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Review

Evolution of methicillin-resistant *Staphylococcus aureus* clones in Latin America

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SUMMARY

Objectives: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a prominent nosocomial bacterial pathogen, associated with significant morbidity and mortality. The global incidence is increasing, and Latin America is no exception. This article reviews MRSA clonal distribution in Latin America and implications for clinical practice.

Design: A PubMed literature search (1966–2008) identified 32 articles that characterized MRSA clones in Latin America.

Results: Data from these articles show that since 1990, several epidemic MRSA clones have spread in Latin America. The multidrug-resistant Brazilian clone is widespread, especially in Brazil and Argentina, but more recently clones with susceptibility to a range of antibiotics have been detected in Brazil, whereas in Argentina, as in Chile, Colombia and Paraguay, the multidrug-resistant Cordobes/Chilean clone prevails. In Mexico, the New York/Japan clone is most frequent. Data were not available from every country and, despite the increasing prevalence of community MRSA infections, most were collected from tertiary care centers.

Conclusions: A variety of epidemic MRSA clones are circulating in Latin America, some of which harbor genes that encode multidrug resistance or enhanced pathogenicity. Continued collection and reporting of epidemiological data is crucial for effective prevention and treatment.

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1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) clones have emerged to cause a global public health concern.^{1–7} Several major pandemic MRSA clones have been identified around the world, but despite one such clone having originated in Brazil, the molecular epidemiology of MRSA in Latin America is largely unknown.⁸

1.1. Analysis of the relatedness of clones

MRSA clones (bacterial strains descended from a common ancestor) diversify through point mutations, recombination, or the acquisition/deletion of mobile genetic elements, giving rise to extensive genomic and phenotypic diversity. Discriminating and reproducible typing methods are needed to study the epidemiology of MRSA. Frequently used methods include ribotyping, pulsed-field gel electrophoresis (PFGE), and polymerase chain reaction (PCR) with repetitive element primers, but these methods are inherently prone to produce different results in different laboratories due to the highly variable, rapidly evolving bacterial genome regions that they target. PFGE has commonly been used in studies of MRSA epidemiology in Latin America, to show the relatedness of isolates from recent outbreaks. However, the technique is not well-suited to long-term

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global epidemiology, which requires a highly discriminatory procedure to decipher gene variations that accumulate slowly.

Newer molecular typing methods, including multilocus enzyme electrophoresis (MLEE) and multilocus sequence typing (MLST), are highly discriminatory and easily reproducible. MLST is used to characterize isolates of bacteria and distinguish between clones by targeting the sequences of internal fragments of housekeeping genes, where genetic variations develop gradually.^{9,10} MLST allows related strains recovered in different countries to be readily identified. When MLST results are analyzed using an algorithm known by the acronym BURST (Based Upon Related Sequence Types), groups of isolates with a defined level of similarity in allelic profile can be discerned among large MLST datasets, and a dendrogram can be constructed.^{6,7} BURST has been useful in studying the evolutionary history of MRSA, to predict the ancestral allelic profile (genotype) of each clonal complex (CC), and the pattern of evolutionary descent of all isolates in the group.^{6,11}

1.2. Historical origins and mechanisms of evolution of MRSA

The first MRSA clones had similar genetic and phenotypic properties to methicillin-susceptible *Staphylococcus aureus* (MSSA) clones that were epidemic in the early 1960s in Europe.⁴ The initial appearance of MRSA resulted from the acquisition by successful MSSA clones of *mecA*, the gene that encodes a penicillin-binding protein conferring resistance to methicillin, from an unknown heterologous source.⁴ The mobile genetic element that carries *mecA*, called the staphylococcal cassette chromosome *mec* (SCC*mec*) has five forms (I, II, III, IV and V), which have arisen by the horizontal transfer of *mecA* in independent events.^{6,12}

Five major lineages of MRSA (CC5, CC8, CC22, CC45 and CC30) circulate internationally and cause most nosocomial MRSA infections worldwide.^{5,11,13–15} Within each lineage, putative evolutionary pathways have been proposed by Robinson and Enright,¹¹ based on sequence types (ST) characterized by MLST. A relatively small number of pandemic MRSA clones have caused a majority of MRSA infections. Five predominant clones (Brazilian, Iberian, Hungarian, pediatric and New York/Japan (NYJ) clones) were identified among 3000 MRSA strains collected in surveillance studies and outbreak investigations from 1994 to 2000 (the CENMET initiative); PFGE was used to characterize these strains.³ These five clones accounted for 68% of isolates. The authors hypothesized that these major clones have a unique ability to cope with changing clinical environments.

