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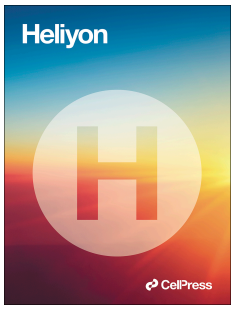

Different evolution of *S. aureus* methicillin-resistant and methicillin-susceptible infections, Argentina

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Different evolution of *S. aureus* Methicillin-Resistant and Methicillin-Susceptible infections, Argentina

Running title

Rising CO-MSSA infections in Argentina

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To be included in Title Page of the Manuscript

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HIGHLIGHTS

- ✓ Since 2009, overall burden of SA infections has risen, driven by CO MSSA, Argentina
- ✓ SA infections rate in 2015: 49.1/100,000 monthly visits, showing a rising evolution
- ✓ Higher (>3 fold) HA/(HACO and HAHO) SA infections rates than CA/(CACO) infections
- ✓ CA-MRSA ST30-IV clone added to rather than replace ST5-IV in HA invasive infections
- ✓ MSSA infections increased by 54.2%, with an ERY resistance rise linked to CC398

ABSTRACT

Staphylococcus aureus-(SA) is widespread among healthcare-associated-(HA) and the community-associated-(CA) infections. However, the contributions of MRSA and MSSA to the SA overall burden remain unclear.

In a nationally-representative-survey conducted in Argentina, 668 SA clinical isolates from 61 hospitals were examined in a prospective, cross-sectional, multicenter study in April 2015. The study aimed to analyze MRSA molecular epidemiology, estimate overall SA infection incidence (MSSA, MRSA, and genotypes) in community-onset (CO: HACO, Healthcare-Associated-CO and CACO, Community-Associated-CO) and healthcare-onset (HO: HAHO, Healthcare-associated-HO) infections, stratified by age groups. Additionally temporal evolution was estimated by comparing this study's (2015) incidence values with a previous study (2009) in the same region. Erythromycin-resistant-MSSA and all MRSA strains were genetically typed.

The SA total-infections (TI) overall-incidence was 49.1/100,000 monthly-visits, 25.1 and 24.0 for MRSA and MSSA respectively (P=0.5889), in April 2015. In adults with invasive-infections (INVI), MSSA was 15.7 and MRSA was 11.8 (P=0.0288), 1.3-fold higher. HA SA infections, both MSSA and MRSA, surpassed CA infections by over threefold.

During 2009-2015, there was a significant 23.4% increase in the SA infections overall-incidence, mainly driven by MSSA, notably a 54.2% increase in INVI among adults, while MRSA infection rates remained stable. The MSSA rise was accompanied by increased antimicrobial resistance, particularly to erythromycin, linked to MSSA-CC398-*t*1451-*erm*T^{+}-IEC^{+}-*pvl*$^{-}$ emergence. The SA-infections rise was primarily attributed to community-onset-infections (37.3% and 62.4% increase for TI and INVI, respectively), particularly HACO-MSSA and HACO-MRSA in adults, as well as CACO-MSSA. The main CA-MRSA-PFGE-typeN-ST30-SCC*mec*IVc-$PVL^{+/-}$ clone along with other clones (USA300-ST8-IV-LV-$PVL^{+/-}$,

PFGE-typeDD-ST97-IV- PVL^{-}) added to rather than replaced CA-MRSA-PFGE-typeI-ST5-SCC*mec*IVa-PVL$^{+/-}$ clone in HA invasive-infections. They also displaced clone HA-MRSA-PFGE-typeA-ST5-SCC*mec*I, mainly in HAHO infections

The overall-burden of SA infections is rising in Argentina, driven primarily by community-onset MSSA, particularly in adults, linked to increased erythromycin-resistance and MSSA-CC398-*t*1451-*erm*T^{+}-IEC^{+}-*pvl*$^{-}$ emergence. Novel knowledge and transmission-control strategies are required for MSSA

Keywords: *S. aureus*, MSSA, MRSA, community-onset-(CO) infections, healthcare-associated-(HA) infections , CA-MRSA-ST30-IV, CA-MRSA-ST5-IV; CA-MRSA-USA300-LV, CC398-MSSA, Argentina

INTRODUCTION

Staphylococcus aureus (SA) infections, particularly methicillin-resistant SA (MRSA) pose a significant challenge to global healthcare, affecting hospitals (healthcare-associated infections/HAIs), communities (community-associated infections/CAIs), and livestock (livestock-associated infections/LAIs) [1,2]. SA causes a spectrum of human diseases, from superficial skin and soft tissue infections (SSTI) to invasive infections (INVI), sepsis, and death. This versatility arises from multiple virulence factors and differential expression abilities, primarily associated with the genotype [2,3]. The escalating concern lies in managing SA infections due to their gradual acquisition of antimicrobial resistance [4]. Notably, the associated mortality with MRSA-HAIs, in both INVI and non-INVI cases, exceeds that of most emerging multidrug-resistant gram-negative pathogens[5]. Remarkably, in 2019, SA, including both MSSA and MRSA, was globally the top bacterial cause of death[6].

Although SA is a global endemic pathogen, new strains can rapidly spread worldwide, driven by high-risk clones (HRCs) that blend increased virulence or transmission potential with multidrug resistance (MDR)[7,8]. Traditional multidrug-resistant HA-MRSA HRCs, identified in hospitals since 1959, mainly affect adult patients, with healthcare-associated risk factors (HRFs). Conversely, emerging MRSA clones (CA-MRSA) in the community since the 1980s were unrelated to healthcare. These genotypes, with diverse clonal lineages and specific geographical patterns, carry smaller SCC*mec* variants and fewer resistance determinants than HA-MRSA, primarily causing SSTI in healthy younger individuals [9]. Furthermore, CA-MRSA genotypes, primarily community-resident [10,11] now also cause healthcare-associated hospital-onset (HAHO) infections [9,12,13]. Therefore, genetic characterization of HRCs is essential for comprehending the evolving molecular epidemiology of SA infections in both hospital and community settings [9].

Despite MRSA HAIs decreasing in some European countries [14-16] and the United States [17-19] over the last decade, the HAHO MRSA infection rate in the US increased by 13% in 2020 compared to 2019, attributed to the impact of COVID-19 pandemic [1].Furthermore, in high-MRSA-prevalent regions of southern and eastern Europe, MRSA bloodstream infections (BSI) persistently rose during 2005-2018 [15] , indicating ongoing challenges in effective MRSA control in highly endemic areas. Additionally, MSSA BSIs have stabilized or increased in the US [18,20] and some European countries [14,15,21,22]. Limited information exists on the global burden of SA infections from both MRSA and MSSA [15,20,21]. Despite high case fatality rates in MSSA-BSI, optimal treatment approaches remain debated [15,21]. Importantly, changes in MRSA and MSSA infection trends become evident when analyzing incidence rates, as they may be overlooked when focusing solely on the MRSA percentage among total SA infections [15].

SA is a worrying problem in hospitals of Latin America[4,9,23]. In Argentina, MRSA accounts for 40-50% of SA isolates in both community-onset (CO) and hospital-onset (HO) infections, [12,13] showing a decreasing trend [24]. Between 2002 and 2007, the HA-MRSA Cordobes/Chilean ST5-SCC*mec*I HRC caused over 60% of HO-MRSA infections [25,26] while over 80% of CA-MRSA infections were associated with the CA-MRSA pulsotypeI-ST5-SSC*mec*IV-PVL$^+$ HRC [26,27]. Since 2009, CA-MRSA ST5-IV-PVL$^+$ HRC has spread in hospitals, coinciding with declining HA-MRSA Cordobes/Chilean ST5-I HRC. Simultaneously, there has been a growing MRSA reservoir in the community linked to two main CA-MRSA HRCs: ST5-IV and ST30-IV, and minor CA-MRSA HRCs, like USA300-ST8-IV-LV (USA300 Latin American variant) [12]. Furthermore, other more recent longitudinal-multicenter study in Córdoba city (Argentina), revealed that, most imported and all hospital-acquired MRSA belonged to CA-MRSA ST30-IV and ST5-IV HRCs, with the community as the primary reservoir [13].

Importantly, there is limited awareness of the incidence evolution over time of invasive and non-invasive infections caused by MSSA and MRSA, in Latin America, and largely unknown in Argentina. The aims of this investigation were: 1) to assess the molecular epidemiology of MRSA infections and estimate overall SA infection incidence (MSSA, MRSA, and genotypes) in community-onset (CO: HACO, Healthcare-associated-CO and CACO, Community-associated-CO) and healthcare-onset (HO: HAHO, Healthcare-associated-HO) infections, stratified by age groups, 2) to evaluate the temporal evolution by comparing this study's (2015) incidence values with a previous study (2009 [12]) in the same region.

MATERIALS AND METHODS

Surveillance Methodology and definitions

To assess the molecular epidemiology of MRSA infections and to estimate overall SA infection incidence (MSSA, MRSA, and genotypes: CA-MRSA$_G$, HA-MRSA$_G$ and principal MRSA clones) in community-onset (HACO and CACO) and healthcare-onset (HAHO) infections, we conducted a prospective-observational cross-sectional multicenter study in Argentina in April 2015. Sixty-one hospitals, including 46 from the WHONET Argentina Network, participated in this study across 20 provinces and Buenos Aires City (CABA). The hospitals characteristics are shown in the Supplementary Table S1. Additionally, a longitudinal-retrospective study was conducted to estimate the overall temporal evolution of SA infection incidence and prevalence (including MSSA, MRSA and genotypes) by comparing this study's (2015) values with a previous study (2009[12]). In the prior study, 591 clinical isolates were recovered from 66 hospitals serving a population of 1,484,505 visits, including 961,424 adults and 523,081 pediatric cases, in November 2009. Briefly, in both studies the patients were prospectively and consecutively identified according to the results of SA clinical cultures, as reported by the microbiology laboratories. Only the first isolate from

each patient was evaluated. A standardized questionnaire was completed for each patient and for this study the following features were analyzed: *i)* demographic characteristics (age and sex, Supplementary Table S2), *ii)* HRFs, CDC criteria [12,28] *iii)* onset of infection (hospital vs. community), *iv)* characteristics and severity of infections (Supplementary Table S2). Invasive infections (INVI) were defined as previously described [12]. Surgical site infections (SSI) were not considered as skin diseases.

We genetically characterized each MRSA clone and, to facilitate comparison between the two studies, we additionally defined traditional CA-MRSA and HA-MRSA strain types genotypically (detailed below), referred to as CA-MRSA$_G$ and HA-MRSA$_G$ (Table 1). Regardless of the strain types involved, cases were classified by infection onset [healthcare-onset (HO) and community-onset (CO)] and healthcare risk factors (HRFs) presence/absence [following epidemiological definitions: Community-associated CO-infections (CACO) and Healthcare-associated (HA) infections, including both HO-infections (HAHO) and CO-infections (HACO) [28]], as described previously [12].

From administrative data provided by each hospital, we determined the total number of patients served in each hospital (stratified by age groups) in both studies (2009 and 2015) across the northern, central, and southern regions of Argentina. We calculated the incidence of SA, MSSA, MRSA, and genotypes (CA-MRSA$_G$, HA-MRSA$_G$, and major clones) infections per 100,000 visits in each period (cases/100,000 monthly visits, including admissions, outpatient facilities, and emergency services). Aggregated data from all hospitals were used to calculate overall incidence rates and compare both periods. The analysis considered all infection cases, stratified by age groups (<19 and ≥19 years, representing pediatric and adult patients, respectively), infection categories (HO [HOHA] and CO [CACO, HACO]), and regions of Argentina (North, Center, and South)[12], Tables 2-5 and Supplementary Tables S3 and S4.

Ethics statement

This study was reviewed and approved by the Ethics Review Board of Health Research for adults and children (CIEIS), Government of the Province of Córdoba, Health Ministry (approval No. 2531, 2551 and 2552 /2015) as well as by the institutional Ethical Review Board of each Hospital listed in acknowledgments. All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study.

Bacterial isolates and antimicrobial susceptibility

SA clinical isolates (n: 668) were identified by standard microbiologic procedures and antimicrobial susceptibility testing was performed by disk diffusion method and/or Vitek2 [29].Vancomycin minimum inhibitory concentrations (MICs), were determined by agar dilution method [29]. Mupirocin susceptibility was determined by E-test method (bioMerieux) with the following definitions: high-level resistance, MIC ≥512 μg/mL; low-level resistance, MIC = 8–64 μg/mL; susceptible, MIC ≤4 μg/mL [30]. High-level resistance to mupirocin was confirmed by detection of the *mup*A gene by PCR as described [31]. To genetically investigate the rising incidence of erythromycin-resistant MSSA detected in the longitudinal study, all such isolates from both periods underwent molecular typing and PCR analysis for erythromycin resistance determinants (*erm*A, *erm*B, *erm*C, *erm*T, and *msr*A1 genes)[32].

Molecular typing

In all MRSA isolates and in erythromycin-resistant MSSA isolates from this study (n: 46) and the pervious one (n:20), PFGE of *Sma*I digests of chromosomal DNA and *spa* typing were performed and interpreted as previously described[12].The *spa*-types were assigned using the RIDOM web server (http://spaserver.ridom.de/). Additionally, the *spa* server was employed to predict sequence types (STs), as previously described [13]. Briefly, when the STs could not be determined using the *spa* server, Multi-locus-sequence-typing (MLST) was performed. Thus, MLST was carried out in at least one strain of each *spa*-type detected. Allele numbers,

sequence types (STs), and clonal complexes (CCs) were assigned using the https://pubmlst.org/organisms/staphylococcus-aureus database.

All MRSA isolates were screened by PCR for accessory gene regulator (*agr*) type, for 24 specific staphylococcal virulence genes (detailed in Table **1**), including Panton-Valentine leukocidin genes *(lukS*-PV-*lukF*-PV), *sas*X and for *arc*A gene (indicator of the arginine catabolic mobile element, ACME), as described elsewhere [12]. All CC398-MSSA isolates (n: 10) were screened by PCR [32] for immune evasion cluster (IEC) genes (*scn, chp, sak, sea*, and *sep*) to determine the potential animal or human origin of our isolates, as well as for *luk*S-PV-*luk*F-PV genes [12].

The SCC*mec* types (including the new variant of SCC*mec* IV/IVNv associated to ST100 in Argentina) were evaluated for all MRSA isolates by multiplex PCR and by allotyping (to identify *mec*, *ccr*, and the J1 region of I-XIV SCC*mec* types) by conventional PCR as described [12,33].

The genotypic definition for the identification of CA-MRSA$_G$ and HA-MRSA$_G$ was used as previously described [12]. Briefly, CA-MRSA$_G$ were defined as belonging to the following genotypes: ST5-IV-*t*311 and related, PVL$^{+/-}$, ST30-IV-*t*019 and related, PVL$^{+/-}$, ST72-IV-*t*148 and related, PVL^{-}, ST8-IV-*t*008, PVL$^{+/-}$, ST97-IV-*t*267 and related, PVL^{-}, ST207-IV-*t*525, PVL^{-}, ST1649 (SLV of ST6)-IV-*t*701, PVL^{-}[12]. All remaining genotypes were considered HA-MRSA$_G$ [9,12].

Statistical analysis

Comparisons between groups were performed with χ^2 test or Fisher`s exact test, as appropriate and $P<0.05$ was considered statistically significant. Data were analyzed using SPSS (version 15.0) and InfoStat (www.infostat.com.ar).

