcus aureus* (MRSA) clone was reported as the dominant strain of MRSA in New York metropolitan hospitals. In 1994, pulsed-field gel electrophoresis (PFGE) and Southern blot hybridization (with *mecA*- and *Tn554*-specific probes) identified the *mecA:Tn554*:PFGE genotype I:A:A MRSA strain (subsequently known as the New York/Japan MRSA clone) in 6 widely dispersed New York hospitals.<sup>1</sup> Within the next 2 years, 42% of MRSA isolates in 12 New York hospitals were characterized as the New York/Japan MRSA clone (hereafter, the New York/Japan clone).<sup>2</sup> The spread of the New York/Japan clone into neighboring states, including New Jersey, Pennsylvania, and Connecticut, was reported by Roberts et al.<sup>3</sup> in 2000. Detected in 29 healthcare facilities, the New

York/Japan clone accounted for 92% of MRSA isolates in Pennsylvania.

In a 2000 Japanese study, 76% of MRSA isolates from a single hospital in Tokyo were characterized as the New York/Japan clone.<sup>4</sup> However, previous epidemiological studies of Japanese MRSA isolates suggest that this clone has been dominant in Japan since the early 1990s,<sup>5,6</sup> indicating that transcontinental spread to the United States may have occurred earlier.

Since 2000, the New York/Japan clone has been reported in several US states,<sup>7-9</sup> Canada,<sup>10</sup> Brazil,<sup>11</sup> Mexico,<sup>12</sup> China,<sup>13</sup> and Korea.<sup>14,15</sup> Although infrequently reported in Europe, the New York/Japan clone has recently been described as a major epidemic MRSA (EMRSA) clone in Hungary.<sup>16</sup>

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In many of these reports, the New York/Japan clone has replaced preexisting EMRSA clones to become the dominant clone. In the recently described US PFGE database of major MRSA lineages, 44% of all MRSA isolates examined were characterized as the New York/Japan clone (referred to as USA100).<sup>17</sup> Typically resistant to erythromycin, clindamycin, and ciprofloxacin, the New York/Japan clone has become the predominant healthcare-associated MRSA clone in the United States and is endemic in many US hospitals.

In Australia, the predominant healthcare-associated MRSA clone is ST239-MRSA-III (colloquially known as Aus-2 or Aus-3 EMRSA). This clone has been endemic in many hospitals in eastern Australian states (including Queensland, New South Wales, and Victoria) since the late 1980s and 1990s, with some spread to hospitals in South Australia, the Northern Territory, and Tasmania,<sup>18</sup> but a statewide "search and destroy" MRSA policy introduced in 1982 has prevented healthcare-associated MRSA from becoming established in Western Australian hospitals. Although the EMRSA clone occasionally causes single-strain outbreaks in Western Australian hospitals, it has to date been eradicated by early and effective infection control interventions.

In a recent article on the molecular epidemiology of MRSA isolates in Western Australia,<sup>19</sup> several New York/Japan clone isolates were characterized. Many of these isolates were recovered from a single-strain outbreak in a regional area. As this has been the only report of the New York/Japan clone in Australia, we describe its epidemiology in Western Australia, discuss the measures used to control a single-strain outbreak, and highlight the potential role of healthcare workers (HCWs) in introducing EMRSA into a population.

## METHODS

### Background

In Western Australia, the public health system is divided into 2 metropolitan health regions and 7 country health regions. The South West Health Region (SWHR) encompasses an area of 24,000 square kilometers (1% of the landmass of Western Australia) and has a population of approximately 141,000 people (7% of the state population). The SWHR is served by 2 hospitals in the regional center of Bunbury (160 kilometers south of the state's capital city, Perth), 13 smaller community hospitals (CHs), and numerous residential care facilities (RCFs). Hospitals and RCFs in the region include both private and government-funded facilities.

