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New patterns of methicillin-resistant *Staphylococcus aureus* (MRSA) clones, community-associated MRSA genotypes behave like healthcare-associated MRSA genotypes within hospitals, Argentina

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) burden is increasing worldwide in hospitals [healthcare-associated (HA)-MRSA] and in communities [community-associated (CA)-MRSA]. However, the impact of CA-MRSA within hospitals remains limited, particularly in Latin America. A countrywide representative survey of *S. aureus* infections was performed in Argentina by analyzing 591 clinical isolates from 66 hospitals in a prospective cross-sectional, multicenter study (Nov-2009). This work involved healthcare-onset infections-(HAHO, >48 hospitalization hours) and community-onset (CO) infections [including both, infections (HACO) in patients with healthcare-associated risk-factors (HRFs) and infections (CACO) in those without HRFs]. MRSA strains were genetically typed as CA-MRSA and HA-MRSA genotypes (CA-MRSA$_G$ and HA-MRSA$_G$) by SCC*mec*- and *spa*-typing, PFGE, MLST and virulence genes profile by PCR. Considering all isolates, 63% were from CO-infections and 55% were MRSA [39% CA-MRSA$_G$ and 16% HA-MRSA$_G$]. A significantly higher MRSA proportion among CO- than HAHO-*S. aureus* infections was detected (58% vs 49%); mainly in children (62% vs 43%). The CA-MRSA$_G$/HA-MRSA$_G$ have accounted for 16%/33% of HAHO-, 39%/13% of HACO- and 60.5%/0% of CACO-infections. Regarding the epidemiological associations identified in multivariate models for patients with healthcare-onset CA-MRSA$_G$ infections, CA-MRSA$_G$ behave like HA-MRSA$_G$ within hospitals but children were the highest risk group for healthcare-onset CA-MRSA$_G$ infections. Most CA-MRSA$_G$ belonged to two major clones: PFGE-type N-ST30-SCC*mec*IVc-t019-PVL$^+$ and PFGE-type I-ST5-IV-SCC*mec*IVa-t311-PVL$^+$ (45% each). The ST5-IV-PVL$^+$/ST30-IV-PVL$^+$ clones have caused 31%/33% of all infections, 20%/4% of HAHO-, 43%/23% of HACO- and 35%/60% of CACO- infections, with significant differences by age groups (children/adults) and geographical regions. Importantly, an isolate belonging to USA300-0114-(ST8-*SCCmec*IVa-*spa*t008-PVL$^+$-ACME$^+$) was detected for the first time in Argentina. Most of HA-MRSA$_G$ (66%) were related to the Cordobes/Chilean clone-(PFGE-type A-ST5-SCC*mec*I-t149) causing 18% of all infections (47% of HAHO- and 13% of HACO-infections).

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Results strongly suggest that the CA-MRSA clone ST5-IV-PVL$^+$ has begun to spread within hospitals, replacing the traditional Cordobes/Chilean-HA-MRSA clone ST5-I-PVL$^-$, mainly in children. Importantly, a growing MRSA reservoir in the community was associated with spreading of two CA-MRSA clones: ST5-IV-PVL$^+$, mainly in children with HRFs, and ST30-IV-PVL$^+$ in adults without HRFs. This is the first nationwide study in Argentina providing information about the molecular and clinical epidemiology of CA-MRSA, particularly within hospitals, which is essential for designing effective control measures in this country and worldwide.

Introduction

Methicillin resistant *Staphylococcus aureus* (MRSA) is one of the most prominent pathogens causing healthcare (HA)-, community (CA)-, and livestock (LA)-associated infections (Stefani et al., 2012; Tavares et al., 2013; Song et al., 2011; Schaumburg et al., 2012; Xiao et al., 2013). In contrast to HA-MRSA strains, which were first detected in hospitals and have affected patients with healthcare associated risk factors (HRFs), the CA-MRSA strains have the ability to infect otherwise healthy younger people outside of the hospital setting (David and Daum, 2010; Klevens et al., 2007), suggesting enhanced virulence and fitness. Recent research revealed that increased virulence and fitness is multifactorial and related to *(i)* acquisition of novel genes on mobile genetic elements, such as smaller staphylococcal cassette chromosome mec (SCC*mec*) type IV or V, the Panton-Valentine leukocidin (PVL)-encoding phage or, in case of USA300 clone, arginine catabolic mobile element (ACME) and *(ii)* the enhanced expression of genome-encoded toxins, including phenol soluble modulins and alpha-toxin (Otto, 2013). Numerous CA-MRSA clones have emerged on every continent (Mediavilla et al., 2012). Importantly, these CA-MRSA strains that initially were associated with community-onset (CO) infections, have begun to enter into hospitals and may be replacing the conventional HA-MRSA strains with significant clinical and public health implications (Otter and French, 2011, 2012). However, CA-MRSA penetration has not been thoroughly explored among a large number of hospitals and knowledge of the risk factors involved in nosocomial transmission of CA-MRSA compared with HA-MRSA remains largely undefined (Murphy et al., 2013; Popoola et al., 2013; Hetem et al., 2012).

MRSA is highly prevalent in hospitals of Latin America. In Argentina, MRSA accounts for approximately 50% of all *S. aureus* isolates recovered from healthcare-onset (HO) infections (WHONET Argentina Network; Quinteros et al., 2009; Sola et al., 2006, 2008) and the Cordobes/Chilean epidemic (ST5-SCC*mec*I) HA-MRSA clone has been considered responsible for most of these infections (>60%) (Sola et al., 2006, 2008). Notably, the proportion of CA-MRSA infections in children has been increasing since 2001, reaching an overall prevalence of 62% of the total CA *S. aureus* infections (38% of which were invasive infections) in central, eastern and northern regions of Argentina during 2007 (Paganini et al., 2008; Sola et al., 2012). This significant increase over time, was associated with the emergence and spread of a CA-MRSA clone, characterized as ST5-SCC*mec*IVa-PVL$^+$ (Sola et al., 2008, 2012). In addition, two international CA-MRSA epidemic clones have been found as minor clones in our previous study: the pandemic Southwest Pacific-(SWP) clone or USA1100-(ST30-SCC*mec*IV-PVL$^+$) and the South American USA300 MRSA-(ST8-SCC*mec*IV-PVL$^+$-ACME$^-$) recently dubbed "Latin American variant USA300-LV" (Nimmo, 2012), accounting for 11.5% and 2% of CA-MRSA isolates, respectively (Sola et al., 2012). However, knowledge of CA-MRSA genotypes (CA-MRSA$_G$) within hospitals remains limited in Latin America and largely unknown in Argentina.

The aims of this investigation were to evaluate the molecular and clinical epidemiology of CA-MRSA and HA-MRSA in both, community and healthcare settings all over Argentina and to explore the transmission of these strains at the hospital setting through a prospective multicenter prevalence survey.

This work was presented in part at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy, 2012 (San Francisco, USA).

Materials and methods

Prospective study design and case definitions

To characterize the CA-MRSA and HA-MRSA genotypes and to evaluate their global prevalence in Argentina in hospital and community settings, a prospective observational cross-sectional multicenter study was conducted during November 2009 in 66 hospitals (46 belonging to the WHONET Argentina Network) from 20 provinces and Buenos Aires City (CABA). The characteristics of hospitals are shown in Table S1 in the Supplemental Material. Patients were prospectively and consecutively identified according to the results of *S. aureus* 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 by previously trained MD members of the *S. aureus* Study Group, Argentina (one or more for each participating hospital). Data collected included the following features (detailed in Table 1): *(i)* socio-demographic characteristics, *(ii)* underlying medical conditions, *(iii)* healthcare-associated risk factors for HA-MRSA colonization or infection (HRFs) (CDC criteria; Klevens et al., 2007), *(iv)* onset of infection (hospital vs. community), *(v)* antibiotic exposure within the previous year, *(vi)* characteristics and severity of infections. In addition, hospitalization characteristics and some factors involved in nosocomial transmission were also analyzed in hospitalized patients (Tables 1 and 2). Invasive infections (INVI) and sepsis were defined as previously described (Sola et al., 2012). Surgical site infections (SSI) were not considered as skin diseases. This study was reviewed and approved by the Ethics Review Board of Health Research of the Ministry of Health, Province of Cordoba (approval No. 1338) as well as by the institutional Ethical Review Board of each Hospital listed in acknowledgments.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijmm.2014.08.002.

For the purpose of this study, CA-MRSA and HA-MRSA strain types were defined genotypically (see below) and were named as CA-MRSA$_G$ and HA-MRSA$_G$, respectively.

Regardless of the strain types involved, cases were classified considering the onset type of infections and the presence/absence of HRFs (epidemiological definitions).

Onset type

We considered an infection to be healthcare-onset (HO) if the culture was obtained >48 h after admission to the hospital and the patient had no evidence of infection at admission time. All other cases were defined as community-onset (CO) infection.

Table 1
Comparison of clinical-epidemiological characteristics of patients with infections (total on top and healthcare-onset at the bottom) caused by CA-MRSA$_G$ and HA-MRSA$_G$ (genotypes) in 66 Argentinean hospitals from one month (Nov), 2009.