RESULTS

Prospective Observational Cross-Sectional Multicenter Study (2015)

a) Characteristics of SA infections cases

The population served by all hospitals (Supplementary Table S1) consisted of 1,360,252 visits, with 880,279 (64.5%) visits from adults and 479,973 (35.3%) visits from pediatric patients with 45,809 admissions during one-month (April 2015). A total of 668 SA clinical isolates were collected, resulting in an overall incidence rate of SA total-infections (TI, including invasive and non-invasive) of 49.1/100,000 monthly visits, with a range of 32.6 to 90.1 (Supplementary Table SS1). The median age of patients was 27 years (range: 1 month to 96 years), with 251 (37.5%) being children (<19 years) and 274 (41%) females (Table 2 and Supplementary Table SS2). Most cases were community-onset (CO) infections (471/668, 70.5%), both in pediatrics (170/251, 67.7%) and adults (301/417, 72.2%, Tables 3 and 4). Of all SA infections, 341 cases (51.0%, 95% CI: 47.2% to 54.8%) were caused by MRSA. Most SA infections were HA (HACO and HAHO), totaling 415 cases (62.1%) with an incidence rate of 30.5/100,000 (P<0.0001, Supplementary Table SS3).

Among 668 patients, there were 817 SA infections: 41.4% SSTI (34.5% uncomplicated, 6.9% complicated), 22.5% bacteremia, 9.2% lower respiratory tract infections, and 8.2% musculoskeletal infections, Supplementary Table SS2 provides additional details.

Among all patients, 55.1% experienced invasive infections, with INVI cases more prevalent among MSSA infections (61.4%, 201 out of 327) compared to MRSA infections (47.5%, 162 out of 341), primarily attributed to musculoskeletal infections (Supplementary Table SS2).

b) Genotyping of MRSA strains and infections

The majority of MRSA isolates (88.6%, 302/341) were classified as CA-MRSA$_G$, with 11.4% as HA-MRSA$_G$ (Table 1). Molecular characteristics, such as CC, ST, MLST, PFGE type and subtype, *spa*A and SCC*mec* types, presence of *pvl* genes, *agr* allotype, virulence gene profiles, and drug resistance patterns for both CA-MRSA$_G$ and HA-MRSA$_G$, are detailed in

Table 1. Prevalence and overall incidence data for TI and INVI caused by SA, MSSA, MRSA, HA-MRSA$_G$, CA-MRSA$_G$, and major MRSA clones from this study are compared with data from the previous one[12], covering the entire population and stratified by age groups, onset type (community or hospital), and epidemiological classifications of infections [CACO or CA, HACO, HAHO, HA (HACO + HAHO)] are shown in in Tables 2-4, Fig.1-2, and Supplementary Table S3 and Fig. S1-S2.

Among CA-MRSA$_G$ isolates (86%, 259/302), two major clones predominated. The PFGE-type N-ST30-SCC*mec*IV accounted for 70.2% (212/302), and the PFGE-type I-ST5-IV-SCC*mec*IV comprised 15.6% (47/302) (Table 1). The remaining CA-MRSA$_G$ isolates belonged to the following genotypes: PFGE-USA300-ST8-IV-LV (6%, n: 18/302), PFGE-D-ST97-IV (4%, n: 12/302), PFGE-R-ST72-IV (3.3%, n: 10/302), PFGE-Y-ST509-IVa (0.7%, n: 2/302), and PFGE-QQ-ST1649-IV (SLV of ST6, one isolate) (Table 1). For HA-MRSA$_G$ isolates (n: 39), the Cordobes/Chilean clone, PFGE-A-ST5-SCC*mec*I, predominated (61.5%, n: 24/39). The second most identified HA-MRSA$_G$ was the Pediatric clone Argentinean variant (PFGE-C-ST100-SCC*mec*INv) (38.5%, n: 15/39) (Table 1).

Furthermore, CA-MRSA$_G$ showed significantly higher rates of TI [22.2 vs. 2.9, P<0.0001, OR (95% CI): 13.3 (9.32-18.99)] and INVI [9.6 vs. 2.4, P<0.0001, OR (95% CI): 4.06 (2.77-5.97)] infections per 100,000 monthly visits compared to HA-MRSA$_G$, primarily due to the increased rate of CA-MRSA ST30-IV clone (15.6), surpassing rates of other major MRSA clones (Table 2).

c) SA infections cases: MSSA, MRSA and MRSA Genotypes

In reference to SA, MRSA and MSSA infection incidence rates stratified by age groups (Table 2), we found similar overall TI rates for MSSA and MRSA in the entire population (24.0 vs. 25.1, *P*=0.5889) and in adults (25.4 vs. 21.9, *P*=0.1289). However, MRSA showed a higher TI rate in children (30.8 vs. 21.4, *P*=0.0045, OR: 1.44), especially in non-INVI cases

where INVI rates were comparable *(P*=0.6494). This difference was evident in CO and CACO infections (Table 4). Conversely, there was a higher incidence of INVI caused by MSSA than by MRSA in the entire population (14.8 vs. 11.9, OR:1.24), especially in adults (15.7 vs. 11.8, OR:1.33), particularly in those older than 30 years (Table 2 and Supplementary Table S2), and among CO infections [entire population (8.7 vs. 6.3, OR:1.38, Table 3) and adults (9.8 vs. 6.2, OR:1.60, Table 4)].

Comparing infection rates across age groups, we observed similar TI and INVI rates caused by SA and MSSA in pediatrics and adults. However, a higher incidence of MRSA-TI was identified in pediatrics (particularly in patients aged 1-18 years) than in adults (30.8 vs. 21.9, OR: 1.44), especially non-INVI cases, in the community setting and linked to CA-MRSA ST30-IV clone (Table 2, Supplementary Fig. S1 and Table S2)

d) SA infections: CO vs. HO infections:

For CO- and HO- SA infections, the community displayed higher overall incidences of SA, MRSA, and MSSA than the hospital (Table 3). The elevated TI and INVI incidences caused by SA and MSSA were observed in adults, especially in HACO invasive infections (SA-HACO: 10.7 vs. SA-CACO: 5.3, MSSA-HACO: 6.4 vs. MSSA-CACO: 3.4, Table 4). Conversely, a higher MRSA-TI incidence in the community than in the hospital (17.3 vs. 7.5) [with comparable MRSA proportions between CO-TI (50.8%) and HO-TI (51.8%) (*P*=0.86), Table 3] was linked to non-invasive MRSA infections, as MRSA-INVI rates were similar (*P*=0.43, Table 3). This finding was observed in both pediatric and adult patients (Table 4), primarily related to a higher CA-MRSA-ST30-IVc (non-INVI)-TI rate in the community (CO: 12.6 vs. HO: 2.9, *P*<0.0001), especially in CACO (non-INVI)-TI (Table 3).

In reference to INVI, while overall MRSA and CA-MRSA$_G$ INVI rates were comparable between community and hospital settings, significant clonal-level differences were identified (Table 3). In the community, ST30-IV clone caused a higher INVI rate than CA-MRSA-ST5-

IV (4.1 vs. 0.73, OR 5.6), with comparable rates in CACO (1.9) and HACO (2.2) infections, *P*= 0.59 across both age groups. Conversely, in the hospital, INVI rates caused by HA-MRSA ST5-I (1.1) and CA-MRSA clones (ST30-IV/1.5, ST5-IV/1.1) were comparable, especially in adults (Table 3 and 4)

e) SA infections: HA vs. CA infections

Regarding HA (HAHO and HACO) and CACO SA infections (Supplementary Table S3), higher SA (MSSA and MRSA) infection rates (TI and INVI) were found in HA compared to CA infections (SA, TI: 1.64 fold, INVI: 3.6 fold; MSSA, TI: 1.80 fold, INVI: 3.3 fold; MRSA, TI: 1.50-fold, INVI: 4.1-fold) with comparable rates between HACO and HAHO infections (Table 3).

The higher MRSA TI and INVI rates in HA infections compared to CACO (Supplementary Table S3) were attributed to *i)* a higher CA-MRSA$_G$ INVI incidence, mainly associated with both CA-MRSA clones (with similar INVI rates between HACO and HAHO infections): ST30-IV and ST5-IV clones, alongside other CA-MRSA clones (USA300-LV and ST97-IV) (Table 3), and *ii)* a greater HA-MRSA$_G$ TI and INVI incidence, linked to ST5-I and ST100-IVNv clones and HAHO infections, particularly in adults (Table 3 and Supplementary Table S3). Notably, in HA MRSA infections (HACO and HAHO), CA-MRSA$_G$ showed higher rates than HA-MRSA$_G$, (Supplementary Table S3).

Evolution of SA infections (longitudinal retrospective study): 2009 *vs*. 2015

1) All Epidemiologic classes and age group

In Argentina, total and invasive SA infection rates increased by 23.4% (from 39.8 to 49.1, OR: 1.2) and 31.2% (from 19.9 to 26.1, OR: 1.3), respectively, from 2009 to 2015 in the entire population. These increases were driven by a 32.5% rise in MSSA TI (from 18.1 to 24.0, OR: 1.3) and a 54.2% growth in MSSA INVI (from 9.6 to 14.8, OR: 1.5), mostly in adults, while MRSA infection rates remained stable [Fig. 1 (A, B), Table 2, Supplementary

Table S4]. This stability in adults was linked to a CA-MRSA-ST30-IV rates increase and a HA-MRSA-ST5-I rates decrease. Notably, CA-MRSA-ST5-IV rates unchanged [Table 2, Fig. 1 (A, B)], Supplementary Table S4).

In pediatrics, there was a 26.7% increase in MRSA-TI incidence (24.3 to 30.8, OR:1.4), particularly non-INVI, while MSSA infection rates remained unchanged [Fig. 1 (A, B), Table 2, Supplementary Table S4]. This rise was linked to a CA-MRSA-ST30-IV clone rates increase and a CA-MRSA ST5-IV rates decline, [Table 2, Fig. 1 (A, B), Supplementary Table S4].

2) Community-onset cases, (CACO and HACO)

Community-onset SA TI and INVI rates rose by 37.3% (25.2 to 34.6, OR: 1.4) and 62.4% (9.3 to 15.1, OR: 1.6) in this period. This increase was related to *i)* a rise in CO-MSSA TI and INVI incidence [59.8% (10.7 to 17.1, OR: 1.6) and 97.7%, (4.4 to 8.7, OR: 1.9) respectively, Table 3, Fig. 2 (A, B)], detected in both HACO and CACO MSSA infections, especially in adults (for children, only a significant increase in CACO MSSA INVI incidence was noted, Table 4), and *ii)* a rise in CO MRSA TI overall rate [20.5%, 14.6 to 17.6, OR: 1.2, Table 3, Fig. 2 (A, B)], particularly INVI in adults (82.3%, 3.4 to 6.2, OR: 1.8, Table 4), and among HACO infections. The increase in CO-MRSA infection incidence was primarily driven by the CA-MRSA-ST30-IV clone, while CA-MRSA-ST5-IV community-onset TI and INVI rates remained unchanged (mainly in adults in HACO and CACO infections) or decreased (mainly in children among CACO TI and INVI and HACO non-INVI TI), [Table 3 and 4, Fig. 2 (A, B) Supplementary Table S4].

3) Hospital-onset cases, (HAHO)

Between 2009 and 2015, overall rates of HAHO SA TI and INVI remained stable in the entire population and among adults for both MRSA and MSSA infections (Table 3 and 4, Fig. 2). Notably, there was a 70.4% increase in pediatric HAHO MRSA TI, (5.4 to 9.2, OR: 1.7),

especially in non-invasive MRSA infections like uncomplicated skin and soft tissue infections (Table 4, Supplementary Table S4).

The HAHO CA-MRSA$_G$ TI and INVI rates significantly increased in the entire population, with pediatrics predominantly experiencing non-invasive infections. This rise was mainly attributed to the hospital introduction and spread of the CA-MRSA-ST30-IV clone. The persistence of the CA-MRSA-ST5-IV clone and, to a lesser extent, other CA-MRSA clones such as USA300-LV and ST97-IV, also contributed to this evolution [Fig. 2 (A, B) Table 3 and 4, Supplementary Table S4, and Fig. S2]. Furthermore, a displacement of the traditional HA-MRSA$_G$, particularly the HA-MRSA-ST5-I clone, by the CA-MRSA clones was evidenced, primarily in adults, resulting in the stability of HAHO MRSA infections in this age group [Table 3 and 4, Fig. 2 (A, B), Supplementary Table S4, and Fig. S2].

4) Healthcare associated Cases (HA: HAHO + HACO)

The overall rates of healthcare-associated SA TI increased by 22.5% (24.9 to 30.5, OR: 1.2), and INVI increased by 30.6% (16.0 to 20.9, OR: 1.3) during this period [Fig. 2 (A, B), Supplementary Table S3]. These increases were primarily driven by MSSA, showing a 26.0% rise in TI (12.3 to 15.5, OR: 1.3) and a 41.3% increase in INVI (8.0 to 11.3, OR: 1.4), mainly among adults with HACO infections. In the entire population and adults, healthcare-associated MRSA TI and INVI incidence remained unchanged. However, pediatric patients saw a significant 57% increase (11.3 to 17.7, OR: 1.6, Supplementary Table S3) in MRSA TI (non-INVI) related to HAHO infections (Table 4 and Supplementary Table S4).

This evolution appears linked to decreased adult HAHO HA-MRSA$_G$ infections, especially HA-MRSA-ST5-I. Concurrently, there's a notable rise in both HACO and HAHO TI and INVI infections by CA-MRSA$_G$ strains in both age groups. This is driven by the increasing ST30-IV clone incidence in both TI and INVI cases, along with rising INVI rates of other

minor clones (USA300-LV and ST97-IV), alongside sustained ST5-IV clone rates in INVI cases (Supplementary Tables S3 and S4).

SA infections by Argentina regions

In 2015, the prospective study revealed similar SA TI rates between the northern and southern regions (81.1 vs. 81.4, P=0.98), both surpassing the central region (41.0, P<0.0001). The disparity was due to higher MRSA (59.1) than MSSA (21.9) incidence in the North and higher MSSA (60.5) than MRSA (20.8) rates in the South (P<0.0001, Table 5). MRSA infection rates were 3.0-fold higher in the North (59.1) than the Center (19.9) and 2.8-fold higher than the South (20.8) of Argentina (*P*<0.0001), driven by major CA-MRSA clones, ST30-IV and ST5-IV, with the former showing a 4-5-fold higher rate than the latter clone in both regions. Other CA-MRSA clones (USA300-LV and ST97-IV) also contributed to this difference. In contrast, comparable HA-MRSA$_G$ infection rates were found between the North (5.6) and South (5.2) of the country, particularly related to the ST5-I clone (3.9 vs. 5.2, Table 5).

From 2009 to 2015, in longitudinal analysis, the northern region exhibited stable TI incidence for SA, MSSA, and MRSA (including genotypes and major clones) (Supplementary Fig. S3). In the central region, overall SA infections increased by 18.2% (34.7 to 41.0) and MSSA by 30.9% (16.2 to 21.2), while MRSA rates remained steady (Table 5 and Supplementary Fig. S3). CA-MRSA$_G$ infections rose by 41.6%, linked to increased ST30-IV clone rates and decreased ST5-IV clone rates, primarily in the community (Supplementary Fig. S4). HA-MRSA$_G$ infections declined by 63.3%, driven by decreased ST5-I clone rates, replaced by the ST30-IV clone and other CA-MRSA clones (ST97-IV and USA300-LV) (Table 5 and Supplementary Fig. S4). In the southern region, SA infections increased by 40.3% (58.0 to 81.4), mainly due to a 47.2% rise in MSSA (41.1 to 60.5), with stable MRSA (genotypes and

major clones) rates, except for increased ST30-IV clone rates (Table 5 and Supplementary Fig. S3).

