Epidemiology and clinical characteristics of invasive group A streptococcal infection in the Republic of Korea, 2015–2024: a nationwide multicenter study

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Summary

Background **Invasive group A streptococcal (iGAS) infection has resurged globally following the coronavirus disease 2019 pandemic; however, long-term nationwide data from Asia is limited. This study aimed to investigate the epidemiology, clinical burden and molecular characteristics of iGAS infection in the Republic of Korea (ROK) over a 10-year period.**

Methods **A nationwide multicentre study for iGAS was conducted across 23 university-affiliated hospitals from 2015 to 2024. iGAS was defined as culture-confirmed isolation of *Streptococcus pyogenes* from sterile sites. Clinical data**

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were collected using standardised forms. Available isolates were *emm*-typed and whole genome sequencing was performed for *emm*1 isolates.

Findings A total of 454 iGAS cases were identified. The mean annual incidence was 4.72/100,000 admissions (95% CI 4.26–5.13), declining from 7.03 (95% CI 6.26–7.77) in 2015–2019 to 1.72 (95% CI 1.27–2.26) in 2020–2022. In 2023–2024, the incidence returned to pre-pandemic levels among children (10.45 per 100,000 admissions, 95% CI 5.95–14.39), whereas the adult incidence partially recovered (2.47 per 100,000 admissions, 95% CI 1.76–3.33). Skin and soft tissue infection (22.7%), streptococcal toxic shock syndrome (STSS, 19.6%), and bacteremia without focus (17.0%) were the most common iGAS infections. Intensive care unit admission was required in 28.9% of iGAS cases, and overall mortality was 15.5%. Mortality was independently associated with STSS (aOR 20.07, 95% CI 9.30–43.30; p < 0.0001), older age (aOR 20.07, 95% CI 9.30–43.30; p < 0.0001), chronic medical condition (aOR 2.96, 95% CI 1.41–6.22; p = 0.004), and immunocompromised condition (aOR 2.33, 95% CI 1.07–5.09; p = 0.034) among adults. Among 98 isolates, the predominant strains were *emm*1 (32/98, 32.7%), *emm*12 (13/98, 13.3%), *emm*28 (11/98, 11.2%), and *emm*89 (8/98, 8.2%). Of 32 *emm*1 isolates, two (6.3%) isolates belonged to the epidemic M1UK lineage were identified (2020, 2024).

Interpretation Following marked pandemic-associated suppression, iGAS incidence rapidly rebounded among children in the ROK. This study reports the first detection of the M1UK lineage in the ROK, highlighting the need for statutory notification of iGAS as a nationally notifiable disease to enable continuous national surveillance with molecular characterization for monitoring emerging epidemic-prone strains.

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Keywords: Group A streptococcus; Streptococcal toxic shock syndrome; Epidemiology; COVID 19; Korea

Research in context

Evidence before this study

We searched PubMed for studies on invasive group A streptococcal (iGAS) infections published from January 2020 to December 31, 2024. Search terms included ("invasive group A streptococcal" OR "iGAS" OR "*Streptococcus pyogenes*") AND ("epidemiology" OR "incidence" OR "surveillance" OR "trends") AND ("COVID-19" OR "pandemic" OR "post-pandemic"). Most studies reported increased iGAS incidence during the post-pandemic period, particularly among children in Australia, European countries and North America, with several identifying the emergence and spread of the M1UK lineage associated with increased severity. Although recent studies from Asia have documented post-pandemic surges in iGAS or the emergence of M1UK lineage, long-term clinical data with molecular characterization spanning the pre-pandemic, pandemic, and post-pandemic periods across all age groups from Asia remain limited. No multi-center surveillance study from the Republic of Korea (ROK) has systematically examined iGAS epidemiology and molecular characteristics across a decade-long period including the COVID-19 pandemic.

Added value of this study

This multi-center study provides the first comprehensive 10-year analysis of iGAS infections in Korean children and adults, capturing pre-pandemic, pandemic, and post-pandemic periods (2015–2024). Our findings reveal a significant post-pandemic surge in iGAS incidence, with rates increasing particularly among children. We identified the first emergence of M1UK lineage in the ROK in 2020. We characterized distinct clinical features differentiating streptococcal toxic shock syndrome from non-toxic shock presentations, and identified independent mortality risk factors among iGAS diseases. This study provides the robust evidence supporting the need for integrated clinical and molecular surveillance systems for iGAS infection.

