

## Review

Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in Latin America

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## ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a serious threat to public health worldwide. Ongoing surveillance is essential to support infection control committees and clinicians in the prevention and treatment of infection. However, in Latin America, resources for monitoring the changing epidemiology of MRSA remain limited. In this article, we review the current situation of MRSA in Latin America in order to highlight the need for a more harmonised effort to improve its management. Literature in the PubMed and SciELO databases as well as the website of the Pan American Health Organization were searched for articles and information about the epidemiology of MRSA in Latin America. MRSA is already the leading cause of nosocomial infection in the Latin American region, and the number of reports of community-acquired MRSA infections is also rising. However, the extent of the problem is not fully understood, especially since data tend to come from large hospitals whereas much of the population is served by small community healthcare centres that do not have extensive facilities for performing microbiological surveillance. In conclusion, wider-reaching and co-ordinated programmes to provide regular MRSA surveillance reports are required across the Latin American region.

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## 1. Introduction

*Staphylococcus aureus* is a major global pathogen that can cause severe infections both in healthy and immunocompromised people. Oxacillin and methicillin were first used in the clinic in the early 1960s, but after only a few years strains of *S. aureus* appeared that were resistant to these agents, collectively termed methicillin-resistant *S. aureus* (MRSA). These strains, carrying the *meC*A gene that confers resistance to methicillin and oxacillin, first spread within

the hospital environment and, in more recent times, have also been found circulating in the community [1]. MRSA has been widely disseminated between countries and across continents; >50% of *S. aureus* isolates now show resistance to methicillin in areas of the USA and some European countries [2–4]. The rise in cases of MRSA infection is a significant concern for public health since they are associated with increased morbidity and mortality and use of healthcare resources compared with infections caused by non-resistant strains [5,6].

Knowledge of the local epidemiology of MRSA underpins effective prevention and treatment strategies, including the rational use of antibiotics. In this article, we review the current state of surveillance in the Latin American region where MRSA is highly prevalent but resources are limited. We also discuss the epidemiology and clinical implications both of nosocomial and community-acquired MRSA infections. By summarising currently available data from

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Latin America, we aim to highlight the pervasiveness of MRSA in the region and raise awareness of the need for important changes in clinical and microbiological practice to combat the escalating challenge presented by this organism.

## 2. MRSA surveillance in Latin America

### 2.1. Surveillance programmes and methodology

Until the year 2000, epidemiological surveillance in Latin America was conducted in only a few countries, including Venezuela and Argentina. Since then, with the support of the Pan American Health Organization (PAHO) and the United States Agency for International Development (USAID), a network for surveillance of bacterial resistance has been organised, which includes the majority of Latin American countries: the Monitoring/Surveillance Network for Resistance to Antibiotics. Criteria for admission of surveillance centres to the network include concepts of standardisation, quality control, supervision visits and regular data reporting. Results are published each year on the PAHO website (<http://www.paho.org>) and in a limited edition of hard copies. Data are collected during the daily work of selected laboratories in the region, with strong support from national and regional reference laboratories.

Special efforts to gather surveillance data from the region have also been made by pharmaceutical companies, with initiatives including the Tigecycline Evaluation and Surveillance Trial (TEST) from Wyeth, SENTRY from Bristol-Myers Squibb, and RESISTNET and the Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) from Pfizer. Whilst these studies are valuable, limitations include the fixed number of strains examined per centre and the small numbers of participating centres and countries. As a result, the data do not always accurately reflect the situation in the region.

The methodology used for definition of a given strain as MRSA is different in each country. Some countries work with the Bauer–Kirby method for screening using oxacillin or cefoxitin disks, and others use automated methods such as VITEK 1 or 2 (bioMérieux) and/or MicroScan (Dade Behring). Confirmation tests such as the meticillin screen plate test are not widely used. The high cost of Etest strips does not permit their routine use in laboratories in the region, and rapid methods of *mecA* gene detection are not available in the majority of laboratories. Molecular analysis of MRSA strains is restricted to some centres in Brazil, Argentina, Chile, Mexico and Colombia. In cases of nosocomial outbreaks, the identity of MRSA strains is usually assumed from the phenotypic pattern of antibiotic resistance.

