# MOLECULAR EPIDEMIOLOGY OF METHICILLIN-RESISTANT *STAPHYLOCCOCUS AUREUS* AT A LOW-INCIDENCE HOSPITAL OVER A 4-YEAR PERIOD

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## ABSTRACT

**OBJECTIVE:** To study the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) over a prolonged period of time with the aid of a molecular typing method (ribotyping).

SETTING: A 1,000-bed tertiary university medical center.

***PATIENTS AND METHODS:*** Defined epidemiological data were recorded for all patients culture-positive for MRSA between 1989 and 1992. Ribotyping of MRSA strains was performed using three restriction enzymes: EcoRv, HindHI, and KpnI.

RESULTS: From 1989 to 1992, MRSA was isolated from clinical specimens in 98 patients and from surveillance cultures in 27 patients. Among the 122 isolates available for typing, 26 different ribotypes were identified. In 20% of the cases, MRSA was community-acquired, and a third of these patients never had been hospitalized previously. Nine ribotypes were responsible for more than one case (2 to 64 patients); 17 appeared only once. Epidemiological data correlated with ribotyping results revealed 14 epidemiologic clusters involving six different ribotypes, whereas only three outbreaks were suspected initially. The median follow-up after the last isolation of a given ribotype was 14 months (range, 1 to 42) for clusters and 25 months (range, 1 to 46) for ribotypes that appeared only once. During clusters, only 16% of the cases occurred after the implementation of control measures in the ward (breakthrough cases).

CONCLUSIONS: The high diversity of MRSA strains observed over 4 years suggested that new strains were introduced continuously in our hospital. Furthermore, that 17 ribotypes were isolated only once, that breakthrough cases represented only 16% of the cases in clusters, and that the follow-up duration after the last isolation of a given ribotype was more than 14 months suggest that infection control measures were effective in limiting the nosocomial spread of MRSA over a prolonged period of time (Infect Control Hasp *Epidemiol* 1995;16:260-267).

## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are an important cause of nosocomial infection and are difficult to control once they have been introduced in an institution.' Therefore, it is of utmost importance to improve our knowledge on the epidemiology and control of MRSA.

Recently, molecular techniques have allowed more refined epidemiological studies, and some have been applied to MRSA.[2-14] However, they have been used mostly for the investigation of epidemic situations and over a limited period of time. To our knowledge, only one study used such a typing method to analyze the epidemiology of MRSA in a given hospital and over a prolonged period of time.[4] The method used was the DNA analysis of plasmid markers. However, plasmids may not always be present, and there is evidence that they can be gained or lost by bacteria over time.[14] In this study, we used ribotyping, as it can be used with many bacteria, including

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***This work was presented in part*** at ***the Sixth European Congress of Clinical Microbiology and Infectious Diseases, Sevilla, Spain, 1993.***

***The authors thank J. C. Piffaretti and F. Kayser*** *for* ***providing some*** *of* ***the methicillin-resistant S*** aureus ***strains; D.*** *Raffalli* ***for technical assistance; M.*** *Roulet for* ***typing the manuscript; and P. H. Moreillon*** *for* ***his*** comments.

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*94-OA-072.* ***Lugeon C, Blanc DS, Wenger A, Francioli I? Molecular epidemiology*** *of* ***methicillin-resistant*** Staphylococcus aureus ***at a low-incidence hospital over a*** *4-year period.* Infect Control Hosp Epidemiol *1995;16:260-267.*

MRSA, and has been proven to be discriminative and useful for epidemiological purposes.[7,9-12,14] The purpose of the present study was to use this method to investigate the epidemiology of MRSA in our hospital over a 4-year period.

## MATERIAL AND METHODS

### Institutional Characteristics and Study Period

The University Hospital of Lausanne (Centre hospitalier universitaire vaudois, CHUV) is a 1,000-bed, tertiary-care, teaching hospital. The hospital has 40 intensivecare beds and approximately 30,000 admissions per year. It serves a population of approximately 300,000.

From January 1989 to December 1992, all patients with clinical or surveillance cultures positive for MRSA were included in the study.