Antimicrobial resistance to non-β-Lactam agents

In 2015, CA-MRSA$_G$ had lower resistance than HA-MRSA$_G$, consistent with 2009[12] (P<0.0001, Supplementary Table S5). Multi-resistance was exclusive to HA-MRSA$_G$ as seen in our previous studies [12,13,25-27]. All MRSA isolates were susceptible to teicoplanin, linezolid, and vancomycin (MIC90: 1 µg/mL, range: 0.5-2 µg/mL). Except for one CA-MRSA ST30-IV isolate with high-level mupirocin resistance (MuH, MIC: >1024 µg/mL, *mup*A$^+$), MRSA isolates were mupirocin-sensitive (MIC90: 0.38 µg/mL, range: 0.094-0.5 µg/mL) (Table 1), and mupirocin resistance was only 0.3% (95%CI: 6.2-9) (1/341 MRSA). The ST30-IV clone showed lower CLI and ERY resistance than ST5-IV, decreasing from 2009 to 2015 (Supplementary Table S5). With increased community-onset MSSA infections (2009-2015), resistance rose significantly to GEN (4.4% to 12.5%), ERY (8.2% to 15.9%), and CLI (3.8% to 11.6%, especially CLIi: 1.3% to 8.2%) (Supplementary Table S5). Among 66 ERY-resistant MSSA isolates, CC8 (28.8%), CC398 (15.1%), CC30 (15.1%), CC45 (10.6%), and CC5 (9.1%) were most frequent lineages. CC398-*t*1451-*erm*T+ was exclusive to 2015, constituting 21.7% of ERY-resistant MSSA. All CC398-MSSA isolates (n: 10) were *pvl*-negative and harbored *scn* gene, indicative of IEC system, with IEC types C (n: 6) and B (n: 4) (Supplementary Table S6).

DISCUSSION

Notably, few studies provide information on MSSA and MRSA infection epidemiology, prevalence, and incidence evolution[15,18-20], including shifts in major MRSA clones and their correlation with antimicrobial resistance, both in the general population and across age groups[34-37]. This study is the first nationwide report on the evolving incidence of

MSSA and MRSA infections in Argentina, highlighting on major MRSA clones causing community and hospital-onset infections across age groups. In the national prospective study in 2015, MRSA constituted 51.0% of SA isolates, with an overall TI rate of 24.0/100,000 monthly visits, remaining stable since 2009. In contrast, CO MSSA INVI incidence rose, with increased erythromycin resistance linked to the emergence of MSSA CC398-t1451-*erm*T^{+}

Concerning MRSA genotypes, our results align with previous studies [12,13], showing higher infections rates (over 10-fold) for typical CA-MRSA$_G$ compared to classic HA-MRSA$_G$, especially in non-invasive infections. The molecular characteristics and non-β-lactam drug resistance shared by isolates from each HRC (CA-MRSA clones: ST30-IV, ST5-IV, USA300-LV, and ST97-IV; HA-MRSA clones: ST5-I and ST100-IVNv) correspond to prior reports [12,13]. Recent genomic epidemiology data from Latin America in 2019 [38]align with our results. Moreover, the association of different clonal backgrounds with distinct antibiotic resistance and virulence gene profiles is consistent with other studies [12,13,39,40]. Genetic characteristics of CA-MRSA ST30-IV-*t*019 isolates suggest affiliation with the ARG4 phylogenetic clade, identified in a recent study of CC30 MRSA strains in Argentina [41]. Considerably, this clone had the highest incidence, surpassing the other major clones CA-MRSA/ST5-IV and HA-MRSA/ST5-I. However, incidence rates varied across infection epidemiological classes, patient age groups, and regions, which is crucial insights for guiding MRSA control strategies.

The overall incidence rates of MSSA and MRSA TI were comparable across the entire population and adults. However, MRSA TI rates, particularly non-INVI, were 1.4 times higher in children (1-18 years) compared to MSSA TI rates. This discrepancy was more pronounced in the community setting (1.6 times higher) and CACO infections (1.7 times higher). These results, consistent with previous studies [12,14,15,42], underscore the heightened risk of CA-MRSA non-invasive infections, especially SSTIs, in children, associated with the

CA-MRSA-ST30-IV clone. Conversely, in adults over 30, MSSA invasive infections surpassed MRSA (1.3-fold), notably in musculoskeletal cases and the community (1.6-fold). In line with previous studies from the US and European countries [14,15,18-20,35,37], these findings highlight higher MSSA invasive infection rates than MRSA and variations based on infection site and population characteristics such as patient age.

Additionally, although MRSA proportions were comparable between the community (50.7%) and the hospital setting (51.8%), higher SA TI and INVI incidence rates were detected in the community. This was linked to increased CO-MSSA TI and INVI, especially HACO-MSSA TI and INVI in adults, and higher CO-MRSA infection rates, particularly non-INVI, in both age groups. These findings underscore the importance of targeting not only hospitals but also the community in strategies to control SA transmission [15,18]. The CA-MRSA-ST30-IV clone drove higher incidence of MRSA TI, especially non-INVI, in the community versus the hospital, notably in CACO infections in both age groups. However, MRSA INVI rates were similar between community and hospital settings. In the community, the CA-MRSA-ST30-IV clone caused the highest INVI incidence, with comparable rates between HACO and CACO infections in adults and pediatrics. In the hospital, this clone exhibited similar INVI rates to other major CC5 MRSA clones (CA-MRSA-ST5-IV and HA-MRSA-ST5-I). These findings underscore different behaviors of two key CA-MRSA clones in community and hospital settings, indicating that unique capacities or characteristics may contribute to their success in these settings, consistent with previous reports [11,13,43-45]. Beyond genetic traits [11, 38,41], these clones might have distinct environmental reservoirs and colonization patterns [11,13], impacting their transmission capacity differentially. However, additional studies are needed to confirm this hypothesis.

In Argentina, HA SA infections, particularly invasive cases, caused by both MSSA and MRSA, were over 3 times higher than CA infections. MRSA's higher incidence in HA

infections was mainly driven by CA-MRSA clones (with similar INVI rates between HACO and HAHO infections), particularly the ST30-IV and ST5-IV, alongside other CA-MRSA clones (USA300-LV and ST97-IV). Traditional HA-MRSA$_G$, like ST5-I and ST100-IVNv clones in adults, contributed but to a lesser extent than CA-MRSA clones. These results confirm the infiltration and transmission of CA-MRSA clones in Argentine hospitals, consistent with the previous study [13]. The dissemination of these MRSA clones, along with MSSA, is likely influenced by their virulence and fitness, as well as varying healthcare interventions, differing between high-income countries and low- and middle-income countries like Argentina, with limited resources and a higher burden of HA infections [4,23,46,47].

Importantly, as reported previously[12,13], multidrug resistance patterns were exclusive to HA-MRSA$_G$. The CA-MRSA ST30-IV clone consistently showed lower resistance rates to erythromycin and clindamycin compared to ST5-IV counterparts throughout the analyzed period. However, a longitudinal analysis via the WHONET Argentina Network in 2018-2022 [24] revealed a slight increasing trend in resistance to ERY and CLI among MRSA isolates, highlighting the need for continuous surveillance for MRSA treatment alternatives in community and hospital settings. Additionally, one CA-MRSA ST30-IV clone isolate with mupirocin resistance (MuH, encoding by *mup*A) was identified, constituting 0.3% (95% CI 0.054-1.654) of clinical MRSA isolates nationwide. Notably, the mupirocin resistance prevalence in Argentina (0.3%) falls within the lower range compared to European (0.3%-98.0%), North American (0.5%-30.0% or more), and Asian (0%-75.0%) countries [48-52]. A genomic study of CC30 MRSA strains from Argentine provinces also detected mupirocin resistance associated with the ST30-IV clone [41]. These findings support the potential for transmission of these resistance determinants (*mup*A or *mup*B genes) through plasmids, which can also carry resistance genes to other antimicrobials across major SA lineages (CC5, CC8,

CC22, and CC30) in both human and animal populations [48,49,51,52]. Therefore, ongoing surveillance and a strict mupirocin use policy are recommended in Argentina.

On the other hand, the highly successful CC5 lineage, other prominent MRSA lineage in Argentina[12,13,26], has shown potential for complex competitive interactions, including the acquisition of multidrug resistance, vancomycin resistance, and diverse SCC*mec* types [9,53]. This lineage has undergone dynamic regional evolution, leading to specific sublineages with genomic changes associated with increased antibiotic resistance and decreased virulence [40,54-56]. Notable examples in this region include the spread of the CC5/ST105-II-*t*002 multidrug-resistant MRSA clone in Rio de Janeiro, Brazil, [57] a neighboring country to Argentina. In Argentina, two HA-MRSA clones (CC5/ST5-I-*t*149, CC5/ST100-IVNv-*t*002) and one CA-MRSA clone (CC5/ST5-IV-*t*311 and related) have been circulating since the 2000s[12,26,58]. Previous reports in this country have also indicated that the CA-MRSA ST5-IV clone expresses h-VISA or VISA phenotypes[27,59,60], or exhibits reduced-susceptibility to tigecycline [61]. These findings underscore the need for global molecular surveillance of CC5 MRSA HRCs.

Regarding the evolution in the incidence of SA infections in Argentina, SA total and invasive infection rates increased by 23.4% and 31.2%, respectively, from 2009 to 2015. This rise was driven by a 32.5% increase in MSSA TI and a 54.2% increase in MSSA INVI, mainly in adults. The majority of the MSSA increase was in community-onset MSSA TI (59.8%) and INVI (97.7%), including both HACO-MSSA and CACO-MSSA infections, especially in adults, although in children an increase in CACO MSSA INVI incidence was also noted. Our findings suggest that the overall burden of community-onset MSSA infections is rising in Argentina, contributing to the SA disease burden, with no significant MRSA changes. This pattern aligns with recent data from North America and Europe, including bloodstream and SSTI infections [15,18-,20,22,35]. Importantly, our study has revealed a

simultaneous increase in CO-MSSA infections and resistance to non-β-lactam antibiotics, specifically erythromycin, linked to the emergence and spread of the MSSA-CC398-*t*1451-*erm*T^{+}-IEC^{+}-*pvl*$^{-}$ lineage in Argentina. Another WHONET Argentina Network analysis[24] has identified a significant rise in the MSSA relative proportion of total SA infections from 50.5% (5720 culture-confirmed SA infections) in 2009 to 66.9% (6278 culture-confirmed SA infections) in 2021, along with increased resistance to non-β-lactam antibiotics (clindamycin, erythromycin, and gentamicin). These findings support our longitudinal study data, suggesting a continuous increase in MSSA infections accompanied by the resistance to ERY, CLI and GEN since 2009, including the impact of the COVID-19 pandemic. Furthermore, in a recent study [38], the MSSA-CC398-*t*1451-*erm*T^{+} was detected as the predominant MSSA lineage in bloodstream isolates across Latin America's southern cone countries, including Argentina, during 2019. CC398 is a highly transmissible lineage, associated with both livestock (LA-MRSA) and humans (HA-MSSA). These two phylogenetic clades, LA and HA, exhibit genomic differences, particularly in mobile genetic elements acquisition or loss, influencing host adaptation, antimicrobial resistance and virulence. The HA-ST398-MSSA lineage, globally disseminated, is characterized by macrolide resistance, *spa* types *t*571 or *t*1451, and the IEC cluster presence, linking it to a human origin, in the majority of isolates [62,63]. Our study suggests that, in Argentina, this highly transmissible MSSA-CC398-*t*1451-*erm*T^{+}-IEC^{+}-*pvl*$^{-}$ lineage likely initiated its spread during 2009-2015, driving the increase in macrolide resistance among MSSA infections.

Notably, due to limited evidence on MSSA horizontal transmission, most studies have focused on the importance of transmission control measures with vertical or MRSA-targeted approaches, such as active surveillance or MRSA decolonization[64]. Nevertheless, considering MSSA potential growing role as a healthcare-associated invasive pathogen, especially in community-onset infections, as indicated by our study in Argentina and other research

globally [15,18,19,22,63,65,66], reassessing and thoroughly studying MSSA epidemiology (general and molecular) is advisable for formulating effective control strategies.

On the other hand, the sustained rates of MRSA TI and INVI during this period, particularly in adults, are associated with the stability of HAHO MRSA infections, reflecting an evolution already identified in other countries [18,22]. In Argentina, this stability is linked to the replacement of HA-MRSA-ST5-I (previously linked to HAHO MRSA infections in adults [25,58]) by CA-MRSA ST30-IV and other clones like USA300-LV and ST97-IV. In adults, CA-MRSA-ST30-IV supplements rather than replaces CA-MRSA ST5-IV, particularly in HA (HAHO and HACO) infections. Consequently, while HAHO MRSA infections remained stable in adults, CO MRSA total infections increased (20.5%), driven by a rise in INVI cases (82.3%), primarily due to increased HACO MRSA INVI. Contrastingly, MRSA TI rates in children increased by 26.7%, primarily due to a 1.7-fold rise in HAHO-MRSA TI, driven by CA-MRSAG (non-INVI)-TI associated with the spread of the CA-MRSA ST30-IV clone in hospitals. This, along with the ST5-IV clone, contributed to the surge in HAHO MRSA infections in children, confirming our previous study [13] emphasizing the high risk of CA-MRSA$_G$ colonization and acquisition in children aged 1 to 18 years in hospitals.

The need for reinforced strategies to control HAHO MRSA infections, particularly in children, is underscored once again [12,42,65,67]. On the other hand, the CO MRSA infections rates in children remained consistently higher than MSSA infections and stable from 2009 to 2015. This stability was linked to the ST30-IV clone spread, displacing the CA-MRSA ST5-IV clone in CACO infections (TI and INVI) and HACO non-invasive infections. These findings suggest that the distinct behavior of MRSA clones is influenced by both the infection setting (hospital or community), reflecting differences in transmission capacity, and associations between SA genotypes and patient age, as observed in certain SA lineages [12,57,68].

All these results demonstrate that the increase in SA infections during this period was primarily driven by a rising evolution over time in community-onset SA infections, particularly in adults, related to increased rates of HACO-MSSA and HACO-MRSA infections and a rise in CACO-MSSA infections in both age groups. Conversely, the stability in HAHO SA infections, mainly in adults, and the decreasing MRSA proportion during 2018-2021, as shown by the WHONET database [24], could be attributed to diverse hospital infection control strategies implemented in Argentina (http://www.vihda.gov.ar/). This suggests more effective infection control practices in hospitals compared to the community, aligning with trends reported in some European Union countries [14,15] and the US [18]. Alongside current hospital strategies like contact precautions, it's crucial to consider non-specific approaches for MRSA and focus infection control on SA (MRSA and MSSA) to disrupt the transmission chain between hospitals and communities [18,65,69,] considering it as a One Health issue encompassing humans, the environment, animals, and plants [1,10,70].

The countrywide coverage of this study allowed for detecting similar rates of SA infections in the northern and southern regions, both higher than in the central region of Argentina. The North had a higher MRSA incidence (59.1) than MSSA (21.9), while the South exhibited a higher MSSA incidence (60.5) than MRSA. The MRSA infections rates were comparable between the central and southern regions, but the northern region had a consistently higher MRSA incidence (2-3 fold), mainly due to elevated CA-MRSA$_G$ rates, particularly ST30-IV, although ST5-IV, USA300-LV, and ST97-IV also contributed. These findings suggest that in the North, specific weather conditions (warmer and/or more humid) and socio-demographic factors (overcrowding, low income, among others) would contribute to the spread of CA-MRSA clones, aligning with other studies [71-73]. Conversely, the sparsely populated South, with different weather conditions (cooler and/or drier), has higher MSSA incidence than other regions of Argentina. Furthermore, while MSSA and MRSA infections rates remained stable

in the North between 2009 and 2015, the Centre and the South experienced SA infection rate increases (18.2% and 40.3%, respectively), driven by rising MSSA rates (30.8% and 47.2%, respectively). In line with other studies [15,20,66], these results support the hypothesis that MRSA and MSSA don't compete for the same ecological niche. Then, different factors, including weather conditions, socio-demographics, antibiotic use rates, and the unique genetic background of each clone, may favor the transmission of MSSA or MRSA. Consequently, MRSA and MSSA do not inevitably replace each other.