### 2.2. Nosocomial MRSA in Latin America

MRSA strains are currently classified as nosocomial or hospital-associated (HA-MRSA) and community-associated (CA-MRSA) [7–14]. HA-MRSA strains tend to be multidrug-resistant (MDR) and to colonise and infect patients during hospitalisation or in long-term healthcare facilities, after surgery or following contact with a person who has an MRSA infection or is a carrier of MRSA. Periodic outbreaks of infection were first reported in hospitals where high levels of oxacillin or meticillin were used and in intensive care environments. However, from the 1980s onwards, HA-MRSA has been a significant regional health threat, causing infections initially in large hospitals and later in smaller community hospitals.

Nosocomial MDR MRSA is a growing problem in Latin America (Fig. 1) [15–23]. Information gathered by the PAHO-sponsored programme on nosocomial infections [15] demonstrated that for the year 2004 MRSA prevalence was as follows: Argentina, 42% ( $n=5851$  isolates); Bolivia, 36% ( $n=1167$ ); Chile, 80% ( $n=246$ ); Colombia, 47% ( $n=4214$ ); Costa Rica, 58% ( $n=674$ ); Cuba, 6% ( $n=80$ ); Ecuador, 25% ( $n=1363$ ); Guatemala, 64% ( $n=1483$ );

Honduras, 12% ( $n=393$ ); Mexico, 52% ( $n=497$ ); Nicaragua, 20% ( $n=296$ ); Paraguay, 44% ( $n=980$ ); Peru, 80% ( $n=1407$ ); Uruguay, 59% ( $n=1431$ ); and Venezuela, 25% ( $n=2114$ ).

Similarly, data submitted to the Pan-American Association of Infectious Diseases for the year 2006 [16] showed the following rates of HA-MRSA: Argentina, 51%; Bolivia, 55%; Brazil, 54%; Chile, 29%; Ecuador, 25%; Mexico, 32%; Panama, 28%; Paraguay, 30%; Uruguay, 24%; and Venezuela, 27% (number of isolates not stated).

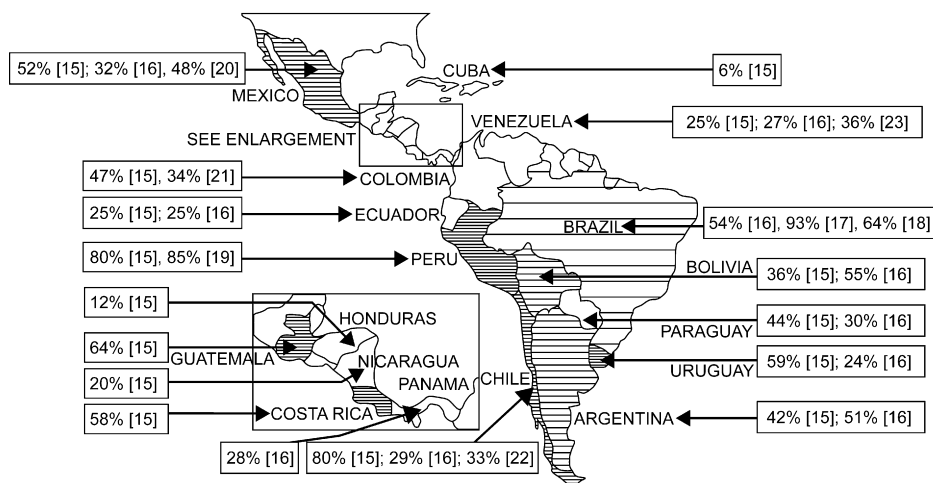
Further data from SENTRY reveal an increase in the proportion of MRSA in Latin American medical centres from 33.8% in 1997 to 40.2% in 2006 [24]. In this programme 41% of MRSA strains were collected from Brazil. Although there was increased resistance to most of the other antibiotics analysed, there was a decrease in the frequency of strains with a minimum inhibitory concentration (MIC) to vancomycin  $\geq 1$   $\mu\text{g}/\text{mL}$ .

