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ORIGINAL RESEARCH

Staphylococcus aureus Nasal Colonization in Spanish Children. The COSACO Nationwide Surveillance Study

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Objective: To assess the prevalence and risk factors for *S. aureus* and methicillin-resistant *S. aureus* (MRSA) nasal colonization in Spanish children.

Methods: Cross-sectional study of patients <14 years from primary care centers all over Spain. Clinical data and nasal aspirates were collected from March to July 2018.

Results: A total of 1876 patients were enrolled. Prevalence of *S. aureus* and MRSA colonization were 33% (95% CI 30.9–35.1) and 1.44% (95% CI 0.9–2), respectively. Thirty-three percent of the children (633/1876) presented chronic conditions, mainly atopic dermatitis, asthma and/or allergy (524/633). Factors associated with *S. aureus* colonization were age ≥5 years (OR 1.10, 95% CI 1.07–1.12), male sex (OR 1.43, 95% CI 1.17–1.76), urban setting (OR 1.46, 95% CI 1.08–1.97) and the presence of asthma, atopic dermatitis or allergies (OR 1.25; 95% CI: 1.093–1.43). Rural residence was the only factor associated with MRSA colonization (OR 3.62, 95% CI 1.57–8.36). MRSA was more frequently resistant than methicillin-susceptible *S. aureus* to ciprofloxacin [41.2% vs 2.6%; p<0.0001], clindamycin [26% vs 16.9%; p=0.39], and mupirocin [14.3% vs 6.7%; p=0.18]. None of the MRSA strains was resistant to tetracycline, fosfomycin, vancomycin or daptomycin.

Conclusions: The main risk factors for *S. aureus* colonization in Spanish children are being above five years of age, male gender, atopic dermatitis, asthma or allergy, and residence in urban areas. MRSA colonization is low, but higher than in other European countries and is associated with rural settings.

Keywords: *S. aureus*, MRSA, child, colonization

Introduction

Staphylococcus aureus is the leading cause of skin and soft tissue infections (SSTIs) in children,[1] and may cause bacteremia and other invasive diseases such as osteoarticular infections and pneumonia.[2]

For the past 20 years, an increase in both community-associated and hospital-acquired infections by *S. aureus* has been observed,[3,4] causing significant morbidity and mortality. Methicillin-resistant *S. aureus* (MRSA) was first isolated in hospitalized and chronically ill patients. In the mid-1990s, community-associated cases started to emerge leading to changes in empirical treatments in areas where methicillin resistance exceeded 10%-15%.

The rate of MRSA among community-acquired *S. aureus* (CA-MRSA) infection in children differs between countries. In Argentina, MRSA causes up to 65% of

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S. aureus community-acquired bacteremia in children.[5] In the US, Sutter et al have reported a 31.6% prevalence of MRSA in community-onset *S. aureus* infections in 2014.[6] In Greece, CA-MRSA has been identified in 35% of children admitted due to *S. aureus* osteoarticular infection, and in 75% of children with *S. aureus* pneumonia.[3,7] The first case of CA-MRSA in a child in Spain was reported in 2006,[8] although current data regarding CA-MRSA infections in children in our country are scarce.

S. aureus colonization is associated with an increased risk of infection and contributes to transmission. Besides, it might be an important reservoir of resistance. A multicenter study performed in nine European countries reported a global prevalence of 21.6% of nasopharyngeal colonization by *S. aureus*. In this study, the prevalence of colonization in Spanish children was 31.5%, but the percentage of MRSA was not specified.[9]

In settings with high CA-MRSA prevalence, empirical treatment of infections likely caused by *S. aureus* should address this potential threat.[10] For all these reasons, we designed this study in order to estimate the prevalence of MRSA colonization in Spanish children who attend primary health-care centers for routine health screenings, as well as the risk factors associated with CA-MRSA nasal carriage. This will help to establish a proper empirical therapeutic approach in children with suspected community-acquired *S. aureus* infections.