### Microbiology

MRSA was identified by standard methods. Except for five patients who harbored MRSA for a long period of time, only the first isolate of each patient was selected for further work-up. Susceptibility testing was performed by disk diffusion on Mueller-Hinton agar with a 24-hour incubation at 35°C. An inhibition diameter of less than 13 mm was considered indicative of resistance to methicillin.[15] Resistance was confirmed by growing the isolates on Mueller-Hinton agar supplemented with NaCl (40 g/L) and oxacillin (6 mg/L).[15] Surveillance cultures were inoculated onto blood agar and Mueller-Hinton agar supplemented with NaCl and oxacillin.[15]

### Ribotyping

Ribotyping was performed as previously described.[13] Briefly, cells were lysed by lysostaphin, and DNA was extracted with phenol-chloroform. Approximately 1 kg of DNA was digested with a restriction enzyme (RE), and fragments were separated by horizontal agarose gel electrophoresis. DNA then was transferred to a nylon membrane, and hybridization was performed with biotinylated plasmid pKK3535 containing an rRNA operon of E coli.‘~,i~ Hybrids were revealed on the membrane using a nonradioactive nucleic acid detection system. For each restrictive enzyme, the DNA fingerprint of each isolate was scored visually for the presence and the position of bands. Similarity between isolates was evaluated by the presence or absence of bands using the mismatch coefficient.[17] The construction of a dendrogram from the similarity data was performed using the unweighted pair group method of analysis (UPGMA).[17] The discriminatory power of the typing method was evaluated by the index of discrimination (D) proposed by Gaston and Hunter.[18]

### Epidemiology

For each patient, the following data were collected: demographic data, geographic origin, date of admission and discharge, location and transfer in the hospital, previous admissions, diagnosis, bacteriological results, and infection control measures.

Cases were defined as epidemiologically related if they were present on the same nursing unit during the same period as another patient colonized or infected with the same ribotype and if no epidemiological link could be found with patients of other units (eg, common staff or transfer of cases). Cases without epidemiological link were considered sporadic. MRSA was considered community-acquired if isolated less than 48 hours after admission, provided that no patient with MRSA was present in the same unit. Breakthrough MRSA cases were defined as patients initially negative for MRSA (documented by surveillance cultures performed because MRSA cases were identified in the same unit) but who became positive on subsequent cultures, despite the implementation of control measures. In other words, breakthrough cases were nosocomial cases of acquisition of MRSA despite the implementation of control measures. A pseudocluster was defined as a temporary increase in the number of patients with MRSA (suggesting a cluster), but with isolates that belonged to different ribotypes.

### Infection Control Strategies

Patients with MRSA were identified by daily surveillance of microbiological laboratory data and by surveillance cultures of readmitted patients known to have been positive for MRSA. Surveillance cultures also were obtained from patients who had been roommates of patients who were infected or colonized with MRSA. When a cluster was suspected, relevant staff and their patients also were screened. Cultures were obtained of the following sites: anterior nares, axillary and inguinal areas, and infected sites or open wounds.

Patients with MRSA were placed on strict isolation: single room with gloves, gown, and masks for staff and visitors. Daily control measures were implemented for a minimum of 7 days and included total body wash with chlorhexidine, intranasal application of antimicrobials three times a day (bacitracin ointment in 1989 and mupirocin since 1990), and systemic oral antibiotic (co-trimoxazole [320 mg:1200 mg/day] and rifampicin [600 mg/day], if the strain was sensitive). Patients with clinically relevant infection were treated with vancomycin (duration according to clinical situation). Isolation was discontinued when surveillance cultures were negative on two occasions, the first being obtained at least 2 days after the end of treatment. If cultures still were positive, the same

treatment was repeated once. If the patient still was harboring MRSA after the second treatment, isolation and local antimicrobial treatment were maintained until discharge. Upon readmission, patients known to have carried MRSA were isolated until results of surveillance cultures were available.