Other reports from hospitals in Latin America demonstrate that MRSA poses a common problem. In Intensive Care Units in Rio Grande do Sul, Brazil, in 2003, *S. aureus* was the most prevalent organism in nosocomial infections and 64% of isolates were MRSA [18]. Between 1997 and 1999, 93.3% of *S. aureus* isolates in bloodstream infections in a newborn unit in Rio de Janeiro, Brazil, were meticillin-resistant [17]. Of note, Melo et al. [25] found that in Uberlândia, Brazil, 9 of 41 patients receiving treatment with vancomycin were infected with MRSA isolates that met criteria for heteroresistance to vancomycin, and one of the isolates had a MIC of 8  $\mu\text{g}/\text{mL}$ . In a large teaching hospital in Lima, Peru, 85% of 73 hospital-acquired *S. aureus* infections were reported to be due to MRSA in 2002 [19]. More recent data from Mexico coming from the TEST study show a prevalence of MRSA of 48% [20]. Reports from the Colombian network of surveillance of resistance have revealed that MRSA prevalence was 38% in 2001, 46% in 2002, 45% in both 2003 and 2004, 38% in 2005 and 34% in 2006 [21]. Data from Valdivia, Chile, showed that in 2006, 33% of *S. aureus* isolates from hospitalised patients were MRSA [22]. In a Venezuelan surveillance programme, 36.4% of 730 isolates of *S. aureus* from hospitalised patients were meticillin-resistant in 2005 [23].

### 2.3. MRSA in the community in Latin America

MRSA infections that are acquired in the community are classified into two categories, with and without healthcare-associated risk factors, the latter category representing the true CA-MRSA infections [10]. Recognised healthcare-associated risk factors are admission to hospital in the previous year, residence in a long-term care facility, dialysis, surgery, permanent indwelling catheters or the use of medical devices inserted through the skin. The distinction between community-acquired MRSA infections with and without healthcare-associated risk factors and HA-MRSA infections is relevant, as these infections are caused by strains that show different epidemiological, clinical, microbiological, genetic and therapeutic behaviours. Community-acquired MRSA in patients with healthcare-associated risk factors tends to be genetically closer to HA-MRSA strains than to CA-MRSA strains [26]. Current evidence suggests that CA-MRSA strains that are acquired in the absence of healthcare-associated risk factors evolved from meticillin-susceptible *S. aureus* in the community that acquired specific genotypic features, including the staphylococcal cassette chromosome *mec* (SCC*mec*) IV element, a mobile and easily transferred element [27].

Although this classification of HA-MRSA and CA-MRSA is commonly used, there is confusion over the terminology, especially between terms such as acquired and associated. Experts propose to use the term acquired to refer to the location of exposure and the term associated to refer to specific *S. aureus* strains [28]. Additionally, the utility of searching for healthcare-associated risk factors to distinguish between MDR strains (HA-MRSA) and CA-MRSA strains



**Fig. 1.** Percentage of nosocomial *Staphylococcus aureus* isolates with resistance to meticillin in studies in Latin American countries. Shading indicates countries where >50% of nosocomial *S. aureus* isolates were found to be meticillin-resistant in at least one report. References are indicated in brackets [15–23]. Pan American Health Organization, 2004 [15]; Casellas, 2006 [16]; Loureiro et al., 2002 [17]; Lisboa et al., 2007 [18]; Seas et al., 2006 [19]; Ponce de Leon et al., 2008 [20]; Buitrago et al., 2008 [21]; Otth et al., 2008 [22]; and Provenra.org [23].

has been challenged more recently, as this approach seems not to have a high discriminative value [29].

The first published report of CA-MRSA infections in Latin America came from Brazil [30], where three well-characterised strains isolated from patients with skin and soft-tissue infection (SSTI) or septic arthritis in 2003 harboured SCCmec type IV, Panton–Valentine leukocidin (PVL), enterotoxin and  $\beta$ -haemolysin genes. A further report followed of a large outbreak of CA-MRSA infection that affected inmates in jails and people from the community in Montevideo, Uruguay, beginning in January 2002 [31]. At the end of the outbreak more than 1000 patients had been affected and 12 deaths had occurred. SSTIs accounted for >65% of the cases, but severe forms of pneumonia were reported, including 4 deaths. In this outbreak, trimethoprim/sulfamethoxazole was very active in the treatment of skin infections [32].