Total infections	No. (%) of patients			*P* value/univariate odd of CA-MRSA$_G$, OR (95% CI)	*P* value/multivariate odd of CA-MRSA$_G$, OR (95% CI)
	All patients *N*: 322	CA-MRSA$_G$ no: 229	HA-MRSA$_G$ no: 93		
Socio-demographic characteristics					
Age, years, Mean ± SD/Median (range)	31.3 ± 24.4 28 (0–95)	24.4 ± 21.2 18 (0–83)	48.3 ± 23.3 55 (0–95)	**<0.0001**	<0.0001
Age group, <19	127 (39.4)	115 (50.2)	12 (12.9)	**<0.0001** 6.81 (3.6–13.0)	<0.0001 12.33 (3.81–39.92)
Proportion female	134 (41.6)	96 (41.9)	38 (40.9)	0.89	
Overcrowding[a]	73 (26.7)	63 (32.3)	10 (12.7)	0.0009 3.3 (1.61–6.70)	
Household monthly income[a] <u$ 800	210 (76.5)	160 (81.5)	50 (63.3)	0.0009 2.4 (1.41–4.72)	
Household density[a], ≥5 cohabitants	117 (42.6)	102 (52.3)	15 (18.8)	<0.0001 4.7 (2.53–8.72)	
Underlying diseases[b]	139 (43.1)	70 (30.7)	69(74.2)	**<0.0001** 0.15 (0.09–0.29)	0.002 0.16 (0.05–0.49)
Healthcare-associated risk factors (HRFs)[c]					
Hospitalization in the past 12 months	109 (38.5)	57 (28.9)	52 (60.4)	<0.0001 0.27 (0.16–0.47)	
History of MRSA infection/colonization	18 (6.3)	8 (4.0)	10 (11.6)	0.010 0.32 (0.13–0.83)	
Surgery in the past 12 months	82 (28.9)	32 (16.2)	50 (58.1)	<0.0001 0.14 (0.08–0.25)	
Hemodialysis in the past 12 months	10 (3.5)	3 (1.5)	7 (8.1)	0.007 0.17 (0.05–0.64)	
Residence in a day care or rehabilitation center	7 (2.5)	6 (3.0)	1 (1.1)	0.34	
Onset type					
Hospital onset	106 (32.9)	34 (14.9)	72 (77.4)	**<0.0001** 0.05 (0.03–0.09)	<0.0001 0.14 (0.05–0.39)
Community onset	216 (67.1)	195 (85.1)	21 (22.6)	**<0.0001** 19.7 (10.81–35.92)	<0.0001 6.97 (2.51–19.36)
Previous antibiotic exposure[d]					
Any β-lactam	99 (35.9)	68 (34.6)	31 (38.7)	0.52	
Any quinolone	15 (5.4)	2 (1.2)	13 (16.3)	<0.0001 0.05 (0.01–0.21)	
Vancomycin	21 (7.6)	13 (6.6)	8 (9.6)	0.38	
Infection characteristics					
Type and severity of Infection					
Skin and soft-tissue SSTI uncomplicated	146 (45.3)	140 (61.1)	6 (6.5)	**<0.0001** 21.2 (9.21–49.10)	0.016 6.24 (1.40–27.85)
Severe sepsis or septic shock[e]	62 (21.9)	38 (19.4)	24 (27.9)	0.11	
30-day all-cause mortality[f]	16 (5.5)	4 (2.0)	12 (13.1)	0.0001 0.14 (0.04–0.41)	

Healthcare-onset infections	No. (%) of patients			*P* value/Univariate odd of CA-MRSA$_G$, OR (95% CI)	*P* value/Multivariate odd of CA-MRSA$_G$, OR (95% CI)
	All patients *N*: 106	CA-MRSA$_G$ no: 34	HA-MRSA$_G$ no: 72		
Socio-demographic characteristics					
Age, years, Mean ± SD/	40.6 ± 27.8	21.4 ± 28.2	49.8 ± 22.6	**<0.0001**	
Median (range)	45 (0–95)	3.5 (0–83)	56 (0–95)		
Age group < 19	28 (26.4)	21 (61.8)	7 (9.7)	**0.0001** 15.0 (5.43–41.47)	0.0001 13.90 (3.54–54.42)
Proportion female	47 (44.3)	19 (55.9)	28 (38.9)	0.14	
Underlying diseases[d]	76 (71.7)	25 (73.5)	51 (70.8)	0.77	
Infection characteristics					
Non-skin-related infection	96 (90.6)	29 (85.3)	67 (93.0)	0.35	
Severe sepsis or septic shock[e]	35 (36.8)	12 (40.0)	23 (35.4)	0.66	
In ICU during hospitalization	52 (49.0)	13 (38.2)	39 (54.1)	0.12	
Length of stay (days)	17.78 ± 17.12	21.31 ± 19.5	16.33 ± 15.69	0.22	
Mean ± SD/Median (range)	14 (1–90)	14 (1–90)	13 (2–90)		
Length of stay > 10 days	61 (57.5)	22 (65.4)	39 (54.9)	0.30	
30-day all-cause mortality[f]	14 (13.5)	3 (8.8)	11 (15.7)	0.33	
Factors involved in nosocomial transmission					
Time to infection, median[e] (days)	16.04 ± 22.56	15.41 ± 24.38	16.33 ± 21.82	0.84	
Mean ± SD/Median (range)	7 (3–130)	4.5 (3–123)	8 (3–130)		
Time to infection[e] ≤ 5 days	43 (40.5)	19 (56.9)	24 (33.3)	0.027 2.53 (1.11–5.78)	

Table 1 (*Continued*).

Healthcare-onset infections	No. (%) of patients			*P* value/Univariate odd of CA-MRSA$_G$, OR (95% CI)	*P* value/Multivariate odd of CA-MRSA$_G$, OR (95% CI)
	All patients *N*: 106	CA-MRSA$_G$ no: 34	HA-MRSA$_G$ no: 72		
Previous invasive procedures[g]					
Indwelling catheters	89 (93.6)	27 (93.1)	61 (93.8)	0.92	
Mechanical respiratory assistance	40 (42.1)	12 (40.4)	28 (43.0)	0.77	
Urinary catheter	45 (47.3)	10 (33.3)	35 (53.8)	0.06	
Parenteral feeding	18 (18.9)	5 (17.2)	13 (19.7)	0.70	

CA-MRSA$_G$ and HA-MRSA$_G$ community-associated and healthcare-associated methicillin-resistant *S. aureus* genotypes; HO, healthcare-onset; CI, confidence interval. Variables associated with CA-MRSA$_G$ with a *P* value of ≤ 0.05 in multivariate analysis are shown in boldface font.
NA: Not applicable.

[a] Data were available for 274 patients: 95 with CA-MRSA$_G$ and 79 with HA-MRSA$_G$ infections. Overcrowding: households with more than three people per room.

[b] Underlying diseases: diabetes, heart disease or stroke, liver or kidney disease, chronic central nervous system disease, cancer or immunodeficiencies (HIV, AIDS and rheumatoid arthritis).

[c] Data were available for 283 patients: 197 with CA-MRSA$_G$ and 86 with HA-MRSA$_G$ infections.

[d] Data were available for 276 patients 196 with CA-MRSA$_G$ and 80 with HA-MRSA$_G$ infections.

[e] Data were available for 282 patients (95 with HO infections): 196 with CA-MRSA$_G$ (30 HO) and 86 with HA-MRSA$_G$ (65 HO) infections. Time to infection: Length of stay until *S. aureus* positive culture of patients with HO infections.

[f] Data were available for 290 patients (104 with HO infections): 199 with CA-MRSA$_G$ (34 HO) and 91 with HA-MRSA$_G$ (70 HO) infections.

[g] Data were available for 95 patients: 30 with CA-MRSA$_G$ and 65 with HA-MRSA$_G$ HO infections.

Epidemiological definitions

Community-associated (CA) infections were defined as cases of CO-infections (CACO) from patients without HRFs during the previous year, according to the CDC criteria (Klevens et al., 2007). Healthcare-associated (HA) infections include: *(i)* hospital-onset infections regardless the presence of other HRFs (HAHO) and *(ii)* community-onset infections occurring in patients with at least one HRF (HACO) (Klevens et al., 2007).

Bacterial isolates and antimicrobial susceptibility

Staphylococcus aureus clinical isolates (*n*: 591) were identified by standard microbiologic procedures and antimicrobial susceptibility testing was performed by disk diffusion method (CLSI, 2009). Vancomycin, teicoplanin, tigecycline and fosfomycin minimum inhibitory concentrations (MICs) were determined by agar dilution method, (CLSI, 2009) and daptomycin was evaluated by E-test (bioMérieux). *S. aureus* strain ATCC 29213, *E. faecalis* 29212 and *E. coli* 25922 were used as reference strains.

Molecular typing

For all MRSA isolates, PFGE of *Sma*I digests of chromosomal DNA were performed and interpreted as previously described (Sola et al., 2008). All MRSA isolates were screened by PCR for accessory gene regulator (*agr*) type, for 23 specific staphylococcal virulence genes (detailed in Table 3), including Panton-Valentine leukocidin genes (*lukS*-PV-*lukF*-PV) and for *arc*A gene (indicator of the arginine catabolic mobile element, ACME), as described elsewhere (Sola et al., 2012 and references therein). Additionally, all MRSA were also tested for the presence of the *sas*X gene by PCR as previously described (Li et al., 2012). Representative MRSA isolates of the most prevalent subtypes (defined

Table 2
Association of factors with healthcare- versus community-onset CA-MRSA$_G$, hospitalized patients, Argentina, 66 hospitals, Nov, 2009.