## RESULTS

### Population

From 1989 to 1992, 1,000 to 1,200 patients had a positive culture for S *aureus* each year. MRSA was isolated from 4.2% of these patients in 1989, 3.9% in 1990, 1.8% in 1991, and 2.2% in 1992. Overall, 125 patients were colonized or infected with MRSA (107 hospitalized patients and 18 outpatients). Among these, 98 (78%) were identified by clinical specimens and 27 (22%) by surveillance cultures (890 samples in 202 patients). Positive specimens were wounds, 38%; anterior nares, 23%; inguinas, 7%; axilla, 1%; urine, 11%; sputum, 3%; oropharyngeal, 6%; and miscellaneous, 11%. At the time of the first isolation of MRSA, the location of the patients was medical wards, 25%; surgical wards, 25%; dermatology ward, 16%; ear-nose-throat (ENT) ward, 8%; burn unit, 6%; intensive care units, 4%; pediatric ward, 4%; and outpatient clinics, 12%. None were intravenous (IV) drug abusers.

Among the 125 patients, there were 25 cases (20%) of deep infection that required vancomycin treatment and 100 cases (80%) of superficial infection or colonization. Deep infections were surgical wound infection, 6 cases; pneumonia, 5; super-infected pressure sore or leg ulcer, 5; bacteremia, 3; urinary tract infection, 2; abscesses, 2; peritonitis, 1; and empyema, 1.

#### *Ribotyping*

To select restriction enzymes that would give the highest discrimination between isolates, ribotyping initially was performed on 20 isolates that were epidemiologically unrelated (either because they originated from different geographic areas around the world or because they had been isolated <48 hours after the first admission of patients with no link to other known MRSA carriers in the hospital or elsewhere). Fifteen restriction enzymes were tested: *ApaI*, BamHI, CfoI, CIaI, *DraI*, *EcoRI*, *EcoRV*, *HaeI*, HindIII, KpnI, PstI, SfuI, *SmaI*, *XbaI*, and XhoI. Three enzymes, *EcoRV*, HindIII, and KpnI, gave the greatest number of types when their restriction patterns were combined. Therefore, DNA of all isolates were digested with these three enzymes.

The reproducibility of ribotyping was evaluated by testing 20 isolates several times at different periods. Identical banding patterns (relative position and intensity of bands) were observed for each isolate and with all restriction enzymes. The discriminatory power of ribotyping for MRSA was evaluated by the index of discrimination proposed by Gaston and Hunter.[s] This index was calculated from the data obtained from 40 unrelated strains[g] and was found to be 0.954.

During the study period, most isolates of MRSA were cryopreserved. Among the 125 patients, 122 had at least one isolate available for ribotyping. Among these 122 isolates, 20 different ribotyping patterns were obtained with *EcoRv;* 17 with HindIII; and 23 with KpnI. Isolates were considered to belong to the same ribotype when they shared the same patterns for all three REs. On this basis, the 122 isolates were distributed into 32 different ribotypes. For five patients harboring MRSA for a long period of time (range, 6 to 12.5 months; median 7.6 months), several isolates were typed. Three patients were constantly colonized with the same ribotype; for the remaining two patients, the last isolate differed by only one band position from previous isolates. These minor changes observed in ribotype most likely were due to a genetic change of the strain. Therefore, for epidemiological purposes, isolates that differed by no more than one band for the three RE were considered similar (Figure 1). Thus, the 122 MRSA isolates were grouped into 26 main ribotypes (Figure 2). Nine ribotypes included isolates from more than one patient, whereas 17 ribotypes were found in only one patient each.

### Epidemiology

The monthly incidence of affected patients according to their ribotype is shown in Figure 3. Epidemiological data correlated with ribotyping results disclosed 14 epidemiologic clusters involving 6 different ribotypes, whereas only three outbreaks were suspected initially. Ribotype 1 accounted for seven clusters (2 to 17 patients, total 47 patients). The two largest clusters concerned the dermatologic ward (17 patients) and ENT ward (9 patients). These two wards were located on two wings of the same floor, but hospital staff were different, and the outbreaks were separated by 1 year. Ribotype 1 also was isolated from 15 additional patients, who were considered sporadic cases. Ribotype 8 was isolated only in a burn unit outbreak. Four other ribotypes (Nos. 10, 13, 16, and 17) were found in five other clusters (2 to 6 patients), as well as in 8 sporadic cases. All other ribotypes were found in sporadic cases. All strains obtained from patients identified by surveillance culture belonged to the nine ribotypes responsible for clusters.