Significantly, most changes in MRSA clone infections rates occurred in the central region, where the hospital entry of the ST97-IV clone, causing HAHO infections, was identified. This clone, also identified as a minor colonizer during hospital admissions in Córdoba in a prior study [13], is likely genetic related to livestock-associated MRSA (LA-MRSA), CC97 [9,74]. The central region, Argentina's primary agricultural and livestock area [75],would require further studies to investigate livestock as a possible reservoir of this lineage in Argentina.

In conclusion, our study has identified an increasing burden of SA infections in Argentina from 2009 to 2015, predominantly in the central and southern regions, driven by a rise in community-onset infections. This surge was primarily attributed to growing rates of MSSA infections, accompanied by increased resistance to macrolides and gentamicin, while the proportion of MRSA remained stable. The emergence and spread of the erythromycin-resistant MSSA CC398-*t*1451 lineage contributed to this evolution, adding to the overall burden of invasive SA disease. The rise in SA infections was associated with increased rates of HACO MRSA and HACO MSSA total and invasive infections in adults, as well as a rise in CACO MSSA infections across age groups. Conversely, CACO MRSA infections remained stable. While overall rates of HAHO MRSA infections showed no significant changes in the entire population and adults, there was a notable 1.7-fold increase in children, contributing to the overall rise in healthcare-associated (HA) SA infections. Our study also identified the

entry and spread of the ST30-IV clone in hospitals, along with other CA-MRSA clones (USA300 LV and ST97-IV). Importantly, these clones complemented rather than replaced the ST5-IV clone in HA (HACO and HAHO) invasive infections in both age groups, with the ST30-IV clone displacing the HA-MRSA ST5-I clone, particularly in adult HAHO infections.

The strengths of this study include: *i*) the first-time assessment of overall SA disease incidence throughout the country. *ii*) a prospective 2015 study with a retrospective longitudinal investigation comparing SA infection incidence between 2015 and the previous 2009 study [12], *iii*) molecular characterization of isolates with sociodemographic and clinical patient data. Both studies (2009 and 2015) covered hospitals distributed nationwide (most from WHONET Argentina Network), serving 3.5% of the Argentine population[76]. Importantly, the analysis has also been stratified by age groups, epidemiological classes, and country regions.

The main limitation of the comparative study is the relatively short inclusion period for infection cases in each study (one month). Monthly values of the pooled estimated incidence rates were compared across all surveillance sites. The limited number of monthly cases may have led to underpowered statistical analysis, potentially missing changes in incidence rates, especially for minor clones. However, the identified changes were sufficient to demonstrate increases or decreases in the burden of MRSA, MSSA, and principal MRSA clones. Furthermore, the analysis involved only two points separated by 6 years, lacking consecutive intermediate points to demonstrate a continuous trend throughout the period. Nevertheless, the annual results of the national surveillance on antimicrobial resistance evolution [24] provided by the WHONET Argentina Network (to which most of the hospitals that participated in both studies belong) align with the evolutionary results on MRSA and MSSA infections from our longitudinal analysis, supporting the continuity of this evolution until at least the year 2021. Additionally, for comparability between the results of both

studies, 85% of the hospitals participated in both studies, with only an 8.3% difference in the populations served.

The analysis of MRSA and MSSA incidence in Argentina adds to existing literature, underscoring the community's role as a growing reservoir for successful MSSA and CA-MRSA clones, resulting in healthcare-associated community-onset infections. These findings provide valuable insights for improving *S. aureus* infection prevention and control programs, guiding transmission control priorities in Argentina and globally, and addressing antimicrobial resistance on a global scale.

DECLARATIONS

Author contribution statement

CS, AC and JLB conceived and designed the study. CS, AC, DB, RL, AG, CSA, PG, CL and DF participated in coordination of the study. RL, AG, CSA and SGroup contributed bacterial strains, carried out the identification and antibiotic susceptibility of the isolates, contributed to clinical care of the patients and the collection and analyses of the clinical and demographic data. DB, EB and MJG carried out the molecular typing of the isolates. DT, DB, EB, MJG and CS performed data analysis. CS, AC, DB, EB and JLB drafted the manuscript. All authors read and approved the final manuscript

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

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Figure Legends

Figure 1: Incidence of cases of (A) total and (B) invasive infections caused by *S. aureus* (SA), MSSA, MRSA and MRSA genotypes (including CA-MRSA$_G$ and HA-MRSA$_G$ and major MRSA clones) in the total population and by age group, 2009 and 2015, Argentina

Abbreviation: n*: $P < 0.05$ by χ^2 test for the comparison between 2009 and 2015 of infections incidence.

Incidence: Number of cases /100,000 monthly visits. Number of visits (V): include outpatient facility, emergency service and admissions during one month.

Figure 2: Incidence of cases of (A) total and (B) invasive infections caused by *S.aureus* (SA), MSSA, MRSA and MRSA genotypes (including CA-MRSA$_G$ and HA-MRSA$_G$ and major MRSA clones) by onset type and epidemiological criteria (CDC) of infections, 2009 and 2015, Argentina.

Abbreviation: n*: $P < 0.05$ by χ^2 test for the comparison between 2009 and 2015 of infections incidence, by onset type and epidemiological criteria (CDC) of infections.

Incidence: Number of cases /100,000 monthly visits. Number of visits (V): include outpatient facility, emergency service and admissions during one month

Table 1. Characteristics of 341 MRSA isolates belonging to HA-MRSA and CA-MRSA genotypes, Argentina, 2015.

Genetic background	ST	PFGE type/no. (%/%)[a]	PFGE Subtype/no. (%)[b]	RIDOM *spa* type/ no.(%)[b]	SCC*mec* no. (%)[b]	*pvl* no. (%)[b]	*agr* type	virulence genes[c] profile	Drug resistance[d] non-β-Lactam (%)
CA-MRSA n: 302									
CC30	30	N/212 (62.1/70.2)	N4/101 (47.6), N6/23(10.8), N30/22(10.4) N13/20 (9.4), and 26 minor subtypes.	t019: 208 (98), t021: 1, *t*3037: 1, *t*433: 1, *t*2529: 1	IVc: 209 (98.5), IVh: 2(1), IVNT: 1	203 (96)	3	*egc-lukDE-bbp-cna*	GEN 24 (11.4), ERY 6 (3)[e], CLIi 3 (1.4)[e], CLIc 3 (1.4), Cip 7(3.3), RIF 1, MUP 1
CC5	5	I/47 (13.8/15.6)	I1/28 (59.6), I29/4 (8.5), I26/2 (4.3), I47/2 (4.3), I68/2 (4.3), and 9 minor subtypes	*t*311: 29 (61.7), *t*002: 15 (31.9), *t*1265: 1, *t*1215: 1, *t*062: 1	IVa: 43 (91.5), IVc: 3 (6.4), IVB: 1	32 (68.1)	2	*sea-egc-lukDE* 32 (68.1), *egc-lukDE* 15 (31.9)	GEN 5 (10.6), ERY 12 (25.5)[e], CLIi 8 (17)[e],CLIc 3(6.4), Cip 1
CC8	8	USA300/18 (5.3/6.0)	USA300-5/4 (22), USA300-17/ 2(11), USA300-19/ 2(11) and 10 minor subtypes	*t*008: 14 (77), *t*024: 2(11), *t*723: 1, *t*068: 1	IVc: 9 (50), V[g]: 3(16.5) IVNT[h]:3(16.5) IVa: 2(11) IVb: 1	10 (56)	1	*pvl-lukDE-sek-seq-bsa*: 5 (28), *lukDE-bsa:* 3 (17), l*ukDE-sea-bsa*: 3 (17), *pvl-lukDE-sea-sek-seq-bsa:* 2(11), *lukDE-sea-sek-seq-bsa:* 1(5), *pvl-lukDE-sec-sek-seq-bsa:* 1(5), *lukDE-sec- bsa:* 1(5), *pvl-lukDE-sed-sej-sek-seq-bsa:*1(5) *pvl-sed-sej-bsa:* 1(5)	GEN 5(28), ERY 4(22.2), CLIi 2(11), CLIc 1, CIP 6(33.3)
CC97	97	DD/12 (3.5/4.0)	DD1/5 (42), DD21/2 (17) and 4 minor subtypes	*t*267: 3(25), *t*359: 2(17), t1190: 2(17), *t*521*:* 1, *t*8870: 1, *t*1247: 1, *t*2445: 1, *t*2383: 1	IVa: 10 (83), IVc: 2(17)	0(0)	1	l*ukDE* 12(100)	GEN 3(25), ERY 1, CLIi 1
CC8	72	R/10 (2.9/3.3)	R1/6 (60) and 4 minor subtypes	t148: 10 (100)	IVc: 9 (90), IVa: 1	0 (0)	1	*egc-lukDE* 10(100)	GEN 4(40), ERY 1(10), CLIi 1 (10), CIP 2(20), RIF 2 (20) TMS 1
CC509	207	Y/2 (0.6/0.7)	Y1/ 1(50), Y4 1(50)	*t*525	IVa: 2(100)	0 (0)	3	*egc*[f]*-etaa-* 1(50), *egc*[f]-cna 1(50)	
CC6	1649	QQ/1 (0.1/0.3)	QQ2	t701	IVNT[h]	0 (0)	1	*lukDE-seb-sea-bsa-cna*	TMS
HA-MRSA n: 39									
CC5	5	A/24 (7.0/61.5)	A102/3 (12.5), A10/2 (8.3), A40/2 (8.3), and 15 minor subtypes	*t*149 22(92), *t*15913: 1, *t*17035: 1	I: 24 (100)	0 (0)	2	*egc-lukDE*	GEN 21 (88), ERY 24 (100), CLIc 24 (100), CIP 23 (96), TMS 1, RIF 1
CC5	100	C/15 (4.4/38.5)	C30/6 (40), and 9 minor subtypes	*t*002: 9 (60), *t*045: 2(13) *t*1084, t1791, t548	NT 11 (73) IVNv: 4 (27)	0 (0)	2	*egc-lukDE*	GEN 14 (93), ERY 8 (53), CLIc 6 (40), CLIi 2 (13), CIP 9 (60), RIF 13 (87) MIN 1

CC, Clonal Complex; ST, Sequence Type, PFGE type/subtype, Pulsed Field Gel Electrophoresis type and subtypes; RIDOM *spa* type: staphylococcal protein A (*spa)* type assigned through the RIDOM databases (http://spaserver.ridom.de); The *spa* type was used to predict sequence types (STs). MLST was carried out in at least one strain of each *spa*-type detected, https://pubmlst.org/organisms/staphylococcus-aureus database, SCC*mec*: Type of Staphylococcal Cassette Chromosome *mec* (SCC*mec* NT: it was not possible to ascertain a class of *mec* complex or a type of *ccr*); *pvl,* Panton Valentine leukocidin genes *(lukS*-PV-*lukF*-PV); *agr* type, type of accessory gene regulator allotype.

[a] no. (%/%), number and % of total MRSA (n: 668)/% of each genotype [CA-MRSA$_G$ (n: 302) or HA-MRSA$_G$ (n: 39)]

[b] no. (%), number and % of strains with this molecular characteristic [PFGE subtype (only those more frequent are indicated) or *spa* type or *SCCmec* type or *pvl* genes] belonging to each genetic background: CA-MRSA$_G$ (n: 302) or HA-MRSA$_G$ (n: 39) genotypes. % is not expressed when only one isolate with this characteristic was detected

[c] Virulence genes profile: The enterotoxins: *sea, seb, sec, sed, see, seg, seh, sei, sej, sen, seo, sem, seq* and *sek;* toxic shock syndrome toxin 1(TSST-1): *tst;* exfoliative toxins: *eta* and *etb*; leukocidin: *lukE-lukD* and the class F leukocidin: *lukM;* bacteriocine (*bsa*), adhesins: for collagen (*cna*) and for bone sialoprotein-binding protein (*bbp*) and the *arc*A gene (indicator of the arginine catabolic mobile element, ACME) were analyzed and those detected are indicated (number and % of positive isolates is expressed when not all isolates harbor this virulence factor).

[d] Drug resistance to non-β-Lactams (%), is indicated as follows: Gentamicin (GEN), Erythromycin (ERY), Clindamycin (CLIc and CLIi: constitutive and inducible resistance to macrolide, lincosamide and streptogramine B, respectively), Ciprofloxacin (CIP), Rifampin (RIF), Trimethoprim/Sulfamethoxazole (SXT), Minocycline (MIN) and Mupirocin (MUP), (%) of strains resistant to these antibiotics within each genetic background is indicated when more than one isolate was detected.

[e] *$P < 0.01$ by χ^2 test,* for comparison between MRSA isolates characterized as pulsotype N and those with pulsotype I for resistance to clindamycin and erythromycin antibiotics

[f] The *egc* locus appears to be present in a variant or truncated form with only genes *sem*, *sei* and *seo* being detectable.

[g] SCC*mec* Vv: positive for *ccrC* locus and class C2 *mec* gene complex and negative for J1 region of SCC*mec* V and for other SCC*mec* regions analyzed.

[h] IV NT: SCC*mec* type IV non typable.

Table 2: Percentage and incidence of total (TI) and invasive (INVI) infections caused by *S. aureus* (SA), including MSSA, MRSA and MRSA-genotypes in Argentine hospitals by age group: 2009 vs. 2015, with comparisons in 2015 between pediatric vs. adult patients and MRSA vs. MSSA for TI and INVI.