### Western Australia Department of Health MRSA Policy

The Western Australia Department of Health administers and sets policy for the government-funded healthcare facilities in Western Australia. In addition, it licences all private healthcare facilities. Since the 1980s, the Western Australia Department of Health has promoted a comprehensive MRSA management policy throughout Western Australia. The policy is based on selective screening, isolation, and decolonization.

The objective of the policy is the early identification, containment, and eradication of MRSA infection and colonization, primarily in acute care hospitals.

In Western Australia, screening for MRSA carriage is recommended for 3 groups. The first group comprises patients admitted to Western Australian hospitals who have been an inpatient of a hospital or a resident in an RCF outside Western Australia in the previous 12 months. One set of MRSA screening swab samples is collected from the anterior nares and from all broken skin areas. The second group is made up of HCWs who have worked in a hospital or RCF outside of Western Australia in the 12 months prior to commencing employment in Western Australia. A set of MRSA screening swab samples is collected from the anterior nares, from the throat, and from all broken skin areas. The third group consists of patients and HCWs who are epidemiologically linked to a single-strain outbreak in a healthcare facility.

All patients or HCWs who are colonized or infected with MRSA are reported to the Western Australia Department of Health and included in an electronic microbiology alert system to which the majority of the state's public hospitals have access. As a prescribed minimum standard, contact isolation infection control precautions are recommended for patients in acute care facilities who are the subject of an EMRSA alert. Individual institutions and infection control professionals can use their discretion to apply similar measures in other environments and for patients with other MRSA clones.

The Western Australia MRSA policy also recommends procedures for decolonization and criteria for determining whether an individual can be considered cleared of MRSA. The recommended decolonization treatment for both inpatients and outpatients includes nasal antiseptics (mupirocin 2% nasal ointment 3 times per day for 10 days), whole-body antiseptics (hexachlorophane 3% emulsion once daily for 10 days), and hair antiseptics (25 mL of cetrimide 20% shampoo followed by a conditioner on days 1, 4, 7, and 10). After decolonization treatment, the individual's screening swab samples must be negative for MRSA for at least 10 weeks before the individual can be considered cleared and have the electronic alert removed. There are no formal audits of compliance with the state policy, although anecdotal evidence suggests strong support for maintaining this approach.

All MRSA isolates recovered in the state are referred to the Gram-Positive Bacteria Typing and Research Unit (GPTU) for epidemiological typing and are characterized as EMRSA or non-EMRSA strains. Basic epidemiological data, including the residential area code of the infected or colonized person, is recorded for all isolates by the GPTU. These results are forwarded to the referring laboratory and to the Western Australia Department of Health. Prior to 2005, however, there had been no significant involvement of public health personnel or epidemiological expertise applied to the comprehensive laboratory-based surveillance data.

Although MRSA is increasing in prevalence in the Western Australia community, especially in RCFs, thus far MRSA is

not endemic in any Western Australia acute care hospital, and single-strain outbreaks are promptly detected and controlled.

### Outbreak Investigation

In May 2005, multilocus sequence typing (MLST) and staphylococcal cassette chromosome *mec* (SCC*mec*) typing identified 3 isolates with a unique contour-clamped homogeneous electric field electrophoresis (CHEF) pattern as ST5-MRSA-II. Subsequent comparison of the isolates' CHEF pattern with that of the New York/Japan clone showed greater than 80% similarity by dendrogram. It was noted that all of these isolates were recovered from patients at the same SWHR community hospital (CH1). Contact screening at this hospital was conducted, and further cases of infection and/or colonization (in patients and HCWs) were detected. The GPTU database was then used to identify other cases retrospectively. Between 2003 and 2005, a total of 18 cases of infection or colonization with the New York/Japan clone had been identified in Western Australia, most of which involved patients who had residential area codes in the SWHR. Isolates with a similar antibiogram that were referred to the GPTU before MLST was introduced were reassessed, resulting in the identification of an additional 4 cases dating from 2002. All of the isolates that were recovered earlier also came from patients who lived in the SWHR.