Overall, epidemiological links eventually could be found for 80 (66%) of 122 patients, whereas 42 (34%) of 122 were considered sporadic cases. Ribotyping allowed us to recategorize as pseudoclusters four groups of cases that had been suspected to be clusters on the basis of increased MRSA incidence (April and

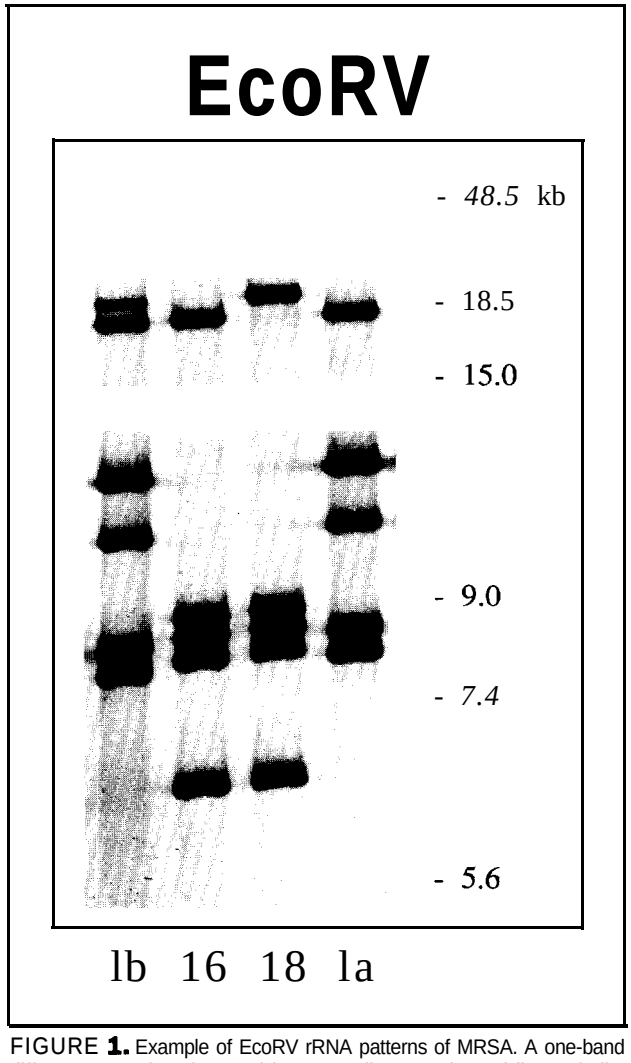


FIGURE **1.** Example of EcoRV rRNA patterns of MRSA. A one-band difference can be observed between ribotypes la and lb. A similar difference is observed between ribotypes 16 and 18, but these two ribotypes differed also by two bands with the restriction enzyme ***KpnI,*** whereas ribotypes la and lb had similar pattern with HinDIII and KpnI (data not shown).