Gathering accurate data about the distribution and evolution of these clones in the Latin American region is necessary to support the use of treatments effective against the most prevalent clones in each local region. Such data also provide insight into possible mechanisms of dissemination across Latin America and help to explain the predominance of certain clones over others, an understanding of which may guide strategies to control the spread of MRSA. Evaluation of existing epidemiological data is also useful for predicting future trends. By summarizing available data on the clonal distribution of MRSA within Latin America, we hope to promote awareness of local differences in epidemiology that impact on the success of prevention and treatment protocols, and thereby encourage more effective infection control and rational use of antibiotics in the region.

2. Evolution of MRSA in Latin America

We performed a literature search to evaluate the history and distribution of MRSA clones within Latin America. The PubMed database was searched for the years 1966–August 2008 for published articles relating to the clonal evolution of MRSA in Latin America. Search terms were: 'MRSA clones', 'Methicillin-resistant *Staphylococcus aureus* clones', 'Latin America', and 'Country name' (country names were Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela).

Most of the pertinent, published data on MRSA in Latin America come from only eight countries. Twenty-nine relevant published articles reporting data collected from single Latin American countries were included: 18 from Brazil (1994–2008), six from Argentina (1998–2008), two from Colombia, two from Mexico and one from each of Uruguay, Paraguay, and Trinidad and Tobago. A further three published studies evaluated MRSA clones collected from several countries: Brazil, Argentina, Uruguay, Mexico and Chile;¹⁶ Brazil and Argentina¹⁷ and Brazil and Uruguay.¹⁸ Additionally, recent data were obtained from Chile^{19,20} and the Colombian–Caribbean region.^{21,22}

Figure 1 shows the sequence of MRSA clonal evolution and dissemination across Latin America, as it is known from the available published data.^{8,16–50} Most of the MRSA clones circulating in Latin America are related to the five major MRSA international clones: NYJ, pediatric, Brazilian, Iberian, and Hungarian (Figure 2).^{8,16–37,39–50}

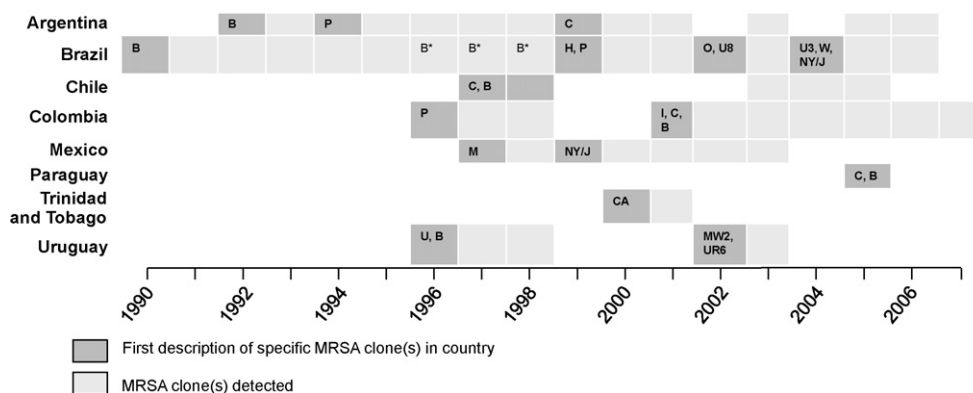


Figure 1. Evolution of MRSA clones in Latin American countries: time line to show where and when clones were isolated.^{8,16–50}

B = Brazilian MRSA clone and variants; C = Cordobes/Chilean MRSA clone; CA = CMRSA-6 (Canadian MRSA clone); H = Hungarian MRSA clone; I = Iberian-related MRSA clone; M = Mexican MRSA clone; MW2 = MW2-related MRSA clone; NY/J = New York/Japan-related MRSA clone; P = pediatric-related MRSA clone; O = Oceania Southwest Pacific MRSA clone; U = Uruguayan hospital MRSA clone; UR6 = Uruguayan community outbreak MRSA clone; U3 = USA-300 MRSA clone; U8 = USA-800 MRSA clone; W = Western Australia 1 MRSA clone.