As a result of the information from the GPTU, an outbreak investigation was initiated in May 2005 by infection control and prevention staff members based in the SWHR, in collaboration with Western Australia Department of Health staff in Perth. Objectives included managing the outbreak identified at CH1 in May 2005 and delineating the epidemiology of what appeared to be an ongoing outbreak in the SWHR that began in 2002.

Relevant epidemiological and clinical information was obtained from the hospital medical records of each case patient, which were reviewed in detail by the investigating team. The information collected included demographic characteristics, medical conditions, and the presence of infection due to the organism. As the isolate had not previously been detected in Australia and had primarily been linked with healthcare institutions, specific attention was paid to recording contacts with healthcare facilities or HCWs, both locally and overseas. HCWs and case patients without available hospital records were contacted in person by members of the investigating team to obtain this information.

### Outbreak Management

Outbreak management followed standard principles,<sup>20</sup> including screening all patients and staff in CH1 for infection or colonization with MRSA. The use of contact isolation precautions and topical therapy for decolonization was recommended for all persons in CH1 who were culture positive for MRSA. The current location of all other persons known to be culture positive for MRSA was ascertained, and their mi-

crobiology alert status was confirmed. Contact tracing, contact isolation precautions, and decolonization therapy were recommended for all infected or colonized individuals who remained in any healthcare facility. If patients known to be culture positive were readmitted to a healthcare facility, they were placed under contact isolation precautions until successive MRSA screening samples were negative for MRSA on culture. Similar measures were applied to all subsequently identified cases (ie, elucidation of contact with healthcare facilities or HCWs, contact isolation precautions, decolonization treatment, and contact tracing). Contact isolation precautions were not applied at all RCFs, many of which do not have single-room accommodations available, but all RCFs were advised to promote excellent adherence to standard precautions and to consider further measures if patients were thought to be at particularly high risk for transmission.

As case patients were identified, details of their contact with healthcare facilities and residential care facilities in the 2 years prior to first detection were entered on a Gantt chart. Retrospectively identified case patients were included, allowing retrospective and then prospective identification of links in time and place between patients.

### Characterization of MRSA

Methicillin susceptibility testing was performed on Mueller-Hinton agar by the disk diffusion method with a 30- $\mu$ g ceftoxitin disk, in accordance with Clinical and Laboratory Standards Institute (CLSI) recommendations.<sup>21</sup> An antibiogram was created on Mueller-Hinton agar by the disk diffusion method, in accordance with CLSI recommendations, against a panel of the following 8 antimicrobial drugs<sup>21</sup>: erythromycin (15  $\mu$ g), tetracycline (30  $\mu$ g), trimethoprim (5  $\mu$ g), ciprofloxacin (5  $\mu$ g), gentamicin (10  $\mu$ g), rifampin (5  $\mu$ g), fusidic acid (10  $\mu$ g), and mupirocin (5  $\mu$ g). The interpretive criterion for susceptibility testing established by the Antibiogram Committee of the French Society of Microbiology was used for fusidic acid,<sup>22</sup> and the suggested interpretive criterion by Finlay et al.<sup>23</sup> was used for mupirocin. CLSI interpretive criteria were used for the remaining antimicrobial drugs.<sup>24</sup>

Urease production was tested on Christensen agar in diagonally oriented test tubes that were incubated for 24 hours at 35°C. Polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) typing of the coagulase gene was performed as described elsewhere.<sup>25</sup> CHEF pattern analysis was performed as described elsewhere, by use of the CHEF-DR III System (Bio-Rad Laboratories).<sup>26</sup> Chromosomal patterns were examined visually, scanned with a Fluor-S Multimager (Bio-Rad Laboratories), and digitally analyzed with Multi-Analyst/PC (Bio-Rad Laboratories). The chromosomal pattern for *S. aureus* NCTC8325 was used as the size marker. MLST was performed on selected isolates as specified by Enright et al.<sup>27</sup> To assign a sequence type (ST), the sequences obtained were compared with the sequences described in the MLST database (available at: <http://www>