	***S. aureus* infections** % (n) / incidence of total cases and % (INV) / incidence of invasive cases									
	Total			**Adults** (≥ 19)			**Pediatrics** (<19)			
	2009 N[a]: 591 INV[b]:296 %(n)/ In[c]/ %(INV)/InI[d]	2015 N[a]: 668 INV[b]:363 %(n)/ In[c]/ %(INV)/InI[d]	*2015 vs. 2009* *P* value/OR (95%CI)	2009 N[a]: 366 INV[b]:188 %(n)/ In[c]/ %(INV)/InI[d]	2015 N[a]: 417 INV[b]: 242 %(n)/ In[c]/ %(INV)/InI[d]	*2015 vs. 2009* *P* value/OR (95%CI)	2009 N[a]: 225 INV[b]: 108 %(n)/ In[c]/ %(INV)/InI[d]	2015 N[a]: 251 INV[b]: 121 %(n)/ In[c]/ %(INV)/InI[d]	*2015 vs. 2009* *P* value/OR (95%CI)	Pediatric vs. Adults 2015 *P* value/OR (95%CI)
SA Total	100(591)	100(668)		100(366)	100(417)		100(225)	100(251)		
	39.8	49.1	**0.002/1.2 (1.10-1.38)**	38.1	47.4	**0.0022/1.2 (1.08-1.43)**	43.0	52.3	**0.033/1.2 (1.02-1.46)**	0.2155
SA INV	100(296)	100(363)		100(188)	100(242)		100(108)	100(121)		
	19.9	26.1	**0.0002/1.3 (1.15-1.56)**	19.6	27.5	**0.0004/1.4 (1.16-1.70)**	20.6	25.2	**0.14**	0.44
MSSA Total	45.5(269)	49.0(327)	0.22	46.7(171)	53.7(224)	0.07	43.6(98)	41.0(103)	0.63	**0.0015/0.60 (0.44-0.82)**
	18.1	24.0	**0.0006/1.3 (1.13-1.56)**	17.8	25.4	**0.0004/1.4 (1.17-1.75)**	18.7	21.4	0.33	0.15
MSSA INV	48.3(143)	55.4(201)	0.08	50.5(95)	57.0(138)	**0.21**	44.4(48)	52.1(63)	0.30	0.44
	9.6	14.8	**0.0001/1.5 (1.24-1.90)**	9.9	15.7	**0.0005/1.6 (1.22-2.06)**	9.2	13.1	0.06	0.24
MRSA Total	54.5(322)	51.0(341)	0.23	53.3(195)	46.3(193)	0.07	56.4(127)	59.0(148)	0.56	**0.0015/1.7 (1.22-2.29)**
	21.7	25.1	0.06	20.3	21.9	0.44	24.3	30.8	**0.047/1.3 (1.00-1.61)**	**0.0017/1.4 (1.14-1.74)**
MRSA INV	51.7(153)	44.6(162)	0.42	49.5(93)	43.0(104)	0.21	55.5(60)	47.9(58)	0.30	0.44
	10.3	11.9	0.45	9.7	11.8	0.17	11.5	12.1	0.82	0.89
In MSSA vs. MRSA *P* value/ OR (95%CI)	**0.0292/0.84 (0.71-0.98)**	0.59		0.21	0.13		0.06	**0.0045/0.70 (0.54-0.89)**		
InI MSSA vs. MRSA *P* value/ OR(95%CI)	0.5610	**0.041/1.2 (1.01-1.53)**		0.8840	**0.028/1.3 (1.03-1.71)**		0.2482	0.6494		
CA-MRSA$_G$ Total	38.7(229)	45.2(302)	**<0.0001/1.7 (1.32-2.06)**	31.1(114)	38.8(162)	**0.0210/1.4 (1.04-1.89)**	51.1(115)	55.8(140)	**0.33**	**<0.0001/2.0 1.45-2.73)**
	15.4	22.2	**<0.0001/1.4 (1.21-1.71)**	11.9	18.4	**0.0003/1.5 (1.22-1.97)**	21.9	29.2	**0.024/1.3 (1.04-1.70)**	**0.0001/1.6 1.26-2.00)**
CA-MRSA$_G$ INV	26.4(78)	35.8(130)	**0.009/1.6 (1.12-2.18)**	16.0(30)	32.2(78)	**0.0001/2.5 (1.56-4.01)**	44.4(48)	43.0(52)	0.93	0.06
	5.2	9.6	**<0.0001/1.8 (1.37-2.41)**	3.1	8.9	**<0.0001/2.8 (1.87-4.31)**	9.2	10.8	0.42	0.26
HA-MRSA$_G$ Total	15.7 (93)	5.8(39)	**<0.0001/0.3 (0.22-0.49)**	22.1 (81)	7.4(31)	**<0.0001/0.3 (0.18-0.44)**	5.3 (12)	3.2(8)	0.44	**0.0234/0.41 (0.19-0.89)**
	6.2	2.9	**<0.0001/0.5 (0.32-0.66)**	8.4	3.5	**<0.0001/0.4 (0.28-0.63)**	2.3	1.7	0.48	0.06
HA-MRSA$_G$ INV	25.3 (75)	8.8 (32)	**0.0001/0.3 (0.18-0.44)**	33.5 (63)	10.7(26)	**<0.0001/0.2 (0.14-0.40)**	11.1 (12)	5.0(6)	0.14	0.10
	5.1	2.4	**0.0002/0.5 (0.31-0.70)**	6.6	3.0	**0.0001/0.4 (0.26-0.65)**	2.3	1.3	0.21	0.06
N-ST30-IV[e] Total	17.6(104)	31.7(212)	**<0.0001/2.2 (1.67-2.84)**	17.5(64)	25.7(107)	**0.0057/1.6 (1.15-2.30)**	17.8(40)	41.8(105)	**<0.0001/3.3 (2.2-5.1)**	**<0.0001/2.1 (1.49-2.91)**
	7.0	15.6	**<0.0001/2.2 (1.76-2.81)**	6.6	12.1	**<0.0001/1.8 (1.34-2.49)**	7.6	21.9	**<0.0001/2.9 (1.9-4.1)**	**<0.0001/1.8 (1.38-2.35)**
N-ST30-IV[e] INV	7.8(23)	21.2(77)	**<0.0001/3.2 (2.25-5.48)**	5.3(10)	17.8(43)	**0.0001/3.9 (1.9-7.77)**	12.0(13)	28.1(34)	**0.0027/2.8 (1.43-5.71)**	**0.0232/1.8 1.08-3.02)**
	1.5	5.7	**<0.0001/3.7 (2.30-5.80)**	1.0	4.9	**<0.0001/4.7 (2.39-9.21)**	2.5	7.1	**0.0008/2.9 (1.52-5.35)**	0.10
I-ST5-IV[e] Total	17.2(102)	7.0(47)	**<0.0001/0.4 (0.25-0.52)**	10.7(39)	5.8(24)	**0.0119/0.5 (0.30-0.87)**	28.0(63)	9.2(23)	**<0.0001/0.3 (0.2-0.4)**	0.13
	6.9	3.4	**0.0001/0.5 (0.36-0.71)**	4.1	2.7	0.12	12.0	4.8	**0.0001/0.4 (0.3-0.6)**	0.06
I-ST5-IV[e] INV	14.2(42)	6.9(25)	**0.0020/0.4 (0.27-0.75)**	7.4(14)	6.2(15)	**0.76**	25.9(28)	8.3(10)	**0.0003/0.3 (0.12-0.55)**	0.46
	2.8	1.8	0.08	1.5	1.7	0.84	5.4	2.1	**0.0079/0.4 (0.19-0.79)**	0.62
A-ST5-I[e] Total	10.3(61)	3.6(24)	**<0.0001/0.3 (0.20-0.52)**	15.8(58)	4.8(20)	**<0.0001/0.3 (0.16-0.47)**	1.3(3)	1.6(4)	0.91	0.06
	4.1	1.8	**0.0003/0.4 (0.27-0.69)**	6.0	2.3	**0.0001/0.4 (0.23-0.62)**	0.6	0.83	0.62	0.06
A-ST5-I[e] INV	15.9(47)	5.2(19)	**<0.0001/0.3 (0.17-0.51)**	23.4(44)	6.6(16)	**<0.0001/0.2 (0.13-0.42)**	2.8(3)	2.5(3)	0.78	0.10
	3.2	1.4	**0.0020/0.4 (0.26-0.75)**	4.6	1.8	**0.0113/0.4 (0.23-0.70)**	0.6	0.6	0.92	0.08
C-ST100-IVNv[e], Total	3.6(21)	2.2(15)	0.18	3.6(13)	2.6(11)	0.18	3.6(8)	1.6(4)	0.27	0.56
	1.4	1.1	0.46	1.3	1.2	0.84	1.5	0.8	0.39	0.48
C-ST100-IVNv[e], INV	5.7(17)	3.6(13)	0.09	4.8(9)	4.1(10)	0.90	7.4(8)	2.5(3)	0.15	0.63
	1.1	0.96	0.58	0.9	1.1	0.85	1.5	0.6	0.17	0.41
USA300-ST8-IV[e] Total	0.8(5)	2.7(18)	**0.0145/3.3 (1.24-8.46)**	1.1(4)	2.9(12)	0.08	0.4(1)	2.4(6)	0.13	0.71
	0.3	1.3	**0.0035/3.9 (1.52-10.18)**	0.4	1.4	**0.0294/3.3 (1.12-9.62)**	0.2	1.2	0.06	0.86
USA300-ST8-IV[e] INV	1.0(3)	1.3(9)	0.12	1.6(3)	2.9(7)	0.38	0(0)	1.7(2)	NA	0.47
	0.2	0.7	0.06	0.3	0.8	0.16	0	0.4	NA	0.41
DD-ST97-IV[e] Total	0.7(4)	1.8(12)	0.08	0.8(3)	1.7(7)	0.29	0.4(1)	2.0(5)	0.13	0.77
	0.3	0.9	**0.0295/3.3 (1.11-9.62)**	0.3	0.8	0.16	0.2	1.0	0.11	0.76
DD-ST97-IV[e] INV	1.0(3)	1.5(10)	0.08	1.1(2)	2.1(5)	0.42	0.9(1)	4.1(5)	0.21	0.31
	0.2	0.7	**0.035/3.6 (1.10-12.20)**	0.2	0.6	0.21	0.2	1.0	0.11	0.51

CA-MRSA$_G$ and HA-MRSA$_G$ community-associated and healthcare-associated methicillin-resistant *S. aureus* genotypes.

% (n) of cases and % (n) of INV isolates, NA: Not applicable.

[a]**N**: Total number of patients with *S. aureus* infections in each category (total, adults, pediatrics).

[b]INV: Total number of patients with *S. aureus* invasive infections in each category (total, adults, pediatrics).
[c]In: Incidence: Number of cases /100.000 monthly visits. Number of visits (V): include outpatient facility, emergency service and admissions during that month.
[d]InI: Invasive infections incidence: Number of cases of invasive infections/100.000 monthly visits. Number of visits (V): include outpatient facility, emergency service and admissions during that month.
[e]Genotypes (major clones) are denoted as: type (by PFGE)-Sequence Type (ST by MLST)-SCC*mec* type
P values ≤ 0.05 for all comparisons are shown in boldface font.

Table 3: Percentage and incidence of total (TI) and invasive (INVI) infections caused by *S. aureus* (SA), including MSSA, MRSA and MRSA-genotypes in Argentine hospitals, by onset type and epidemiological criteria: 2009 vs. 2015, with comparisons in 2015 between infection types and MRSA vs. MSSA for TI and INVI.