*First identification of Brazilian MRSA isolates with vancomycin and teicoplanin heterogeneous resistance (1996–1998).

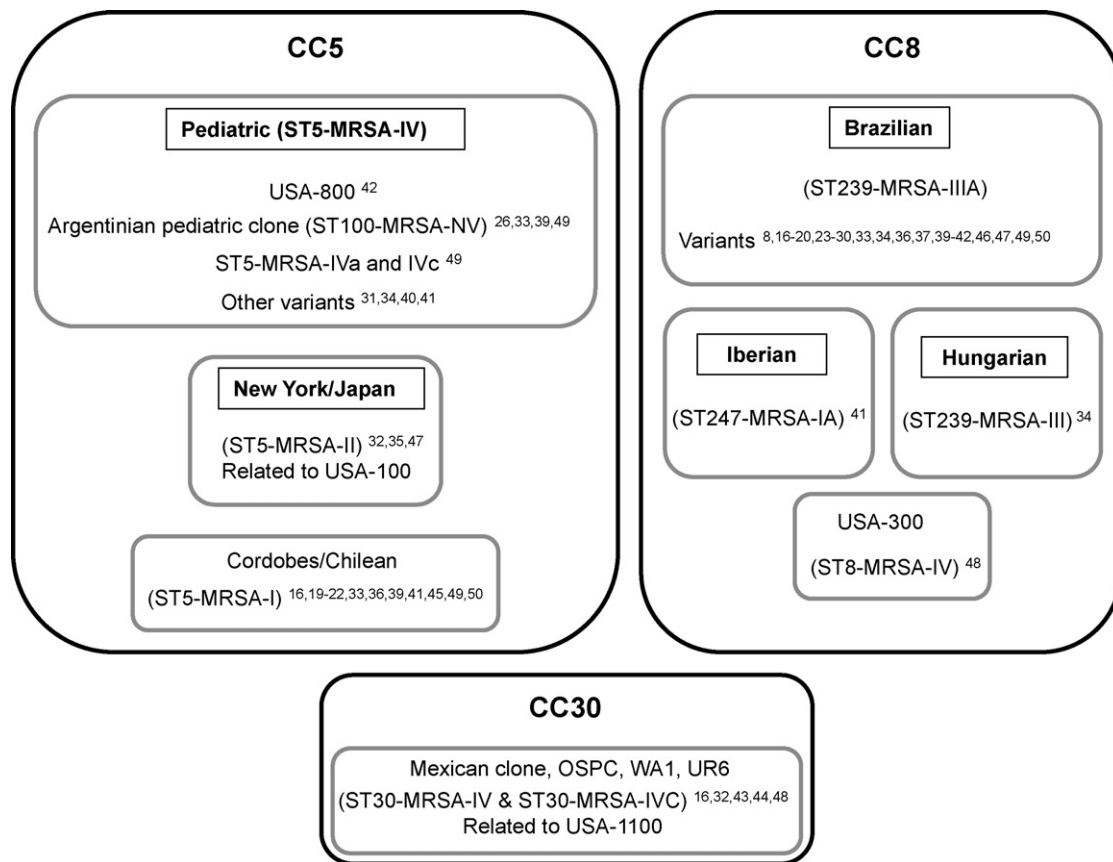


Figure 2. Relationship of Latin American MRSA strains to clonal complexes (CC5, CC8 and CC30) and international MRSA clones according to the model put forward by Robinson and Enright (2003).¹¹ Major international clones are indicated in bold type. Sequence types (ST) and SCCmec types (I to IV and variants) of MRSA clones are indicated where known. Reference numbers are shown in superscript. No Latin American isolates belonging to CC22 or CC45 were described. UR6 = Uruguayan community outbreak MRSA clone; OSPC = Oceania Southwest Pacific MRSA clone; WA1 = Western Australia 1 MRSA clone.