.mlst.net). *SCCmec* typing was performed by polymerase chain reaction with primers described elsewhere that identified the class of *mec* complex and the type of cassette chromosome recombinase (*ccr*) encoded on the element.<sup>28,29</sup>

## RESULTS

### MRSA Characterization

Between August 2002 and September 2005, a total of 31 MRSA isolates that were referred to the GPTU were characterized as the New York/Japan clone. All of these isolates were urease positive as well as erythromycin and ciprofloxacin resistant, and PCR-RFLP analysis showed coagulase gene sequence type 36. MLST and *SCCmec* typing of selected isolates identified the strain as ST5-MRSA-II.

The isolates had a CHEF pattern similar to that of a known New York/Japan clone (Figure 1) and were classified into 6 pulsotypes (A1-A6). Twenty-six isolates shared a common pulsotype (A4), and another showed greater than 95% similarity by dendrogram (A5).

### Epidemiological Characterization

The results of the epidemiological investigation described are shown in Figures 2 and 3. Figure 2 is an outbreak curve beginning from the time the first New York/Japan clone was isolated. Figure 3 illustrates the presumed spread of this clone as established by the epidemiological investigation.

### Identification of the Index Subject

The case patients from 2002 and 2003 included an HCW from the regional hospital (RH) who was first identified as being colonized in December 2002. The colonization was detected as a result of screening all ward staff at the RH following a cluster of infections in RH inpatients in November 2002. This was prior to the introduction of MLST, and none of these isolates were identified as the New York/Japan clone at that time.

This investigation subsequently established that the HCW had had surgery in 2001 in New York and was treated there for a postoperative wound infection due to MRSA. No other