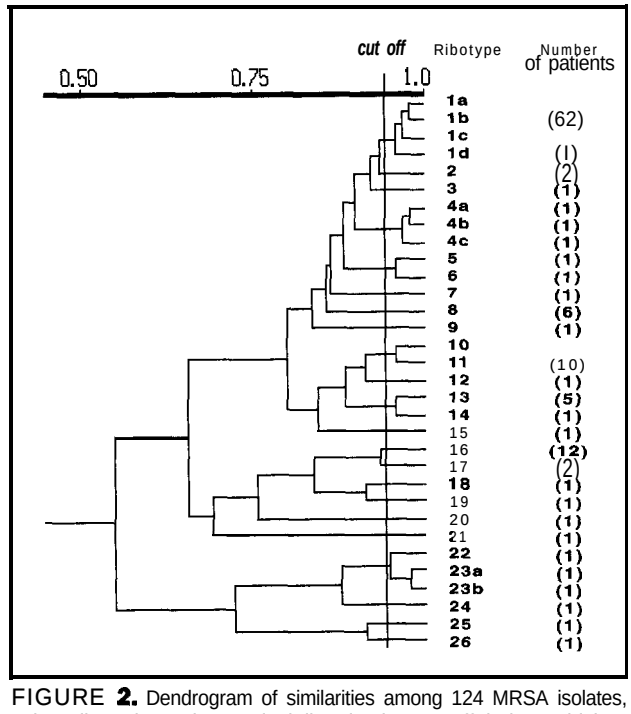


FIGURE **2.** Dendrogram of similarities among 124 MRSA isolates, using ribotyping. The vertical line is the cut-off below which a difference of one band or less between isolates is observed.

November 1989, January and November 1992). In fact, 4 to 5 different ribotypes were involved in each of these pseudoclusters (Figure 3).

Among the 97 nosocomial cases, 24 were from a ribotype observed for the first time in the hospital and were considered index cases. MRSA was considered community-acquired in 25 cases (20%). Among these, 17 (68%) came from the geographical area served by the hospital and 8 (32%) came from foreign countries. Of these 25 patients, 9 (36%) had never been hospitalized before and one came from a nursing home.

### Control *of MRSA*

The complete set of control measures was applied to 83% of the 107 hospitalized patients, whereas 11% had isolation measures only and 6% were discharged before the end of the treatment. Of the 96 hospitalized patients still alive at the time of discharge, 32 (33%) were considered culture-negative (2 consecutive negative cultures), whereas 40 patients (42%) still were considered positive; in 24 patients (25%), the presence of MRSA could not be assessed. Among the 40 patients who still were positive, 28 (70%) received local and systemic antibiotics and 12 (30%) received no treatment. This was significantly different from the 32 patients who became negative and among whom only three (9%) received no systemic antibiotics. Overall, 7% of the strains were resistant to co-trimoxazole; 33% to rifampicin. The proportions of strains resistant to these antibiotics were similar in patients with negative or positive control cultures after treatment. No strain was resistant to mupirocin.

Among the 52 patients who were readmitted to the hospital (3 days to 7 months later, median 5.7 months), 22 had positive cultures at the end of their first stay. Out of the 19 cases who had surveillance cultures obtained upon readmission, 10 still were positive. Among these 10 patients, two were found to have epidemiological links with subsequent cases and might have been the sources of their MRSA

Among the 80 epidemiologically related patients, only 13 were breakthrough cases. Most of these breakthrough cases occurred soon after the identification of a cluster, suggesting that some of them probably already were colonized at the time of implementation of control measures.