Implications of all the available evidence

This nationwide study, supported by Korea Disease Control and Prevention Agency, provides the foundational evidence establishing the need for systematic iGAS surveillance in the ROK. The post-pandemic surge with M1UK lineage emergence, consistent with global reports from Europe and North America, necessitates heightened clinical vigilance and regular surveillance. The identified mortality risk factors enable early risk stratification and should prompt aggressive management including intensive supportive care. This study establishes the scientific basis for national iGAS surveillance policy, supporting the implementation of a national surveillance system to monitor emerging strains and guide evidence-based interventions.

Introduction

Group A streptococcus (GAS) causes many diseases, ranging from mild illnesses, such as tonsillitis, scarlet fever, and impetigo, to life-threatening invasive infections. Invasive group A streptococcal (iGAS) infections, which encompass streptococcal toxic shock syndrome (STSS), sepsis, and necrotising fasciitis, are associated with substantial morbidity and mortality.[1] Despite advances in antimicrobial therapy and supportive care, the incidence of iGAS has shown an increase since the 1980s with a further resurgence reported in several high-income countries reported from 2014.[1–3] This resurgence has been partly attributed to the emergence and expansion of hypervirulent strains, most notably the M1UK lineage initially identified in the United Kingdom, further underscoring the evolving public health significance of iGAS infections.[4]

During the coronavirus disease 2019 (COVID-19) pandemic, widespread non-pharmaceutical interventions led to a marked global decline in both scarlet fever and iGAS incidence.[5] The subsequent relaxation of these measures created a unique epidemiological inflection point: beginning in early to mid-2022, multiple countries reported a rapid resurgence of both non-invasive GAS and iGAS infections, particularly among children.[6–8] Countries with established nationwide surveillance systems, including Canada, Australia, Europe, Japan, and the United States, were able to promptly detect changes in iGAS epidemiology and respond with targeted public health measures.[9]

In the Republic of Korea (ROK), while comprehensive surveillance systems exist for scarlet fever, systematic monitoring of iGAS infections is lacking. Several single-centre and limited multi-centre studies have reported clinical and microbiological characteristics of iGAS infections.[10,11] However, population-based or nationwide surveillance data remain unavailable, despite the substantially higher morbidity and mortality associated with iGAS. This gap highlights an important limitation in national infectious disease surveillance.

In this context, this study aimed to establish the clinical and molecular epidemiological evidence base for iGAS in the ROK. Specifically, we sought to: (1) document temporal trends in iGAS incidence over the past decade and contextualize the post-pandemic upsurge within the global literature; (2) characterize the clinical presentations and severity of iGAS across paediatric and adult populations; (3) identify risk factors for mortality and disability to inform the prioritization of high-risk groups; and (4) describe the molecular epidemiology of circulating GAS strains, including the first identification of the M1UK lineage in the ROK — underscoring the need for sustained clinical and genomic surveillance. Together, these findings are intended to support the designation of iGAS as a nationally notifiable disease in the ROK and to provide the foundation for a systematic national surveillance programme integrating both clinical and molecular data.

Methods

Study design

Given the recent epidemiologic changes in iGAS infections reported in countries with established surveillance systems, we conducted a multi-centre cohort study using a hybrid design combining prospective and retrospective data collection to assess temporal trends in the ROK. iGAS cases were retrospectively identified from January 2015 to May 2024 through microbiology laboratory databases at each participating hospital, based on isolation of *Streptococcus pyogenes* from normally sterile sites. During the prospective period, June to December 2024, cases were identified through active surveillance at each participating hospital, with real-time reporting of microbiologically confirmed isolates. A total of 23 university-affiliated hospitals across the ROK participated in this study (Appendix p 2). These centers were major referral hospitals with established microbiological capacity. Both paediatric and adult patients were included across all participating sites. The hospitals participating in this study covered regions accounting for over 90.0% of the population. Data were obtained using a standardised case report form developed based on the core data elements proposed by the Strep A Vaccine Global Consortium working group, which recently reported surveillance standards for iGAS.[12] Demographic and clinical data included age, sex, underlying medical conditions, clinical diagnosis, site of isolation, antibiotic susceptibility results at each hospital, treatment received (including surgery), severity, and outcome. Morbidity was defined as the presence of persistent clinical sequelae or disability at the time of hospital discharge, including amputation, skin necrosis or scarring, chronic kidney disease or dialysis dependency, and other clinically significant complications. Data on potential risk factors, including preceding illness, social history, and epidemiologic exposures, were also collected. Culture isolates were collected from previously stored specimens at six institutions and were longitudinally collected from all institutions during the prospective study period. This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (IRB No. B-2407-914-302). The IRB waived informed consent requirements for retrospective anonymised surveillance data, and written informed consent was obtained from patients or guardians for prospective case collection.