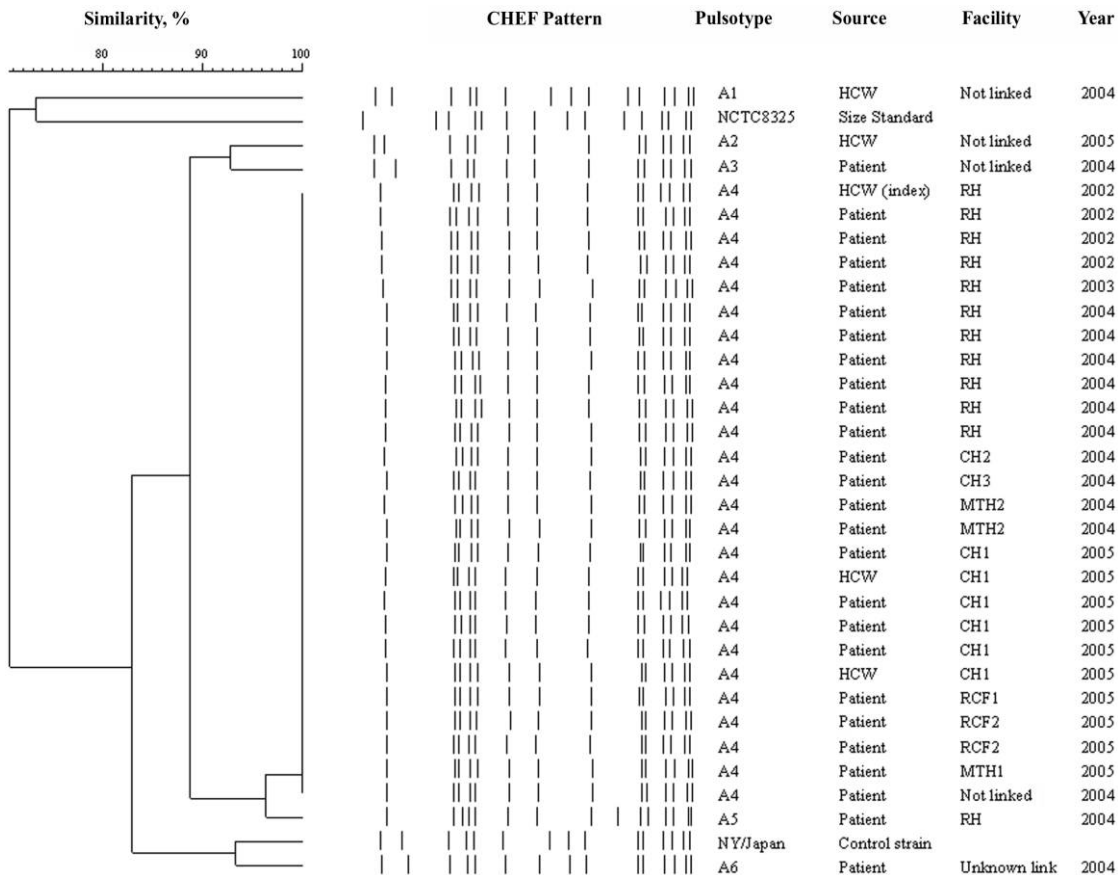


FIGURE 1. Dendrogram comparing contour-clamped homogeneous electric field electrophoresis (CHEF) pulsotypes A1-A6 of the New York/Japan methicillin-resistant *Staphylococcus aureus* clone. CH1, community hospital 1; CH2, community hospital 2; CH3, community hospital 3; HCW, healthcare worker; MTH1, metropolitan teaching hospital 1; MTH2, metropolitan teaching hospital 2; RCF1, residential care facility 1; RCF2, residential care facility 2; RH, regional hospital.

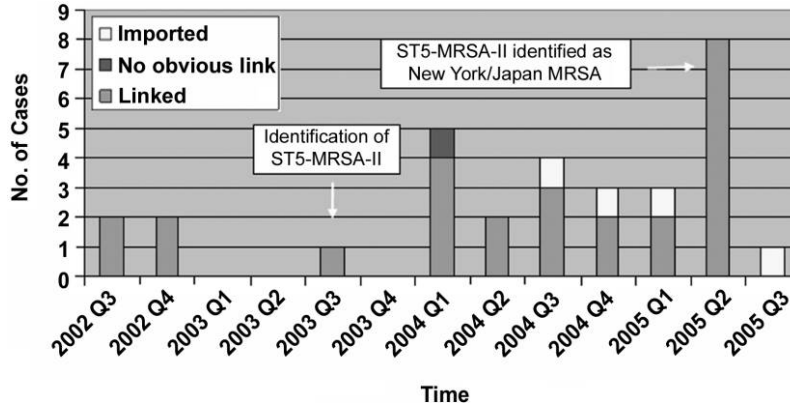


FIGURE 2. Outbreak curve of the New York/Japan methicillin-resistant *Staphylococcus aureus* (MRSA) clone isolated in Western Australia. Periods are given as year and quarter.

overseas travel or contact with HCWs or healthcare facilities could be identified for any case patients identified prior to 2005. We therefore concluded that this HCW was the index subject.

The index subject underwent decolonization treatment in early 2003. The New York/Japan clone was detected again from follow-up swab samples obtained in January 2004, requiring further treatment. Screening swab samples remained negative in June 2005.

Investigations revealed that 11 of the case patients had been cared for by this HCW at the RH during 2002-2004. Many of the patients had been transferred to RCFs and to other hospitals, including CH1. The Gantt chart of healthcare facility and RCF contacts revealed that the case patients subsequently identified in CH1, 2 residential care facilities (RCF1 and RCF2), and a metropolitan teaching hospital (MTH2) could also be retrospectively linked directly to the initial cases at the RH. Further transmission could be demonstrated from these secondary cases in both CH1 and in another metropolitan teaching hospital (MTH1).

