Chapter

The Molecular Epidemiological Study of MRSA in Mexico

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Abstract

The rapid spread of infections by methicillin-resistant *Staphylococcus aureus* (MRSA) emerged in the early 1960s, and this pathogen is one of the most common agents of nosocomial infections. As a reaction to the appearance and spread of multi-drug-resistant MRSA in Mexico, some hospitals have established molecular epidemiological surveillance, where pandemic clones of MRSA have been detected in different states in the north, the center, and the south of Mexico. The pandemic clones detected in Mexico are the Iberian, the New York/Japan, the pediatric, the EMRSA-16, and the USA-300. The surveillance or evolutionary studies carried out in Mexico, using different molecular methodologies, have shown a predominance of the New York/Japan clone, which has even displaced other MRSA clones. Therefore, it is necessary to continue establishing molecular surveillance and diagnostic programs as a special management for the confirmed MRSA infections, if these measures are not carried out to understand and control the changing lineages of MRSA, in the future, it may become an important public health problem, since the New York/Japan clone, which is the most predominant in our country, clearly demonstrates its great capacity for geographical expansion, multi-resistance, and virulence.

Keywords: *Staphylococcus aureus*, MRSA, clones, CA-MRSA, HA-MRSA, Mexico

1. Introduction

In Mexico, la Red Hospitalaria de Vigilancia Epidemiologica (RHVE) reported that mortality rates among patients infected with *S. aureus* show a variability between 5 and 70%, in addition to high attributable mortality rates, approximately 50% [1]. *S. aureus* produces a wide variety of exoproteins that contribute to its ability to colonize and cause disease in humans [2]. MRSA strains are characterized by the presence of a mobile genetic element called the staphylococcal cassette cromosoma *mec (SCCmec)*, which includes the *mecA* gene [3]. The structural *mecA* gene codes for penicillin-binding protein (PBP) 2a, which determines resistance to methicillin [4]. Modifications in PBP2a prevent PBP-penicillin binding, causing cell wall synthesis to proceed normally [5].

Nosocomial infections (NI) are considered a public health problem worldwide. For example, in the Latin American region, the SENTRY Surveillance Antimicrobial Program reported an increase in the proportion of MRSA in medical centers from

33.8% in 1997 to 40.2% in 2006. In Mexico, some studies show an increase in the prevalence of MRSA in recent years, and the incidence of NI ranges between 3.8 and 26.1 cases per 100 discharges; mortality associated with nosocomial infections is an average of 5%, and in 2001, it was the seventh leading cause of death for the general population in 2001 [6]. Reports from the Pan American Health Organization (PAHO) for Mexico informed that there was a prevalence of 52% of MRSA in 2004, while the Pan American Association of Infectious Diseases reported 32% in 2006, and data from the study of the TEST program (Tigecycline Evaluation and Surveillance Trial) showed a prevalence of 48% of MRSA in 2008 [7].

2. The molecular epidemiology of MRSA

Monitoring and stopping the intra- and inter-hospital distribution of MRSA clones require the use of efficient and accurate epidemiological typing systems that allow discrimination between unrelated isolates and recognition of isolates that descend from a common ancestor (i.e., that belong to the same clone). Currently, multiple phenotypic and genotypic typing methods have been developed to type MRSA. The choice of a typing method depends on the needs, the level of skills, the resources of the laboratory, and the type of question to be answered (short-term or long-term analysis) [8].

On the other hand, the molecular epidemiological study of MRSA aims to determine the clonal relationship that exists between several isolates of the same species. This information is very useful, especially when epidemic outbreaks caused by multi-resistant strains occur because it makes it possible to determine the number of circulating clones, evaluate the effectiveness of control measures aimed at preventing their spread, and differentiate between infection and reinfection [9]. Identification of MRSA clones is based on a combination of different typing methods, such as DNA hybridization with *mecA* and Tn554 probes, PFGE, RAPD, *SCCmec typing*, *spa typing*, and *MLST* [10].