Characteristics	No. (%) of patients			*P* value/Univariate odd of HO OR (95% CI)	*P* value/Multivariate odds of HO OR (95% CI)
	Total *N*: 139	HO *n*: 34	CO *n*: 105		
Age group <19	79 (56.8)	21 (61.8)	58 (55.2)	0.50 1.31 (0.60–2.86)	
Proportion female	58 (41.7)	19 (55.9)	39 (37.1)	0.06 2.14 (0.95–4.65)	
Underlying diseases[a]	56 (40.3)	25 (73.5)	31 (29.5)	<0.0001 6.63 (2.82–15.61)	0,016 4.71 (1.34–16.55)
Infection characteristics					
Non-skin-related infection	91 (65.5)	29 (85.3)	62 (59.0)	0.0051 4.02 (1.50–10.82)	0,038 7.14 (1.12–45.53)
Severe sepsis or septic shock[b]	34 (25.8)	12 (40.0)	22 (21.6)	0.0424 2.42 (1.03–5.71)	
Hospitalization characteristic					
In ICU during hospitalization	23 (16.9)	13 (38.5)	10 (9.5)	0.0001 5.88 (2.31–14.94)	
Length of stay (days)	13.77 ± 13.7	21.31 ± 19.5	11.29 ± 10.18	0.017	
Mean ± SD/Median (range)	10 (1–90)	14 (1–90)	9 (1–60)		
Length of stay > 10 days	64 (46.0)	22 (64.7)	42 (40.0)	0.012 2.75 (1.24–6.08)	
30-day all-cause mortality	4 (2.9)	3 (8.8)	1 (1.0)	0.045 10.06 (1.43–71.01)	

CA-MRSA, community-associated methicillin-resistant *S. aureus*; CI, confidence interval.

[a] Underlying diseases: diabetes, heart disease or stroke, liver or kidney disease, chronic central nervous system disease, malignancies or immunodeficiencies (HIV, AIDS and rheumatoid arthritis).

[b] *n*: 132 Severe sepsis or septic shock not available for: 7 patients (3 CO and 4 HO infections).

Table 3
Characteristics of 322 MRSA isolates belonging to HA-MRSA and CA-MRSA genotypes, Argentina.

Genetic background	ST	PFGE type/no. (%)	PFGE Subtype/no. (%)[a]	RIDOM *spa* type/no. (%)[a]	SCC*mec* no. (%)[a]	*pvl* no. (%)[a]	*agr* type	Virulence genes[b] profile no. (%)	Drug resistance[c] non-β-lactam *n*. (%)
CA-MRSA, *n*: 229									
CC30	30	N/104(45)	N4/73 (71), N6/10 (10), N17/7 (7), N13/6 (6) and 8 minor subtypes	t019: 102 (99), t021: 2 (1)	IVc: 103 (99) IVNT: 1	104 (100)	3	*egc-lukDE-bbp-cna*	GEN 12 (12), ERY 12 (12)[d], CLIi 7 (7)[d], CLIc 1 (1), RIF 2 (2)
CC5	5	I/102(45)	I1/66 (64), I4/6 (6), I47/6 (6), I2/3 (3), I26/2 (2), I44/2 (2) and 17 minor subtypes	t311: 84 (82), t002: 17 (17), t2049: 1	IVa: 99 (96), IVc: 3 (3), Vv[f]: 1	79 (77)		*sea-egc-lukDE* 79 (77), *egc-lukDE 23 (23)*	GEN 7 (7), ERY 29 (28)[d], CLIi 25 (24)[d], CIP 2 (2), RIF1 (1), CHL1 (1)
CC8	72	R/10(4)	R1/5 (50), R4/2 (20) and 3 minor subtypes	t148: 5 (50), t1346: 4 (40), t3092: 1	IVNv1[h]: 5 (50) IVc: 3 (30), IVa: 1, IVNT: 1	0 (0)	1	*egc-lukDE*	GEN 8, ERY 4, CLIi 3
CC8	8	USA300/5(2)	USA300-5/2 (40) and 3 minor subtypes	t008: 5 (100)	IVc: 2 (40), IVb: 1, Vv[g]: 1 IVa: 1	4 (80)	1	*lukDE-sek-seq-bsa*: 2 (40), *lukDE-sea-sec-bsa*: 1 (20), l*ukDE- bsa*: 1 (20), *lukDE-sek-seq-bsa-ACME*: 1 (20)	GEN 1, ERY 2, CLIi 1
CC97	97	D/3(1.5)	DD1/2 (66) and 1 minor subtypes	t359, t267, t2734	IVc: 3 (100)	0	1	l*ukDE*	GEN 1, ERY 2, CLIi 1, CIP1
CC88	88	G/1	BB1	t186	IVg	0	3	l*ukDE*	
CC6	1649 (SLV ST6)	Q/1	QQ1	t701	IVc	0	1	*lukDE-seb-bsa-cna*	
CC1	1	F/1	FF1	t127	Vv[g]	1	3	*lukDE-seb-seh-bsa-cna*	GEN 1, CIP 1
CC121	1210	V/1	V1	t812	IVE	1	4	*egc-lukDE-seb-bbp-cna*	
CC121	121	V/1	V2	t159	Vv[g]	0	4	*egc-lukDE-seb-bbp-cna-eta-etb*	
HA-MRSA, *n*: 93									
CC5	5	A/61(66)	A4/8 (13), A15/6 (10), A5/4 (7), A3/4 (7), A10/3 (5), A8/2 (3), A42/2 (3), A71/2 (3), A85/2 (3), A86/2 (3) and 26 minor subtypes	t149 61(100)	I: 61 (100)	0 (0)	2	*egc-lukDE*	GEN 60 (98), ERY 60 (98), CLIc 59 (97), CLIi 1 (1), CIP 58 (95), RIF 12 (20), CHL 4 (7)
CC5	5	E/3(3)	EE1/3 (100)	t12090 [e]	I: 3 (100)	0 (0)	2	*sea-egc-lukDE*	GEN 3, ERY 3, CLIc 3, CIP 3
CC5	100	C/21(23)	C15/2 (10), C40/2 (10) and 17 minor subtypes	t002: 17 (81), t067, t1341, t3152, t548	IVNv: 17 (81), NT 4 (19)	0 (0)	2	*egc-lukDE*	GEN 19 (91), ERY 11 (52), CLIc 5 (23), CLIi 6 (29), CIP 7 (33), RIF 5 (24)
CC8	239 *n*: 7 2266[f] *n*:1 (SLV ST239)	B/8(8)	B17/3 (29) and 5 minor subtypes	t037	IIIA: 7(86), NT: 1	0 (0)	1	*lukDE-bsa*	GEN 8, ERY 8, CLI 7, CIP 8, RIF 7, SXT 8, CHL1, MIN1

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); 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 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*: 229) or HA-MRSA$_G$ (*n*: 93) genotypes. (%) is not expressed when only one isolate with this characteristic was detected.

[b] 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*), surface protein sasX (*sas*X) 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).

[c] 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 Chloramphenicol (CHL), (%) of strains resistant to these antibiotics within each genetic background only is indicated when more than 10 total isolates with this genetic background were detected.

[d] $P < 0.01$ 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.

[e] New *spa*-type.

[f] New ST.

[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] SCC*mec* IVNv1: New variant 1: positive for the *ccr2* gene complexes and for a larger-than normal class B *mec* gene complex (negative for the *Tn*4001 transposon within this element).

by PFGE) were also characterized by multilocus sequence typing (MLST) and *spa* typing, as previously described (Sola et al., 2012 and references therein). The *spa* types were attributed using the RIDOM web server (http://spaserver.ridom.de/). Allele numbers and sequence types (ST) were assigned using the database maintained at http://saureus.mlst.net/, while clonal complexes (CC)s were inferred using eBURST analysis. The SCC*mec* types [I–VI, including the new variant of SCC*mec* IV (IVNv) associated to ST100 in Argentina] were evaluated for all MRSA isolates by multiplex PCR and allotyped by conventional PCR through the identification of *mec*, *ccr*, and the J1 region as previously described (Sola et al., 2012 and references therein).

Genotypic definitions

For the purpose of this study, CA-MRSA$_G$ were defined as belonging to the following genotypes: ST5-IV/V-t311 and related, PVL$^{+/-}$, ST30-IV-t019 and related, PVL$^+$, ST72-IV-t148 and related, PVL$^-$, ST8-IV-t008, PVL$^+$, ST97-IV-t267 and related, PVL$^-$, ST88-IV-t186, PVL$^-$, ST1649 (SLV of ST6)-IV-t701, PVL$^-$, ST1-V-t127, PVL$^+$, ST121/ST1210 (SLV of ST121)-IV/V, t159 and related, PVL$^{+/-}$ (Mediavilla et al., 2012; Sola et al., 2012; Chuang and Huang, 2013; Spoor et al., 2013; Monecke et al., 2011; Kurt et al., 2013). All remaining genotypes were considered HA-MRSA$_G$ (Stefani et al., 2012, Sola et al., 2012).

Statistical analysis

Bacteriologic and patient data were compiled in an electronic database using Access (Microsoft). Univariate and multiple logistic regression analyses were used to investigate characteristics independently associated with CA-MRSA$_G$ infections in total and HO-infections. Comparisons were made between strain groups genotypically defined as CA-MRSA$_G$ and HA-MRSA$_G$ for all MRSA infections and repeated for HO-infections to describe factors associated with transmission of CA-MRSA$_G$ in the hospital setting. We also carried out comparisons between onset type of infection (community and hospital) for CA-MRSA$_G$ among hospitalized patients, to determine those characteristics independently associated with healthcare-onset CA-MRSA$_G$ infections.