Figure 3 shows that 22 cases of infection and/or colonization with the New York/Japan clone that were identified between November 2002 and September 2005, involving 20 patients and 2 HCWs, could be epidemiologically linked directly to the index subject. An additional 2 cases of infection and/or colonization with the New York/Japan clone were identified in patients who received care at another 2 SWHR community hospitals (CH2 and CH3). Although no direct link could be found to either the index subject or known culture-positive case patients, isolates recovered from both patients had the same pulsotype as that recovered from the index subject, and transmission from unidentified colonized case subjects serving as reservoirs seems likely.

From February 2004 through September 2005, we identified 5 cases of infection and/or colonization with the New York/Japan clone that could not be linked to this outbreak. There were 2 HCWs detected by pre-employment MRSA

screening who had previously been employed in the United States, 2 patients from Western Australia with documented skin infections who reported developing these infections overseas (in the United States and in Réunion), and 1 patient with no apparent epidemiological link to either the sporadic or outbreak cases in Western Australia or the SWHR and no history of overseas travel or contact with HCWs or healthcare facilities. No secondary cases associated with these 5 cases of infection and/or colonization with the New York/Japan clone have been detected.

### Typing Results

The isolates recovered from all case patients who were linked epidemiologically to the HCW who was the index subject or to SWHR healthcare facilities had the same CHEF patterns. Conversely, isolates recovered from the 4 case patients who had had recent contact with overseas HCWs and/or overseas healthcare facilities all had dissimilar CHEF patterns. The isolate recovered from the patient without a clear link to any culture-positive case patients, to the SWHR, or to overseas travel had the same CHEF pattern as the majority of isolates, which suggested unidentified local contact.

### DISCUSSION

Because of their ability to spread within hospitals, some strains of MRSA are known as EMRSA strains, differentiating them from other MRSA strains that do not necessarily cause epidemics.<sup>30</sup> The explosive ability of some EMRSA clones to replace existing methicillin-susceptible *S. aureus* and MRSA clones highlights the important role of epidemiological typing in surveillance systems.

EMRSA strains are endemic in acute care hospitals in most parts of the world, including the east coast of Australia.<sup>31</sup> Particular challenges to the detection and control of MRSA outbreaks include the large proportion of colonized, add therefore clinically unrecognized, case subjects.<sup>32,33</sup> Prolonged

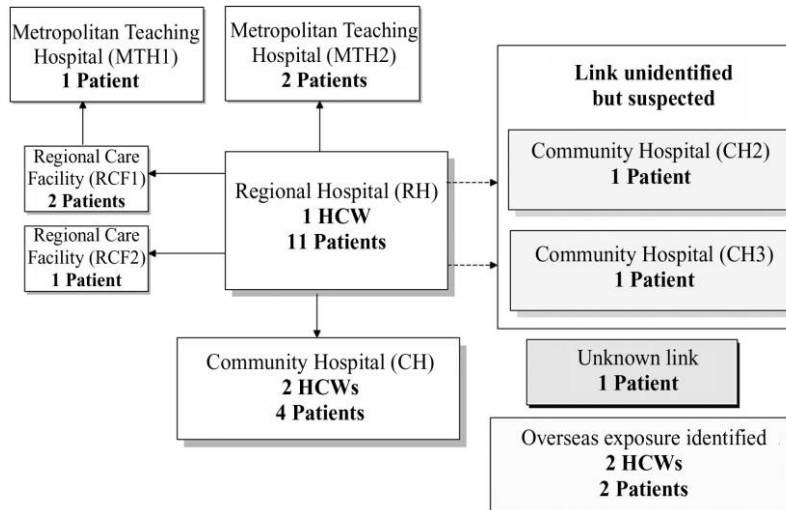


FIGURE 3. Frequency and distribution of cases of infection and/or colonization with the New York/Japan methicillin-resistant *Staphylococcus aureus* clone among healthcare workers (HCWs) and patients in different geographic locations.

carriage by these colonized case subjects provides a long-term reservoir for ongoing, unrecognized transmission. Even when clinically apparent infection does occur, thus providing a chance for detection, there is usually a delay between acquisition and infection; as a result, the MRSA infection may only be detected after a patient is discharged. In this investigation, for example, on at least 6 occasions MRSA infection and/or colonization was not detected until after the individual was discharged from the healthcare facility where acquisition had probably occurred. A full understanding of the links between case patients, and consequently, the ability to detect an outbreak, are therefore unlikely in the absence of a central universal surveillance system.