Case definition

iGAS infection was defined as the isolation of *Streptococcus pyogenes* from a normally sterile site using culture. Eligible clinical diagnoses included primary bacteremia without source, skin and soft tissue

infection (SSTI), necrotising fasciitis, STSS, osteoarticular infection (OAI), deep-seated abscess, respiratory tract infection, carditis, intra-abdominal infection, central nervous system infection, pelvic inflammatory disease, and other site infections with bacteremia. A clinical diagnosis with a focal lesion—such as central nervous system infection, pneumonia, OAI, or deep-seated abscess—was assigned when the pathogen was isolated from the corresponding sterile site or, if identified only in blood, when clinical features were compatible with the diagnosis. STSS was defined as the presence of hypotension and involvement of multiple organ systems, with isolation of *S. pyogenes* according to the definition by the Centres for Disease Control and Prevention (CDC).[13]

emm typing and sequencing

All available *S. pyogenes* isolates were *emm*-typed at the central research laboratory. Whole-genome sequencing (WGS) was subsequently performed for *emm*1 isolates, and M1UK lineage characterization was conducted in collaboration with the Korea Disease Control and Prevention Agency (KDCA). *emm* gene sequences were analysed according to the CDC protocol.[14] DNA was extracted using PrepMan Ultra Sample Preparation Reagent (ThermoFisher Scientific, Waltham, MA, USA). Polymerase chain reaction (PCR) was performed using MBAE-110 Axen H Taq PCR Master Mix (2×) with initial denaturation at 95 °C for 5 min, followed by 35 cycles (95 °C for 30 s, annealing for 30 s, 72 °C for 1 min), and final extension at 72 °C for 10 min. PCR products were sequenced using the BigDye Terminator v3.1 Cycle Sequencing Kit on an ABI PRISM 3730XL DNA Analyser (Applied Biosystems, Foster City, CA, USA). Whole-genome sequencing was performed using TruSeq Nano DNA Library Prep Kit (Illumina, San Diego, CA, USA) as 150 bp paired-end reads on the NovaSeq X platform (Macrogen, Seoul, ROK). M1UK lineage determination was based on characteristic single-nucleotide polymorphism profiles and lineage-specific genomic markers described in prior reports.[5]

Statistical analysis

Differences in epidemiologic and clinical features according to age group and period were analysed using the chi-square or Fisher's exact test. Age-based analyses were conducted using two approaches: (1) a two-group comparison between children (<19 years) and adults (≥19 years), and (2) a three-group comparison subdividing adults into younger (19–64 years) and older adults (≥65 years). Annual incidence was calculated using two methods: (1) the number of cases per 100,000 inpatients at each hospital for each year, and (2) the number of cases per 100,000 mid-year population based on ROK national statistics.[15] For the population-based incidence, the annual mid-year population by sex and age group was obtained from Statistics Korea (Korean Statistical Information Service, KOSIS) for each corresponding year and used as the denominator; therefore, the denominator varied annually reflecting changes in the national population.[15] To evaluate the impact of the COVID-19 pandemic, cases were categorised across three time periods: pre-COVID-19 (2015–2019), during COVID-19 (2020–2022), and post-COVID-19 (2023–2024). Poisson regression models with offsets for population size and total hospital admissions were used to estimate incidence rate ratios (IRR) across the three periods, with the pre-COVID-19 period as the reference. Logistic regression analyses were conducted to identify risk factors for mortality. For adult patients, variables with $p < 0.1$ in univariate analysis were included in the multivariable logistic regression model. Sex and period were additionally included a priori as a recognised confounder regardless of its univariate p-value. For paediatric patients, the limited number of deaths (n = 8) precluded reliable multivariable analysis; therefore, only univariate analyses are presented for this subgroup. We performed statistical analyses using R version 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria), and $p < 0.05$ was considered statistically significant.