The long-term efficacy of the control measures

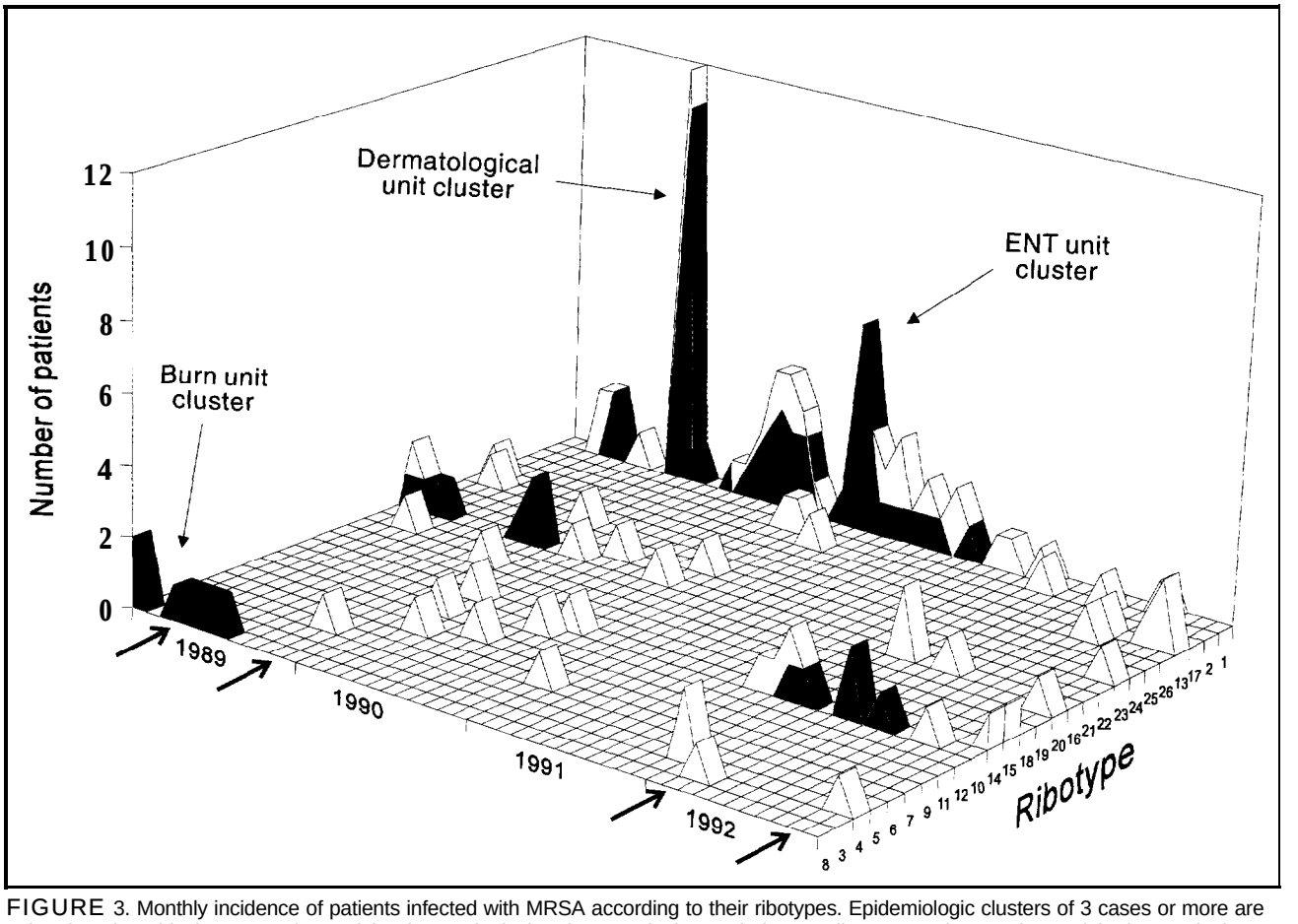


FIGURE 3. Monthly incidence of patients infected with MRSA according to their ribotypes. Epidemiologic clusters of 3 cases or more are pointed out by a black area. Patients of the dermatological and ENT unit clusters belong to ribotype 1, whereas those of the burn unit cluster belong to ribotype 8. Arrows on the x-axis show pseudoclusters.

was estimated by the median follow-up duration after the last positive culture for a given ribotype in the hospital. At the end of 1992, the median follow-up duration was 14 months (range, 1 to 42 months) for the ribotypes involved in clusters, and 25 months (range, 1 to 46 months) for the 17 ribotypes isolated only from one patient. Moreover, ribotype 1, which accounted for approximately one half of the patients with MRSA, was observed only in three cases during the last 12 months, whereas it was observed in 12 unrelated wards and in 65 cases during the first 3 years of the study. The other 8 ribotypes involved in clusters were much more limited in time and space.

### Hospital Staff

Surveillance cultures performed during clusters among the staff in contact with patients (701 samples in 489 individuals) identified only four nurses colonized with MRSA. Isolates from three nurses were available for typing, and the same ribotype was observed in these nurses and in their patient(s). All four positive nurses became persistently negative after nasal instillation of mupirocin for 1 week.