Several countries, in particular The Netherlands, Denmark, and Finland, have successfully controlled the nosocomial spread of EMRSA strains by implementing strict and comprehensive “search and destroy” MRSA management policies. These policies include the systematic screening of patients and staff members exposed to MRSA, including all patients and staff members who are transferred from hospitals abroad or from hospitals known to harbor MRSA.<sup>34</sup> Western Australia has similar policies in place. First isolated in Japan in the 1990s, the New York/Japan clone has the ability to replace existing MRSA strains and consequently has become the dominant EMRSA clone in Japan,<sup>35</sup> Taiwan,<sup>36</sup> Hungary,<sup>16</sup> and the United States.<sup>17</sup>

In 2005, by use of CHEF pattern analysis, MLST, and SCC*mec* typing, the GPTU identified a single-strain outbreak of infection and colonization due to the New York/Japan clone in a small community hospital in the state’s SWHR. This prompted a broader investigation that resulted in the detection of an outbreak that had been taking place since 2002, involving a large geographic area and numerous dif-

ferent healthcare facilities. An HCW who had been a patient in an overseas hospital was identified as the index subject.

The role of HCWs in MRSA transmission and management is contentious. However, HCWs colonized with EMRSA have been linked to single-strain outbreaks in individual institutions. We previously reported a link between ST22-MRSA-IV (EMRSA-15) and staff carriage in Western Australia.<sup>37</sup> Similarly, there have been reports outside Australia that have demonstrated the role of HCWs in causing outbreaks of MRSA infection and/or colonization.<sup>38,39</sup> In 2003, Blok et al.<sup>40</sup> reported that colonized HCWs acted as vectors in transmitting MRSA to patients and were the index subjects for a number of outbreaks of infection and/or colonization with MRSA; they subsequently recommended an active screening policy for HCWs who were at risk for MRSA carriage. Although not linked to this outbreak, pre-employment screening identified 2 other HCWs carrying the New York/Japan clone during 2004-2005. Decolonization of these HCWs may have prevented further outbreaks of infection and/or colonization with the New York/Japan clone in Western Australia hospitals and justifies continued pre-employment screening of HCWs as part of the ongoing management of MRSA in Western Australia.

The challenges of managing this outbreak were numerous. Apart from the cluster of case patients in the RH in December 2002, until the outbreak investigation began in mid-2005, none of the case patients had been recognized as being part of an outbreak. Delayed recognition of the presence of a novel EMRSA clone in Western Australia by both laboratory and epidemiological surveillance methods resulted in a missed opportunity for early intervention. An additional challenge was posed by the involvement of multiple institutions over a large geographical area and over an extended period. Pol-

icies, practices, and the availability of clinical experts varied among the private and public facilities involved. At least 15 different consultants' opinions had been sought regarding individual cases, but as there had hitherto not been significant investment in regional or statewide resources to act on typing information, the linkages between case patients had not been recognized. Clinicians caring for individual patients and infection control staff at individual hospitals cannot recognize and manage such a situation in isolation. The need for clear and consistent policies created yet another challenge. The Western Australia Department of Health policy document was not felt to be clearly understood by all HCWs, particularly those in smaller facilities with less expertise in MRSA management. Outbreak management was further complicated by the nature of MRSA transmission, which is often clinically unrecognized.

MRSA is thus far not endemic in Western Australia acute care hospitals, unlike those of most Australian states. The continued success of this policy is dependent on the control of MRSA being recognized as a regional and state public health responsibility, not just the task of individual hospital staff members. The incorporation of a central epidemiological typing laboratory that uses molecular techniques to enable the rapid identification of EMRSA clones not previously reported in the region is pivotal to this policy.

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