3. International MRSA clones

At the present time, it has been shown that multiple clonal lineages of MRSA exist because of the successful horizontal transfer of *mecA* [11]. Six types of HA-MRSA hospital-acquired pandemic clones have been reported (Iberian, Brazilian, Hungarian, New York/Japan, Pediatric, and EMRSA-16), and they are scattered in different regions of the world [12]. The Iberian clone was the first one to be identified in 1989, in a massive outbreak of MRSA in a hospital in Barcelona, Spain [13]; but it seems to have already been present in Belgium and France at least since 1984 [14]. The Brazilian clone is widely distributed in Brazilian hospitals and has spread to neighboring countries in South America: Argentina, Uruguay and Chile and in Europe: Portugal, the Czech Republic, and Greece, where it displaced the main local clones [15]. The Hungarian clone has been widely disseminated in Hungarian hospitals since 1993 [16]. The New York/Japan clone was identified as the main clone in different regions in the United States of America [17], and in a hospital in Tokyo [18]. EMRSA-16 clone was found in the United Kingdom hospitals [19]. This clone has been widely spread in Greece, Mexico, and Canada [20]. The Pediatric clone was reported in Portugal in 1991 and since then, it has been found in Poland, France, the United Kingdom, the United States (EU), Argentina, and Colombia [21].

Reports of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) infections in healthy people began to appear in the 1990s. In 2000, it was described that these types of strains were genetically different from bacteria isolated in hospital settings. Currently, CA-MRSA strain types possess more bacterial resistance genes, and more virulence factors, leading to more severe infections [22]. There are multiple clones of CA-MRSA worldwide, as well as a segregation of these clones based on the MLST technique. For example, USA300 (ST8), which predominates in the USA, USA400 (STI), USA1100 (ST30), and USA1000 (ST59), is clone notable for causing CA-MRSA infections. STI and ST30 are the cause of the main CA-MRSA infections in Australia and Oceania, while clone ST80 predominates in Europe [23].

The MRSA clones were once confined to hospitals for the last 20 years. MRSA infections have emerged in the community in people with no previous exposure to hospitals. Genotypically, CA-MRSA is a newer and more virulent strain, emerging in the late 1990s as leading the cause of skin and soft tissue infections in young healthy