Methods

We conducted a nationwide observational, cross-sectional multicenter study in children from community settings all over Spain (the COSACO study –Colonization by *S. aureus* in the Community). All research was performed in accordance with local regulations. Informed consent in accordance with the Declaration of Helsinki was obtained from the parents or guardians of all children before their inclusion, as well as from those patients aged 12 years or older. The study was approved by the Clinical Research Ethics Committee at La Paz University Hospital (Madrid) (*PI18/00372*).

Study Participants

Between March and July 2018, children under 14 years of age attending primary care for routine preventive assessments were recruited. Children presenting with an active infection during the visit (either confirmed or suspected) were excluded from the study. Seventy primary care centers from all the Spanish regions took part in the study. According to region features and population density, at least two health-care centers (from rural, urban and mixed areas) were selected to take part in the study. The number of included patients was proportional to the pediatric population living in that region.

Primary care pediatricians from a pre-existing research network (PAPenRED) recruited patients in accordance with the study protocol, which included a homogeneous age distribution. Children were included every Tuesday and Thursday until recruitment was completed. Sample size was calculated for a 95% confidence level and a 3% margin of error, assuming a prevalence of nasal colonization of 20% for *S. aureus* and of 3% for MRSA. According to these data and taking into account a 15% of possible losses during the inclusion process, a minimum target of 1745 samples was established.

A survey was performed for each patient to collect clinical and epidemiological data including age; gender; siblings; household members; habitat type; child's and parents' origin; school/day-care attendance; exposure to livestock or pets; underlying chronic conditions; hospital admissions; antibiotic treatment in the previous month; and/or previous skin infections affecting the child or any of the household members.

Study Samples

Nasal swabs from every patient were collected following a standardized protocol, inserting the swab tip into the two nostrils and rotating it for five seconds in each one. ESwab™ flocked swabs with Liquid Amies Medium (Copan, Brescia, Italy) were used. Nasal samples were submitted from each primary care center to its microbiology laboratory of reference belonging to hospitals of the National Health Service in Spain. Isolation and identification of *S. aureus* were based on standard microbiological procedures. For methicillin resistance screening, disk diffusion method with cefoxitin (30 μg) was used. Susceptibility testing to other antibiotics was performed by microdilution or disk diffusion. Methods and antimicrobial susceptibility interpretations were in accordance with the EUCAST guidelines.[11]

Statistical Analysis

Values are expressed as percentages for discrete variables or as the mean and standard deviation for continuous variables. Categorical variables were compared using χ^2 and Fisher's exact test, and continuous variables with Student's *t* test or non-parametric tests, as appropriate.

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Logistic regression for multivariate analysis was performed according to the distribution and characteristics of the variables. A two-sided value of $p \leq 0.05$ was considered statistically significant. Odds ratio (OR) was used as measures of association, with 95% confidence interval (CI) to assess its precision. All analyses were performed using the Statistical Package for the Social Sciences, version 21.0 (IBM, Armonk, NY).

Results

We included 1876 children and their corresponding samples. The epidemiological and clinical characteristics of the cohort are shown in Table 1. A total of 619 samples were positive, meaning that 33% of children (95% CI: 30.9–35.1) were colonized by *S. aureus*. MRSA was isolated in 27/619 positive samples (4.4%; 95% CI: 2.7–6.0). This implies an MRSA colonization prevalence of 1.4% in Spanish children (95% CI: 0.9–2.0).

The comparison of the epidemiological features of colonized and non-colonized children is shown in Table 2. In the univariate analysis, children colonized by *S. aureus* were: older than 5 years of age; males; living in urban settings; attending school or daycare and having previous skin infections or underlying chronic conditions more frequently than non-colonized patients. Logistic regression analysis indicated a significantly higher risk of colonization by *S. aureus* for children older than five years of age, males, living in urban settings and with chronic diseases (Table 2). Thirty-three percent of the children included in the study presented some type of chronic condition (633/1876), mostly atopic dermatitis, asthma and/or allergy (82.7%; 524/633). The presence of asthma, atopic dermatitis or allergies increased the risk of *S. aureus* colonization (OR 1.25; 95% CI: 1.093–1.43).

S. aureus colonization prevalence by age and sex is reported in Supplementary materials (https://www.dovepress.com/get_supplementary_file.php?f=282880.pdf). In children older than 10 years, we observed the greatest difference in the colonization rate between males and females [49.3% vs 31.7%; OR 2.09 (95% CI; 1.49–2.94)]. In our cohort, the number of household members and siblings, foreign origin of children or parents, livestock or pet exposure and antibiotic treatment in the previous month had no impact on the carrier status.

Regarding MRSA colonization, a significantly higher rate was observed among children living in rural environments (OR 3.49; 95% CI: 1.46–8.37) (Supplementary materials https://www.dovepress.com/get_supplementary_file.php?f=282880.pdf). No other risk factors related to CA-MRSA colonization were found. Children aged 0–4 years had a CA-MRSA colonization rate of 7.4% (9/122), whereas 5–9 years and 10–14 years had 3.4% (9/263) and 3.8% (9/234)

Table 1 Epidemiological and Clinical Characteristics of the Study Cohort (n=1876)

		n (%)
Age group (years)	0–4 5–9 10–14	651 (34.7) 647 (34.5) 578 (30.8)
Mean age in years (SD)*		7.01 (4.38)
Female gender		946 (50.4)
Child's origin	Foreign Spanish	77 (4.1) 1799 (95.9)
Mother's origin	Foreign Spanish	387 (20.6) 1489 (79.4)
Father's origin	Foreign Spanish	357 (19) 1519 (81)
Number of siblings	0 1 2 3 ≥4	517 (27.5) 1016 (54.2) 252 (13.5) 59 (3.2) 32 (1.7)
Mean number of individuals per household (SD)		4.01 (0.99)
Habitat type	Rural Urban Mixed	296 (15.8) 1188 (64.3) 392 (20.9)
Livestock exposure Pets at home School or daycare attendance		192 (10.2) 867 (46.2) 1539 (82)
Antibiotic treatment in the previous month		105 (5.6)
Previous skin infection	Yes No Unknown	361 (19.2) 1418 (75.6) 97 (5.2)
Other household members with previous skin infections	Yes No Unknown	94 (5) 1720 (91.6) 62 (3.3)
Hospital admission in the last year		97 (5.2)
Underlying chronic disease	Atopic dermatitis (with no other atopic manifestations) Asthma and/or allergies Others	316 (16.8%) 208 (11.1%) 109 (5.8%)

Abbreviation: SD, standard deviation.

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Table 2 Variables Analyzed as Possible Risk Factors for *S. aureus* Colonization

Total Population (n=1876)		***S. aureus* Colonized (n=619) n (%) (95% CI) or Mean (SD)**	**Magnitude (CI 95%)**
Age group (years)	0–4 (n=651) 5–9 (n=647) 10–14 (n=578)	122 (18.7) (15.7–21.7) 263 (40.7) (36.9–44.4) 234 (40.5) (36.5–44.5)	**OR 5–14 years: 2.96 (2.36–3.72)***
Mean age (years)	Colonized Not colonized	8.19 (3.96) 6.44 (4.50)	**MD: 1.75 (1.35–2.15)***
Gender	Male (n=930) Female (n=946)	339 (36.5) (33.4–39.5) 280 (29.6) (26.7–32.1)	**OR male: 1.36 (1.12–1.66)***
Child's origin	Foreign (n=77) Spanish (n=1799)	26 (33.8) (23.2–44.3) 591 (32.8) (30.8–35.1)	OR: 1.04 (0.64–1.68)
Mother's origin	Foreign (n=387) Spanish (n=1489)	115 (29.7) (25.2–34.3) 502 (33.7) (31.4–36.2)	OR: 0.83 (0.65–1.05)
Father's origin	Foreign (n=357) Spanish (n=1519)	123 (34.5) (29.5–39.4) 494 (32.5) (30.3–35.0)	OR: 1.09 (0.85–1.38)
Number of siblings	Colonized Not colonized	2.00 (0.98) 1.97 (1.01)	MD: 0.03 (−0.07–0.13)
People per household	Colonized Not colonized	4.03 (0.95) 4.00 (1.01)	MD: 0.03 (−0.06–0.12)
Habitat	Urban (n=1580) Rural (n=296)	538 (34) (31.7–36.4) 81 (27.4) (22.3–32.4)	**OR urban: 1.37 (1.03–1.81)***
Livestock exposure	Yes (n=192) No (n=1679)	66 (34.4) (27.7–44.1) 553 (32.9) (30.6–35.1)	OR: 1.07 (0.78–1.47)
Pets at home	Yes (n=867) No (n=1002)	282 (32.5) (29.4–35.6) 333 (33.2) (30.3–36.2)	OR: 0.97 (0.80–1.18)
School/daycare attendance	Yes (n=1539) No (n=336)	551 (35.8) (33.4–38.2) 68 (20.2) (16.0–24.5)	**OR 2.19 (1.65–2.92)***
Previous antibiotic treatment	Yes (n=105) No (n=1761)	28 (56.7) (18.2–35.1) 588 (33.4) (31.2–35.6)	OR no antibiotic: 1.38 (0.88–2.15)
Previous skin infection	Yes (n=361) No (n=1418)	136 (37.7) (32.8–42.8) 455 (32,1) (29.7–34.6)	**OR: 1.29 (1.01–1.63)***
Hospital admission last year	Yes (n=97) No (n=1774)	26 (26.8) (18.0–35.6) 591 (33.3) (31.1–35.5)	OR: 1.36 (0.86–2.16)
Underlying chronic disease	Yes (n=633) No (n=1240)	242 (38.2) (34.7–42.3) 375 (30.2) (27.7–32.8)	**OR: 1.44 (1.18–1.76)***
MULTIVARIATE ANALYSIS			
Age Male gender Urban habitat Underlying chronic disease			**OR: 1.10 (1.07–1.12)*** **OR: 1.43 (1.17–1.76)*** **OR: 1.46 (1.08–1.97)*** **OR: 1.27 (1.02–1.57)***

Note: *Significant results are represented in bold letters.
Abbreviations: SD, standard deviation; MD, mean difference; OR, odds ratio; CI, confidence interval.

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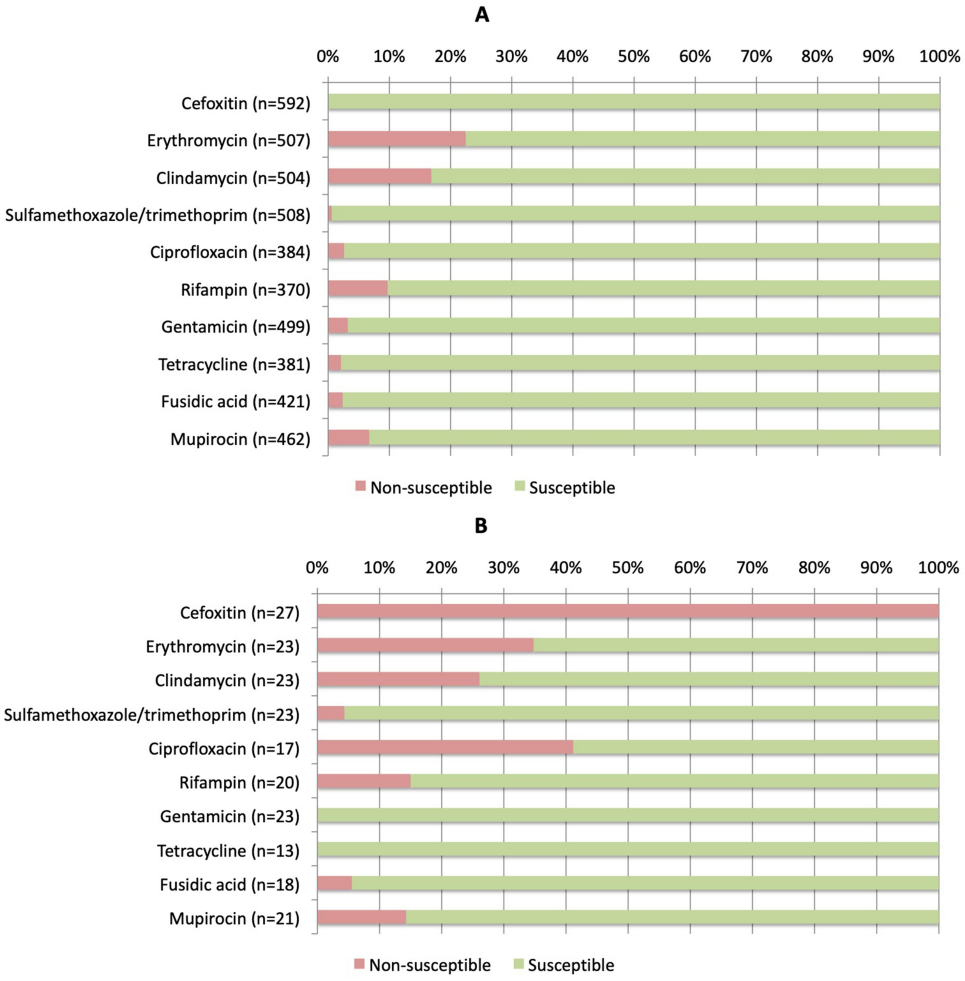

Figure 1 Antibiotic susceptibility results of methicillin-susceptible *S. aureus* (**A**) and methicillin-resistant strains (**B**).

respectively, although this trend was not statistically significant [OR 0–4 years vs 5–14: 2.12 (0.93–8.45)].

Antibiotic susceptibility results are shown in Figure 1 and Supplementary materials (https://www.dovepress.com/get_supplementary_file.php?f=282880.pdf). MRSA was more frequently resistant than methicillin-susceptible *S. aureus* (MSSA) to other antibiotics, including ciprofloxacin [41% (7/17) vs 2.6% (10/384); p<0.0001], erythromycin [34% (8/23) vs 22% (114/507); p=0.17], clindamycin [26% (6/23) vs 16.9% (85/504); p=0.39], and mupirocin [14.3% (3/21) vs 6.7% (31/462); p=0.18]. None of the MRSA strains associated resistance to tetracycline (n=13), fosfomycin (n=17), vancomycin (n=21) or daptomycin (n=20). Only one out of 18 strains was linezolid-resistant.

Discussion

This is the first study performed in Spain to determine the national prevalence and antibiotic resistance of commensal *S. aureus* in children, and one of the largest in Europe analyzing more than 1,800 nasal swabs obtained in primary care centers. The prevalence of nasal carriage was higher than 30% among Spanish children. The main risk factors for colonization were: age above 5 years; male gender; atopic dermatitis; asthma or allergy and residence in urban areas. MRSA prevalence was 1.4% and increased among children younger than 4 years and those living in rural areas.

Older children and young adults, as well as males, are known to be more frequently colonized by *S. aureus*.[9,12–15] As we have observed, other authors have also reported higher colonization rates in urban settings in asymptomatic children or among adults with SSTIs.[16,17] In our study, patients with chronic conditions presented higher rates of colonization, although most of them were atopic children. Patients with atopic dermatitis are mainly colonized by *S. aureus*, in contrast to children with healthy skin, who are more frequently colonized by *S. epidermidis* or

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S. hominis.[18] It has been described in the past that early-life skin colonization by *S. aureus* may contribute to the onset of atopic dermatitis.[18] *S. aureus* colonization has also been associated with asthma, food sensitization and allergy.[19,20] As neither previous antibiotic treatments nor hospital admissions were associated with colonization, atopy itself seems to increase the risk for *S. aureus* colonization, and no other chronic conditions with frequent use of health-care services.

Higher colonization prevalence has also been reported among patients with SSTIs compared to controls.[17] In our study, previous SSTI was a risk factor for colonization in univariate analysis but not in logistic regression analysis. Nevertheless, as patients with atopic dermatitis suffer more SSTIs than non-atopic children,[18] it is likely that atopy is the real risk factor for colonization, as we have previously mentioned. Several authors have reported that children living in crowded settings or attending school are more likely to be colonized,[15,21,22] as these settings increase human contact and the possibility of transmission. The contamination of inert surfaces and objects could have a major role in cross-transmission of pathogens in school settings, as with nosocomial infection acquisition.[23] Some of the *Staphylococcus* strains have the ability to produce biofilms, which allow the bacteria to adhere to surfaces and foreign bodies. This is a virulence factor, which favors subsequent colonization and infection as previously reported.[24] Univariate analysis revealed that colonized children attended school or daycare more frequently than non-colonized ones, although this could not be proved by logistic regression analysis. Maternity leave lasted less than 20 weeks in our country, and following this period, many infants were admitted to day-care centers.[25] Almost all children go to school at the age of three in our country (96.5%),[25] which could favor higher colonization rates.

Regarding CA-MRSA, multiple factors have been proposed that increase the risk of colonization, such as low socioeconomic status, living in crowded conditions, previous exposure to antibiotics and livestock exposure or pets.[26–30] In our cohort, we observed a higher percentage of MRSA carriage among children younger than 4 years of age.

Our observation is coincident with that reported by other authors, who have observed higher rates of CA-MRSA infections in younger children,[6,27] as higher colonization rates seem to increase the risk for subsequent infections.[18] We did not find any other epidemiological factors that increased the risk of MRSA carriage, except for children living in rural areas, although the low number of MRSA strains isolated in our study could be a limitation for relevant conclusions.

None of the MRSA strains was associated with tetracycline resistance, a marker of livestock-associated MRSA.[31] In addition, no relationship was observed between the presence of pets in the household and MRSA colonization, suggesting that MRSA carriage is not a zoonotic problem among Spanish children.

In 2013, den Heijer et al reported the results of a large cross-sectional study (APRES study)[9] performed by family doctors that compared the prevalence of nasal *S aureus* carriage in patients (aged 4 years or older) across nine European countries, including Spain. More than 4,000 Spanish patients were included, but only 12% were younger than 20 years. The global prevalence of *S. aureus* nasopharyngeal colonization was 19% in our country, but it was higher in populations between 4 and 19 years of age (31.5%). MRSA was isolated in 0.3% of the Spanish patients.

We have observed a slightly higher prevalence of *S. aureus* colonization in Spanish children, even with younger patients included in our study who usually have lower colonization rates, as we have previously described. Recent studies performed in different regions of Europe have also reported high *S. aureus* colonization rates in children (34% to 53%).[13,32] These data suggest that *S. aureus* colonization could be increasing in children in our continent. In addition, although the isolation of MRSA was low in our cohort (1.4%), it is substantially higher than the rates reported by several authors in European children and even in adults (0.14–0.8%)[9,13,26,32] which is a concerning issue.

S. aureus carriage increases the risk of subsequent *S. aureus* infections,[14,29,33] and most of the children who develop life-threatening *S. aureus* infections are young and previously healthy.[6,27] Accordingly, the surveillance of *S. aureus* and MRSA colonization in children is important.

In the last decades, countries in the American continent and in the Asia–Pacific region have faced a dramatic increase of infections caused by CA-MRSA strains,[27,29,34–36] which has led to changes in the initial empirical treatment upon *S. aureus* suspicion.[35] In Europe, surveillance data show a general trend towards increasing MRSA infection from north to south, with higher prevalence in Spain, Italy and Greece.[29] Several authors have reported high rates of MRSA in community-associated infections in children in southern Europe, with high ICU

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admission rates and longer hospitalizations.[3,7] The different prevalence rates observed across Europe could be explained by different lifestyle conditions, infection control practices and antimicrobial use.[9,15,26,29] Spain was the country with the highest rate of antibiotic use per habitant of all the countries included in the APRES study. It was also the one with the lowest percentage of pan-susceptible *S. aureus* strains.[9] Our study found a higher resistance to clindamycin, ranging from 17% in MSSA to 26% in MRSA strains. Several authors have also reported a worrisome increase in clindamycin resistance in both MSSA and MRSA strains isolated from children with *S. aureus* infection in different countries. These rates were much higher than 15%,[6,7,37] exceeding 30% to 50% in some cases.[6] We have additionally observed a high erythromycin resistance rate in our study, especially in MRSA strains, which can imply inducible clindamycin resistance. For all these reasons, when the local susceptibility rate drops below 85%, clinicians should not use clindamycin in the empirical treatment of *S. aureus* infections,[6] unless inhibition of toxin production is required.[38]

Rapid development of resistance to mupirocin has also been described over the last years.[6,39,40] As intranasal mupirocin is the cornerstone for eradication therapy, the increasing rates of resistance are worrisome.[40] Less than 1% of *S. aureus* strains from our study were resistant to sulfamethoxazole/trimethoprim, similarly to other European studies.[9,38] This antibiotic can be a good alternative for non-severe infections, as its efficacy is similar to clindamycin.[41]

Our study has some limitations. Samples were taken only from the anterior nares, leaving out other sites of colonization such as throat, groin, perineal region or rectum. Some authors have reported that oropharyngeal screening could increase the identification of *S. aureus* carriage by about 14%, since some children are colonized exclusively in the throat.[33] Previous studies have reported that staphylococcal strains colonizing the pharynx display more aggressive traits compared to those colonizing the anterior nares, which might have important implications on the risk of developing disease following colonization.[42] Therefore, we could have underestimated the prevalence of *S. aureus* colonization in Spanish children. Secondly, we were not able to demonstrate a different rate of colonization in children of foreign origin, although the risk of CA-MRSA infection is higher in patients from Latin America and very low in Sub-Saharan Africa.[43] As only 4% of our patients were immigrants, a comparison between individual countries was not feasible.

The microbiological methods were not performed in a single reference laboratory, which could have contributed to homogenizing study results. However, we chose to carry out the microbiological studies in each primary care centers' reference laboratories to facilitate the organization and execution of the study. All the participating laboratories were accredited to carry out these microbiological procedures.

The 27 strains of MRSA detected in the study were not typified, which would have made it possible to confirm the community origin of the strains, or to suggest the possible hospital or livestock association. The epidemiology of MRSA is transforming into a blurry boundary between HA-MRSA and CA-MRSA due to a constant transfer of strains between the community and hospitals, as previously documented.[44] Nevertheless, the main strength of this surveillance study is that it includes children of all ages, who live in rural and urban settings all over Spain. It provides important and reliable information regarding *S. aureus* carriage in the pediatric population, as well as updated and relevant antibiotic resistance data in a European Mediterranean country.

Abbreviations

CA, community-acquired; CI, confidence interval; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus*; OR, odds ratio; SSTIs, soft tissue infections.

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Disclosure

The authors declare that they have no potential conflicts of interest.

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