2.1. Brazil

Twenty studies described clonal MRSA in Brazil (Figure 3).^{8,16–18,23–25,27–30,34,37,40,42,43,46–48,50} The earliest publication from Brazil described the inter-hospital spread of a single MRSA clone in eight of nine hospitals under surveillance in Sao Paulo between 1990 and 1992.⁸ A year later, MRSA isolates collected from five large teaching hospitals in different parts of Brazil shared a common PFGE pattern, again indicating that a single, epidemic clone (the ‘Brazilian’ clone) was widespread in Brazil.²⁴ Since then, the Brazilian clone and related variants, collectively termed the ‘Brazilian epidemic clonal complex’ (BECC),²⁸ have been highly prevalent in Brazilian hospitals each year between 1990 and 2004 (Figure 3). In recent studies of nosocomial MRSA isolates in Brazil,^{42,46} the frequency of BECC clones has remained above 50% of all *S. aureus* isolates.

The BECC MRSA clones have acquired multi-resistance genes, and isolates have demonstrated resistance to chloramphenicol, cephalothin, ciprofloxacin, clindamycin, erythromycin, gentamicin, lincomycin, penicillin, tetracycline and trimethoprim–sulfa-methoxazole (TMP–SMX).^{2,24} In 1999, the acquisition of a novel mupirocin resistance gene (*ileS*) was described.²⁹ As many as 74% of Brazilian clone isolates from teaching hospitals in Brazil between 1992 and 1994 were reported to be sensitive only to vancomycin,²⁴ and this pattern of resistance was also observed in isolates collected in other studies.^{17,25,27–29} The emergence of a subpopulation of BECC isolates with vancomycin and teicoplanin heterogeneous resistance in the northeast of Brazil was observed in 1996–1998.³⁰

In addition to multi-resistance, isolates of the predominant BECC variant that were collected between 1995 and 1998 in Belém, developed an enhanced ability to produce biofilm on inert polystyrene surfaces and to adhere to and invade epithelial airway cells.²⁸ In another study in Rio de Janeiro, BECC isolates had acquired the gene for production of Panton–Valentine leukocidin (PVL) toxin, which was suggested to have occurred by horizontal transfer from a reservoir of PVL-positive MSSA isolates.³⁴

Although BECC MRSA clones are widespread in Brazil, other clones are also in circulation. In Rio de Janeiro in 1999–2000, the Brazilian clone coexisted with other clones, one resembling the Hungarian clone and one similar to the pediatric clone.³⁴ In 2004, a gentamicin-susceptible MRSA clone resembling the NYJ MRSA clone was reported in the same city.⁴⁷ Other nosocomial MRSA strains have been described with susceptibility to four or more antimicrobials and harboring SCCmec type IV – traits that are usually associated with community-associated MRSA (CA-MRSA).⁵¹ This suggests that CA-MRSA clones have been introduced into the hospital and are now circulating as nosocomial pathogens. In 2007, non-multiresistant MRSA isolates were identified in hospitals in two cities in Brazil;⁴² these caused severe nosocomial infections and displayed PFGE patterns similar to USA-800, with a high growth rate, an ability to produce biofilm, and enterotoxin genes. International CA-MRSA strains with genes encoding PVL and enterotoxin have been identified in Rio de Janeiro and Porto Alegre, causing both community- and hospital-acquired infections.^{43,48}

Conversely, MRSA strains isolated within 6 h of hospital admission from the nasopharyngeal passages of 686 Brazilian children between 2000 and 2001 were multidrug-resistant and