Continuous variables were compared using Student's *t*-test or one-way analysis of variance (ANOVA) and the Mann–Whitney *U* test or the Kruskal Wallis test for nonparametric data, as appropriate. Dichotomous or categorical variables were compared using χ^2 analyses or Fisher's exact test, as appropriate. $P < 0.05$ was considered statistically significant. Categorical variables that were significant on each univariate analysis ($P < 0.05$) performed between paired strain groups, were included in the multiple logistic regression analysis for each situation compared. In all comparisons, the information about the variables considered was available for over 80% of the cases. A Hosmer and Lemeshow Goodness of Fit test indicated an acceptable fit to the data. Data were analyzed using SPSS (version 15.0) and InfoStat (www.infostat.com.ar).

Results

MRSA infections in the community and healthcare settings

The population served by all hospitals was 1,484,505 visits and 47,329 admissions during this month (Table S1). A total of 591 isolates from patients with *S. aureus* infections were collected during a one month surveillance study period in 2009. Median age of the patients was 30 years (range, 1 month to 96 years), 225 were children (<19 years) (38%) (Fig. S1A) and 248 were female (42%). Of all 591 cases, 322 (55%) were MRSA and 375 (63%) were CO-infections (Fig. S1A). The proportion of MRSA differed significantly ($P = 0.045$) between CO- (58%, 216/375) and HO- (49%, 106/216) infections, particularly in children (62%, 99/160 in CO- vs 43%, 28/65 in HO-infections, $P = 0.01$). A total of 266 patients (45%) presented skin and soft-tissue infections (SSTI) and among these, the MRSA proportion was 62% (164/266).

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Using the CDC criteria (Klevens et al., 2007), 222 (38%) infections were classified as CACO: 61% CACO-MRSA (*n*: 136) and 39% CACO-MSSA (*n*: 86); 153 (26%) as HACO: 52% HACO-MRSA (*n*: 80) and 48% HACO-MSSA (*n*: 73) and 216 (36%) as HAHO: 49% HAHO-MRSA (*n*: 106) and 51% HAHO-MSSA (*n*: 110) (Fig. S1A). Hence, the MRSA proportion differed significantly ($P = 0.01$) between CA (61%) and HA (50%) infections (Fig. S1A).

MRSA genotypes: CA-MRSA$_G$ and HA-MRSA$_G$ by epidemiological criteria, age group and geographic region

The combination of the results obtained by all the typing methods used showed that the majority of MRSA (229/322 isolates, 71%) were classified as CA-MRSA$_G$, while 93 (29%) as HA-MRSA$_G$ (Table 3).

Considering all cases (*n*: 591), 39% (*n*: 229) were caused by CA-MRSA$_G$ and 16% (*n*: 93) by HA-MRSA$_G$ (Fig. S1A). Additionally, the overall rate of MRSA, CA-MRSA$_G$ and HA-MRSA$_G$ were 15.4-(range 2.5–301.4), 6.2-(range 0–46.4) and 21.7-(range 2.6–321.9) cases/100,000 monthly visits, respectively (Table S1).

Regarding, CO- and HO-*S. aureus* infections (*n*: 375 and 216, respectively), 52% (*n*: 195) and 16% (*n*: 34) were caused by CA-MRSA$_G$, 6% (*n*: 21) and 33% (*n*: 72), by HA-MRSA$_G$, respectively. On the other hand, considering the CDC criteria (Klevens et al., 2007), CA-MRSA$_G$/HA-MRSA$_G$ accounted for the 60.5% (*n*: 135)/0.5% (*n*: 1) of CACO infections, 39% (*n*: 60)/13% (*n*: 20) of HACO infections and 16% (*n*: 34)/33% (*n*: 72) of HAHO infections. Hence, 31% (60/195) of patients with CO infections by CA-MRSA$_G$ had at least one HRF (HACO infections) and importantly, 16% of HAHO-*S. aureus* infections were caused by CA-MRSA$_G$. Then, among healthcare-associated *S. aureus* infections (HACO and HAHO, *n*: 369), CA-MRSA$_G$ and HA-MRSA$_G$ accounted roughly for 25% each (*n*: 94 and 92, respectively).

In addition, the relative proportion of CA-MRSA$_G$ differed significantly between pediatrics (<19 years) and adults in total *S. aureus* infections (51% vs 31%, $P < 0.0001$) and in both HA-infections (HACO and HAHO) (38% vs 19%, $P = 0.0001$) and CACO-infections (68% vs 55%, $P = 0.045$) (Fig. S1A). Most CA-MRSA$_G$ infections occurred in pediatric patients (<19 years) both in the community setting (48%) and in the hospital setting (62%). However, 47% of the HO group was <1 year of age compared with 4% in the CO group (Fig. S1B).

The percentages of CA-MRSA$_G$ and HA-MRSA$_G$ were stratified by regions of Argentina (Fig. 1): Northern (8 provinces, 10 hospitals, 86 isolates), Central (7 provinces and Buenos Aires city, 49 hospitals, 433 isolates) and Southern (5 provinces, 7 hospitals, 72 isolates). The proportion of MRSA differed significantly from northern (81%) to central (53%) and southern (29%) regions of Argentina ($P < 0.0001$). This finding was largely associated to the spread of CA-MRSA$_G$ due to the proportion of CA-MRSA$_G$ differed significantly ($P < 0.0001$) from the North to the South of the country (72% vs 16%, respectively), while the proportion of HA-MRSA$_G$ infections were similar between both regions ($P = 0.08$) (Fig. 1). Likewise, the overall rate of MRSA infections was increased (3.6 fold) in the North [62.3 (range 27.3–321.9) cases/100,000 monthly visits] compared to the South [16.9 (range 10.5–26.9) cases/100,000 monthly visits] of Argentina ($P < 0.0001$). This fact was associated with greater rate (6.2 fold) of CA-MRSA$_G$ in northern [55.1 (range 14.1–301.2) cases/100,000 monthly visits] than in southern regions [8.9 (range

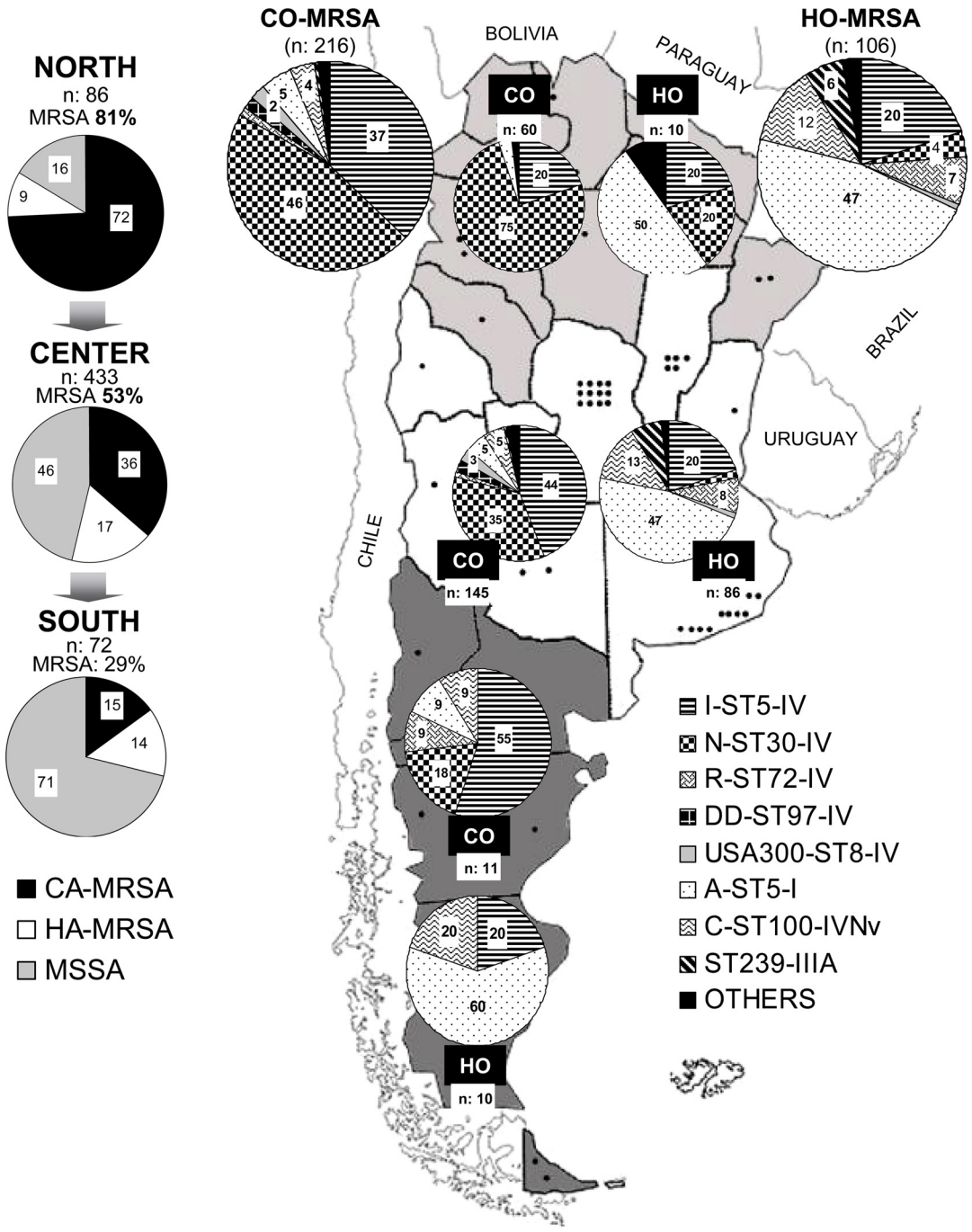

Fig. 1. Prevalence of CA-MRSA$_G$, HA-MRSA$_G$ and MSSA (left) in total infections and distribution of the most frequent MRSA clones in both, community (CO) and healthcare (HO) setting (right), by regions of Argentina: North (dark gray), Center (white) and South (light gray). CA-MRSA$_G$ and HA-MRSA$_G$: community-associated and healthcare-associated methicillin-resistant *S. aureus* genotypes, MSSA, methicillin-susceptile *S. aureus*.