Role of the funding source

The Korea Disease Control and Prevention Agency contributed to molecular characterisation of selected isolates, including identification of the M1UK lineage, however had no role in the study design, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 454 cases of iGAS infection were identified during the 10-year study period (Table 1). The median age was 54 years (range, 11 days to 94 years), and 269 patients (59.3%) were male. Children (<19 years) accounted for 21.4% (n = 97/454), younger adults (19–64 years) for 44.5% (n = 202/454), and older adults (≥65 years) for 34.1% (n = 155/454) of the participants. Detailed clinical data were available for all adults and 76 children, accounting for 95.4% of all cases. The overall mortality rate was 15.5% (67/454; 10.5% for children and 26.5% for older adults), and 11.5% (50/454) of the cases experienced long-term sequelae.

Annual incidence

The mean annual incidence of iGAS infection was 4.72 events per 100,000 admissions (95% CI 4.26–5.13) overall, 7.04 events per 100,000 admissions (95% CI 5.96–8.97) for children and 4.33 events per 100,000 admissions for adults (95% CI 3.83–4.72). The annual incidences by age group are depicted in Fig. 1, and IRRs

Characteristics	No. of cases (%)				p value[a]
	Total	Children (<19 years)	Younger adults (19–64 years)	Older adults (≥65 years)	
Total	454	97 (21.4)	202 (44.5)	155 (34.1)	NA
Sex, male	269 (59.3)	58 (59.8)	118 (58.4)	93 (60.0)	0.948
Age, median (Q1–Q3)	54 (25.2–69)	6 (4–9)	47 (37–57)	73 (69–79)	NA
Cases with detailed clinical information	433 (95.4)	76 (78.4)	202 (100)	155 (100)	NA
Hospitalisation	396 (91.5)	74 (97.4)	180 (89.1)	142 (91.6)	0.090
Risk factor					
Underlying medical condition	241 (55.7)	10 (13.2)	109 (54.0)	122 (78.7)	<0.001
Chronic underlying disease	184 (42.5)	7 (9.2)	79 (39.1)	98 (63.2)	<0.001
Immunocompromised	101 (23.3)	5 (6.6)	49 (24.3)	47 (30.3)	<0.001*,†
Pregnancy	3 (0.7)	0 (0.0)	3 (1.5)	0 (0.0)	0.178
Acute skin breakage[b]	81/381 (21.3)	7/70 (10)	34/177 (19.2)	40/134 (29.9)	0.003†
Chronic skin disease[c]	36/366 (9.8)	4/71 (5.6)	21/168 (12.5)	11/127 (8.7)	0.228
Pharyngitis within 7 days	33/336 (9.8)	13/65 (20.0)	14/150 (9.3)	6/121 (5.0)	0.004†
Smoking	50/375 (13.3)	.	29/165 (17.6)	21/134 (15.7)	0.66
Alcohol use	37/375 (9.9)	.	23/169 (13.6)	14/130 (10.8)	0.46
IV drug user	10/321 (3.1)	.	6/144 (4.2)	4/104 (3.8)	NA
Clinical diagnosis[d]					
SSTI	103 (22.7)	12 (12.4)	49 (24.3)	42 (27.1)	0.019
STSS	89 (19.6)	9 (9.3)	39 (19.3)	41 (26.5)	0.004†
Bacteremia without focus	77 (17.0)	24 (24.7)	28 (13.9)	25 (16.1)	0.062
Deep-seated abscess	72 (15.9)	19 (19.6)	36 (17.8)	17 (11.0)	0.112
OAI	69 (15.2)	24 (24.7)	24 (11.9)	21 (13.5)	0.012
Respiratory tract infection	67 (14.8)	9 (9.3)	31 (15.3)	27 (17.4)	0.198
Necrotizing fasciitis	60 (13.2)	8 (8.2)	26 (12.9)	26 (16.8)	0.148
Intra-abdominal infection	27 (5.9)	3 (3.1)	16 (7.9)	8 (5.2)	0.224
Carditis	9 (2)	0 (0.0)	5 (2.5)	4 (2.6)	0.287
CNS infection	6 (1.3)	3 (3.1)	1 (0.5)	2 (1.3)	0.183
Pelvic inflammatory disease	5 (1.1)	0 (0.0)	5 (2.5)	0 (0.0)	0.043
Pregnancy-related infection	3 (0.7)	0 (0.0)	3 (1.5)	0 (0.0)	0.152
Others	8 (1.8)	2 (2.1)	4 (2.0)	2 (1.3)	0.858
Severity					
ICU admission	125 (28.9)	18 (23.7)	49 (24.3)	58 (37.4)	0.014
Ventilator support	84 (19.4)	13 (17.1)	32 (15.8)	39 (25.2)	0.075
IVIG	44 (10.2)	13 (17.1)	18 (8.9)	13 (8.4)	0.087
Inotropic	138 (31.9)	14 (18.4)	54 (26.7)	70 (45.2)	<0.001†,‡
ECMO	10 (2.3)	3 (3.9)	4 (2.0)	3 (1.9)	0.578
CRRT	60 (13.9)	6 (7.9)	26 (12.9)	28 (18.1)	0.094
Surgery	179 (41.3)	37 (48.7)	86 (42.6)	56 (36.1)	0.169
Amputation	6 (1.4)	1 (1.3)	4 (2.0)	1 (0.6)	0.563
Outcome					
Death	67 (15.5)	8 (10.5)	18 (8.9)	41 (26.5)	<0.001†,‡
Disability	50 (11.5)	6 (7.9)	21 (10.4)	23 (14.8)	0.235