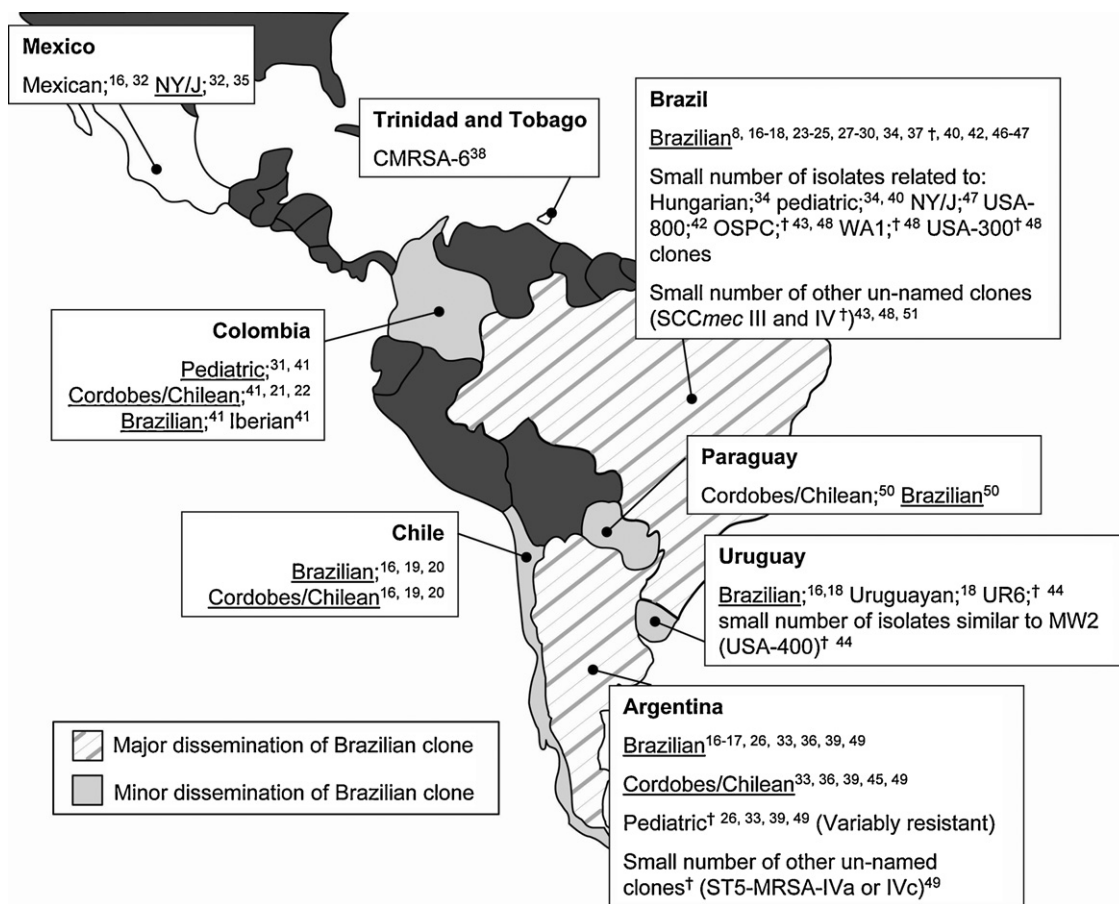


Figure 3. Distribution and dissemination of MRSA clones in Latin American countries and the Caribbean. Shading indicates the dissemination of the Brazilian clone. Data were not available for countries shaded in dark gray. Reference numbers are shown in superscript. Underlined text shows multidrug-resistant clones.

[†]Includes isolates from community-acquired infection or colonization.

MW2 = MW2-related MRSA clone; NY/J = New York/Japan-related MRSA clone; OSPC = Oceania Southwest Pacific MRSA clone; UR6 = Uruguayan community outbreak MRSA clone; WA1 = Western Australia 1 MRSA clone.

harbored SCCmec type III, characteristics that suggested that clones of hospital origin were now spreading in the community.³⁷

2.2. Argentina

Eight studies described the clonal epidemiology of MRSA in Argentina (Figure 3).^{16,17,26,33,36,39,45,49} The presence of the Brazilian clone was confirmed,^{16,17,26} but over time an increasing proportion of other epidemic clones have been detected.

The year 2002 marks the first published report of the Cordobes/Chilean clone, co-existing with the Brazilian clone in the second largest city in Argentina.³³ Of isolates collected in 1999 from six hospitals in Córdoba, 34% were the Brazilian clone and 38% of isolates belonged to a major clonal type with a novel PFGE pattern (later found to be closely related to the Chilean clone).^{16,33} Most Cordobes/Chilean clone isolates had a multiresistant phenotype, although the resistance profile differed between subtypes and all were susceptible to TMP–SMX and minocycline. This clone caused outbreaks of nosocomial infection in Córdoba and Buenos Aires, and its prevalence increased over time.^{33,36,39,45,49}

Variants of the pediatric clone were detected in Buenos Aires, Tucumán and Córdoba in the late 1990s.^{26,33,39,49} In Córdoba, isolates related to the pediatric clone were associated with a new variant SCCmec element, type IVNv.^{33,39,49} Most of these were resistant to β-lactam antibiotics and gentamicin, and by 2001, most were also resistant to rifampin. The clone caused approxi-

mately 15% of nosocomial infections and a variable proportion of community-acquired infections.^{33,39,49} Related clones (ST5-MRSA-SCCmec IVa or IVc) were the most frequent CA-MRSA isolates detected in 2005–2006, and some harbored genes for PVL and enterotoxin A.⁴⁹