5.2–13.4) cases/100,000 monthly visits] ($P < 0.0001$), while the incidences of HA-MRSA$_G$ infections were comparable between these regions (Table S1).

Univariate comparisons of socio-demographic and clinical characteristics of MRSA infections: CA-MRSA$_G$ vs. HA-MRSA$_G$

The basic socio-demographic and clinical characteristics of the patients with CA-MRSA$_G$ and HA-MRSA$_G$ infections are summarized in Table 1. Overall, 41.6% (134/322) of MRSA were isolated from female patients; with no significant difference in the gender distribution between HA-MRSA$_G$, and CA-MRSA$_G$ either in the total as in HO infections.

Total MRSA infections

Considering all MRSA infections, compared with HA-MRSA$_G$, the CA-MRSA$_G$ infections were associated with the community setting, in younger patients without comorbidities (Table 1). In addition, these patients with CA-MRSA$_G$ infections, were more likely to have households with ≥ 3 persons per room (overcrowding), ≥ 5 persons per household, to be economically disadvantaged (household monthly income < US$ 800) and to develop SSTI (Tables 1 and S2).

All these characteristics were also associated with CA-MRSA$_G$ infections when only the CO infections (CA-MRSA$_G$: 195 and HA-MRSA$_G$: 21 cases) were evaluated (data not shown).

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On the other hand, compared with CA-MRSA$_G$, the patients infected with HA-MRSA$_G$ were associated with older patients and HO infections (Table 1), they had more co-morbid conditions, mainly malignancies (solid tumors and hematological malignancy, 18.5% vs 5%, $P = 0.011$) and diabetes (17.2% vs 4.4%, $P = 0.001$) and they had higher rates of at least one HRF (98.9% vs 41.0%, $P < 0.0001$) (Table 1). Addtionally, they were more likely to develop INVI (80.6% vs. 34.1% $P < 0.0001$), mainly in lungs, bacteriemia and catheter-associated infections and were less likely to present a SSTI (Table S2).

HO-infections

Among patients with HO infections, compared with HA-MRSA$_G$, those infected with CA-MRSA$_G$ were also associated with younger patients, particularly <1 year (Fig. S1B and Table 1). Importantly, at the hospital setting, the two groups of patients infected with CA-MRSA$_G$ and HA-MRSA$_G$, were comparable regarding most of the clinical variables and factors involved in nosocomial transmission (Tables 1 and S2), including the proportion of INVI [67.6% (23/34) vs 80.6% (58/72) $P < 0.15$].

Univariate comparisons of characteristics of hospitalized patients with CA-MRSA$_G$ infections: CO- vs. HO-infections

Regarding patients with CO-infections, 53.8% (105/195), 90.5% (19/21) and 64.8% (103/159) of CA-MRSA$_G$, HA-MRSA$_G$ and MSSA were hospitalized, respectively. Considering only hospitalized patients with CA-MRSA$_G$ infections (n: 139, 105 with CO-infections as cause of hospitalization and 34 with HO-infections), the variables that differed significantly ($P < 0.05$) between patients with CO- and HO-infections are shown in Table 2. Among these, ICU admission, non-SSTI infections, patients with comorbidities, presentation with sepsis and a length of stay longer than 10 days were more common in the HO than in the CO group ($P < 0.05$). Infection type also differed between the HO and CO groups; skin infections dominated the CO group, whereas most HO infections were surgical site (SSI) and invasive infections (Table S3).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijmm.2014.08.002.

Multivariate analyses

In multivariate analyses, compared with HA-MRSA$_G$, CA-MRSA$_G$ were independently associated with age <19 years (OR 12.33), lower frequency of comorbidities (OR 0.16), CO-infections (OR 6.97), and presentation with SSTI (OR 6.24). Furthermore, only the age group <19 years (OR 13.90) was associated to CA-MRSA$_G$ among HO-infections (Table 1).

In a multivariate model of hospitalized patients with CA-MRSA$_G$ infections (Table 2) only the presence of any kind of underlying disease (OR 4.71) and non-skin/soft-tissue infection (OR 7.14) were independently associated with healthcare-onset CA-MRSA$_G$ infections.

Molecular characterization of MRSA strains

The molecular characteristics: clonal complex (CC) and sequence type (ST), as defined by MLST, PFGE type and subtype, *spa*A and SCC*mec* types, presence of *pvl* genes, *agr* allotype, virulence genes profile along with the drug resistance pattern of all CA-MRSA$_G$ and HA-MRSA$_G$ are shown in Table 3. In addition, the distribution of the most predominant genotypes of MRSA isolates involved in invasive and non invasive infections for the entire population and stratified by age groups, according to the onset type of infections (community or healthcare) are shown in Table 4.

Most of CA-MRSA$_G$ isolates (n: 206, 90%) belonged to two major clones (about 45% each): PFGE type N-ST30-IV (n: 104) and PFGE type I-ST5-IV (n: 102,), which accounted for 33% and 31% of all MRSA, 46% and 37% of CO-MRSA infections and 4% and 20% of HO-MRSA infections, respectively (Table 4). The remaining CA-MRSA$_G$ isolates belonged to the following genotypes: R-ST72-IV (n: 10, 4%), USA300 ST8-IV (n: 5, 2%), D-ST97-IVc (n: 3, 1.5%), G-ST88-IVg, Q-ST1649-IVc (SLV of ST6), F-ST1-Vv (5C2), V-ST1210-IVE and V-ST121-Vv (one isolate each) (Tables 3 and 4).

The CA-MRSA isolates clonally related by PFGE to the USA300 MRSA epidemic strain (n: 5) belonged to ST8, CC8, *spa*-t008 and to *agr* 1. Two of these isolates were associated with SCC*mec*IVc and shared the virulence genes profile *pvl-lukDE-sek-seq-bsa*, one isolate with SCC*mec*IVb carried *luk*DE-*sea-sec-bsa* and other one with SCC*mec*Vv harbored *pvl-lukDE-bsa* genes. Only one isolate with subtype SCC*mec*IVa, carrying *lukDE-sek-seq-bsa* genes, also harbored the *arc*A gene which is an indicator of the presence of the ACME 1.

Additional minor CA-MRSA clones were also detected and their molecular features are included in Table 3.

The majority of the HA-MRSA isolates were related with the Cordobes/Chilean clone, pulsotype A, ST5-SCC*mec*I-t149 (61 isolates, 66%). The second most commonly identified HA-MRSA genotype was the Pediatric clone Argentinean variant (pulsotype C-ST100-IVNv) (23%, Table 3). These two clones represented 18% and 7% of all MRSA, 5% and 4% of CO-MRSA infections and 47% and 12% of HO-MRSA infections, respectively (Table 4). Other HA-MRSA isolates only accounted for 3% of all MRSA: (*a*) Brazilian clone: 7 isolates with B-ST239-IIIA genotype and 1 isolate with B-ST2266 (new ST, SLV of ST239)-IIIA genotype and (*b*) E-ST5-SCC*mec*I-t12090 (new *spa*-type) 3 isolates.

MRSA clones by epidemiological criteria (CDC) and age group

The distributions of the most predominant genotypes of MRSA isolates by epidemiological criteria (CACO-, HACO- and HAHO-MRSA infections) are shown in Fig. 2. The ST5-IV clone accounted for 35% and 30% of CACO-MRSA and HA-MRSA infections (43% HACO; 20% HAHO), respectively. Importantly, this CA-MRSA clone was the second more frequent one causing HA-MRSA infections, following HA-MRSA clone ST5-I. Not surprisingly, ST5-I clone was only involved in HA-infections (33% of total,: 13% of HACO- and 47% of HAHO-infections). On the other hand, the ST30-IV represented 60% of CACO-MRSA infections and 12% of HA-MRSA infections (23% HACO; 4% HAHO).

When stratified by age (Table 4), the proportion of all MRSA infections (total and INVI) caused by ST5-IV CA-MRSA clone was greater for children than for adults (50% vs. 20% for total infections and 48% vs. 15% for INVI, $P < 0.0001$). The opposite scenario was detected for the ST5-I HA-MRSA clone, which affected in greater proportion adults than children (30% vs. 2% for total infections and 47% vs. 4.5% for INVI, $P < 0.0001$) (Table 4). In contrast, the percentage of infections caused by ST30-IV CA-MRSA was similar in children and adults (31% vs 33% $P = 0.80$, for total infections and 22% vs 11% $P = 0.07$, for INVI) (Table 4).