## DISCUSSION

Ribotyping of MRSA satisfied relevant criteria for any epidemiological typing system: typability and reproducibility were 100%. In preliminary experiments, we evaluated a wide panel of restrictive enzymes and chose the 3 enzymes that gave the highest number of types. Combining the results of the 3 enzymes, 32 different ribotypes were obtained, whereas the greatest number of different ribotypes obtained with the use of a single enzyme was only 23. Thus, combining the results of 3 RE clearly enhanced the discriminatory power of the method. It appears to be a valuable approach for improving the performance of the typing method.

With the use of this method and of classic epidemiological investigation, the present study disclosed several interesting features of endemic and epidemic MRSA. Over a 4-year period, 26 different ribotypes, often represented by only one strain, were identified in 122 patients, suggesting that new strains were introduced regularly into the hospital from outside sources. Moreover, among the patients who

were considered to have acquired their MRSA in the community (20%) one third had not been hospitalized in an acute or chronic care facility, suggesting that MRSA circulating in the community may be a significant source of MRSA for hospitals.

Little is known of the epidemiology of MRSA within the community. In a recent study, community-acquired cases admitted directly from their own home represented 60% of all MRSA cases, but 88% of these patients had at least one admission in the same hospital within the previous 12 months.[4] Epidemics in the community have been described in some particular populations such as drug addicts[2023] and children.[24] It also has been shown that discharged patients still carrying MRSA may spread it further in the community.[25] Transmission in the community also has been postulated to explain certain epidemic patterns observed in hospitals, such as simultaneous occurrence of cases in different wards without obvious hospital epidemiological link.[2]

The diversity of strains observed in the present study, as well as in other recent studies,[4*5] and the fact that a substantial proportion of community-acquired cases had never been hospitalized, suggest that asymp tomatic carriers in the community (other than IV drug users) may constitute a significant reservoir of MRSA for hospitals. However, it is of interest that in our study, only two readmitted patients colonized with MRSA were suspected to have spread their MRSA to other patients. This possibly was due to the application of early control measures. In the present study, only 4 of the 489 investigated staff members were found to harbor MRSA, of which 3 isolates could be typed. Although the nurses shared the same ribotypes as their patients, the direction of transmission could not be determined. In the meantime, the low number of positive staff members suggests that chronic carriage by the staff was not a main source of MRSA in our setting.

Ribotyping also proved to be a useful complement to traditional epidemiological investigations. Indeed, several unsuspected clusters were discovered, which helped us in focusing appropriate control and educational interventions. Others also observed that detection of small outbreaks by using a typing method permitted concentration of infection control efforts.[4] In the same way, ribotyping allowed us to exclude the existence of epidemic clusters that could have been suspected on the basis of an increase of MRSA incidence, thus avoiding unnecessary epidemiological investigations.

Many studies have investigated the short-term efficacy of infection control measures in the control of outbreaks.[2c28] In some studies, cohorting and isolation alone was shown to be effective in controlling epidemics, but not in eradicating the epidemic strain from the hospita1.[2gv30] In other studies, only the combination of isolation, extended screening, and mupirocin treatment of carriers[31] or systemic treatment[32*33] was able to contain epidemics. In a long-term prospective study, combined measures were able to terminate several epidemics, to control undetected clusters, and to limit nosocomial transmission. Moreover, this program was found to be cost-effective.[33] Only one study assessed the efficacy of control measures over a long period of time and with the aid of molecular typing.[4] In the present study, standardized control measures were applied during the 4-year period. The number of MRSA isolated in our hospital remained essentially unchanged over these years.

Although the contribution of the control measures in limiting the spread of MRSA is difficult to assess, the use of ribotyping allowed several interesting observations. First, 17 of 26 ribotypes were found only once, with a median follow up of 25 months. Second, breakthrough cases accounted for only 16% of the cases observed in clusters. Third, most of the clusters due to a given ribotype were limited in time, with a median follow up after the occurrence of the last case of 14 months. Fourth, during clusters, there was a clear temporal association between initiation of control measures and the decrease in the number of new cases.