	***S. aureus* infections** % (n) / incidence of total cases and % (INV) / incidence of invasive cases														
	Hospital onset (HO) (HAHO)			**Community onset (CO)** (CACO + HACO)			2015	**Community-associated-community-onset** (CACO)			**Healthcare-associated community-onset** (HACO)			2015	
	2009 N[a]: 216 INV[b]:158 %(n)/ In[c] %(INV)/InI[d]	2015 N[a]: 197 INV[b]:158 %(n)/In[c] %(INV)/InI[d]	*2015 vs. 2009* *P* value/ OR (95%CI)	2009 N[a]: 375 INV[b]:138 %(n)/ In[c]/ %(INV)/InI[d]	2015 N[a]: 471 INV[b]: 205 %(n)/In[c] %(INV)/InI[d]	*2015 vs. 2009* *P* value/ OR (95%CI)	***CO vs. HAHO*** *P* value/OR (95%CI)	2009 N[a]: 222 INV[b]:58 %(n)/ In[c]/ %(INV)/InI[d]	2015 N[a]: 253 INV[b]: 79 %(n)/In[c] %(INV)/InI[d]	*2015 vs. 2009* *P* value/ OR (95%CI)	2009 N[a]: 153 INV[b]:80 %(n)/ In[c]/ %(INV)/InI[d]	2015 N[a]: 218 INV[b]: 126 %(n)/In[c] %(INV)/InI[d]	*2015 vs. 2009* *P* value/ OR (95%CI)	***HACO vs. CACO*** *P* value/OR (95%CI)	***HACO vs. HAHO*** *P* value/OR (95%CI)
SA Total	100(216)	100(197)		100(375)	100(471)			100(222)	100(253)		100(153)	100(218)			
	14.6	14.5	0.54	25.2	34.6	**<0.0001/1.4 (1.21-1.63)**	**<0.0001/2.4 (2.03-2.82)**	15.0	18.6	**0.0175/1.2 (1.04-1.49)**	10.3	16.0	**<0.0001/1.6 (1.27-1.91)**	0.10	0.30
SA INV	100(158)	100(158)		100(138)	100(205)			100(58)	100(79)		100(80)	100(126)			
	10.6	11.6	0.77	9.3	15.1	**<0.0001/1.6 (1.31-2.01)**	**0.0136/1.3 (1.05-1.60)**	3.9	5.8	**0.0210/1.5 (1.06-2.08)**	5.4	9.2	**<0.0001/1.7 (1.30-2.27)**	**0.0010/1.6 (1.59-1.20)**	0.06
MSSA Total	50.9(110)	48.2(95)	0.65	42.4(159)	49.3(232)	0.053	**086**	38.7(86)	45.8(116)	0.14	47.7(73)	53.2(116)	0.35	0.13	0.31
	7.5	7.0	0.41	10.7	17.1	**<0.0001/1.6 (1.31-1.98)**	**<0.0001/2.4 (1.92-3.10)**	5.8	8.5	**0.0063/1.5 (1.11-1.94)**	4.9	8.5	**0.0002/1.7 (1.30-2.32)**	0.99	0.15
MSSA INV	48.7(77)	51.2(82)	0.57	47.8(66)	58.0(119)	0.062	**024**	41.4(24)	59.5(47)	**0.0360/2.1 (1.05-4.12)**	52.5(42)	57.1(72)	0.57	**0.73**	0.46
	5.2	6.0	0.54	4.4	8.7	**<0.0001/1.9 (1.46-2.66)**	**0.0091/1.5 (1.10-1.92)**	1.6	3.5	**0.0019/2.1 (1.31-3.48)**	2.8	5.3	**<0.0010/1.9 (1.28-2.73)**	**0.0201/1.53 (1.06-2.21)**	0.42
MRSA Total	49.1(106)	51.8(102)	0.65	57.6(216)	50.8(239)	0.053	0.8075	61.3(136)	54.2(137)	0.11	52.3(80)	46.8(102)	0.35	0.13	0.31
	7.1	7.5	0.96	14.6	17.6	**0.044/1.2 (1.01-1.45)**	**<0.0001/2.3 (1.86-2.95)**	9.2	10.1	0.43	5.4	7.5	**0.0263/1.4 (1.04-1.86)**	**0.0236/0.7 (0.58-0.96)**	>0.99
MRSA INV	51.3(81)	48.1(76)	0.57	52.2(72)	42.0(86)	0.062	0.24	58.6(34)	40.5(32)	**0.0360/0.5 (0.24-0.95)**	47.5(38)	42.9(54)	0.57	0.73	0.46
	5.5	5.6	0.54	4.9	6.3	0.09	0.43	2.3	2.4	0.98	2.6	3.9	**0.0367/1.6 (1.03-2.34)**	**0.0177/1.70 1.09-2.61)**	0.06
In: MSSA vs. MRSA *P* value/ OR (95%CI)	0.79	0.62		**0.0032/0.74 (0.60-0.90)**	0.75			**0.0008/0.6 (0.48-0.83)**	0.19		057	0.34			
InI: MSSA vs. MRSA *P* value/ OR (95%CI)	0.75	0.63		0.61	**0.021/1.38 (1.05-1.82)**			019	0.09		0.65	0.11			
CA-MRSA$_G$ Total	15.7(34)	38.6(76)	**<0.0001/3.4 (2.1-5.3)**	52.0(195)	48.0(226)	0.27	**0.026/1.5 (1.05-2.06)**	60.8(135)	53.8(136)	0.14	39.2(60)	41.3(90)	0.77	**0.007/0.6 (0.42-0.87)**	0.57
	2.3	5.6	**<0.0001/2.4 (1.63-3.65)**	13.1	16.6	**0.0161/1.3 (1.04-1.53)**	**<0.0001/3.0 (2.3-3.9)**	9.1	10.0	0.43	4.0	6.6	**0.0028/1.6 (1.18-2.27)**	**0.0022/0.7 (0.51-0.86)**	0.28
CA-MRSA$_G$ INV	14.5(23)	34.2(54)	**<0.0001/2.3 (1.8-5.3)**	39.8(55)	37.1(76)	0.60	0.56	58.6(34)	39.2(31)	**0.0248/0.5 (0.23-0.90)**	26.3(21)	35.7(45)	0.15	0.61	0.79
	1.5	3.9	**0.0001/2.6 (1.58-4.16)**	3.7	5.6	**0.0194/1.5 (1.07-2.13)**	0.054	2.3	2.3	0.98	1.4	3.3	**0.0009/2.3 (1.40-3.91)**	0.11	0.37
HA-MRSA$_G$ Total	33.3(72)	13.2(26)	**<0.0001/0.3 (0.2-0.5)**	5.6 (21)	2.8(13)	0.06	**<0.0001/0.19 0.09-0.37)**	0.5(1)	0.4(1)	0.59	13.1 (20)	5.5(12)	0.0174/**0.4 (0.19-0.81)**	**0.0007/14.68 2.67-80.64)**	**0.0067/0.4 (0.19-0.77)**
	4.9	1.9	**<0.0001/0.4 (0.25-0.61)**	1.4	1.0	0.26	**0.037/0.50 (0.26-0.96)**	0.1	0.07	0.95	1.3	0.9	0.25	**0.0023/12.0 2.21-65.27)**	**0.0231/0.5 (0.24-0.90)**
HA-MRSA$_G$ INV	36.7(58)	13.9(22)	**<0.0001/0.3 (0.2-0.5)**	12.3 (17)	4.5(10)	**0.0121/0.4 (0.2-0.8)**	**0.002/0.3 (0.15-0.68)**	0 (0)	1.2(1)	NA	21.3 (17)	7.1(9)	**0.0030/0.3 (0.12-0.66)**	0.06	0.07
	3.9	1.6	**0.0001/0.4 (0.25-0.67)**	1.1	0.7	0.26	**0.033/0.50 0.22-0.95)**	0	0.07	NA	1.1	0.7	0.17	**0.0114/9.0 1.61-50.36)**	**0165/0.4 (0.19-0.87)**
N-ST30-IV[e] Total	1.9(4)	20.3(40)	**<0.0001/13.5 (4.9-36.5)**	26.7(100)	33.5(172)	**0.0023/1.6 (1.2-2.3)**	**<0.0001/2.3 (1.52-3.34)**	36.5(81)	42.3(107)	0.23	11.8(18)	29.8(65)	**<0.0001/3.2 (1.81-5.61)**	**0.0005/0.6 (0.40-0.85)**	**0.0260/1.7 (1.06-2.62)**
	0.3	2.9	**<0.0001/10.9 (4.12-28.90)**	6.7	12.6	**<0.0001/1.9 (1.5-2.4)**	**<0.0001/4.3 3.1-6.1)**	5.5	7.9	**0.0125/1.4 (1.08-1.92)**	1.2	4.8	**<0.0001/3.9 (2.35-6.60)**	**0.0014/0.61 0.45-0.83)**	**0.0147/1.6 1.10-2.40)**
N-ST30-IV[e] INV	1.3(2)	13.3(21)	**<0.0001/12.0 (3.2-45.2)**	15.2(21)	27.3(56)	**0.0084/2.1 (1.2-3.6)**	**0.0012/2.5 1.42-4.24)**	27.6(16)	32.9(26)	0.50	6.3(5)	23.8(30)	**0.00811/4.7 (1.80-12.20)**	0.09	**0.0218/2.0 1.11-3.75)**
	0.1	1.5	**<0.0001/11.9 (3.09-42.5)**	1.4	4.1	**<0.0001/2.9 (1.77-4.78)**	**0.0001/2.7 1.62-4.38)**	1.1	1.9	0.06	0.3	2.2	**<0.0001/6.6 (2.64-16.24)**	0.59	0.21
I-ST5-IV[e] Total	9.7(21)	8.6(17)	0.38	21.6(81)	6.4(30)	**<0.0001/0.25 (0.2-0.4)**	0.40	21.6(48)	6.3(16)	**<0.0001/0.2 (0.14-0.44)**	22.2(34)	6.4(14)	**<0.0001/0.24 (0.12-0.46)**	0.88	0.51
	1.4	1.2	0.58	5.5	2.2	**<0.0001/0.4 (0.3-0.6)**	0.06	3.2	1.2	**0.0003/0.4 (0.21-0.64)**	2.3	1.0	**0.0097/0.45 (0.24-0.83)**	0.71	0.59
I-ST5-IV[e] INV	9.5(15)	9.5(15)	>0.99	19.6(27)	4.9(10)	**<0.0001/0.2 (0.1-0.5)**	0.085	25.9(15)	2.5(2)	**<0.0001/0.07 (0.02-0.30)**	15.0(12)	6.3(8)	**0.0410/0.38 (0.15-0.96)**	0.21	0.33
	1.0	1.1	0.92	1.8	0.7	**0.0114/0.4 (0.20-0.82)**	0.31	1.0	0.15	**<0.0029/0.15 (0.04-0.55)**	0.8	0.6	**0.48**	0.06	0.14
A-ST5-I[e] Total	23.6(51)	9.1(18)	**<0.0001/0.3 (0.2-0.5)**	2.7(10)	1.3(6)	0.22	**<0.0001/0.13 0.05-0.32)**	0(0)	0(0)	NA	6.5(10)	2.8(6)	**0.14**	**ND**	**0.0054/0.3 0.11-0.70)**
	3.4	1.3	**0.0003/0.4 (0.23-0.66)**	0.67	0.44	0.44	**0.0143/0.33 0.14-0.81)**	0	0	NA	0.7	0.4	0.41	**ND**	**0.0143/0.3 0.14-0.81)**
A-ST5-I[e] INV	25.3(40)	9.5(15)	**0.0002/0.3 (0.2-0.6)**	5.0(7)	1.9(4)	0.11	**0.0014/0.19 0.06-0.55)**	0(0)	0(0)	NA	8.8(7)	3.2(4)	0.08	**ND**	**0.0342/0.3 0.11-0.92)**
	2.7	1.1	**0.0023/0.23 (0.23-0.73)**	0.5	0.3	0.39	**0.0116/0.3 0.09-0.76)**	0	0	NA	0.5	0.3	0.44	**ND**	**0.0116/0.3 0.09-0.76)**
C-ST100-IVNv[e] Total	6.0(13)	4.0(8)	0.48	2.1(8)	1.5(7)	0.15	**0.08**	0.5(1)	0.4(1)	0.59	4.6(7)	2.8(6)	0.52	0.08	0.69
	0.9	0.6	0.30	0.5	0.5	0.92	0.81	0.1	0.07	0.95	0.5	0.4	0.90	0.06	0.59
C-ST100-IVNv[e] INV	6.3(10)	4.4(7)	0.45	5.0(7)	2.9(6)	0.31	0.44	0(0)	1.2(1)	ND	8.8(7)	3.9(5)	015	0.26	0.69
	0.7	0.5	0.50	0.5	0.4	0.85	0.78	0	0.07	ND	0.5	0.4	0.67	0.1	0.56
USA300-ST8-IV[e] Total	0.5(1)	3.6(7)	**0.0228/7.9 (1.36-46.22)**	1.9(4)	4.6(11)	0.10	0.36	1.3(3)	2.8(7)	0.34	0.7(1)	1.8(4)	0.65	0.50	0.26
	0.07	0.5	**0.0246/7.6 (1.32-44.10)**	0.3	0.8	**0.048/3.0 (1.01-8.92)**	0.36	0.2	0.5	0.16	0.07	0.3	0.15	0.37	0.37
USA300-ST8-IV[e] INV	0.6(1)	3.8(6)	0.06	1.5(2)	1.5(3)	0.95	0.96	1.7(1)	1.3(1)	0.59	1.3(1)	1.6(2)	0.83	0.48	0.32
	0.07	0.4	**0.045/6.6 (1.11-38.65)**	0.1	0.2	0.58	0.32	0.07	0.07	0.95	0.07	0.2	0.41	0.57	0.1573
DD-ST97-IV[e] Total	0.0(0)	4.1(8)	NA	1.9(4)	1.7(4)	0.88	**0.0044/0.2 0.06-0.64)**	0.9(2)	1.2(3)	0.78	1.3(2)	0.5(1)	0.80	0.39	**0.0119/0.1 0.02-0.62)**
	0.0	0.6	NA	0.3	0.3	0.98	0.25	0.1	0.2	0.58	0.13	0.07	0.61	0.32	**0.0230/0.1 0.02-0.74)**
DD-ST97-IV[e] INV	0.0(0)	5.1(8)	NA	2.2(3)	1.0(2)	0.65	**0.0183/0.2 0.04-0.77)**	3.4(2)	1.3(1)	0.81	1.3(1)	0.8(1)	0.68	0.91	**0.0413/0.2 0.03-0.86)**
	0.0	0.6	NA	0.2	0.1	0.53	0.06	0.1	0.07	0.42	0.07	0.07	0.98	0.99	**0.0230/0.1 0.02-0.74)**

$CA\text{-}MRSA_G$ and $HA\text{-}MRSA_G$ community-associated and healthcare-associated methicillin-resistant *S. aureus* genotypes.
% (n) of cases and % (n) of INV isolates, NA: Not applicable.
[a]N*:* Total number of patients with *S. aureus* infections in each category [healthcare onset (HO or HAHO), community onset (CO: including CACO + HACO), community-associated community-onset infections (CACO) and healthcare-associated community-onset (HACO)].
[b]INV*:* Total number of patients with *S. aureus* invasive infections in each category.
[c]In: Incidence: Number of cases /100,000 monthly visits. Number of visits (V): include outpatient facility, emergency service and admissions during that month.
[d]InI: Invasive infections Incidence: Number of cases of invasive infections/100.000 monthly visits. Number of visits (V): include outpatient facility, emergency service and admissions during that month.
[e]Genotypes (major clones) are denoted as: type (by PFGE)-Sequence Type (ST by MLST)-SCC*mec* type.
P values ≤ 0.05 for all comparisons are shown in boldface font.

Table 4: Percentage and incidence of total (TI) and invasive (INVI) infections caused by *S. aureus* (SA), including MSSA, MRSA and MRSA-genotypes in Argentine hospitals, by age group, onset type and epidemiological criteria: 2009 vs. 2015, with comparisons in 2015 between infection types, pediatric vs. adult patients and MRSA vs. MSSA for TI and INVI.