Abbreviations: CNS, central nervous system; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; GAS, group A streptococcus; ICU, intensive care unit; IV, intravenous; IVIG, intravenous immunoglobulin; NA, not applicable; OAI, osteoarticular infection; SSTI, skin and soft tissue infection; STSS, streptococcal toxic shock syndrome. [a]*indicates a statistically significant difference between children and younger adults; † between children and older adults; and ‡ between younger adults and older adults. [b]Includes injection-related injuries, bee-venom therapy, penetrating trauma, and skin defects due to preceding traffic accidents. [c]Includes sores, diabetic foot ulcers, tinea-related wounds, and atopic dermatitis. [d]Case patients may have had >1 syndrome, with the exception of bacteremia without focus.

Table 1: **Demographics and clinical characteristics of invasive group A streptococcal infection cases by age group.**

compared to the pre-pandemic period are shown in Appendix pp 3–4. The overall incidence significantly declined from 7.03 cases per 100,000 inpatients in 2015–2019 to 1.72 in 2020–2022 (IRR 0.25 [95% confidence interval, CI 0.15–0.41]) and then rose to 3.43 in 2023–2024. Among children, the incidence dropped from 9.34 cases per 100,000 inpatients in 2015–2019 to 0.95 in 2020–2022 (IRR 0.10 [95% CI 0.02–0.37]), but returned to pre-pandemic levels at 10.45 in 2023–2024 (IRR 1.10 [95% CI 0.39–3.40]). In contrast, adult