Since those first reports, MRSA has been identified as the cause of community-acquired infections in several more countries across South America. In Lima, Peru, 27% resistance to meticillin was reported in isolates collected from 30 community-acquired infections in 2002 [19]. Two cases of SSTI caused by CA-MRSA strains were reported from Bogotá, Colombia, in 2006 [33], and a report from the Colombian network of resistance surveillance showed an increase in CA-MRSA from 1% of *S. aureus* isolates in 2001 to 5.4% in 2006 [21]. The PAHO programme has also included surveillance of community-acquired MRSA infections since 2005, and in Venezuela 12.4% of 845 *S. aureus* isolates from the community were resistant to oxacillin [23]. However, no clinical information is available for these cases. A few isolated cases of CA-MRSA infection have been reported in Chile, but some of these were in people returning from cities in Uruguay or Brazil with a high incidence of MRSA [34,35].

### 3. Conclusions

MRSA is an increasing problem in Latin America, both in the healthcare environment and in the community. In nosocomial *S. aureus* infections the frequency of meticillin resistance has surpassed 50% in over one-half of the Latin American countries for which data were identified (Fig. 1). Community-acquired MRSA has been reported in Latin America and even though large outbreaks such as the one that occurred in Uruguay, causing 12 deaths, have not been reported elsewhere, this example highlights the problem.

Surveillance programmes are only recently beginning to record CA-MRSA, and the true incidence of MRSA in the community is still largely unknown in the region.

Although surveillance systems in Latin America are improving, many limitations remain. Data are unavailable from several countries, and even in countries participating in regional surveillance programmes the data recorded may not reflect the general situation and may not be widely accessible. Much of the population of Latin America is served by small community hospital centres where resources and facilities for microbiology are very limited, whereas data tend to come only from a few large hospitals and reference laboratories. In some countries there are marked differences in the MRSA frequencies detected by different studies. This may reflect real changes in the incidence of MRSA over time (for example, the impact of improved infection control practice or importation of an epidemic strain), differences between the populations studied (populations that are geographically separated or with different risk factors for MRSA), or changes in standards of microbiology and the availability of technologies.

If surveillance data are to be useful in practice, they must be accurate. Reference laboratories are vital in this regard for ensuring quality control in microbiology, but microbiologists in all centres require sufficient training and resources to identify MRSA and to perform susceptibility tests. In particular, Etests for vancomycin susceptibility testing are not widely available in Latin America. Reduced susceptibility to vancomycin has been reported in HA-MRSA strains in some studies, which may be associated with a greater rate of clinical failure. However, the situation in Latin America is not fully known and this represents a challenge to decision-making in clinical practice. An apparent decrease in strains with a vancomycin MIC  $\geq 1$   $\mu\text{g}/\text{mL}$  [24] suggests a shift in clonal dissemination and further data are required to follow this trend, which has important implications for treatment. The role of vancomycin as the first-choice agent for the treatment of severe infection caused by MRSA is being questioned, especially since there are now new options for treatment such as the oxazolidinones, glycylicyclines and lipopeptides. Guidelines or recommendations for the appropriate diagnosis of MRSA, vancomycin-intermediate *S. aureus* (VISA) and *S. aureus* with reduced susceptibility to vancomycin can support the correct use of newer treatment options such as linezolid, daptomycin or tigecycline based on local resistance data.

Early empirical therapy may reduce the risk of mortality in severe MRSA infections [36] but therapy should be based on local

epidemiology. Clinicians can use local surveillance data to predict the risk of infection with MRSA, as well as the most likely strains, in order to aid the appropriate choice of antibiotics. The choice will not only depend upon clinical presentation and case history but also whether prevailing *S. aureus* strains in the local area are methicillin-resistant, and community- or healthcare-associated, as well as the susceptibility profiles of those strains.

Clinicians and microbiologists need to be aware of the high prevalence of MRSA in Latin America and must be alert to the evolving epidemiology in their local region. Infection control committees play a key role in advising clinicians in this respect. Ongoing surveillance of the MRSA situation in each healthcare centre and in the community in Latin America, in order to provide up-to-date information, is essential to the success of infection control programmes and treatment protocols. More rigorous monitoring and reporting of epidemiological data is required, including use of the Internet to make real-time reports of outbreaks and special situations available. This will enable infection control committees to tackle the spread of MRSA with a co-ordinated effort in order to implement appropriate antibiotic policies, screening and decolonisation protocols, and other preventive strategies.

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