	***S. aureus* infections in pediatric** (<19)**and adult** (≥19) **patients** % (n) / incidence of general cases and % (INV) / incidence of invasive cases																
	Community onset (CO) (CACO + HACO)							**Hospital onset (HO)** (HAHO)							2015		
	Adults			Pediatrics			2015	Adults			Pediatrics			2015	Adults	Pediatrics
	2009 Nª: 215/ INVᵇ:75 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 301/ INVᵇ:141 %(n)/ Inᶜ/ %(INV)/InIᵈ	*2015 vs. 2009* *P* value/OR (95%CI)	2009 Nª: 160/ INVᵇ: 63 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 170/ INVᵇ: 64 %(n)/ Inᶜ/ %(INV)/InIᵈ	*2015 vs. 2009* *P* value/OR (95%CI)	Pediatric vs. Adults *P* value/OR (95%CI)	2009 Nª: 151/ INVᵇ:113 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 116/ INVᵇ:101 %(n)/ Inᶜ/ %(INV)/InIᵈ	*2015 vs. 2009* *P* value/OR (95%CI)	2009 Nª: 65/ INVᵇ:45 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 81/ INVᵇ:57 %(n)/ Inᶜ/ %(INV)/InIᵈ	*2015 vs. 2009* *P* value/OR (95%CI)	Pediatric vs. Adults *P* value/OR (95%CI)	***CO vs. HO*** *P* value/OR (95%CI)	***CO vs. HO*** *P* value/OR (95%CI)
SA Total	100(215)	100(301)		100(160)	100(170)			100(151)	100(116)		100(65)	100(81)				
	22.4	34.2	**<0.0001/1.5 (1.28-1.82)**	30.6	35.4	0.18	0.72	15.7	13.2	0.15	12.4	16.9	0.07	0.08	**<0.0001/2.6 (2.10-3.20)**	**<0.0001/2.1 (1.61-2.73)**
SA INV	100(75)	100(141)		100(63)	100(64)			100(113)	100(101)		100(45)	100(57)				
	7.8	16.0	**<0.0001/2.1 (1.55-2.72)**	12.0	13.3	0.56	0.22	11.8	11.5	086	8.6	11.9	0.10	0.83	**0.0101/1.4 (1.08-1.80)**	0.53
MSSA Total	45.6(98)	55.1(166)	**0.0321/1.5 (1.03-2.09)**	38.1(61)	38.8(66)	0.97	**0.0007/0.52 (0.35-0.76)**	48.3(73)	50.0(58)	0.86	56.9(37)	45.7(37)	0.23	0.65	0.4086	0.37
	10.2	18.8	**<0.0001/1.9 (1.44-2.37)**	11.7	13.8	0.35	**0.0293/0.73 (0.55-0.97)**	7.6	6.6	0.18	7.1	7.7	0.73	0.51	**<0.0001/2.9 (2.12-3.86)**	**0.0043/1.9 (1.20-2.66)**
MSSA INV	56.0(42)	61.0(86)	0.57	38.1(24)	51.6(33)	0.17	0.27	46.9(53)	51.5(52)	0.59	53.3(24)	52.6(30)	0.89	0.89	0.1801	0.94
	4.4	9.8	**<0.0001/2.2 (1.55-3.23)**	4.6	6.9	0.45	0.08	5.5	5.9	0.62	4.6	6.2	0.25		**0.0038/1.7 (1.17-2.33)**	0.71
MRSA Total	54.4(117)	44.9(135)	**0.0321/0.68 (0.48-0.97)**	61.9(99)	61.2(104)	0.97	**0.0007/1.9 (1.32-2.84)**	51.7(78)	50.0(58)	0.86	43.1(28)	54.3(44)	0.23	0.66	0.41	0.34
	12.2	15.3	0.07	18.9	21.7	0.33	**0.0078/1.4 (1.09-1.82)**	8.1	6.6	0.22	5.4	9.2	**0.0243/1.7 (1.07-2.74)**	0.09	**<0.0001/2.3 (1.71-3.16)**	**<0.0001/2.4 (1.66-3.36)**
MRSA INV	44.0(33)	39.0(55)	0.57	61.9(39)	48.4(31)	0.17	0.27	53.1(60)	48.5(49)	0.59	46.7(21)	47.4(27)	0.88	0.89	0.18	0.86
	3.4	6.2	**0.0058/1.8 (1.19-2.80)**	7.4	6.5	0.45	0.88	6.2	5.6	0.56	6.2	5.2	0.24	0.81	0.56	0.60
In: MSSA vs. MRSA *P* value/ OR (95%CI)	0.1950	0.07		**0.0027/0.62 (0.45-0.85))**	**0.0036/0.63 (0.47-0.86)**			0.68	0.99		0.26	0.44				
InI: MSSA vs. MRSA *P* value/ OR (95%CI)	0.2988	**0.009/1.60 (1.12-2.19)**		0.06	0.80			0.51	0.77		0.65	0.69				
CA-MRSA$_G$ Total	47.0(101)	40.9(123)	0.19	58.8(94)	60.6(103)	0.79	**<0.0001/2.2 1.52-3.26)**	8.6(13)	33.6(39)	**<0.0001/5.4 (2.7-10.6)**	32.3(21)	45.7(37)	0.13	0.09	0.21	0.0262/**1.8 (1.07-3.11)**
	10.5	13.9	**0.0312/1.3 (1.02-1.73)**	17.9	21.5	0.21	**0.0012/1.5 (1.18-1.99)**	1.4	4.4	**0.0001/3.3 (1.77-6.08)**	4.0	7.7	**0.0151/1.9 (1.13-3.26)**	**0.0145/1.7 (1.11-2.72)**	**<0.0001/3.2 (2.20-4.51)**	**<0.0001/2.9 (1.92-4.05)**
CA-MRSA$_G$ INV	28.0(21)	31.9(45)	0.66	54.0(34)	48.4(31)	0.65	0.0232/**2.0 (1.10-3.65)**	8.0(9)	32.7(33)	**<0.0001/5.6 (2.56-12.26)**	31.1(14)	36.8(21)	0.69	0.56	0.94	0.27
	2.2	5.1	**0.0009/2.3 (1.40-3.91)**	6.5	6.5	0.99	0.31	0.9	3.7	**<0.0001/4.0 (1.95-8.23)**	2.7	4.4	0.15	0.56	0.17	0.17
HA-MRSA$_G$ Total	7.4 (16)	4.0(12)	0.19	3.1(5)	0.6(1)	0.21	0.0306/**0.14 (0.03-0.78)**	43.0 (65)	16.4(19)	**<0.0001/0.3 (0.14-0.46)**	10.8 (7)	8.6(7)	0.84	0.11	<0.0001/**0.2 (0.10-0.45)**	0.0009/**0.1 (0.01-0.32**
	1.7	1.4	0.66	1.0	0.2	0.26	0.0421/**0.15 (0.03-0.81)**	6.8	2.2	**<0.0001/0.3 (0.19-0.53)**	1.3	1.5	0.88	0.37	0.21	0.0339/**0.1 (0.02-0.82)**
HA-MRSA$_G$ INV	16.0 (12)	7.1(10)	0.07	7.9(5)	0(0)	NA	NA	45.1 (51)	15.8(16)	**<0.0001/0.2 (0.12-0.44)**	15.6 (7)	10.5(6)	0.69	0.35	0.06	NA
	1.2	1.1	0.85	1.0	0	NA	NA	5.3	1.8	**0.0001/0.3 (0.20-0.60)**	1.3	1.3	0.99	0.43	0.24	NA
N-ST30-IV^e Total	27.9(60)	30.6(92)	0.51	25.0(40)	47.1(80)	**<0.0001/2.7 (1.67-4.25)**	**0.0004/2.0 (1.37-2.97)**	2.6(4)	12.9(15)	**0.0012/5.5 (1.9-16.1)**	0(0)	30.9(25)	NA	**0.0007/3.3 (1.63-6.70)**	**0.0002/3.0 (1.65-5.34)**	**0.0150/2.0 (1.14-3.47)**
	6.2	10.4	**<0.0017/1.7 (1.21-2.32)**	7.6	16.7	**<0.0001/2.2 (1.49-3.18)**	**0.0021/1.6 (0.47-0.85)**	0.4	1.7	**0.0066/4.1 (1.43-11.70)**	0(0)	5.2	NA	**0.0003/3.1 (1.63-5.75)**	**<0.0001/6.1 (3.58-10.50)**	**<0.0001/3.2 (2.05-5.00)**
N-ST30-IV^e INV	10.7(8)	23.4(33)	**0.023/2.6 (1.14-5.76)**	20.6(13)	35.9(23)	0.086	0.09	1.8(2)	9.9(10)	**0.0145/6.1 (1.49-24.90)**	0(0)	19.3(11)	NA	0.09	**0.0067/2.8 (1.32-5.87)**	0.0679
	0.83	3.7	**<0.0001/4.5 (2.12-9.56)**	2.5	4.8	0.054	0.36	0.2	1.1	**0.0137/5.5 (1.37-21.69)**	0(0)	2.3	NA	0.10	**0.0005/3.3 (1.65-6.60)**	**0.0396/2.1 (1.03-4.23)**
I-ST5-IV^e Total	14.4(31)	5.0(15)	**0.0002/0.3 (0.16-0.59)**	31.3(50)	8.8(15)	**<0.0001/0.2 (0.11-0.40)**	0.15	5.3(8)	7.8(9)	0.56	20.0(13)	9.9(8)	0.083	0.79	0.39	0.98
	3.2	1.7	**0.0321/0.53 (0.29-0.97)**	9.6	3.1	**0.0001/0.3 (0.19-0.58)**	0.09	0.8	1.0	0.85	2.5	1.7	0.36	0.31	0.22	0.14
I-ST5-IV^e INV	10.7(8)	4.3(6)	0.12	30.2(19)	6.3(4)	**0.0005/0.2 (0.05-0.46)**	0.79	5.3(6)	8.9(9)	044	20.0(9)	10.5(6)	0.28	0.92	0.23	0.61
	0.83	0.7	0.71	3.6	0.8	**0.0035/0.23 (0.08-0.64)**	0.85	0.6	1.0	0.34	1.7	1.3	0.35	0.70	0.45	0.52
A-ST5-I^e Total	4.7(10)	2.0(6)	0.12	0(0)	0(0)		NA	31.8(48)	12.1(14)	**<0.0001/0.09 (0.04-0.17)**	2.8(3)	2(4)	0.95	0.14	<0.0001/**0.2 (0.06-0.38**	NA
	1.0	0.7	0.42	0	0		NA	5.0	1.6	**<0.0001/0.3 (0.18-0.57)**	0.6	0.8	0.62	0.32	0.08	NA
A-ST5-I^e INV	9.3(7)	2.8(4)	0.08	0(0)	0(0)		NA	32.7(37)	11.9(12)	**0.0004/0.29 (0.14-0.58)**	6.7(3)	5.3(3)	0.89	0.26	0.0177/**0.3 (0.09-0.81)**	NA
	0.7	0.5	0.44	0	0		NA	3.8	1.4	**0.0011/0.3 (0.19-0.67)**	0.6	0.6	099	0.21	**0.0455/0.3 (0.11-0.98)**	NA
C-ST100-IVNv^e Total	2.8(6)	2.0(6)	0.23	2.5(4)	0.6(1)	0.20	0.45	6.0 (9)	4.3(5)	0.54	6.2(4)	3.7(3)	0.49	0.87	0.33	0.19
	0.6	0.5	0.62	0.7	0.2	0.37	0.21	0.9	0.6	0.35	0.7	0.6	0.78	0.71	0.74	0.31
C-ST100-IVNv^e INV	4.0(3)	4.3(6)	0.88	6.3(4)	0(0)	NA	NA	5.3 (6)	4.0(4)	0.89	8.9(4)	5.3(3)	0.74	0.89	0.89	NA
	0.3	0.7	0.25	0.8	0	NA	NA	0.6	0.5	0.85	0.8	0.6	0.79	0.86	0.53	NA
	Healthcare -associated-community-onset (HACO)							**Community-associated-community-onset (CACO)**							2015	
	Adult			Pediatric			2015	Adult			Pediatric			2015	Adult	Pediatric
	2009 Nª: 93/ INVᵇ:46 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 147/ INVᵇ:94 %(n)/ Inᶜ/ %(INV)/InIᵈ	*2015 vs. 2009* *P* value/ OR (95%CI)	2009 Nª: 60/ INVᵇ:34 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 71/ INVᵇ:32 %(n)/ Inᶜ/ %(INV)/InIᵈ	*2015 vs. 2009* *P* value/ OR (95%CI)	Pediatric vs. Adults *P* value/ OR (95%CI)	2009 Nª: 122/ INVᵇ:29 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 154 INVᵇ: 47 %(n)/Inᶜ %(INV)/InIᵈ	*2015 vs. 2009* *P* value/ OR (95%CI)	2009 Nª: 100/ INVᵇ:29 %(n)/ Inᶜ/ %(INV)/InIᵈ	2015 Nª: 99 INVᵇ: 32 %(n)/Inᶜ %(INV)/InIᵈ ᶠ	*2015 vs. 2009* *P* value/ OR (95%CI)	Pediatric vs. Adults *P* value/ OR (95%CI)	***HACO vs. CACO*** *P* value/OR (95%CI)	***HACO vs. CACO*** *P* value/OR (95%CI)
SA Total	100(93)	100(147)		100(60)	100(71)			100(122)	100(154)		100(100)	100(99)				
	9.7	16.7	**<0.0001/1.7 (1.33-2.24)**	11.5	14.8	0.15	0.40	12.7	17.5	**0.0078/1.4 (1.09-1.75)**	19.2	20.6	0.5920	0.20	0.69	**0.0317/0.7/ (0.53-0.97)**
SA INV	100(46)	100(94)		100(34)	100(32)			100(29)	100(47)		100(29)	100(32)				
	4.8	10.7	**<0.0001/2.2 (1.57-3.17)**	6.5	6.7	0.92	**0.0011/0.6 (0.42-0.93)**	3.0	5.3	**0.0142/1.8 (1.12-2.80)**	5.5	6.7	0.4712	00.33	**0.0001/2.0 (1.41-2.83)**	>0.99
MSSA	47.3(44)	58.5(86)	0.12	48.3(29)	42.3(30)	0.49	**0.0242/0.5 (0.29-0.92)**	44.3(54)	51.9(80)	0.26	32.0(32)	36.4(36)	0.6137	**0.0152/0.53 (0.32-0.88)**	0.30	0.43

Total	4.6	9.8	**<0.0001/1.5 (1.49-3.06)**	5.5	6.3	0.65	**0.0337/0.6 (0.42-0.97)**	5.6	9.1	**0.0058/1.6 (1.15-2.28)**	6.1	7.5	00.5561	0.39	0.64	0.46
MSSA INV	50.0(23)	59.6(56)	0.37	55.9(19)	50.0(16)	0.63	0.34	65.5(19)	63.8(30)	0.92	17.3(5)	53.1(17)	**0.0036/5.44 (1.72-17.18)**	0.34	0.77	0.80
	2.4	6.4	**<0.0001/2.7 (1.64-4.30)**	3.6	3.3	0.56	**0.0204/0.5 (0.30-0.91)**	2.0	3.4	0.06	1.0	3.5	**0.0057/3.7 (1.42-9.66)**	0.89	**0.0051/1.9 (1.20-2.90)**	0.86
MRSA Total	52.7(49)	41.5(61)	0.12	51.7(31)	57.7(41)	0.49	**0.0242/1.9 (1.09-3.41)**	55.7(68)	48.1(74)	0.26	68.0(68)	63.6(63)	0.6137	**0.0152/1.9 (1.13-3.17)**	0.30	0.43
	5.1	6.9	0.11	5.9	8.5	0.12	0.29	7.1	8.4	0.30	13.0	13.1	0.9561	**0.0088/1.6 (1.12-2.18)**	0.26	**0.0310/0.7 (0.44-0.96)**
MRSA INV	50.0(23)	40.4(38)	0.37	44.1(15)	50.0(16)	0.63	0.34	34.5(10)	36.2(17)	0.956	82.7(24)	46.9(15)	**0.036/0.18 (0.06-0.58)**	0.34	0.7650	0.80
	2.4	4.3	**0.0234/1.8 (1.08-3.01)**	2.9	3.3	0.66	0.38	1.0	1.9	0.11	4.6	3.1	0.2404	0.17	**0.0046/2.2 (1.27-3.93)**	0.86
In: MSSA vs MRSA *P* value/ OR (95%CI)	0.6041	**0.039/1.40 (1.02-1.96)**		0.79	0.19			0.21	0.63		**0.0003/0.47 (0.31-0.71)**	**0.0067/0.57 (0.38-0.86)**				
InI: MSSA vs MRSA *P* value/ OR (95%CI)	0.9999	0.063		0.49	0.99			0.09	0.06		**0.0004/0.21(0.08-0.53)**	0.72				
CA-MRSA$_G$ Total	36.6(34)	34.0(50)	0.79	43.3(26)	56.3(40)	0.14	**0.0017/2.5 (1.41-4.45)**	54.9(67)	47.4(73)	0.63	68.0(68)	63.6(63)	0.6137	**0.0115/1.9 (1.16-3.25)**	**0.0182/0.6 (0.36-0.91)**	0.34
	3.5	5.7	**0.0314/1.6 (1.04-2.48)**	4.0	8.3	0.0380/1.7 (1.03-2.74)	0.07	7.0	8.3	0.31	13.0	13.1	5.0	**0.0082/1.6 (1.13-2.21)**	**0.0381/0.7 (0.48-0.98)**	**0.0234/0.6 (0.43-0.94)**
CA-MRSA$_G$ INV	23.9(11)	30.9(29)	0.51	29.4(10)	50.0(16)	0.09	0.06	34.5(10)	34.0(16)	0.97	82.7(24)	46.9(15)	**0.036/0.18 (0.06-0.58)**	0.25	0.86	0.80
	1.1	3.3	**0.0018/2.9 (1.46-5.69)**	1.9	3.3	0.16	0.96	1.0	1.8	0.16	4.6	3.1	0.2404	**0.0011/2.8 (1.47-5.14)**	0.05	0.86
HA-MRSA$_G$ Total	16.1(15)	7.5(11)	0.06	8.3 (5)	1.4(1)	0.09	0.12	0.9(1)	0.6(1)	0.67	0(0)	0(0)		NA	0.0025/12.4 **(2.22-68.91)**	NA
	1.6	1.2	0.57	1.0	0.2	0.13	0.24	0.1	0.1	0.99	0.0	0.0		NA	**0.0039/11.0 (2.01-60.30)**	NA
HA-MRSA$_G$ INV	26.1 (12)	9.6(9)	**0.0206/0.3 (1.12-0.76)**	14.7 (5)	0(0)	NA	NA	0(0)	2.1(1)	NA	0(0)	0(0)		NA	0.20	NA
	1.3	1.0	0.66	1.0	0.0	NA	NA	0.0	0.1	NA	0.0	0.0		NA	**0.0114/9.0 (1.61-50.36)**	NA
N-ST30-IV^e Total	12.9(12)	23.1(34)	0.07	10(6)	43.7(31)	**<0.0001/6.9 (2.73-17.81)**	**0.0019/2.6 (1.41-4.70)**	39.3(48)	37.7(58)	0.88	34.0(34)	49.5(49)	**0.0267/1.9 (1.08-3.36)**	0.09	**0.0062/0.5 (0.30-0.82)**	0.45
	1.2	3.8	**0.0004/3.1 (1.62-5.91)**	1.1	6.5	**0.0004/5.6 (2.42-13.10)**	**0.0363/1.7 (1.03-2.71)**	5.0	6.6	0.15	6.5	10.2	**0.0410/1.6 (1.02-2.4)**	**0.0022/1.6 (1.06-2.26)**	**0.0123/0.6 (0.38-0.89)**	**0.0442/0.6 (0.40-0.99)**
N-ST30-IV^e INV	6.5(3)	20.2(19)	**0.0366/3.6 (1.10-12.02)**	5.9(7)	34.4(11)	**0.0036/8.4 (1.92-35.53)**	0.10	17.2(5)	29.8(14)	0.33	37.9(11)	37.5(12)	0.9897	0.45	0.29	0.79
	0.3	2.2	**0.0003/6.9 (2.22-21.58)**	0.4	2.3	**0.0080/5.9 (1.53-23.54)**	0.88	0.5	1.6	**0.02342/3.06 (1.15-8.16)**	2.1	2.5	0.9561	0.25	0.38	0.83
I-ST5-IV^e Total	16.1(15)	4.8(7)	**0.0029/0.26 (0.10-0.65)**	30.0(18)	9.9(7)	**0.0035/0.26 (0.10-0.65)**	0.26	13.1(16)	5.2(8)	**0.0204/0.36 (0.15-0.86)**	32.0(32)	8.1(8)	**<0.0001/0.19 (0.08-0.42)**	0.57	0.91	0.69
	1.7	0.8	0.13	3.4	1.5	**0.0469/0.4 (0.18-0.99)**	0.25	1.7	0.9	**015**	6.1	1.7	**0.0004/0.27 (0.13-0.58)**	0.23	0.79	0.79
I-ST5-IV^e INV	10.9(5)	5.3(5)	0.39	20.6(7)	9.4(3)	0.20	0.41	10.3(3)	2.1(1)	0.30	41.4(12)	3.1(1)	**0.0003/0.05 (0.01-0.27)**	0.78	0.66	0.81
	0.5	0.6	0.85	1.4	0.6	0.26	0.87	0.3	0.1	0.36	2.3	0.2	**0.0037/0.09 (0.02-0.49)**	086	0.10	0.31
A-ST5-I^e Total	10.7(10)	4.1(6)	0.08	0(0)	0(0)			0(0)	0(0)		0(0)	0(0)			NA	
	1.0	0.7	0.41	0.0	0.0			0.0	0.0		0.0	0.0			NA	
A-ST5-I^e INV	15.2(7)	4.2(4)	0.05	0(0)	0(0)			0(0)	0(0)		0(0)	0(0)			NA	
	0.7	0.5	059	0.0	0.0			0.0	0.0		0.0	0.0			NA	
C-ST100-IVNv^e Total	3.2(3)	3.4(5)	0.78	6.7(4)	1.4(1)	0.50	0.69	0.8(1)	0.6(1)	0.60	0(0)	0(0)		NA	0.18	NA
	0.3	0.6	0.41	0.8	0.2	0.21	0.34	1.0	0.1	0.99	0.0	0.0		NA	0.10	NA
C-ST100-IVNv^e INV	6.5(3)	5.3(5)	0.99	11.7(4)	0(0)	NA	NA	0(0)	2.1(1)	NA	0(0)	0(0)		NA	0.66	NA
	0.3	0.6	0.41	0.8	0	NA	NA	0.0	0.1	NA	0.0	0.0		NA	0.10	NA

CA-MRSA$_G$ and HA-MRSA$_G$ community-associated and healthcare-associated methicillin-resistant *S. aureus* genotypes.

