Editorial

Patterns of Methicillin-Resistant Staphylococcus aureus Prevalence

John M. Boyce, MD

Strains of methicillin-resistant *Staphylococcus aureus* (MRSA), which were initially described in England in 1961, emerged as important nosocomial pathogens in parts of Ireland, France, Switzerland, Belgium, Denmark, and some eastern European countries between 1965 and 1970.[1,2] Then, for reasons that are not entirely clear, the prevalence of MRSA decreased appreciably in these countries between 1970 and 1975.[1,2]

However, in the late 1970s and early 1980s, there was a resurgence of MRSA, and outbreaks occurred in Europe, the Middle East, Africa, Australia, Asia, and North and South America.35 In the United States, the number of MRSA outbreaks increased dramatically after 1975.[6] Interestingly, a majority of MRSA strains that caused outbreaks after 1976 were resistant to gentamicin as well as other antibiotics.

Currently, estimated prevalence rates vary greatly among countries, and within affected countries, rates vary substantially among hospitals. In some parts of northern Europe, MRSA presently accounts for 1% or less of S *aureus* included in antibiotic resistance surveys, while in other areas, strains of MRSA account for more than 25% of S *aureus* isolates included in such surveys (Table) .[7-13]

In this issue of *Infection Control and Hospital Epidemiology,* Rosdahl and Knudsen[7] describe the secular trends in the prevalence of MRSA in Denmark. Their report represents an update of surveillance studies conducted for more than 20 years at the Statens Seruminstitut in Copenhagen, where phage typing is performed on S *aureus* isolates submitted from hospitals throughout Denmark.

Earlier studies conducted in the 1960s at the same institution documented that MRSA emerged as a nosocomial pathogen in Denmark at the same time as it did in other parts of Europe.'" By 1967, 16% of all Danish S *aureus* strains submitted for phage typing were resistant to methicillin.[14] However, resistance to methicillin peaked in 1968 and then declined in Denmark as it did in other European countries during the early 1970s. By 1974, only 6% of Danish S *aureus* strains were resistant to methicillin.[14] The report by Rosdahl and Knudsen[7] documents that the overall prevalence of MRSA has continued to decline steadily since 1974 and that MRSA has accounted for less than 0.2% of Danish S *aureus* isolates submitted for phage typing since 1984.

These findings are noteworthy for several reasons. First, there was no resurgence of MRSA in Denmark in the late 1970s and early 1980s, when major outbreaks of nosocomial infection were seen throughout the world. And second, large nosocomial outbreaks have not occurred, even though patients with MRSA have been transferred from endemic areas into Denmark on multiple occasions. Unfortunately, the authors are unable to provide an adequate explanation for these findings.

Factors that must be considered in attempting to understand the prevalence of MRSA in a given locale include the phenotypic characteristics of the strains, antibiotic use patterns in hospitals and the community, host factors of patients in affected institutions, local infection control practices, the frequency of transfer of colonized or infected patients between facilities, methods of detecting MRSA, and the num-

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TABLE
REPORTED PREVALENCE OF MRSA IN SELECTED COUNTRIES

Country	Year(s)	No. Hospitals Included	No. S *aureus* Tested	Prevalence of MRSA	Range
Denmark[7]	1988	NA*	13,227	**0.1%**	NA
Sweden	1989	NA	NA	<1%	NA
Switzerland (Zurich)	1989	1	2,977	2%	
Germany[8]	1989(?)	19	3,800	4%	0.59622%
France	1989	3	3,184	26%	16%-42%
Italy"	1986	24	3,867	26%	6%-44%
Greece (Athens)")	1986	12	NA	32%	17%-60%
Spain	1989	2	2,547	13%	4%-19%
Australia"	1986-1987	14	7,554	14%	0.4%-25%
Malaysia[12]	1986	14	NA	NA	<5%-25%
United States[13]	1987-1988	40	1,408	15%	0%->15%

* Not available

ber and type of hospitals reporting MRSA.

Many investigators believe that some strains of MRSA have enhanced transmissibility (i.e., they are more efficient at colonizing patients and spreading through hospitals than other strains).[3-5,15-18] The increased "epidemiologic virulence" of such strains may be due to their antibiotic resistance patterns, resistance to disinfectants or antiseptics, or to other unidentified properties.[2,3,16,17] For example, a majority of the MRSA strains that caused serious nosocomial infections in Denmark during the late 1960s belonged to phage group 83A complex and were resistant to streptomycin and tetracycline. When phage group 83A strains were largely replaced by other phage types in Denmark, the prevalence of MRSA also decreased, as pointed **out** by Rosdahl and Knudsen.[7] The streptomycin- and tetracycline-susceptible MRSA that supplanted phage group 83A strains seems to have less propensity to spread within hospitals.'" More recently, "epidemic" strains of MRSA that appear to have enhanced transmissibility have been described in England, Ireland, and Australia.[3-5,17-18] The appearance and disappearance of such strains in an area can greatly affect local prevalence rates.

Why do such strains become very common, only to decline in prevalence after a variable period of time? The answer to this question is not clear. Changes in the resistance patterns of S *aureus* may be due in part to changes in antibiotic use practices.[2] For example, it has been suggested that a marked reduction in the amounts of streptomycin and tetracycline used in Denmark during the early 1970s may have reduced the selection pressure against streptomycin- and tetracycline-resistant type 83A MRSA, and caused the decline of such strains between 1969 and 1974.19 However, others have postulated that the increased use of gentamicin may have led to a reduction of the gentamicin-susceptible strains that were common in the early 1970s. Some authorities have suggested that the amount of cephalosporins used or the total amount of β-lactam antibiotics consumed may have an impact on MRSA prevalence. Most feel that the prevalence of MRSA cannot be related directly to the consumption of methicillin.[2,19] Widespread gentamicin use may have served as a selective pressure for the gentamicin-resistant strains of MRSA that have emerged since 1976. Unfortunately, Rosdahl and Knudsen[7] did not provide data regarding antibiotic use patterns in Denmark during the 1970s and 1980s.

Interestingly, only one gentamicin-resistant strain of MRSA was detected in Denmark in 1977. A few cases occurred in 1979 and, subsequently, such strains have been rare.[15] If the use of gentamicin (or possibly cephalosporins) was lower in Denmark than in other countries during the late 1970s, there may have been less selective pressure favoring gentamicin-resistant MRSA. Alternatively, the lack of resurgence of MRSA in Denmark in the late 1970s may be due to the fact that such strains did not become endemic in large tertiary referral centers, which often serve as reservoirs of MRSA in affected locales.

Why didn't gentamicin-resistant MRSA strains become entrenched in large hospitals in Denmark? Once again, the answer to this question is not evident from the data presented in the companion article.[7] The extent to which MRSA spreads within a facility and to nearby facilities is related to patient mix, local infection control practices, and referral patterns. Nosocomial transmission is more likely to occur if MRSA is introduced into burn units or other intensive care

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units.20 Other risk factors that favor acquisition of MRSA include prolonged hospitalization and receipt of multiple courses of antibiotics.[20] In institutions with many high-risk units, critically ill patients, and limited infection control resources, MRSA often causes epidemics or becomes highly endemic. However, effective infection control programs can limit transmission and prevent MRSA from becoming endemic.[20] Rosdahl and Knudsen[7] **suggest** that the continued low prevalence of MRSA in Denmark may be due to the rapid implementation of control measures when MRSA is detected. Their claim is difficult to assess, since the infection control practices used were not described.