Regarding the CO-infections and presence of HRFs, the prevalence of ST5-IV CA-MRSA clone was about the same among children without/with HRFs [n: 68 (47%) vs. n: 31 (58%), respectively, $P > 0.3$]

Table 4
Most frequent genotypes of Methicillin Resistant *S. aureus* (MRSA) isolates by onset type of infections (total and invasive), for the entire sample and for isolates stratified by patient age group, Argentina, November 2009.

Genotypes[c]	MRSA infections			no. (%) of cases/no. (%) of INVI isolates					
	All MRSA infections			Community-onset infections			Healthcare-onset infections		
	Total	Pediatric patients	Adult patients	Total	Pediatric patients	Adult patients	Total	Pediatric patients	Adult patients
N-ST30-IV	104 (33) 23 (15)	40 (31) 13 (22)	64 (33) 10 (11)	100 (46) 21 (29)	40 (40) 13 (33)	60 (51) 8 (24.5)	4 (4) 2 (2.5)	0 (0) 0 (0)	4 (5) [d] 2 (3)
I-ST5-IV	102 (31) 42 (27.5)	63 (50)[a] 28 (48)[b]	39 (20)[a] 14 (15)[b]	81 (37) 27 (37)	50 (50)[a] 19 (49)[b]	31 (27)[a] 8 (24.5)[b]	21 (20) 15 (19)	13 (46)[a,d] 9 (43)[b]	8 (10)[a,d] 6 (10)[b]
A-ST5-I	61 (18) 47 (31)	3 (2)[a] 3 (4.5)[b]	58 (30)[a] 44 (47)[b]	10 (5) 7 (10)	0 (0) 0 (0)	10 (9) 7 (21.5)	51 (47) 40 (49)	3 (11)[a] 3 (14)[b]	48 (61)[a] 37 (62)[b]
C-ST100-IVNv	21 (7) 17 (11)	8 (6) 8 (13)	13 (7) 9 (10)	8 (4) 7 (10)	4 (4) 4 (10)	4 (3.5) 3 (9)	13 (12) 10 (12)	4 (14) 4 (19)	9 (11.5) 6 (10)
R-ST72-IV	10 (3) 6 (4)	7 (5) 5 (8)	3 (1) 1 (1)	3 (1.5) 1 (1)	0 (0) 0 (0)	3 (2.5) 1 (3)	7 (7) 5 (6)	7 (25)[d] 5 (24)	0 (0) 0 (0)
ST239-IIIA	8 (2) 7 (5)	0 (0) 0 (0)	8 (4) 7 (7.5)	1 (0.5) 1 (1.5)	0 (0) 0 (0)	1 (1) 1 (3)	7 (6) 6 (7.5)	0 (0) 0 (0)	7 (9) 6 (10)
USA300-ST8-IV	5 (2) 3 (2)	1 (1) 0 (0)	4 (2) 3 (3)	4 (2) 2 (3)	1 (1) 0 (0)	3 (2.5) 2 (6)	1 (1) 1 (1.5)	0 (0) 0 (0)	1 (1.5) 1 (2)
Others	11 (4) 8 (4.5)	5 (5) 3 (4.5)	6 (3) 5 (5.5)	9 (4) 6 (8.5)	4 (5) 3 (8)	5 (3.5) 3 (9.5)	2 (3) 2 (2.5)	1 (4) 0 (0)	1 (2) 2 (3)
Total Infections Invasive Infections (INVI)	*n*: 322 INVI: 153	*n*: 127 INVI: 60	*n*: 195 INVI: 93	*n*: 216 INVI: 72	*n*: 99 INVI: 39	*n*: 117 INVI: 33	*n*: 106 INVI: 81	*n*: 28 INVI: 21	*n*: 78 INVI: 60

[a] $P<0.001$ by χ^2 test, for comparison between pediatric and adult cases of all MRSA infections, in both hospital and community setting, for each genotype.
[b] $P<0.001$ by χ^2 test, for comparison between pediatric and adult cases of invasive MRSA infections, in both hospital and community setting, for each genotype.
[c] Genotypes are denoted as: type (by PFGE)-Sequence Type (ST by MLST)-SCC*mec* type.
[d] CA-MRSA$_G$ isolates (*n*: 32) distributed in micro-outbreaks (≥ 2 isolates with the same genotype) from nine hospitals.

and among adults without/with HRFs [*n*: 68 (23%) vs. *n*: 49 (33%), respectively, $P>0.27$]. In addition, the ST30-IV CA-MRSA clone in both, children and adults, was significantly more frequent among patients without HRFs than in those with HRFs (50% vs. 19% for children, $P=0.0039$ and 69% vs. 24% for adult patients, $P<0.0001$).

MRSA clones and geographic distribution

While isolates belonging to Cordobes/Chilean ST5-I HA-MRSA clone were recovered throughout Argentina in the healthcare setting with similar frequencies, the proportions of ST30-IV

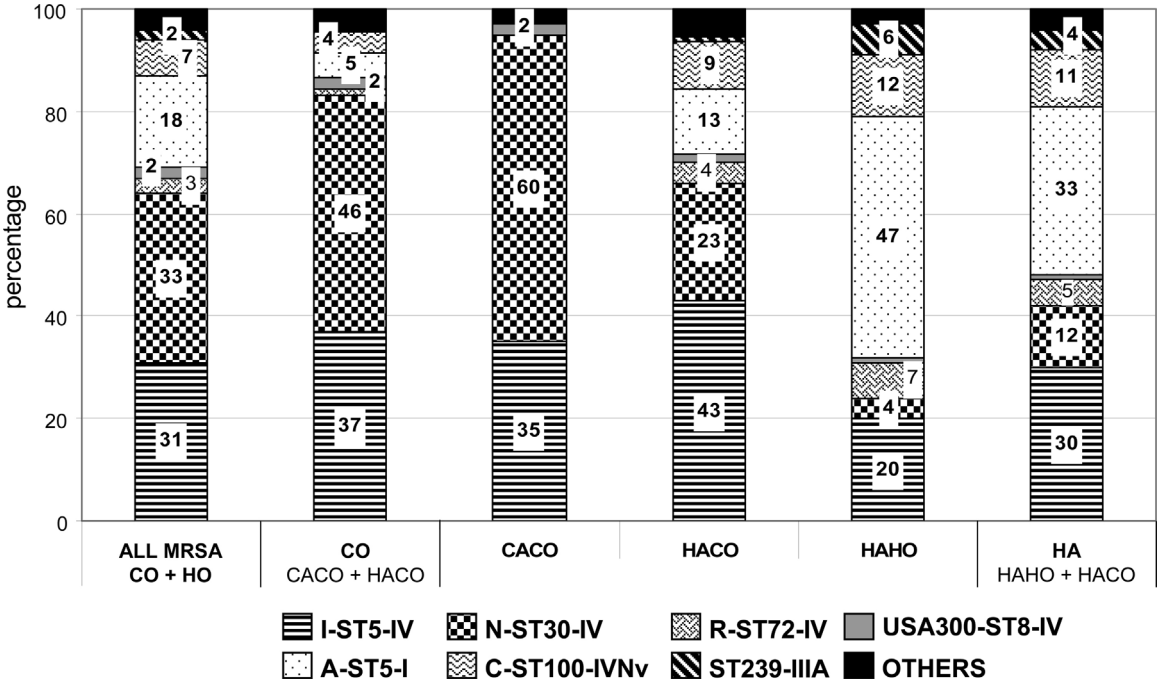

Figure 2. Prevalence of major HA-MRSA and CA-MRSA clones by epidemiological criteria and onset type of infection in entire population, Argentina. CACO: community-associated community-onset infections, HA: healthcare-associated infections: including HACO: healthcare-associated community-onset and HAHO: healthcare-associated hospital-onset infections.

Table 5
Antimicrobial resistance rates of CA-MRSA$_G$ and HA-MRSA$_G$ isolates from all cases and by onset type of infections in Argentina, November 2009.

Antimicrobial[a]	CA-MRSA$_G$				HA-MRSA$_G$[b]	*P* value
	CO, no. (%)*n*: 195	HO, no. (%)*n*: 34	*P* value CO vs. HO	Total, no. (%)*N*: 229	Total, no. (%)*N*: 93	CA-MRSA vs HA-MRSA
Gentamicin	16(8.2)	13(38.2)	**<0.0001**	29(12.7)	90(96.8)	**<0.0001**
Ciprofloxacin	2(1.0)	1(2.9)	0.37	3(1.3)	75(80.6)	**<0.0001**
Clindamycin	27(13.8)	11(32.4)	**0.007**	38(16.6)	79(84.9)	**<0.0001**
CLIi	26(13.3)	11(32.4)	**0.0054**	37(16.2)	1(1.2)	**<0.0001**
CLIc	1(0.5)	0(0)	NA	1(0.4)	78(83.2)	**<0.0001**
Erythromycin	34(17.4)	15(44.1)	**0.0005**	49(21.4)	79(84.9)	**<0.0001**
Rifampicin	1(0.5)	2(5.9)	0.058	3(1.3)	23(24.7)	**<0.0001**
Trimethoprim/sulfamethoxazole	0(0)	0(0)	–	0(0)	8(8.6)	NA
Chloramphenicol	0(0)	1(2.9)	–	1(0.4)	6(6.5)	**0.0028**
Minocycline	0(0)	0(0)	–	0(0)	1(1.1)	NA
Linezolid	0(0)	0(0)	NA	0(0)	0(0)	NA

CA-MRSA$_G$ and HA-MRSA$_G$ community-associated and healthcare-associated methicillin-resistant *S. aureus* genotypes; CO and HO: community-onset and healthcare-onset infections.
CLIc and CLIi: constitutive and inducible resistance to macrolide, lincosamide and streptogramine B, respectively, NA: Not applicable.
[a] All MRSA isolates were susceptible to (MIC_{90} and range in μg/mL): vancomycin (1; 0.5–2), teicoplanin (1; 0.5–2), tigecycline (0.25; 0.03–0.25), fosfomycin (4; 0.5 to >512) and daptomycin (0.25; 0.06–0.5).
[b] $P > 0.05$ by χ^2 test, for comparison between *S. aureus* isolates from patients with CO infections and those from HO infections.
Significant differences ($P < 0.05$) for each comparison between the resistances (%) are shown in boldface font.