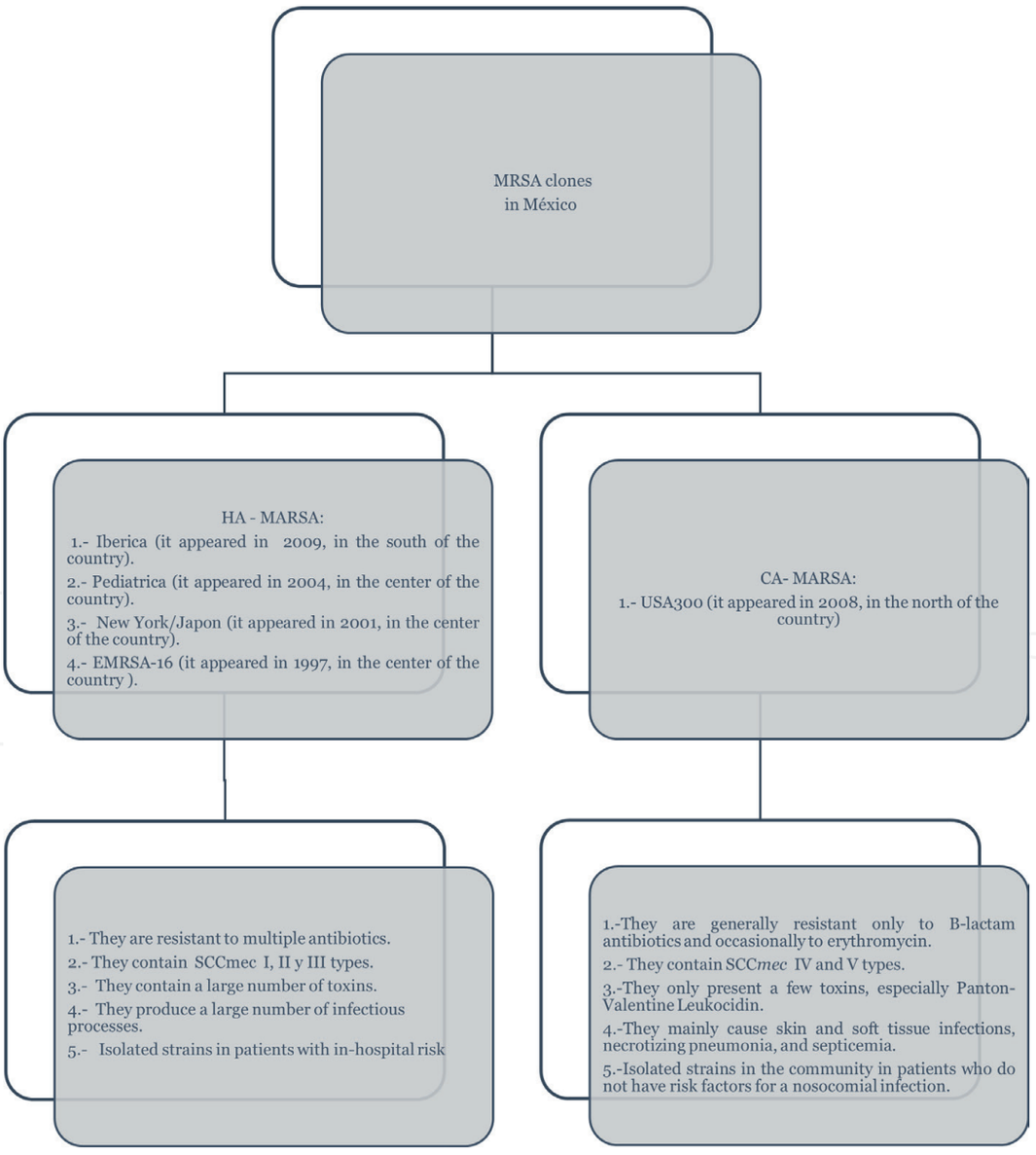

Figure 1.
Main differences between HA-MRSA and CA-MRSA strains detected in Mexico. (Modified by Bustos et al. [25]).

people. CA-MRSA strains typically carry *SCCmec types IV* or *V* and are generally susceptible to β-lactam antimicrobials. In addition, CA-MRSA carries Panton-Valentine Leukocidin (PVL), which is associated with increased pathogenicity. In relationship to HA-MRSA clones, they carry *SCCmec types I*, II, or III and do not have PVLs. HA-MRSA clones are associated with nosocomial infections, for example, endocarditis, urinary tract infections, and surgical infections, and are resistant to β-lactam antibiotics, especially aminoglycosides, macrolides, lincosamides, and fluoroquinolones. Although CA-MRSA has been predicted to replace HA-MRSA in hospitals, mathematical models predict the coexistence between the two strains given hospital-community interactions [24].

The molecular epidemiological study of MRSA clones has been insufficient in Mexico since there is not a systematized surveillance system, where the appearance or distribution of these clones is reported, monitored, and controlled. There have been few studies in Mexico over the years and they have randomly detected HA-MRSA and CA-MRSA clones in different states of the country, which have described their main phenotypic and genotypic characteristics, which are observed in **Figure 1**.

4. MRSA clones in Mexico

In Mexico, The Instituto Nacional de Salud Pública in México has been confirmed as a network of tertiary hospitals, which have carried out studies aimed at understanding the molecular epidemiology of MRSA [26] and it is coordinated by Dra. Velázquez-Meza and et al. Studies carried out between 1997 and 2003 at the Hospital de Pediatría del Centro Médico Nacional (CMN), Siglo XXI-IMSS (Mexican Institute of Social Security) in Mexico City, 659 strains of *S. aureus* were analyzed, with a variation in the prevalence of MRSA from 17 to 23% until 2001. It subsequently decreased drastically to a prevalence of 4% in 2002, which was due to nosocomial infection control measures. During this investigation, the presence of the clone EMRSA-16 (*SCCmec type IV*) was detected, and the clone New York/Japan (SCCmec *type II*) was introduced into the hospital in 2001, which completely displaced clone EMRSA-16 in 2002 [27].

At the Hospital Civil de Guadalajara, "Fray Antonio Alcalde" between 1999 and 2003, 839 strains of MRSA were isolated from adult and pediatric patients. A total of 216 MRSA strains showed antimicrobial resistance to β-lactams, macrolides, chloramphenicol, and imipenem, and sensitivity to gentamicin, rifampicin, trimethoprim-sulfamethoxazole, and vancomycin. The New York/Japan clone was also detected in the 216 MRSA strains studied, like the one found in the Hospital de Pediatría del CMN-Sigloi XXI [28]. The New York/Japan clone may have been transferred from the United States to Mexico.