Movement of colonized or infected patients or healthcare workers from an affected hospital can result in spread to other neighboring facilities. In some cities, MRSA has become highly endemic in many hospitals. In other cities, MRSA prevalence rates of 20% to 40% occur at large tertiary referral centers or veterans' hospitals but remain at 2% to 10% at affiliated hospitals."' Transfer of colonized or infected patients also may lead to transmission of MRSA across state, national, or continental boundaries. This point is illustrated by the fact that 48% of recent MRSA isolates in Denmark were traced to sources outside Denmark.[7]

The methods used for detecting MRSA may affect the apparent prevalence of MRSA in a given area. The heterogeneous resistance to β-lactams manifested by most strains of MRSA may result in unreliable detection of such strains by some susceptibility testing systems." Factors that affect detection of methicillin resistance include the method of inoculum preparation, inoculum size, media composition and pH, presence or absence of NaCl, incubation time and temperature, break-points used for categorizing isolates as methicillin-resistant, and the level of heterogeneous resistance of the strain being tested.[22,23]

Currently, many different antimicrobial susceptibility testing methods are used by countries reporting MRSA. For example, six different systems for antimicrobial susceptibility testing are currently used in Europe, and those used in Scandinavia differ from those used in central and southern Europe.[24] If the prediffusion paper disk and tablet methods widely used in Denmark have low sensitivity for detecting MRSA, the low reported prevalence of MRSA in Denmark could represent a surveillance artifact. However, this possibility was taken into consideration by Rosdahl and Knudsen,[7] and the additional tests performed on *S aureus* isolates by the investigators revealed that susceptibility testing methods used by local hospitals were unlikely to have missed MRSA.

In contrast, a comparison of susceptibility methods used in the United States and in Japan revealed that the latter system produced false-susceptible results for nearly half of the MRSA strains tested.[25] As a result, MRSA prevalence estimates for Japan could be spuriously low. Even when sensitive and accurate methods are used, surveillance artifacts are possible. In 1987, our laboratory found that methicillin-susceptible *S aureus* isolates were being miscategorized as MRSA on the basis of defective oxacillin disks of diminished potency, leading to a spuriously high rate of methicillin resistance at our hospital.[26] The implicated lots of disks were voluntarily recalled by the manufacturer, and a new manufacturing process is now used for producing oxacillin disks. When the low-potency disks were replaced by the new formulation in our hospital, the proportion of *S* aureus isolates reported as intermediate or resistant to oxacillin dropped from 9.1% to 2% (unpublished data).

Finally, the number and type of hospitals contributing data to surveillance statistics also influences reported prevalence rates. In some of the countries listed in the Table, data were provided by only a few "high-risk" institutions where MRSA is highly endemic. In contrast, in Denmark, about 13,000 S *aureus* isolates from throughout the country were tested in 1988, or about 250 isolates per 100,000 population.[7] The authors did not state what percentage of Danish hospitals contributed data. In the United States, susceptibility results for more than *628,000 S aureus* isolates from 5,000 to 5,500 acute-care hospitals would have to have been compiled in 1988 to achieve a similar rate of ascertainment. If this were done, the overall prevalence of MRSA in the United States probably would have been appreciably lower than the 15% reported,[13] because data from many smaller "low-risk" institutions would be included. However, it should be pointed out that calculating average or overall prevalence rates for an entire country may obscure the fact that MRSA may be causing major problems in some referral centers. Therefore, in most instances, it is preferable to stratify prevalence rates by hospital size and give the range of prevalence rates observed in individual hospitals.

In summary, the reported prevalence of MRSA in Denmark may appear lower than other areas because of the large number of isolates tested from hospitals of all sizes. However, there is no doubt that there has been a remarkable decline in the occurrence of MRSA in Denmark. In order to compare MRSA prevalence rates from different geographic areas in a more meaningful way, rates would need to be stratified using a standardized method of classifying hospitals by their level of risk (e.g., bed size, number and type of intensive care units, case-mix index, medical school affiliation), and ascertainment would need to be comparable in all areas being compared. Currently, no

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such reporting system exists. At present, prospective surveillance in each healthcare facility and rapid implementation of control measures when cases occur remain our best defense against these unpredictable pathogens.

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