($P = 0.0006$) and ST5-IV ($P = 0.02$) differed significantly between the North (75% and 20%) and the South (18% and 55%) of the country in the community setting (Fig. 1). Then, the CA-MRSA clone ST30-IV has mainly spread in the North whereas the CA-MRSA clone ST5-IV has remained in the South of Argentina.

Antimicrobial resistance to non-β-lactam agents

CA-MRSA$_G$ isolates were associated with lower rates of resistance to erythromycin, clindamycin, ciprofloxacin, gentamicin, rifampicin, trimethoprim/sulfamethoxazole and chloramphenicol than HA-MRSA$_G$ isolates ($P < 0.0001$ for most comparisons, Table 5). As opposed to HA-MRSA$_G$ strains, among CA-MRSA$_G$ isolates, those recovered from patients with HO-infections had significantly higher rates of resistance to gentamicyn, erythromycin and clindamycin than those obtained from patients with CO-infections (Table 5).

From all CA-MRSA$_G$ isolates (*n*: 229), 25% were resistant to at least one and 5% to at least two non-β-lactam antibiotics. From all HA-MRSA$_G$ isolates, 93% were resistant to two or more non-β-lactam antibiotics. Multi-resistance occurred exclusively in HA-MRSA$_G$ and their antimicrobial resistance profiles (Table 3) were similar to those described in our previous studies (Sola et al., 2006, 2008, 2012).

All MRSA isolates were susceptible to: vancomycin, teicoplanin, tigecycline, fosfomycin and daptomycin (Table 5).

Discussion

Surprisingly, there are not many studies reporting data about all types of *S. aureus* infections in a general population in the last decade, covering isolates from children and adults in the community and hospital settings (Ray et al., 2012; Klein et al., 2013). Moreover, unlike in North America and Europe, few studies have documented the epidemiology of CA-MRSA$_G$ as cause of healthcare-onset infections in Latin America (Benoit et al., 2008; Alvarez et al., 2010; Jimenez et al., 2012; Caboclo et al., 2013). This study provides the first nationwide comprehensive description about the epidemiology of CA-MRSA$_G$ and HA-MRSA$_G$ as cause of both, CO- and HO-infections in Argentina.

In this prospective cross-sectional, multicenter, nationwide study, MRSA accounted for 55% of the *S. aureus* isolates. Importantly, a significantly higher proportion of MRSA among CO- than HO-infections was detected, particularly in children, in patients without HRFs and in patients with SSTI. Moreover, more than 50% of HA-MRSA infections were caused by CA-MRSA$_G$, mainly in pediatrics (> 70%). Furthermore our results from a longitudinal analysis evaluating the trends in *S. aureus* infections between 2001 and 2011 in Argentina (49,909 culture-confirmed *S. aureus* infections, WHONET national database, Fig S2A–C) suggest that the proportion of MRSA has risen significantly from 39.7% in 2001 to 52.1% in 2011 having peaked at 55.2% in 2010. This increase was largely related to CA-MRSA strain types (6.4% in 2001 to 38.9% in 2011), which is consistent with our prospective cross-sectional study. All these results, strongly suggest that in Argentina, typical *CA*-MRSA lineages appear to be replacing classical HA-MRSA clones as causes of HO-infections along with an increasing reservoir in the community. These important findings are in line with mathematical models predicting the replacement of HA-MRSA in hospitals by epidemic CA-MRSA (D'Agata et al., 2009; Skov and Jensen, 2009), harboring a smaller staphylococcal cassette chromosome mec (SCCmecIV) with a lower fitness cost. However, the possibility of coexistence of both CA- and HA-MRSA has also been suggested (Kouyos et al., 2013). Importantly, multi-resistance occurred exclusively in isolates with HA-MRSA$_G$ and 95% of all CA-MRSA$_G$ isolates were only resistant to no more than 1 of the non-beta-lactam antibiotics. Furthermore, all these epidemiological changes have significant implications for the diagnosis and treatment of both CO- (it is necessary to consider MRSA for empiric therapy) and HO- (more treatment options with non-beta-lactam antimicrobial are possible) *S. aureus* infections.

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In agreement with previous studies from other countries (David and Daum, 2010), specific socio-demographic characteristics (overcrowding, to have ≥5 persons per household and to be economically disadvantaged) were associated with CA-MRSA$_G$ in Argentina. However, multivariate analysis showed that CA-MRSA$_G$, were only independently associated with CO-infections, particularly SSTI, in younger patients (<19 years) without comorbidities. Additionally, CA-MRSA strain types detected in this study also caused invasive infections, particularly osteomyelitis and severe pneumonia in otherwise healthy people, which supports the virulent nature of predominant CA-MRSA genotypes in Argentina.

Importantly, the CA-MRSA$_G$ penetration into hospitals, as it was strongly suggested in this work, may require implementation of new infection control strategies, as previously advised (Otter and

French, 2012). In addition there is some evidence that they may cause more severe disease than HA-MRSA strains (Otto, 2013). In this study, in the healthcare setting, CA-MRSA$_G$ compared with HA-MRSA$_G$ were only independently associated with younger children, all other clinical and demographic factors assessed yielded no differences. In addition, HO-infections caused by CA-MRSA$_G$, like those caused by the HA-MRSA$_G$, were more likely to be non-skin related diseases and to occur in patients with comorbidities, than CO-infections caused by CA-MRSA$_G$. All these results support that: *(i)* the CA-MRSA strains behave more like to HA-MRSA strains when they enter into hospitals, as it was already suggested (Otter and French, 2011; Benoit et al., 2008; Popoola et al., 2013) *(ii)* the pediatric population, particularly <1 year, remains as the highest risk group for HO-infections caused by CA-MRSA$_G$, in agreement with a recent report (Iwamoto et al., 2013).

On the other hand, in line with previous studies (David and Daum, 2010; Otter and French, 2011) the patients infected with HA-MRSA$_G$ had significantly higher rates of most HRFs compared with those with CA-MRSA$_G$. However 31% of patients with CO infections by CA-MRSA$_G$ had at least one HRF. This highlights the limitations of epidemiological definitions, but also of genotypic classifications to define epidemiological reservoirs and shows that both molecular typing data and epidemiological data have to be considered together when performing surveillance of *S. aureus* infections.

The molecular characteristics and drug resistance to non-β-Lactams (Table 3) shared by the isolates belonging to each one of two major CA-MRSA clones (ST5-IVa-PVL$^+$-t311 and ST30-IVc-PVL$^+$-t019), which accounted for 90% of CA-MRSA isolates (45% each) and two major HA-MRSA clones (ST5-I-t149 and ST100-IVNv-t002) largely correspond to those reported in our previous paper (Sola et al., 2012). Notably, the ST30-IV-PVL$^+$ clone, has lower rates of resistance than their ST5-IV-PVL$^+$ counterparts to erythromycin (12% vs. 28%) and clindamycin (8% vs. 24%), which has important implications for empirical antimicrobial treatment, particularly SSTI in the community setting.

On the other hand, the mobile genetic element-encoded gene, *sas*X was not identified in any of the MRSA clones analyzed in this study. This is consistent with the finding that, although *sas*X was recently recognized as a crucial factor related to the epidemiological success of MRSA clones at the hospital setting in China (particularly ST239-III), it was absent from other major global MRSA strains from divergent clonal and geographical backgrounds (Li et al., 2012). It is likely that the South American isolates associated to ST239-III MRSA are clustered within a uniform phylogenetic clade highly distinct than the Asian clade (Harris et al., 2010). Although the Brazilian HA-MRSA clone (ST239-IIIA), only accounts for 6% of HO-infections in Argentina, surveillance over time for detection of *sas*X is strongly recommended.