At the Instituto de Cardiología "Dr. Ignacio Chavez" (ICh), located in Mexico City, which is a 246-bed tertiary teaching hospital between 2002 and 2009, 90 MRSA strains were collected from bronchial secretions, wound secretions, blood, catheter, pleural fluid, peritoneal fluid, and others, from pediatric and adult populations. MRSA isolates were resistant to amoxicillin, cefotaxime, cephalothin, cefazolin, chloramphenicol, imipenem, clindamycin, erythromycin, clarithromycin, penicillin, and oxacillin, while only 94.4% of isolates were also resistant to ciprofloxacin. The New York/Japan clone, which was isolated from a variety of sites of infection, was identified in 50% of MRSA isolates. The studies showed that the New York/Japan clone had *SCCmec type II*. EMRSA-16 was found in 2002 and it presented *SCCmec IV*, and this chromosomal cassette is related to CA-MRSA clones [29].

In the north of Mexico, an investigation was carried out to identify MRSA responsible for nosocomial infection in five medical centers in Monterrey, Nuevo León (NL) Mexico, between 2005 and 2009, and 190 strains of MRSA were isolated from five hospitals affiliated to the Mexican Institute of Social Security. This study clearly documented the high dissemination capacity and persistence of the New York/Japan clone in these centers [30].

At the Hospital San José Tec de Monterrey, Nuevo León, Mexico, the first five cases of a clone of community MRSA were described in 2008, and three of the patients were children. The first patient with a history of retinoblastoma in the left eye was diagnosed in November 2007, when he just started chemotherapy. In 2008, he returned to the hospital with a fever for 2 weeks of evolution. Blood cultures showed MRSA and vancomycin was started for 1 week. Two other children who were considered as healthy ones previously arrived at the hospital with abscesses and with a severe local reaction from where MRSA was isolated. After drainage, both were treated with clindamycin. Two other patients who were considered healthy adults previously had abscesses and because of it, they required hospitalization. The drainage of the lesions showed MRSA in the culture and the patients were treated with linezolid. All patients recovered. This study revealed that the pattern was similar to that observed for the CA-MRSA clone USA300 genotype [31].

On the other hand, at the Hospital Universitario Dr. José Eleuterio González, in Monterrey, between 2012 and 2013, a prophylactic protocol was carried out that consisted of applying a solution with chlorhexidine gluconate (CXG), throughout his body, with the aim of reducing nosocomial infections, where 158 strains of MRSA were collected. During these CXG washouts, antibiotic resistance significantly decreased for clindamycin, levofloxacin, and norfloxacin. During the pre-intervention period, 65.7% of the isolates were resistant to oxacillin, and in the post-intervention period, this percentage was reduced to 32.6%. This result indicates a significant reduction in the frequency of MRSA isolates as a result of the lavage with CXG. The presence of two clones descending from clone ST5-MRSA-II (New York/Japan) and clone ST8-MRSA-IV (USA300) was evidenced. The New York/Japan clone decreased significantly in the intervention period but recovered in the post-intervention period, while the USA300 clone was established under pressure from CXG [32].

Although in Monterrey, Mexico, the first clone of community origin of MRSA with a history in previously hospitalized patients was identified. In another study carried out in 2013 at the Universidad Autónoma Metropolitana-Xochimilco, in which healthy volunteers from schools and factories in Mexico City were recruited, to whom nasal or throat sampling was applied, a total of 131 strains of MRSA are obtained from 1039 strains of *S. aureus*. Considerable diversity in PFGE patterns in CA-MRSA isolates was observed in clonal analysis, allowing only a small number of clones to be detected: USA300 and USA100. This study provides the first description of CA-MRSA in healthy people in Mexico City, suggesting that community MRSA clones could replace hospital MRSA clones in the future [33].

At the Hospital de Oncología (INCAN), a tertiary care hospital in Mexico City in 2006 and later in 2010, the New York/Japan clone was isolated as the cause of an outbreak of nosocomial infections that arose from an index case [34, 35].