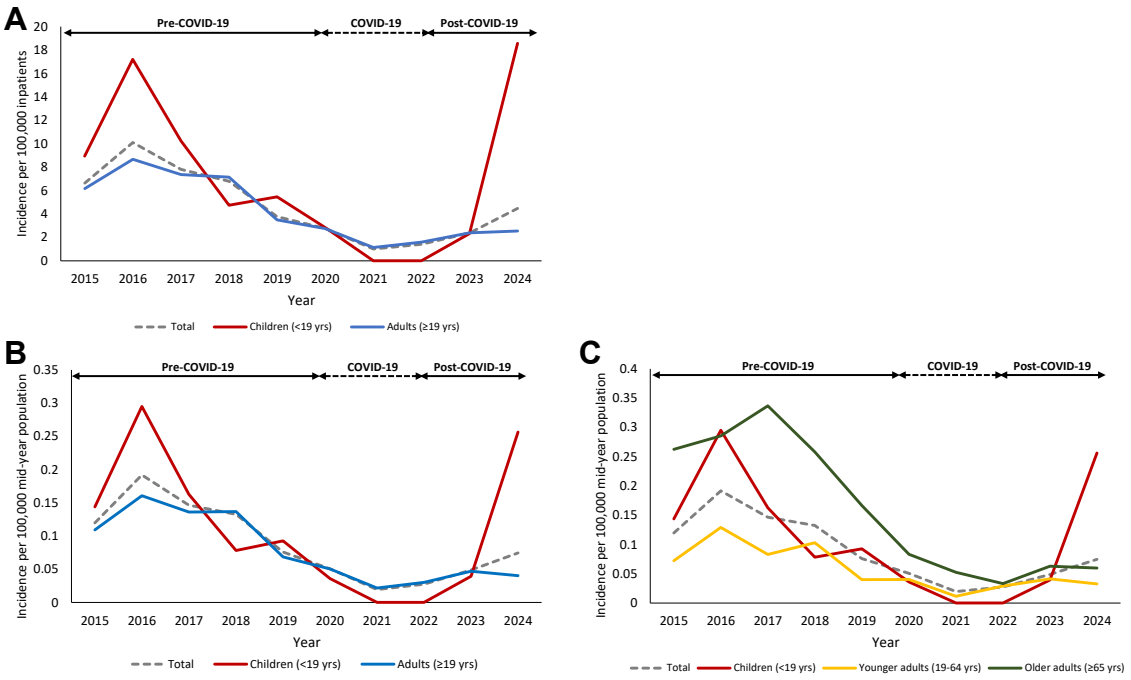


***Fig. 1:* Annual incidence of invasive group A streptococcal infection in the Republic of Korea, 2015–2024.** (A) Annual incidence per 100,000 inpatients among children and adults. (B) Annual incidence per 100,000 mid-year population among children and adults. (C) Annual incidence per 100,000 mid-year population by age group: children (<19 years, red line), younger adults (19–64 years, yellow line), and older adults (≥65 years, green line). The dashed grey line represents the total population. In panels A and B, the red line represents children, the blue line represents adults, and the dashed grey line represents the total population. The pre-COVID-19 period refers to 2015–2019; the COVID-19 period, 2020–2022; and the post-COVID-19 period, 2023–2024. COVID-19, coronavirus disease 2019; yrs, years.

incidence decreased from 6.57 to 1.83 during the pandemic (IRR 0.28 [95% CI 0.18–0.43]), and slightly increased to 2.5 in 2023–2024. Similar age-related patterns were observed using mid-year population rates and the raw number of annual iGAS cases (Fig. 1B, C, and Appendix p 4–5). Comparison with national scarlet fever surveillance data (KDCA) revealed that increases in iGAS incidence preceded rises in scarlet fever notifications between 2015 and 2024 (Appendix p 6).

Clinical characteristics

Among the 454 cases, the most common clinical diagnosis was SSTI (103/454, 22.7%), followed by STSS (89/454, 19.6%), bacteremia without a source (77/454, 17.0%), deep-seated abscess (72/454, 15.9%), OAI (69/454, 15.2%), respiratory tract infection (67/454, 14.8%), and necrotising fasciitis (60/454, 13.2%). SSTI and STSS were more common in adults than in children ($p = 0.009$ and $p = 0.006$, respectively), whereas OAI was more common in children ($p = 0.012$) (Table 1 and Appendix p 8–9). The distribution of clinical diagnoses did not differ significantly across the three epidemiological periods (Appendix p 10), with SSTI, STSS, and bacteremia without focus remaining the three most common presentations throughout. Among the 433 cases with detailed clinical data, 396 (396/433, 91.5%) were hospitalised, and 241 (241/433, 55.7%) had underlying medical conditions. Children less frequently had underlying medical conditions (10/76, 13.2%) than younger (109/202, 54.0%) and older adults (122/155, 78.7%) ($p < 0.001$). Among adults, diabetes mellitus was the most common underlying medical condition (92/357, 25.7%), followed by chronic heart disease (66/357, 18.5%). Chronic neurological disease (6/76, 7.9%) and malignancy (3/76, 3.9%) were the most frequent among children. A potential infection route was identified in 127 cases (127/433, 29.3%), predominantly acute skin breakage (81/381, 21.3%). Recent pharyngitis within 7 days was reported in 20.0% (13/65) of children (Table 1, Appendix pp 8–9).

Clinical severity and outcome

Among the 433 cases with detailed clinical data, fever was observed in 79.9% (346/433), hypotension in 36.5% (158/433), and acute kidney injury in 26.3% (114/433) (Appendix pp 6–7). Intensive care unit management was required in 125 cases (125/433, 28.9%), including mechanical ventilation (84/433, 19.4%), continuous renal replacement therapy (60/433, 13.9%), and extracorporeal membrane oxygenation (10/433, 2.3%).