The Cordobes/Chilean HA-MRSA clone ST5-I has spread from the South (Argentina and Chile) to the North of Latin America through the Andean region (Perú, Ecuador, Venezuela and Colombia) as well as in Paraguay and Brazil (Sola et al., 2006, 2008; Reyes et al., 2009; Becker et al., 2012; Medina et al., 2013). In this study, it accounted for 66% of HA-MRSA$_G$. Hence, in Argentina, HO-infections were associated with this HA-MRSA clone mainly in adults (47% in the entire population, 61% for adults), but followed by the CA-MRSA-ST5-IVa-PVL$^+$ clone, particularly in children (20% in the entire population, 46% for children). On the other hand, two CA-MRSA clones: ST30-IVc-PVL$^+$ and ST5-IVa-PVL$^+$ have accounted for 46% and 37% of CO-MRSA infections in the entire population, respectively. However, the ST30-IVc-PVL$^+$ clone was predominant in adults (51%), mainly in those without HRFs (69%) in the previous year and the second one in children (50%), both with (58%) and without (47%) HRFs. All these results strongly suggest that ST5-IV-PVL$^+$ is the dominant CA-MRSA clone that has entered into the hospital setting, replacing the Cordobés/Chilean HA-MRSA clone, particularly in pediatrics. A resembling situation was described in Medellin city (Colombia), where the Cordobes/Chilean clone is being displaced in the hospital setting, but in this case, by the USA300-LV clone (Jimenez et al., 2012). The transmission into the hospital of ST5-IV-PVL$^+$ CA-MRSA clone constitutes a concern for public health due to: *(i)* its high transmissibility in the community (Sola et al., 2008, 2012) *(ii)* its great ability to cause invasive infections particularly in children (Sola et al., 2012) and *(iii)* its capacity to express the h-VISA or VISA phenotypes, (Sola et al., 2011, 2012; Errecalde et al., 2013), being vancomycin the mainstay of treatment for this invasive CA-MRSA infections (Liu et al., 2011). This work also supports the age preferences of two clones belonging to CC5 (ST5-IV-PVL$^+$ and ST5-I). Associations between *S. aureus* genotypes and patient age have recently been described in certain MSSA lineages (CC5 or CC45) (Blomfeldt et al., 2013) and in some MRSA clones (Nichol et al., 2013; Williamson et al., 2013).

The nationwide coverage of our study allowed for detecting a higher proportion of MRSA in Northern (81%), than in Central (53%) and Southern (29%) regions of Argentina. Moreover, the incidence of MRSA was increased 3.6-fold in the North compared to the South of the country. This finding was largely related to the spread of CA-MRSA strains types in the North (72%) compared to the South (15%) of Argentina, with a rate of CA-MRSA$_G$ 6.2-fold higher in northern (mainly due to ST30-IV clone) than in sourthen regions. This situation might indicate that this CA-MRSA clone is spreading not only from Uruguay (Benoit et al., 2008; Sola et al., 2012), but also from other neighboring regions in the North and Northeast of Argentina, such as Brazil, where it is highly prevalent in the community (Scribel et al., 2009). As far as we know, there is no data about CA-MRSA infections in Bolivia and Paraguay. Additionally, while Argentinean health system ensures basic coverage, access levels are particularly related to differences in the economic area of each region. According to general and health indicators, the northeast and northwest are the most impoverished and backward regions (PNUD, 2010). Lower socioeconomic status (and crowded living conditions) along with a lower health coverage and weather conditions (warmer and/or wetter) contributing to a greater density of these strains on the skin, are likely important factors that might be involved in the spread of the CA-MRSA strains in the northern region of Argentina.

The results of this study agree with another one (Fernandez et al., 2013), showing that the CA-MRSA ST30-IV clone has been the most prevalent during 2010–2011 among CACO-MRSA invasive infections in adult population in Argentina (Fernandez et al., 2013). However, that study (Fernandez et al., 2013), was limited not only in geographical scope (central region), but also in the population analyzed (only adults without HRFs with CO-infections).

Another important finding of our study was the identification of the CA-MRSA clone ST72-IV-PVL$^-$ as a minor one (3% of all MRSA), which has also entered into hospitals causing 7% of HO-infections mainly in children (25%), as opposed to South Korea where it was described as the major CA-MRSA clone (Chuang and Huang, 2013). The USA300 clone (ST8-IV), which has become a major international epidemic clone, commonly causing CO- and HO-infections in the USA, is now the dominant CA-MRSA strain in other countries and it has also been identified in all continents except Antarctica (Nimmo, 2012). The variants, USA300-0114 (ACME$^+$) and USA300-LV (ACME$^-$) have been dominant in the CA-MRSA epidemics in the USA and in the North of Latin America, respectively (Nimmo, 2012; Sola et al., 2012; Medina et al., 2013; Reyes et al., 2009). In Argentina, unlike in the northern areas of South America, the USA300-LV remains as a minor clone since 2007 (4 cases) (Sola et al., 2012) and only 4 cases were identified in this study with a high degree of genetic diversity. Then, other factors, such as sociodemographic, socioeconomic, environmental and ethnicity, in addition to bacterial factors, related with the competition with

other established epidemic clones by the same ecological niche, could influence its spread, but further investigation is needed. Importantly, one isolate with all characteristics of variant USA300-0114-ACME$^+$ was also identified in this study, representing the first case in Argentina of CA-MRSA infection caused by this highly virulent and transmissible strain. This isolate was recovered from an uncomplicated SSTI in a previously healthy patient, 30 years old, who traveled to the USA in the previous year, suggesting that this clone likely was imported from that country. Whether the spread of this strain in Argentina will occur and in what extent it will impact on illness and mortality rates, remains to be seen.

Although CC121-MSSA is a common cause of SSTI worldwide and one of the dominant CC *S. aureus*, MRSA from this lineage appear to be very rare (Monecke et al., 2011). Recently, two isolates recovered in unrelated pediatric patients from Cambodia with CA infections were CC121/ST121 MRSA-V-PVL$^+$ (Chuang and Huang, 2013). Importantly, we report here CA-MRSA isolates belonging to CC121 in Argentina. One of those isolates was characterized as ST1210 (SLV of ST121), *spa*-t812, SCC*mec*IVE, PVL$^+$, *eta*$^-$ and *etb*$^-$, and the other as ST121, *spa*-t159, SSC*mec*V, PVL$^-$, *eta*$^+$ and *etb*$^+$. They were recovered from children, with deep-seated (abscess) and superficial (impetigo) skin infections, respectively. Moreover, two CA-MRSA strains belonging to CC121/ST1210 *spa*-t645, SCC*mec*IVE, PVL$^+$, *eta*$^-$, *etb*$^-$, were also isolated in Argentina (central region) six months before this study from children with osteomyelitis; (Egea and Sola, et al., unpublished results). The characteristics of all these cases support the mutually exclusive nature of the *eta*/*etb* and *pvl* genes in CC121 and the association of superficial and deep-seated skin infections with either exfoliative toxins ETA and ETB or the PVL toxin, respectively (Kurt et al., 2013 and references there in). Moreover, a recent study (Kurt et al., 2013) reported the presence of a phylogenetic clade within the CC121 (clade C) associated geographically with South and Central America, in which several *spa* types such as *spa*-t159 and *spa*-t645 and both, isolates *eta*/*etb*$^+$-*pvl*$^-$ and *eta*/*etb*$^-$-*pvl*$^+$, were detected. Then, the local emergence of the CC121-CA-MRSA isolates detected in Argentina by independent acquisitions of different SCC*mec* types (IV and V) by the ancestor CC121 clade C, could be hypothesized.

Interestingly, as a minor or sporadic CA-MRSA clone, the genotype ST97-IV was also identified in this study. It is important to remark that this clone is likely related to clones of human epidemic CA-MRSA which resulted from livestock-to-human host jumps by the major bovine *S. aureus* CC97 (Spoor et al., 2013; Mediavilla et al., 2012).

Hence, this finding suggests that the livestock, one of the big props of the Argentinean economy, may be an additional reservoir of MRSA strains. However, regular molecular surveillance of the microbiota in livestock in this country would be needed to demonstrate this hypothesis. In Argentina there is a national program of epidemiology and control of healthcare-associated infections (VIHDA, Ministry of Health-Government of Argentina, INE and ANLIS, http://www.vihda.gov.ar/), covering almost all regions of the country. The aims of VIHDA program include the establishment of standards and guidelines for the control of nosocomial infections, according to national data. Considering the results of this study, household-based interventions should be developed to control these infections by CA-MRSA$_G$ in the community, and coordination between medical and veterinary providers could be beneficial.

The strengths of this study include the prospective design, the extent of socio-demographic and clinical information collected from all over the country and the extensive molecular characterization of isolates causing infections. However, this study was subject to some limitations. We based our definition of healthcare-onset CA-MRSA genotype infections on time from hospital admission to culture. Because surveillance cultures on admission are not routinely performed, there is no reliable way to determine the actual time and origin of MRSA acquisition, implying that misclassification was possible. However, 32 of 34 cases of healthcare-onset CA-MRSA infections were clustered in micro-outbreaks of infections caused by the same genotype in only 9 of 66 hospitals in one month. In addition, no patient treated for a community onset CA-MRSA$_G$ infection was present at the same time and ward service where these micro-outbreaks were detected. Thereby, it is unlikely that these cases of healthcare onset infections caused by CA-MRSA$_G$ were acquired outside of the hospital or by cross transmission from a patient with a community onset CA-MRSA infection and hospitalized at the same time and ward.

In conclusion, the results from this study strongly suggest the rapid emergence and introduction of CA-MRSA$_G$ strains into hospitals in Argentina, supplanting the traditional HA-MRSA lineages, along with a growing reservoir in the community. Importantly, CA-MRSA$_G$ strains behave more like HA-MRSA$_G$ strains when they are inside hospitals. While two CA-MRSA clones were disseminated in the community setting, the ST30-IV-PVL$^+$and the ST5-IV-PVL$^+$, the latter one seems to be spreading also into hospitals, replacing the Cordobes/Chilean ST5-I HA-MRSA clone, mainly in children.

By means of local molecular and clinical surveillance of MRSA infections our study extends the existing literature, providing information about the factors associated with CA-MRSA clones spreading in the community, penetration and transmissibility in hospitals. These contributions will be useful particularly in children, to evaluate infection control strategies and prevention, targeting community and hospital sources.

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