2.3. Other Latin American countries and the Caribbean

We identified 13 published studies from other Latin America countries and the Caribbean (Figure 3).^{16,18–22,31,32,35,38,41,44,50} In Chile, Aires de Sousa et al.¹⁶ detected a variant of the Brazilian clone, existing together with a novel clone, the Chilean clone (known later as the Cordobes/Chilean clone, mentioned above). Recent data presented in Chile showed that the Cordobes/Chilean clone has become the predominant clone.^{19,20}

The first report from Colombia found that MRSA isolates from five hospitals in Bogotá (1996–1998) had 80% genetic homology to the pediatric clone, although these isolates were recovered from patients of all ages and had a multiresistant phenotype.³¹ However, later studies detected the Cordobes/Chilean clone in Colombia between 2001 and 2006,^{22,41} and Espinal et al.²¹ observed this clone among clinical isolates recovered in the Colombian–Caribbean region. It is of note that Buitrago et al. observed that isolates with the characteristics of CA-MRSA strains were increasing in prevalence in Colombia between 2001 and 2006.²²

The Cordobes/Chilean clone was also the predominant clone in Paraguay in 2005, where it co-existed with the Brazilian clone.⁵⁰

Aires de Sousa et al.¹⁶ detected a unique clone associated with pediatric infections in Mexico, resistant to penicillin, oxacillin, and gentamicin. This Mexican clone predominated in Mexico City between 1997 and 2000, but was entirely substituted by the multidrug-resistant NYJ clone by 2002.³² Isolates collected between 1999 and 2003 in Guadalajara were also similar to the NYJ clone.³⁵

In Trinidad and Tobago, the Canadian MRSA clone, CMRSA-6, was detected in three major hospitals between 2000 and 2001, a possible result of dissemination through tourism.³⁸

Between 1996 and 1998, Aires de Sousa et al. demonstrated the presence of the Brazilian clone in Uruguayan hospitals (100% of MRSA isolates),¹⁶ and this clone was also detected in four of five hospitals in Montevideo by Senna et al.,¹⁸ although it only predominated in one hospital. The large outbreak of community infections caused by MRSA in Montevideo in 2002–2003 was associated with a novel clone, UR6, although other CA-MRSA strains were also identified.⁴⁴ The highly virulent nature of these CA-MRSA clones is associated with the production of PVL toxin.⁴⁴

3. Discussion

The introduction of methicillin and other antibiotics has provided a selective pressure for the evolution of new and diverse MRSA clones, which have spread in countries around the world,¹ and Latin America has been no exception. In this review, we have found that the pandemic Brazilian clone and variants continue to circulate throughout hospitals in Brazil and are also disseminated in neighboring countries. Several other clones have been detected in the region and in particular, clones related to the NYJ and the pediatric clones, belonging to CC5, have successfully spread. The Cordobes/Chilean clone was first detected in isolates from Chile in 1997, and in Argentina in 1999; this quickly became the predominant clone in Argentina, Chile, Colombia and Paraguay. The NYJ clone has been detected in Brazil, and has completely displaced the Mexican clone in certain Mexican hospitals. Variants of the pediatric clone have caused infections in the healthcare setting or the community in Brazil, Argentina and Colombia. Several studies characterized clones involved in MRSA infections acquired in the community. CA-MRSA clones in Brazil, Argentina, Colombia, and Uruguay belonged to CC5, CC8 and CC30, and were found to be related to CA-MRSA clones previously described in the USA and Western Australia. Adding to these data, a recent study by Goering and colleagues⁵² identified the hospital-associated MRSA (HA-MRSA) strain, USA-800, in Peru and Costa Rica, and the CA-MRSA strain, USA-300, in Costa Rica.

A combination of factors may have caused the observed pattern of MRSA clones in Latin America. In 1998 Aires de Sousa et al.¹³ demonstrated the intercontinental spread of the Brazilian clone between Brazil and Portugal, and the NYJ clone has also been disseminated between continents, causing infections in New York City, New Jersey, Connecticut, and Pennsylvania, as well as in Tokyo, Japan,¹⁴ and now in Latin America. Explanations for this phenomenon, which could also apply in Latin America, were suggested to include the increased migration of human populations, including healthcare professionals, combined with ineffective practices to control the spread of MRSA from infected or colonized patients.¹³

Antibiotic selection may be a key factor causing the dissemination of predominant MRSA clones in hospitals.⁵³ In the community, other factors may be more influential. In Latin America, the SCCmec element, type IV, has been detected in several clones circulating in the community and in the healthcare setting. Previous analyses

have found that this smallest SCCmec element is the most frequently acquired, suggesting that it may transfer most efficiently or be selectively favored over the larger, more complex elements, and this property is likely to impact on the future evolution of MRSA.¹¹

MRSA clones with enhanced pathogenic properties have important implications for infection control and treatment strategies. The presence of new virulence factors in MRSA in Latin America is a worrisome trend. Virulence factors may promote attachment and persistence, evasion of defense mechanisms, or tissue invasion and penetration, as well as enabling the production of toxins that mediate more aggressive disease (e.g., toxic shock syndrome).⁵⁴ These developments are a significant concern, especially because transfer of virulence genes has been observed between HA- and CA-MRSA strains.⁵⁵ Such virulence genes may be acquired by epidemic MRSA clones to produce new variants with enhanced pathogenesis, a situation that has already been observed in Brazil. As well as harboring genes encoding PVL toxin, a toxin capable of destroying cells, the Brazilian clone has also demonstrated the potential for acquisition of genes for production of biofilm.^{28,34}

S. aureus can rapidly develop resistance to antibiotics. In 2008, more than 90% of *S. aureus* isolates were resistant to penicillin, the incidence of MRSA in Latin America was greater than 50% of all *S. aureus* isolates in some countries,⁵⁶ and strains were found to be prone to develop resistance to additional antibiotics. The Brazilian clone is usually multidrug-resistant and in some cases sensitive only to vancomycin, tigecycline, linezolid and daptomycin; this clone can also develop mupirocin resistance and heterogeneous vancomycin and teicoplanin resistance. The pediatric clone has developed multidrug resistance in some regions of Latin America. The Cordobes/Chilean clone and the NYJ clones are also multidrug-resistant (although both are sensitive to glycopeptides and linezolid, and the Cordobes/Chilean clone is usually susceptible to TMP-SMX, minocycline and rifampin, while the NYJ clone is usually susceptible to TMP-SMX, gentamicin and rifampin). Since there are currently few options available for the treatment of multidrug-resistant MRSA infections, clinicians around Latin America should be prudent in using these antibiotics.

Both *S. aureus* and MRSA can colonize the anterior nares, axilla, groin, and the gastrointestinal tract.⁵⁴ More than 20% of humans have either persistent or intermittent nasal colonization with MRSA. From the colonized sites, *S. aureus* and MRSA can cause infection or be transmitted to other persons. A carrier of *S. aureus* or MRSA is at potential risk, especially when admitted to hospital, of developing an infection involving the colonizing pathogen and of transmitting the MRSA to other patients with risk factors for infection. The need to prevent *S. aureus*/MRSA-colonized patients from entering hospital and causing dissemination of the pathogen has led to the publication of guidelines for what is now known as universal surveillance for MRSA.⁵⁷ Despite most Latin American countries using infection control practices based on the Centers for Disease Control and Prevention (CDC) guidelines, and with some institutions having an antibiotic stewardship program based on guidelines from the Infectious Diseases Society of America,⁵⁸ using mostly education, streamlining of therapy, and intervention and feedback (also known as a 'back-end' approach), MRSA continues to be a major problem.

Our understanding of the molecular epidemiology of MRSA in Latin America remains limited. So far, data have mainly been collected from large tertiary hospitals. Few studies have collected isolates from the community setting, despite evidence that the incidence of CA-MRSA is increasing.²² Epidemiological data are not published frequently from every hospital, and therefore it is difficult to follow evolving trends, and in some countries there are no published data.

The efforts of Latin American investigators are important, and rigorous surveillance is needed in order to prevent further problems caused by MRSA clones. Continuing surveillance, molecular epidemiological studies, and timely dissemination of the findings in our region are vital.

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