In relationship to MRSA clones in Veracruz, Veracruz, Mexico, at the Hospital Regional de Alta Especialidad in Veracruz (HRV) in 2010, the presence of two pandemic clones was identified, the New York/Japan clone (ST5-*SCCmec type II*) and the Iberian clone (ST247-*SCCmec type IA*). The IB1 clonal subtype was isolated from the emergency department in a patient with an ear infection, who stated that he had

traveled to the USA, and on his return, he presented the infection, making it probable that the Iberian clone arrived from the USA to the HRV. The strains with IB2 and IB3 patterns were later isolated in two other patients from the same hospital medical service, which reveals the introduction of this clone from an external service to a critical area of the HRV [36]. Although the New York/Japan clone has been previously identified in other hospitals in Mexico [12, 13, 31], this clearly demonstrates its great capacity for geographical expansion, multi-resistance, and virulence. The importance of this finding lies in the fact that the first strain of MRSA resistant to vancomycin with a minimum inhibitory concentration (MIC) of 1024 μg/ml belongs to the New York/Japan lineage [37, 38].

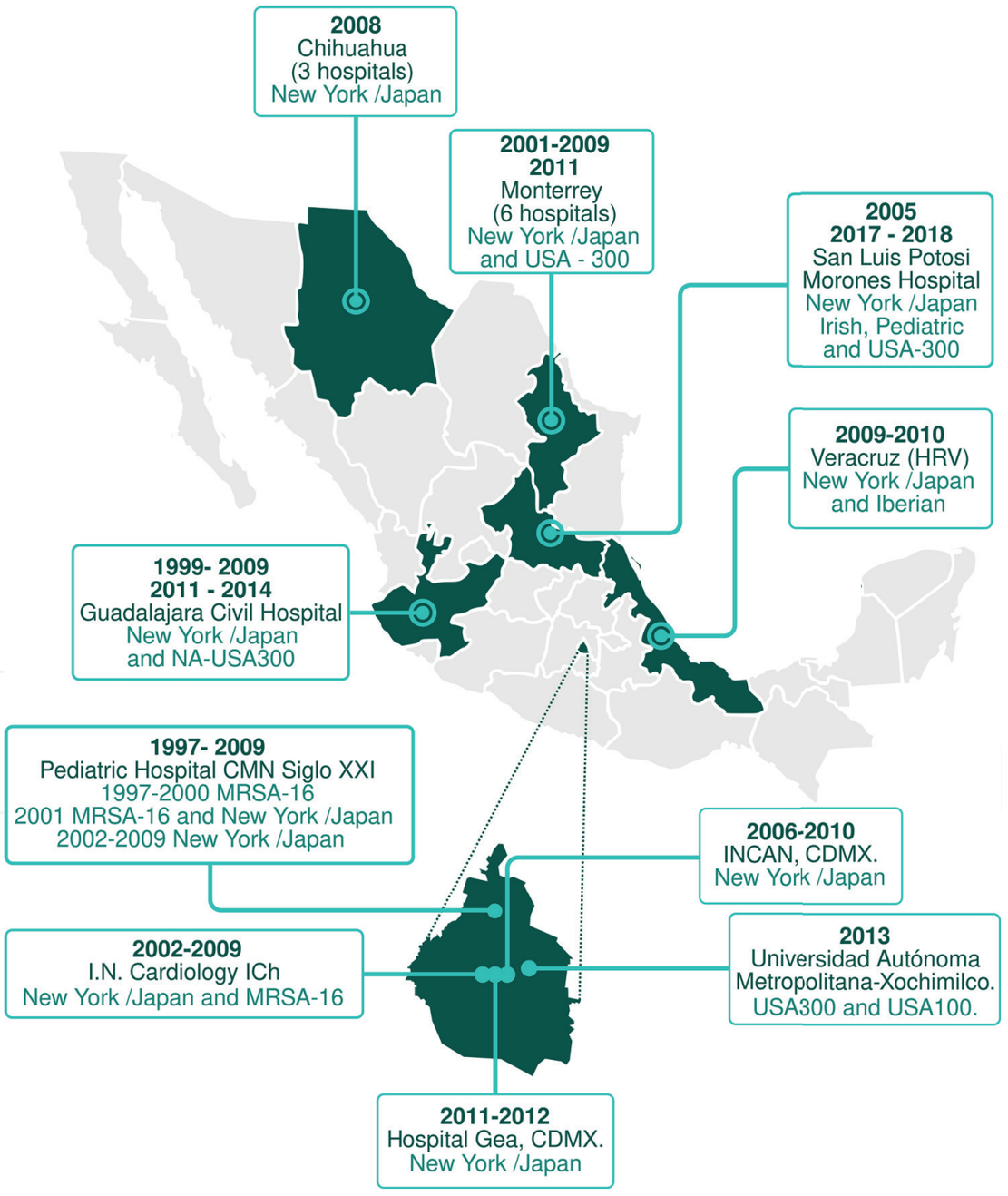

Figure 2.
Distribution of MRSA clones in Mexico.

At the Hospital General "Dr. Manuel Gea González," located in the southern zone of Mexico City, from 2011 to 2012, 109 strains of MRSA were isolated from wound secretions, soft tissues, blood cultures, cerebrospinal fluid, pleural fluid, bone, etc., of hospitalized patients. The most prevalent infection was ventilator-associated pneumonia. The isolated strains were characterized by resistance to β-lactams. A single predominant clone named New York/Japan (NY) was identified [39].

A prospective observational cohort study was carried out and 24 hospitals in Latin America participated from 2011 to 2014 and collected 1346 strains of *S. aureus*. The Hospital Civil de Guadalajara, Fray Antonio Alcalde de Guadalajara, Mexico, participated, and 18% of the MRSA isolates in this hospital showed the typical pattern of USA300, suggesting that this strain is likely circulating in Mexico [40].

In a cross-sectional study carried out at the Hospital Central Dr. Ignacio Morones Prieto, in San Luis Potosí, Mexico, from 2017 to 2018, a total of 191 isolates of *S. aureus* were obtained from different patients in all wards of the hospital, in the pediatric and adult population, coming from the emergency services, surgery, intensive care unit, internal medicine, gynecology, burn unit, and outpatient service. Clinical samples were obtained from skin and soft tissue infections, respiratory tract, blood, bones and joints, and the cerebrospinal fluid. A total of 77% of the strains were considered as coming to the hospital and 23% were classified as community ones. The most frequent *S. aureus* infections were those that affected the skin, soft tissues, and bacteremia. Instead, the type of infection more frequent cause by isolates of MRSA was the infection of the surgical site. The presence of clones ST5-MRSA-II-t895 (clone New York/Japan) and ST1011-MRSA-II-t9364 (clone New York/Japan) was evidenced by the PFGE technique. In addition to the clone mentioned above, the presence of endemic clones of MRSA was evidenced, such as USA300, Irish and Pediatric, these being the ones with the highest prevalence [41].

As seen in previous studies in Mexico, the predominant clone is the New York/Japan [42], which has the ability to spread, cause outbreaks and replace existing clones [43], and this is due, among other things, to its great virulence, since it presents staphylococcal enterotoxins and it also possesses the toxic shock syndrome toxin 1, which enables it to cause a wide variety of clinical syndromes, including toxic shock syndrome and suppurative infections [44]. In addition to this, it is resistant to β-lactams and a wide range of antibiotics [15].

The epidemiological study of MRSA clones acquired in hospitals is an area of little study, which does not allow knowing exactly the behavior or evolution of MRSA pandemic clones, as shown in the following **Figure 2**, which compiles the reported clones in Mexico.

5. Conclusions

It is necessary to promote and encourage the molecular epidemiological surveillance of HA-MRSA and CA-MRSA clones, to prevent and control this pathogen, which causes outbreaks and high mortality rates in Mexico, due to hospital or community infections. Attention shoulder be paid to the detection, surveillance, and control of CA-MRSA due to the increase in the non-hospitalized population, which could displace HA-MRSA and become a health problem.

The molecular epidemiological surveillance of MRSA clones is essential knowledge for its prevention, control, and possible eradication. This type of research allows the nosocomial infection control committees of each institution to be informed. This

in sum would help to strengthen measures, such as the restriction of prescription of broad-spectrum antibiotics, daily supervision of cultures and results, monthly reports of infections, training aimed at health workers in general, and strengthening of medical practices.

In Mexico, the predominant clone is New York/Japan, which has the ability to spread, cause outbreaks and replace existing clones, this is due, among other things, to its great virulence and antimicrobial multi-resistance. The importance of this clone lies in the fact that the first strain of MRSA resistant to vancomycin belongs to the New York/Japan lineage. Vancomycin is considered one of the latest therapeutic alternatives against infections caused by MRSA and other gram-positive microorganisms.

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