% (n) of cases and % (n) of INV isolates, NA: Not applicable

[a]N*:* Total number of pediatric patients with *S. aureus* infections in each category [healthcare onset (HO or HAHO), community onset (CO: including CACO + HACO), community-associated community-onset infections (CACO), healthcare-associated community-onset (HACO)].

[b]INV*:* Total number of patients with invasive *S. aureus* infections in each category .

[c]In: Incidence: Number of cases /100,000 monthly visits. Number of visits (V) include: outpatient facility, emergency service and admissions during that month.

[d]InI: Incidence of Invasive infections: Number of cases of invasive infections/100,000 monthly visits. Number of visits (V) include: outpatient facility, emergency service and admissions during that month.

[e]Genotypes (major clones) are denoted as: type (by PFGE)-Sequence Type (ST by MLST)-SCC*mec* type.

P values ≤ 0.05 for all comparisons are shown in boldface font.

Table 5: *Staphylococcus aureus* (SA) infections across hospitals from Argentine provinces and Buenos Aires city (2015): percentage and incidence by region, including MSSA, MRSA and MRSA genotypes; comparisons with 2009 data.

	***S. aureus* infections** % (n) / incidence of cases of infections											
	North			**Centre**			**South**			**2015**		
	2009 N[a]: 86 %(n)/ In[b]	2015 N[a]: 144 %(n)/ In[b]	*2009 vs. 2015 P* value/OR (95%CI)	2009 N[a]: 433 %(n)/ In[b]	2015 N[a]: 446 %(n)/ In[b]	*2009 vs. 2015 P* value/OR (95%CI)	2009 N[a]: 72 %(n)/ In[b]	2015 N[a]: 78 %(n)/ In[b]	*2009 vs. 2015 P* value/OR (95%CI)	*North vs Centre P* value/OR (95%CI)	*North vs South P* value/OR (95%CI)	*Centre vs South P* value/OR (95%CI)
SA	100(86)	100(144)		100(433)	100(446)		100(72)	100(78)				
	76.5	81.1	0.68	34.7	41.0	**0.0128/1.2 (1.04-1.35)**	58.0	81.4	**0.0370/1.4 (1.02-1.93)**	**<0.0001/2.0 (1.64-2.39)**	0.98	**<0.0001/0.50 (0.40-0.64)**
MSSA	18.6(16)	27.1(39)	0.21	46.7(202)	51.6(230)	0.19	70.8(51)	74.4(58)	0.78	**<0.0001/0.35 (0.23-0.53)**	**<0.0001/0.13 (0.07-0.24)**	**0.0002/0.37 (0.21-0.63)**
	14.2	21.9	0.14	16.2	21.2	**0.0053/1.3 (1.08-1.58)**	41.1	60.5	**0.041/1.5 (1.01-2.14)**	0.82	**<0.0001/0.36 (0.24-0.54)**	**<0.0001/0.35 (0.26-0.47)**
MRSA	81.4(70)	72.9(105)	0.21	53.3(231)	48.4(216)	0.19	29.2(21)	25.6(20)	0.78	**<0.0001/2.9 (1.90-4.32)**	**<0.0001/7.9 (4.19-14.54)**	**0.0002/2.7 (1.59-4.66)**
	62.2	59.1	0.73	18.5	19.9	0.45	16.9	20.8	0.50	**<0.0001/3.0 2.36-3.76)**	**<0.0001/2.8 (1.77-4.55)**	0.83
In: MSSA vs MRSA *P* value/ OR (95%CI)	**<0.0001/0.23 (0.13-0.39)**	**<0.0001/0.37 (0.26-0.54)**		0.1634	0.5073		**0.0004/2.4 (1.47-4.02)**	**<0.0001/2.9 (1.75-4.80)**				
CA-MRSA$_G$	72.1(62)	65.9(95)	0.42	36.0(156)	43.0(192)	**0.0330/1.3 (1.02-1.76)**	15.3(11)	19.2(15)	0.67	**<0.0001/2.6 1.73-3.79)**	**<0.0001/8.1 (4.24-15.64)**	**0.0001/3.1 (1.77-5.70)**
	55.1	53.5	0.85	12.5	17.7	**0.0130/1.4 (1.14-1.75)**	8.9	15.6	0.14	**<0.0001/3.0 2.37-3.87)**	**<0.0001/3.4 (2.00-5.85)**	0.65
HA-MRSA$_G$	9.3 (8)	6.9(10)	0.51	17.3 (75)	5.4(24)	**<0.0001/0.3 (0.17-0.44)**	13.9 (10)	6.4(5)	0.20	0.48	0.88	0.71
	7.1	5.6	0.62	6.0	2.2	**<0.0001/0.4 (0.23-0.58)**	8.1	5.2	0.42	**0.0099/2.6 1.24-5.26)**	0.88	0.07
N-ST30-IV[c]	54.7(47)	44.4(64)	0.13	12.5(54)	31.4(140)	**<0.0001/3.2 (2.27-4.54)**	2.8(2)	10.3(8)	0.07	**0.0042/2.0 1.19-2.57)**	**<0.0001/7.0 (3.20-15.32)**	**<0.0001/4.0 (1.91-8.38)**
	41.8	36.0	0.43	4.3	12.9	**<0.0001/2.4 (1.57-3.61)**	1.6	8.3	**0.0211/5.2 (1.26-21.22)**	**<0.0001/2.8 2.08-3.76)**	**<0.0001/4.3 (2.11-8.83)**	0.22
I-ST5-IV[c]	16.3(14)	9.7(14)	0.14	18.9(82)	6.7(30)	**<0.0001/0.3 (0.20-0.48)**	11.1(8)	3.8(3)	0.09	0.2341	0.11	0.33
	12.5	7.9	0.22	6.6	2.8	**<0.0001/0.4 (0.28-0.64)**	6.4	3.1	0.27	**0.0007/2.8 1.53-5.34)**	0.13	0.83
A-ST5-I[c]	8.1(7)	4.9(7)	0.31	10.8(47)	2.7(12)	**<0.0001/0.2 (0.12-0.438)**	9.7(7)	6.4(5)	0.45	0.1996	0.62	0.08
	6.2	3.9	0.38	3.8	1.1	**<0.0001/0.3 (016-0.55)**	5.6.	5.2	0.89	**0.0040/3.6 1.44-8.83)**	0.63	**0.0013/0.21 (0.08-0.58)**
C-ST100-IVNv[c]	0(0)	2.1(3)	NA	1.8(8)	2.7(12)	0.40	4.2(3)	0(0)	NA	0.6873	NA	NA
	0.0	1.7	NA	0.6	1.1	0.40	2.4	0.0	NA	0.7104	NA	NA
USA300-ST8-IV[c]	0(0)	5.6(8)	NA	1.2(5)	1.6(7)	0.82	0(0)	3.8(3)	NA	**0.0138/3.7 1.36-10.03)**	0.5753	0.1752
	0.0	4.5	NA	0.4	0.6	0.41	0.0	3.1	NA	**<0.0001/7.0 2.62-18.68)**	0.5885	0.0414**/0.21 (0.06-0.73)**
DD-ST97-IV[c]	0(0)	3.5(5)	NA	0.7(3)	1.6(7)	0.35	0(0)	0(0)		0.1596	NA	NA
	0.0	2.8	NA	0.2	0.6	0.20	0.0	0		**<0.0059/4.4 1.45-13.14)**	NA	NA

CA-MRSA$_G$ and HA-MRSA$_G$ community-associated and healthcare-associated methicillin-resistant *S. aureus* genotypes.

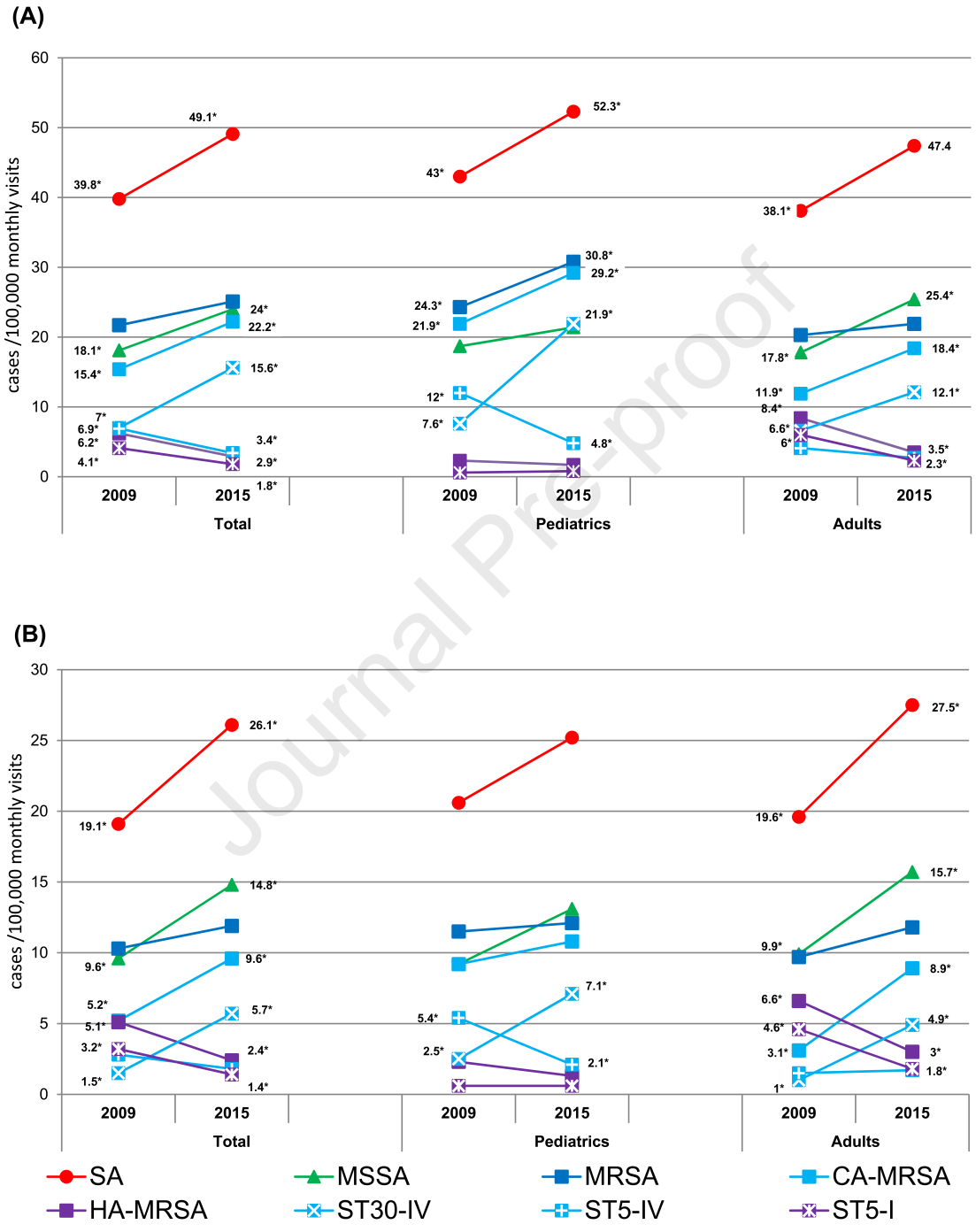
[a]N*:* Total number of patients with *S. aureus* infections in each Argentina region.

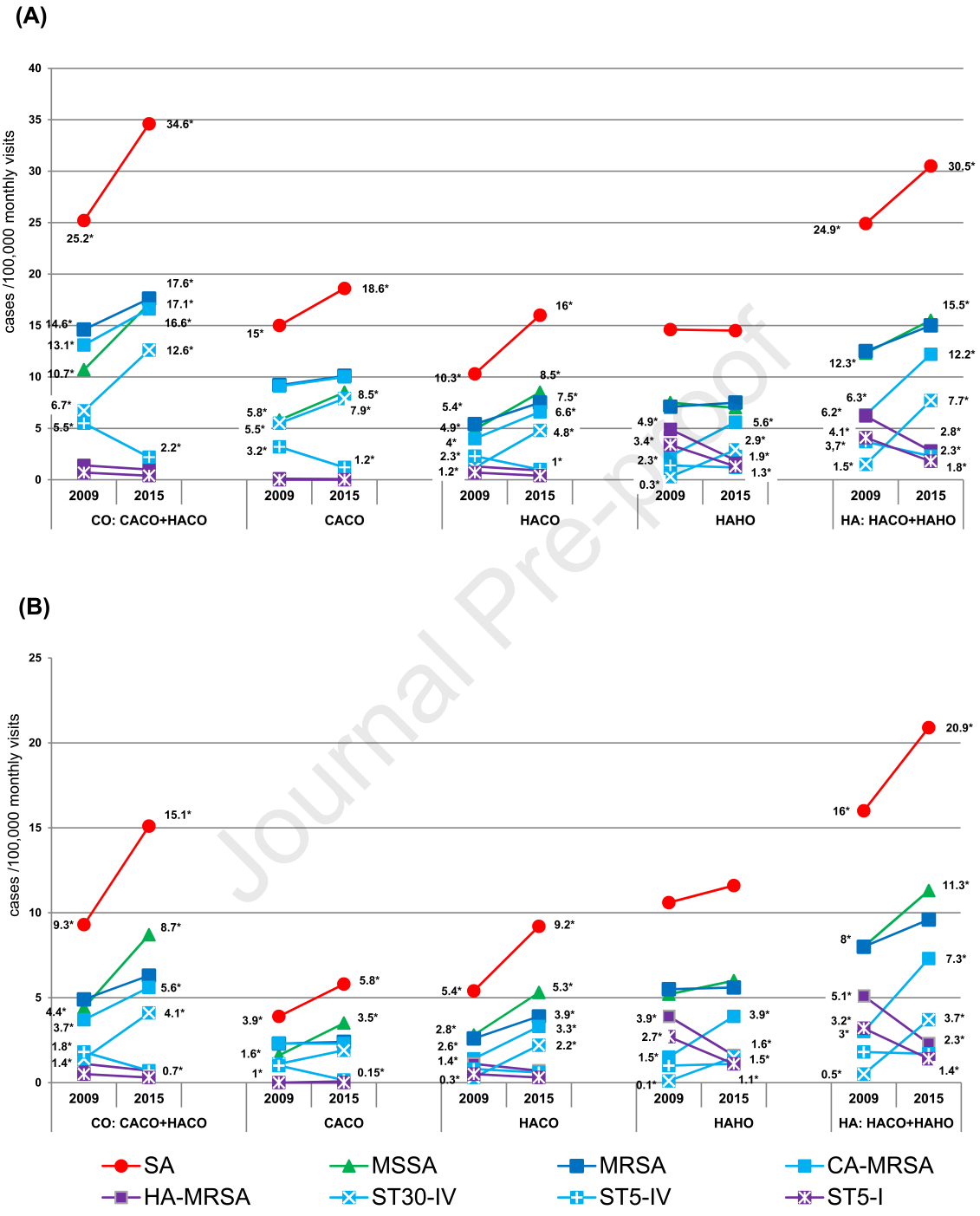
[b]In: Incidence: Number of cases /100,000 monthly visits. Number of visits (V): include outpatient facility, emergency service and admissions during that month.

V_{2009}: North: 112,427; Centre: 1,247,957 and South 124,121 visits

V_{2015}: North: 177,554; Centre: 1,086,859 and South 95,839 visits.

[c]Genotypes (major clones) are denoted as: type (by PFGE)-Sequence Type (ST by MLST)-SCC*mec* type





Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: