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Sharp increase in the incidence and severity of invasive *Streptococcus pyogenes* infections in children after the COVID-19 pandemic (2019-2023): A nationwide multicenter study

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ABSTRACT

Objectives: A global surge in pediatric invasive group A streptococcal infection (iGAS) was reported after autumn 2022. This study analyzed the epidemiology and severity of iGAS in Spain, comparing two periods; P1: pre-outbreak (January 2019-September 2022) versus P2: outbreak (October 2022-July 2023).
Methods: Children ≤16 years with iGAS enrolled in the Spanish PedGAS-net (2019-2023), were included. Bacterial isolates were analyzed for *emm* typing, antibiotic susceptibility, and whole genome sequencing. Multivariate analysis identified risk factors for PICU admission and mortality.
Results: 558 cases were included; 307 (55.1%) were male, with a median age of 43.9 months (IQR:19.3-84.1). There were significantly more iGAS in P2 (35.7 vs. 4.5 cases/month, $P < 0.001$), with higher PICU admissions (51.3% vs. 30.8%, $P < 0.001$). Pneumonia was the most common syndrome (32.3%), with pleural effusion in 58.3%. Of the 130 samples available for *emm*-typing, the most frequent were *emm*1 (56.1%) and *emm*12 (27.1%). 245 (43.9%) required PICU admission. Factors associated with PICU were streptococcal toxic shock syndrome (STSS), pneumonia, necrotizing fasciitis, acute kidney failure, and previous consultation before diagnosis. The *emm*1 (especially $M1_{UK}$) increased PICU risk. 11 children (2.0%) died. STSS, sepsis, and central nervous system infection were associated with mortality.
Conclusion: In Spain, pediatric iGAS cases sharply increased during 2022-2023, with a remarkable increase in severity. Epidemiological surveillance of iGAS remains crucial.

Introduction

Streptococcus pyogenes or group A *Streptococcus* (GAS) is one of the most important pathogens causing community-acquired infections in the pediatric population. It can cause a broad spectrum of diseases, ranging from non-invasive infections (mainly pharyngitis and scarlet fever) to severe clinical syndromes such as pneumonia, osteomyelitis, septic arthritis, meningitis, necrotizing fasciitis (NF), streptococcal toxic shock syndrome (STSS), or sepsis. There are also non-suppurative complications such as rheumatic heart disease or poststreptococcal glomerulonephritis [1].

The virulence of GAS depends primarily on the M protein, encoded by the *emm* gene. This M protein antigen is located on the cell surface and in the fimbria, and can inhibit opsonization and phagocytosis, facilitating tissue invasion. Additionally, GAS produces a variety of extracellular enzymes and toxins, including streptococcal pyrogenic exotoxins (SPEs), which contribute to toxic shock syndrome and severe inflammatory responses. The hyaluronic acid capsule aids in immune evasion, while cytolysins like streptolysin O and S damage host cells, enhancing the bacterium's ability to spread. Over 250 *emm* types have been identified, with some, like the *emm*1, linked to severe outcomes [2,3].

The *emm* types can be grouped into 48 *emm* clusters that share structural and binding properties [4]. As protective antibodies can be generated against M protein, this protein represents one of the most characterized vaccine candidates to date [5].

In recent decades, multiple reports have highlighted a global increase in the incidence of iGAS. As demonstrated by Villalón et al. there was already a rising trend in invasive *S. pyogenes* infections in Spain between 2007 and 2019, prior to the COVID-19 pandemic. Several studies also indicate a decline in iGAS incidence during the first two years of the pandemic, followed by a significant and concerning resurgence in the late months of 2022 and the first quarter of 2023 [6–8]. The reason for this outbreak appears to be multifactorial, potentially including a more susceptible population after the post-COVID-19 pandemic period, rather than by increased transmission per se, as well as a possible emergence of more virulent GAS strains [9–12].

This increase in incidence was also associated with a high proportion of severe infections such as pneumonia, mediastinitis, primary peritonitis and central nervous system (CNS) infections [7,13–15].

In Spain, iGAS is not a notifiable disease. However, we created a pediatric multicenter network registry (PedGAS-net) for the study of iGAS in children. The objective of this study was to provide a

description of epidemiology, microbiological characteristics, clinical features, treatment, and outcomes of iGAS in children, comparing possible differences between two periods: pre-outbreak (P1) and outbreak (P2).

Methods

We included children with iGAS between January 1, 2019, and July 31, 2023, enrolled in PedGAS-net, a multicenter prospective national network with 51 collaborating Spanish hospitals launched in January 2019, aiming to study iGAS in patients ≤16 years old. Participants were excluded if they declined informed consent or had incomplete data. iGAS was defined as an infection where GAS was identified by culture or PCR in a specimen obtained from a normally sterile body site or when a clinical diagnosis of NF or STSS was supported by GAS detection from a non-sterile site isolation (Supplementary Material 2). Upper respiratory tract infections (URTI) were defined as per the criteria outlined in Supplementary Material 2. The testing for respiratory viruses was performed based on clinician's discretion, considering symptoms, patient history, and local protocols. Only positive respiratory viral tests were available and included in the analysis. Although we do not have data of the total number of patients tested, we thought it was an important information to report on cases where respiratory viruses were isolated. Cases were defined as severe if the patient required admission to a pediatric intensive care unit (PICU).

GAS isolates were initially identified at the participating hospitals through laboratory alerts to the attending healthcare providers. Once a child with iGAS was enrolled in the study, the site investigator contacted the corresponding Microbiology laboratory to retrieve the isolate, which had been properly stored frozen according to local laboratory protocols for subsequent microbiological analysis. Each center was subsequently requested to send the strains to the National Microbiology Center (CNM) for *emm* typing, antibiotic susceptibility testing, and whole genome sequencing (Supplementary Material 2). Part of this microbiological data has been recently published by our group [13].

We established two periods to compare clinical characteristics and outcomes of patients; P1: pre-outbreak (January 2019-September 2022) and P2: outbreak (October 2022-July 2023).

This study was approved by the Ethics Committee of the Gregorio Marañón Hospital and ratified in all participating centers. The parents or legal guardians signed an informed consent prior to their inclusion in the study.

Medical records were reviewed, and all data (including demographics, laboratory, imaging, and clinical data), were collected and managed using REDCap (Research Electronic Data Capture) database, hosted at the Gregorio Marañón Hospital [16].

Statistical analysis

Data is summarized as frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for continuous variables. The annual incidence rate of iGAS episodes was calculated as the number of confirmed iGAS cases per 100,000 children aged ≤16 years who were attended at the pediatric emergency departments of the participating hospitals during each calendar year. To calculate this annual incidence of iGAS, we used the number of iGAS cases diagnosed at the 51 participating hospitals as the numerator, and the total number of children ≤16 years attended at the pediatric emergency departments of those hospitals each year as the denominator. The 95% confidence intervals (CIs) for the annual incidence rates were calculated assuming a Poisson distribution. Categorical variables were compared with χ^2 or Fisher's test, and continuous variables with the Wilcoxon-Mann-Whitney test, due to the non-normal distribution of the sample, as assessed by the Shapiro-Wilk test. Factors associated with severity were assessed using logistic regression. All the variables in the entire cohort with a p-value <0.1 in the univariate analysis of PICU admission and mortality were included in a backward, conditional, stepwise, multivariable, logistic regression model. The general goodness of fit of the final models was analysed with Nagelkerke's R-squared. The predictive ability of the final models was examined by calculating its area under the receiver operating characteristic (AUROC) curve with a 95% confidence interval. Monthly case counts of invasive *S. pyogenes* infections were plotted alongside national data on the incidence of influenza and respiratory syncytial virus (RSV) in Spain. Surveillance data for RSV and influenza were obtained from the Spanish SiVIRA system (Surveillance of Acute Respiratory Infections), available at: https://cne.isciii.es/servicios/enfermedades-transmisibles/enfermedades-a-z/gripe-covid-19-y-otros-virus-respiratorios. All calculated p-values were two-sided, and an alpha level of 0.05 was used to assess significance. Data were analyzed using Stata v17 (StataCorp, College Station, TX).

Results

Five hundred and fifty-eight cases were included. All patients were admitted to the hospital, and 307 (55.1%) were male with a median age of 43.9 months (IQR: 19.3-84.1 months). The average annual incidence rate was 13.6 cases per 100,000 children attended at the emergency departments (95% CI: 12.7-14.6), with a marked decrease during the COVID-19 pandemic and a sharp increase in 2022-2023. We observed an increase in iGAS that overlapped temporally with the influenza epidemic in Spain, and a smaller earlier rise that coincided with the circulation of RSV, as shown in Figure 1. Incidence peaked in winter (n= 252, 45.2%) and was lower in summer (n=64, 11.5%).

Of the 558 patients, 178 (31.9%) were also diagnosed with an URTI within the last four weeks prior to iGAS diagnosis. Among all patients, 64 (11.5%) had a virus detected: 49 (8.8%) influenza, 7 (1.2%) RSV, and 9 (1.6%) other respiratory viruses. Preceding trauma, wound or skin lesion was present in 7.5% (n=42) of iGAS, including four patients (0.7%) with varicella infection.

Three hundred and twelve patients (312/558, 55.9%) had visited a healthcare center within 4 weeks before the diagnosis of iGAS. Among these 312 children, 62/312 (19.9%) received antibiotics. The most frequent diagnoses for antibiotic prescription were acute streptococcal pharyngotonsillitis (18/62; 29.0%), acute otitis media (15/62; 24.2%), cellulitis (7/62; 11.3%), and pneumonia (5/62; 8.1%). Previous antibiotic treatment was associated with a lower rate of PICU admission (OR: 0.46 [95% CI: 0.27-0.78], $P = 0.004$), but not with reduced mortality (OR: 0.65 [95% CI: 0.08-5.11], $P = 0.676$).

Most patients (n=495; 88.7%) had fever at iGAS diagnosis. The most common clinical syndrome was pneumonia (n=180, 32.3%); 58,3% (105/180) complicated with pleural effusion. Skin and soft tissue infection (n=85, 15.2%) was the second most common syndrome, followed by primary bloodstream infection (n=67, 12.0%), mastoiditis (n=63, 11.3%), osteoarticular infection (n=54, 9.7%), deep neck infection (n=41, 7.3%) and CNS infection (n=33, 5.9%). Furthermore, 60 (10.8%) children had STSS, and 23 (4.1%) NF, with eight children having both complications.

All patients received intravenous antibiotics. The average duration of antibiotic therapy was 19 days (IQR: 13-28). Protein synthesis-inhibiting antibiotics with toxin-suppressing effects (clindamycin or linezolid) were administered to 256 (45.9%) patients, and intravenous immunoglobulin to 53 (9.5%) patients. Clindamycin was far more frequently used than linezolid (251 vs 5 cases). These antibiotics were more commonly used in severe cases (NF, STSS, pneumonia, and sepsis), and in patients admitted to the PICU (Supplementary Material 3)

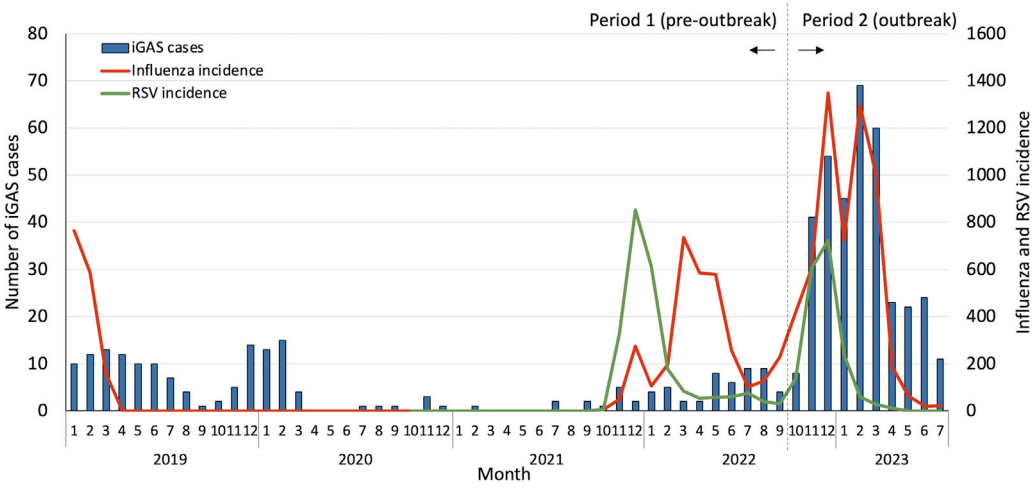

Figure 1. Monthly number of pediatric invasive *S. pyogenes* cases reported through the PedGAS-net (blue bars, left axis), and national surveillance data on RSV (green line) and influenza (red line) incidence per 100,000 population in Spain (right axis), 2019-2023. Incidence of RSV and influenza obtained from the Surveillance of Acute Respiratory Infections (SiVIRA), https://cne.isciii.es/servicios/enfermedades-transmisibles/enfermedades-a-z/gripe-covid-19-y-otros-virus-respiratorios Data on RSV incidence has been available since October 2020.

A surgical procedure was required in 313 (56.5%) patients; 240 in the first 24 hours of hospitalization. The median length of stay in hospital was 11 days (IQR: 7-17).

Information on the occurrence of GAS infection among close contacts was available for 506 (90.7%) cases. Within 30 days of the initial case, 3 of these close contacts (0.5%) developed a subsequent GAS infection: all of them diagnosed with acute streptococcal pharyngotonsillitis, with no cases of iGAS.

GAS was most frequently isolated from blood (n=222, 39.8%). The remaining isolates were obtained from pleural fluid (n=149, 26.7%), joint fluid/bone samples (n=34, 6.1%), cerebrospinal fluid (n=10; 1.8%), and from other intraoperative specimens. In 70 cases (12.5%), GAS was isolated from more than one site. All isolates were susceptible to penicillin, and among isolates available for testing, 2.8% (14/493) were resistant to clindamycin, and 5.2% (25/479) to erythromycin.

Emm typing was available for 130/558 (23.3%) isolates (22 isolates in P1 and 108 isolates in P2), and 96 were sent to CNM for whole genome sequencing. Among the typed isolates, fourteen different *emm* types were detected. The most common were *emm*1 (73, 56.1%), *emm*12 (36, 27.7%), *emm*4 (6, 4.6%) and *emm*6 (4, 3.1%), accounting for 91.5% of all typed isolates. Among the *emm*1 strains sequenced (n=51), 29/51 (56.9%) were classified as $M1_{global}$, and 22/51 (43.1%) as $M1_{UK}$.

When comparing 2022 and 2023, based on the total number of *emm* types analyzed during this period (n=116), the proportion of *emm*1 isolates significantly increased from 26.5% (9/34) in 2022 to 68.3% (56/82) in 2023 ($P < 0.001$). Conversely, the proportion of *emm*12 decreased from 58.8% (20/34) in 2022 to 17.1% (14/82) in 2023 ($P < 0.001$). These findings, although based on a subset of isolates, suggest a possible shift in the distribution of circulating *emm* types. Table 1 summarizes the characteristics of iGAS episodes according to *emm* types and subtypes, including clinical syndromes, exotoxin gene profiles, antimicrobial resistance, and severity.

A significant association was observed between the $M1_{UK}$ strain and STSS, with 38.5% of $M1_{UK}$ cases presenting with STSS compared to 21.4% in the non-$M1_{UK}$ group (OR: 3.68, [95% CI: 1.07-12.58] $P = 0.038$) (Supplementary Material 4). The *emm*1 genotype was also significantly associated with a higher risk of PICU admission (66.2% in *emm*1 vs 46.2% in non-*emm*1, OR: 2.28, [95% CI: 1.12-4.63] $P = 0.023$), particularly among $M1_{UK}$ strains (27.7% in $M1_{UK}$ vs 6.2% in non-$M1_{UK}$, OR: 5.84, [95% CI: 1.85-18.41] $P = 0.003$). The relationships between exotoxins and the requirement for PICU or mortality are detailed in Supplementary Material 5.

Two hundred and forty-five (43.9%) patients were admitted to PICU, 94 (38.4%) required invasive mechanical ventilation, 75 (30.6%) received inotropic support, and 12 (4.9%) extracorporeal membrane oxygenation. The median length of stay in the PICU was 5 days (IQR: 3-9). Characteristics of patients and risk factors of PICU admission are summarized in Table 2. Factors associated with PICU in the multivariate analysis were SSTS (adjusted OR (aOR): 4.49 [95% CI: 1.86-10.83]), pneumonia (aOR: 13.91 [95% CI: 8.63-22.43]), NF (aOR: 5.50 [95% CI: 1.82-16.57]), acute kidney failure (aOR: 4.38 [95% CI: 1.10-17.46]), and evaluation by healthcare professional before iGAS diagnosis (aOR: 1.81 [95% CI: 1.16-2.83]). The final model reported an AUROC curve of 0.85 (95% CI 0.81-0.88) for PICU admission. Overall, the model demonstrated a good level goodness of fit, with a pseudo-R squared (Nagelkerke) of 0.475. (Table 2).

Of the 558 patients included in the study, 31 (5.5%) developed sequelae secondary to iGAS, including 9 who required limb amputation. In addition, 11 children (2.0%, [95% CI: 1.0%-3.5%]) died. Outcome data were available for all patients. STSS (aOR: 7.94 [95% CI: 1.92-32.88]), sepsis at the time of iGAS diagnosis (aOR: 5.55 [95% CI: 1.41-21.79]), and CNS infection (aOR: 11.48 [95% CI: 1.76-75.01]) were associated in multivariate analysis with increased mortality risk. The final model reported an AUROC curve of 0.92 (95% CI 0.86-0.98). Overall, the model demonstrated an acceptable level goodness of fit, with a pseudo-R squared (Nagelkerke) of 0.307 (Supplementary Material 6).

Comparison according to period

There were significantly more iGAS in P2 (n=357, average 35.7 cases/month [95% CI: 20.6-50.8]) compared to P1 (n=201, average 4.5 cases/month [95% CI 3.1-5.9]), ($P < 0.001$). Indeed, February 2023 showed a 4.6-fold rise in incidence compared to the highest average recorded in the preceding months (Figure 1). Cases were also more severe in P2, with significantly higher proportions of patients with CNS infection (7.8% vs 2.5%; $P = 0.010$), pneumonia (38.4% vs 21.45%; $P < 0.001$), and sepsis (25.5% vs 15.4%; $P = 0.006$). Moreover, a higher percentage of children were admitted to PICU in P2 (51.3% vs 30.8%; $P < 0.001$), with also more cases needing mechanical ventilation (21.0% vs 9.5%; $P < 0.001$) (Table 3).

Table 1
Features of the fourteen *emm* types detected.

emm types/ subtypes	Strains (n,%)	*emm* cluster[a]	Secuence type (ST) correlation[b] (n/N,%)	Infection		Exotoxins[b]		Antimicrobial resistance[b] (Type, n)	PICU (n,%)	Death (n,%)
				Type[c]	n,%	Gene profile	n/N,%			
*emm*1	73/130 (56.1%)	A-C3	ST28 (51/52, 98.1%) ST1357 (1/52, 1.9%)	Pneumonia OAI	34 (46.6%) 9 (12.3%)	A-C-G-J-Z A-C-G-J-Z-sic A-G-J-Z-sic A-G-J-Z	15/52, 28.8% 14/52, 26.9% 13/52, 25.0% 10/52, 19.2%	Not detected	43/73, 58.9%	3, 4.1%
■ 1.0	47 (36.4%)									
■ 1.3	25 (19.4%)									
■ 1.159	1 (0.8%)									
*emm*12	36/130 (27.7%)	A-C4	ST36 (20/30, 66.7%) ST242 (7/30, 23.3%)	Pneumonia OAI	12 (34.3%) 9 (25.7%)	C-G-H-I-Z G-H-I-Z C-G-H-I-Z-ssa Others	20/30, 66.7% 5/30, 16.7% 3/30, 10.0% 3/30, 10.0%	TET, ERY, CLI (n=1) ERY, CLI (n=1)	14/36, 38.9%	1, 2.8%
■ 12.0	24 (18.6%)									
■ 12.37	8 (6.1%)									
■ 12.4	2 (1.6%)									
■ 12.19	1 (0.8%)									
■ 12.128	1 (0.8%)									
*emm*4.0	6/130 (4.6%)	E1	ST39 (4/4, 100%)	Primary BSI	3 (50.0%)	C-Z-ssa	4/4, 100%	Not detected	1/6, 16.7%	No
*emm*6.0	4/130 (3.1%)	A-C[d]	ST32 (2/2, 100%)	Pneumonia	2 (50.0%)	A-C-G-H-I-K-Z	2/2, 100%	Not detected	3/4, 75.0%	No
*emm*89.0	2/130 (1.6%)	E4	ST101 (2/2, 100%)	SSTI Mastoiditis	1 (50.0%) 1 (50.0%)	C-G-K-Z C-G-Z	1/2, 50% 1/2, 50%	Not detected	No	No
*emm*22.24	1/130 (0.8%)	E4	ST46 (1/1, 100%)	Pneumonia	1 (100%)	A-G-Z-ssa	1/1, 100%	Not detected	1/1, 100%	No
emm28.0	1/130 (0.8%)	E4	ST458 (1/1, 100%)	Mastoiditis	1 (100%)	C-G-J-K-Z	1/1, 100%	Not detected	No	No
*emm*29	1/130 (0.8%)	A-C[d]	-	OAI	1 (100%)	-	-	Not detected	No	No
*emm*31.12	1/130 (0.8%)	A-C5	ST365 (1/1, 100%)	Pneumonia	1 (100%)	C-G-J-Z	1/1, 100%	TET, ERY, CLI (n=1)	1/1, 100%	No
*emm*44.0	1/130 (0.8%)	E3	ST25 (1/1, 100%)	Mastoiditis	1 (100%)	G-J-Z-ssa	1/1, 100%	Not detected	No	No
*emm*60.11	1/130 (0.8%)	E1	SST53 (1/1, 100%)	SSTI	1 (100%)	K	1/1, 100%	TET (n=1)	No	No
*emm*75	1/130 (0.8%)	E6	-	Pneumonia	1 (100%)	-	-	-	1/1, 100%	No
*emm*77	1/130 (0.8%)	E4	-	OAI	1 (100%)	-	-	-	No	No
*emm*87.0	1/130 (0.8%)	E3	ST62 (1/1, 100%)	DNI	1 (100%)	G-J-K-Z-ssa	1/1, 100%	Not detected	1/1, 100%	No

[a] Sanderson-Smith *et al.* [3].
[b] Conducted only on the strains sent to *National Microbiology Center* (n=96/130).
[c] Most frequent clinical syndromes.
[d] Single protein *emm*-cluster clade Y.
BSI, bloodstream infection; CLI, clindamycin; DNI, deep neck infection; ERY, erythromycin; OAI, Osteoarticular infection; SSTI, skin and soft tissue infection; TET, tetracycline.

Table 2
Characteristics of patients and risk factors of PICU admission.

	PICU (N=245)	Non-PICU (N=313)	OR (95% CI)	aOR* (95% CI)
Demographics				
Gender (male)	135 (55.1%)	172 (55.1%)	1.00 (0.72-1.40)	
Age (months)[1]	38.9 (17.8-75.8)	52.4 (21.3-90.8)	**0.99 (0.99-1.00)**	
Medical background[2]				
Preceding trauma, wound or skin lesion	8 (3.3%)	34 (10.9%)	**0.28 (0.13-0.61)**	
URTI	87 (35.5%)	91 (29.1%)	1.34 (0.94-1.92)	
Influenza virus infection	36 (14.7%)	13 (4.2%)	**3.97 (2.06-7.68)**	2.21 (0.94-5.17)
Previous consultation before diagnosis Consulted a medical center	158 (64.5%)	154 (49.5%)	**1.85 (1.31-2.61)**	1.81 (1.16-2.83)
Previous antibiotic therapy	21 (8.6%)	53 (17.0%)	**0.46 (0.27-0.78)**	0.39 (0.19-0.79)
Symptoms at the time of iGAS diagnosis				
Fever	230 (93.9%)	265 (84.7%)	**2.78 (1.52-5.09)**	
Rash	51 (20.8%)	30 (9.6%)	**2.48 (1.52-4.03)**	1.76 (0.95-3.27)
Respiratory distress	129 (52.7%)	20 (6.4%)	**16.29 (9.71-27.34)**	
Functional impairment/arthralgia.	27 (11.0%)	65 (20.8%)	**0.47 (0.29-0.77)**	
Protrusion of the auricle	6 (2.4%)	42 (13.4%)	**0.16 (0.07-0.39)**	
Cervical pain	9 (3.7%)	24 (7.7%)	**0.46 (0.21-1.01)**	
Laboratory parameters on admission[1]				
White blood cell count (cells/mm3)	15,475.0 (8,000.0-22,390.0)	16,060.0 (12,000.0-20,100.0)	1.00 (1.00-1.00)	
Neutrophil count (cells/mm3)	12,460.0 (5,485.0-18,395.0)	11,700.0 (8,065.0-15,970.0)	1.00 (1.00-1.00)	
CRP (mg/dl)	25.5 (16.1-37.1)	12.3 (5.9-22.9)	**1.00 (1.00-1.00)**	
Procalcitonin (mcg/L)	26.2 (7.2-91.7)	1.4 (0.2-8.2)	**1.03 (1.02-1.04)**	
*emm*1 (%)[3]	43/130 (33.1%)	30/130 (23.1%)	**2.28 (1.12-4.63)**	
$M1_{UK}$ (%)[4]	18/96 (18.7%)	4/96 (4.2%)	**5.84 (1.85-18.41)**	
$M1_{Global}$ (%)[4]	15/96 (15.6%)	14/96 (14.6%)	1.09 (0.48-2.50)	
Clinical syndrome				
Pneumonia	147 (60.0%)	33 (10.5%)	**12.73 (8.18-19.80)**	13.91 (8.63-22.43)
Pleural effusion	96 (39.2%)	9 (2.9%)	**21.76 (10.61- 44.30)**	
Skin and soft tissue infection	13 (5.3%)	72 (23.0%)	**0.19 (0.10-0.35)**	
Osteoarticular infection	9 (3.7%)	45 (14.4%)	**0.23 (0.11-0.47)**	
Mastoiditis	12 (4.9%)	51 (16.3%)	**0.26 (0.14-0.51)**	
Deep neck space infection	10 (4.1%)	31 (9.9%)	**0.39 (0.19-0.81)**	
CNS infection	15 (6.1%)	18 (5.8%)	1.07 (0.53-2.17)	
Sepsis	99 (40.4%)	23 (7.3%)	**4.39 (2.60-7.38)**	
Necrotizing fasciitis	18 (7.3%)	5 (1.6%)	**4.88 (1.79-13.35)**	5.50 (1.82-16.57)
STSS	51 (20.8%)	9 (2.9%)	**8.88 (4.27-18.45)**	4.49 (1.86-10.82)
Treatment and outcome				
Antibiotics with antitoxin-inhibiting properties on admission	177 (72.2%)	79 (25.2%)	**8.41 (5.56-12.73)**	
IV immunoglobulin	49 (20.2%)	4 (1.3%)	**19.13 (6.80-53.86)**	
Total days of antibiotic therapy[1]	22.0 (15.0-30.0)	14.0 (10.0-22.0)	**1.05 (1.03-1.06)**	
Acute kidney failure	25 (10.2%)	3 (1.0%)	**11.74 (3.50-39.38)**	4.38 (1.10-17.46)
Surgery	129 (52.9%)	184 (59.4%)	0.77 (0.55-1.08)	
Death rate	7 (2.9%)	4 (1.3%)	2.27 (0.66-7.85)	

[1] Median [IQR].
[2] Within the last four weeks prior to iGAS diagnosis.
[3] *emm* typing was available for 130 isolates (n=130).
[4] Conducted only on the strains sent to *Centro Nacional de Microbiología* (n=96/130).
CNS, Central nervous system; CRP, C-reactive protein; iGAS, Invasive Group A Streptococcus; PICU, Pediatric intensive care unit; SSTI, Skin and soft tissue infection; STSS, Streptococcal toxic shock syndrome; URTI, Upper respiratory tract infection.
* aOR, adjusted odds ratio for the variables included in the final predictive model for pediatric intensive care admission. Values in bold indicate statistical significance at $P < 0.05$.

Discussion

In this multicenter study, we analyzed the evolving trend of iGAS in children in Spain over the last years, including a period of two years post-COVID-19 pandemic. Our analysis revealed a sharp and alarming surge in iGAS cases starting in October 2022, reaching a peak incidence in February 2023. This outbreak period (P2) was characterized by a significant increase in severe clinical syndromes, including pneumonia, CNS infections, sepsis, SSTS, and other critical conditions, alongside increased PICU admissions.

The cause of this outbreak remains unclear. Some publications have linked previous or concurrent viral respiratory tract infections to the development of iGAS [10,17–19]. In our study, approximately one-third of cases had a history of URTI, including a small proportion with influenza. In P2, we detected more pneumonia cases,

Table 3
Comparison between pre-outbreak and outbreak periods.

	Total iGAS (N=558)	Pre-outbreak (P1: Jan 2019- Sep 2022) (N=201)	Outbreak (P2: Oct 2022 - Jul 2023) (N=357)	p-value
Gender (male)	307 (55.1%)	119 (59.2%)	188 (52.8%)	0.145
Age (months)	43.9 (19.3-84.1)	40.1 (18.7-82.7)	47.8 (19.5-84.1)	0.756
Upper respiratory tract infection	178 (31.9%)	43 (21.4%)	135 (37.8%)	**<0.001**
Varicella infection	4 (.7%)	4 (2%)	0 (0%)	**0.007**
Laboratory parameters at admission[1]				
White blood cell count (cells/mm3)	15,900.0 (10,700.0-21,100.0)	15,800.0 (11,000.0-20,000.0)	15,930.0 (10,400.0-22,025.0)	0.766
Neutrophil count (cells/mm3)	11,946.0 (7,545.0-17,200.0)	11,700.0 (7,510.0-16,330.0)	12,100.0 (7,580.0-17,500.0)	0.737
CRP level (mg/dl)	17.8 (9.4-31.1)	15.3 (7.3-27.5)	20.5 (10.6-32.9)	**0.002**
Procalcitonin level (mcg/L)	9.8 (1.2-50.0)	9.7 (1.2-39.0)	9.8 (1.2-50.0)	0.558
*emm*1[2]	73/130 (56.1%)	8 /22 (36.4%)	65/108 (60.2%)	0.046
Clinical syndrome				
Pneumonia pleural effusion	180 (32.3%) 105 (18.8%)	43 (21.4%) 26 (12.9%)	137 (38.4%) 79 (22.1%)	**<0.001 0.008**
SSTI	85 (15.2%)	46 (22.9%)	39 (10.9%)	**<0.001**
Osteoarticular infection	54 (9.7%)	26 (12.9%)	28 (7.8%)	0.051
Deep neck infection	41 (7.3%)	23 (11.5%)	18 (5.0%)	**0.005**
CNS infection	33 (5.9%)	5 (2.5%)	28 (7.8%)	**0.010**
Sepsis	122 (21.9%)	31 (15.4%)	91 (25.5%)	**0.006**
STSS	60 (10.7%)	19 (9.5%)	41 (11.5%)	0.457
Treatment and outcome				
Length of hospital stay	11.0 (7.0-17.0)	10.0 (6.0-17.0)	12.0 (7.0-17.5)	**0.007**
Antitoxin antibiotic at admission	256 (45.9%)	71 (35.3%)	185 (51.8%)	**<0.001**
Total antibiotic therapy days	19.0 (13.0-28.0)	15.0 (11.0-26.5)	21.0 (14.0-28.0)	**<0.001**
Surgery	313 (56.5%)	103 (51.2%)	210 (59.5%)	0.060
PICU admission	245 (43.9%)	62 (30.8 %)	183 (51.3%)	**<0.001**
Mechanical ventilation	94 (16.8%)	19 (9.5%)	75 (21%)	**<0.001**
Death	11 (2.0%)	3 (1.5%)	8 (2.2%)	0.542

Median [IQR] for quantitative variables.
CNS, central nervous system; CRP, C-reactive protein; iGAS, Invasive Group A *Streptococcus*; PICU, Pediatric Intensive Care Unit; SSTI, Skin and soft tissue infection; STSS, Streptococcal toxic shock syndrome.
[2]*emm* typing was available for 130 isolates (n=130). P values < 0.05 in bold.

possibly associated with the temporal overlap with the influenza epidemic in Spain. However, it is important to note that only a small proportion of patients were tested for influenza, and the observed trend towards higher severity was limited by the small number of patients tested. Therefore, while this suggests that vaccination might help in the prevention of iGAS, further research is needed to confirm this benefit. This finding is in line with other studies reporting an association between influenza infection and increased severity of GAS disease [20]. Other considerations for this rise of incidence may include a large group of susceptible children after the COVID-19 lockdown, which has been defined as "immunity debt", or a more virulent GAS strain [21–23].

The most isolated *emm* types were *emm*1 and *emm*12, consistent with others reports [8,11,24,25]. In 2023, *emm*1 increased to become the most frequent genotype, overtaking *emm*12, which had been dominant at the end of 2022. The dominance of *emm*1 is concerning because of its greater virulence and association with more severe infections, which was also reflected in our data [11,17,21,26].

Beta-lactam antibiotics, especially penicillin, are the main treatment for GAS infections, since this bacterium remains universally susceptible. Although an increase of clindamycin resistance has been shown in other countries, this was not observed in our study [18,27]. In fact, both clindamycin and erythromycin resistance showed a decreasing trend during the study period.

Some international guidelines recommend considering the addition of protein synthesis-inhibiting antibiotics that reduce bacterial toxin production (such as clindamycin or linezolid) in severe cases to decrease mortality [28–30]. However, no randomized controlled trials have demonstrated a clear mortality benefit for these treatments in iGAS. In our study, we observed that these antibiotics were used more frequently during P2, likely reflecting the increased severity of cases (e.g., STSS, NF, and pneumonia with pleural effusion) and a higher number of patients requiring PICU admission. This trend aligns with international guidelines, but further research is needed to clarify the morbidity and mortality benefits of adjunctive therapies.

Eleven deaths (2%) occurred, a case fatality rate consistent with those reported in other countries [8,24,25].

Close contacts of iGAS patients are at increased risk of developing these infections [31,32]. In our cohort, where the policy on close contact prophylaxis varies by center and routine prophylaxis was not uniformly offered, we identified only three (0.5%) secondary GAS cases (streptococcal pharyngotonsillitis) and no iGAS cases. While some experts recommend identifying and treating close contacts, this remains controversial [30]. A review by Khan et al. found limited evidence supporting prophylaxis, while Birck et al. reported no infection rate differences but a threefold higher risk of adverse events with antibiotics [33,34].

No vaccine against GAS is currently available. Among the M protein-based vaccines, StreptAnova, a 30-valent vaccine has completed a phase 1 clinical trial and was found to be immunogenic [5]. This vaccine covers [the] *emm* type of 128 out of the 130 strains of GAS isolates identified in our study (representing 14 distinct *emm* types overall; *emm*60 and *emm*31 would not be covered), resulting in 98.5% coverage [35].

Our study has some limitations. First, *emm* type data from all patients included in the study was not available, and the majority belongs to P2. Second, GAS is not a notifiable infection in Spain and, therefore, we were not able to describe trends in non-invasive presentations. Additionally, the multivariate analysis of mortality risk is limited by the small number of patients included, which impacts the statistical power and generalizability of the findings. Furthermore, information on the total number of patients tested for respiratory viruses was not systematically col-

lected across all centers. However, testing was performed based on clinician discretion, typically in patients with respiratory symptoms, and guided by local institutional protocols. On the other hand, the study has several important strengths, such as its multicenter design, encompassing most of Spain's leading hospitals, and a high number of cases evaluated. Also, its prospective manner of identifying patients makes the data presented here more reliable.

Conclusions

In Spain, a significant surge in pediatric iGAS began in October 2022, reaching its highest peak in February 2023. This outbreak was also marked by a rise in severe illnesses, such as pneumonia, CNS infections, and sepsis, with PICU admissions increasing by 1.7-fold. Pneumonia, acute kidney failure, NF, STSS, and previous visit to a healthcare center before iGAS diagnosis correlated to greater disease severity, resulting in more admissions to the PICU. No new GAS strains were identified during the study period, with *emm*1 and *emm*12 remaining the most prevalent serotypes. However, it is important to highlight the increase in *emm*1 in 2023 and its associated severity, particularly due to the $M1_{UK}$ subtype. Making iGAS a notifiable disease in Spain could improve the detection of invasive cases, strengthen epidemiological surveillance, and support timely public health responses.

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Ethical approval statement

This study was approved by the Ethics Committee of the Gregorio Marañón Hospital and ratified in all participating centers. The parents or legal guardians signed an informed consent prior to their inclusion in the study.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

Author contributions

EC-V, DA-A, CC, and JS-L conceptualized and designed the study. EC-V and DA-A performed the data management. EC-V, DA-A, CC, and JS-L drafted the manuscript. All authors enrolled participants and participated in the collection of data. All authors were involved in the preparation and review of the final manuscript. All authors participated and were involved in the critical review of the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107982.

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