It can be argued that these observations are not related to the control measures that were implanted. Indeed, some authors pointed out that the incidence of MRSA infections may tend to rise and fall without any apparent relationship to control measures.[34] For this reason, criteria were proposed to validate observations on the effectiveness of a strategy for MRSA control (baseline rate of MRSA, mode of transmission, number of interventions, etc.). Most of these criteria were fulfilled in the present study, suggesting that the limitation of the spread of MRSA in our hospital was at least partly due to the infection control program.

Clearly, further studies are needed to assess the efficacy and cost-effectiveness of each individual control measure. Indeed, our program could be considered excessive and costly. However, in a hospital with a low incidence of MRSA, the absolute cost of a comprehensive program is limited, and we have elected to maintain this program while awaiting further data on the efficacy of control measures.

An important limitation of control measures is that MRSA cases often were discovered when they already had caused spread to other patients. Thus, in our study, 80% of the cases were considered hospital-acquired, but most arose before the implementation of control measures. Screening on admission could be applied to certain categories of patients (eg, patients previously known to harbor MRSA or transferred

from other institutions or from countries with high MRSA prevalence). In our setting, this strategy would be of limited efficacy, since new ribotypes were introduced, often identified in patients who did not fall in the above categories.

It is of note that local and systemic antimicrobial treatment was ineffective in eradicating MRSA in a substantial proportion of patients. Better results were obtained in other studies that used mupirocin alone,[31] with no obvious reasons for this difference. This suggests that barrier precautions were the most important contributor to the control of the spread of MRSA. However, even if the bacteria were not eradicated in many patients, antimicrobials may have decreased the load of bacteria.

In the present study, there were relatively more patients who did not receive systemic antibiotic treatment among those who still had positive culture after therapy, suggesting that local and systemic antibiotics might be more effective than local antibiotic alone. However, this effect was marginal and would require further investigation. Indeed, additional interventional studies using molecular typing are needed to better delimit the usefulness of each control measure in controlling the spread of endemic MRSA.

In conclusion, this study suggests that new strains of MRSA were introduced continuously in our hospital and that despite this constant external pressure, the control measures were effective in limiting the spread of MRSA.

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# CDC Reports TB Transmission Between Passengers and Flight Crew on Commercial Aircraft

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The Centers for Disease Control and Prevention (CDC) recently investigated six instances in which passengers or flight crew traveled on commercial aircraft with symptomatic, AFB smear-positive cavitary tuberculosis (TB). In two instances, Mycobacterium tuberculosis isolated from the index patient was resistant to isoniazid and rifampin. Further, in two instances, the index patients were aware of their TB at the time of travel and were on an international flight in transit to the United States to obtain medical care.

More than 2,000 passengers and flight crew potentially were exposed during these incidents. Follow-up investigation can be difficult because the airlines do not keep addresses of passengers unless they are part of frequent flyer programs.

The CDC concluded that transmission did occur in two of the six investigations, from flight attendant to other flight crew and from passenger to passenger. The cases (tuberculin skin-test conversions) involving flight attendants were associated with cumulative flight time exposure (>12 hours) to an infected flight attendant. All cases involving passengers occurred in passengers seated in the same section of the aircraft as the index passenger, suggesting that transmission was associated with proximity of seating.

The risk for TB transmission on an aircraft does not appear to be greater than in other confined spaces. Based on current evidence indicating a low risk for transmission of TB on aircraft, the CDC recommends that the need for notification of passengers be guided by three criteria: first, whether the person with TB was infectious at the time of the flight; second, whether exposure was prolonged (eg, the duration of the flight exceeded 8 hours); third, priority should be given to notifying passengers and flight crew at greatest risk for exposure, based on proximity to the index case (for example, depending on the aircraft design, proximity may be defined as seating or working in the same cabin section as the infected passenger or crew member).

To prevent exposures to TB aboard an aircraft, the CDC recommends that persons known to have infectious TB should travel by private transportation, not commercial aircraft or other commercial carrier. At a minimum, patients with infectious TB should be sputum smear-negative for AFB before being placed in indoor environments conducive to transmission.

FROM: Centers for Disease Control and Prevention. Exposure of passengers and flight crew to Mycobacterium tuberculosis on commercial aircraft, 1992-1995. *MMWR.* 1995;44(8):137-140.