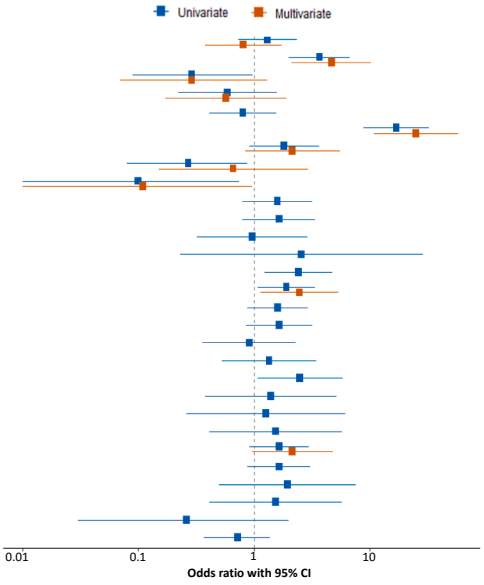
Surgery was performed in 179 cases (179/433, 41.3%), including six amputations (6/433, 1.4%). The overall mortality rate was 15.5% (67/433), with 11.5% (50/433) experiencing long-term disabilities. Mortality was highest among older adults (41/155, 26.5%), followed by children (8/76, 10.5%) and younger adults (18/202, 8.9%) ($p < 0.001$) (Table 1). Severity and outcomes were broadly consistent across the three epidemiological periods, with no statistically significant differences observed (Appendix p 10).

Risk factors for mortality

Risk factors for mortality were analysed in 433 cases with detailed clinical data (Fig. 2). In adults, univariate analysis identified age ≥ 65 years, STSS, chronic medical conditions, and immunocompromised status as associated with mortality. On multivariable analysis, independent predictors were STSS (adjusted OR [aOR] 20.07, 95% CI 9.3–43.3), age ≥ 65 years (aOR 4.67, 95% CI 2.12–10.29), chronic medical conditions (aOR 2.96, 95% CI 1.41–6.22), and immunocompromised status

A

Characteristic	No. of death/ total (%)	Univariate analysis, OR (95% CI)	*p* value	Multivariate analysis, OR (95% CI)	*p* value
Male	38/211 (18.0)	1.31 (0.73-2.34)	0.365	0.93 (0.45-1.92)	0.843
Older adults (≥ 65 years)	41/155 (26.5)	3.68 (2.01-6.71)	<0.001	4.67 (2.12-10.29)	<0.001
During-COVID-19 period	3/47 (6.4)	0.29 (0.09-0.98)	0.046	0.4 (0.1-1.57)	0.188
Post-COVID-19 period	5/41 (12.2)	0.59 (0.22-1.59)	0.298	0.54 (0.16-1.77)	0.307
SSTI	13/91 (14.3)	0.8 (0.41-1.55)	0.505		
STSS	42/80 (52.5)	16.90 (8.75-32.65)	<0.001	20.07 (9.3-43.28)	<0.0001
Bacteremia without focus	13/53 (24.5)	1.82 (0.91-3.67)	0.093	2.12 (0.86-5.22)	0.102
Deep-seated abscess	3/53 (5.7)	0.27 (0.08-0.88)	0.031	0.76 (0.18-3.13)	0.704
OAI	1/45 (2.2)	0.1 (0.01-0.74)	0.024	0.14 (0.02-1.16)	0.068
Respiratory tract infection	13/58 (22.4)	1.59 (0.79-3.18)	0.190		
Necrotizing fasciitis	12/52 (23.1)	1.65 (0.80-3.37)	0.172		
Intra-abdominal infection	4/25 (16.0)	0.96 (0.32-2.9)	0.941		
CNS infection	1/3 (33.3)	2.55 (0.23-28.61)	0.448		
Underlying medical condition	47/231 (20.3)	2.41 (1.23-4.77)	0.010		
Chronic medical condition	37/177 (20.9)	1.9 (1.07-3.37)	0.029	2.96 (1.41-6.22)	0.004
Diabetes mellitus	20/92 (21.7)	1.61 (0.88-2.94)	0.120		
Chronic heart disease	15/66 (22.7)	1.65 (0.85-3.19)	0.136		
Chronic kidney disease	6/39 (15.4)	0.91 (0.36-2.28)	0.839		
Cerebrovascular disease	6/29 (20.7)	1.35 (0.53-3.48)	0.530		
Chronic liver disease	9/29 (31.0)	2.5 (1.08-5.81)	0.033		
Chronic lung disease	3/14 (21.4)	1.4 (0.38-5.17)	0.616		
Chronic neurological disease	2/10 (20.0)	1.27 (0.26-6.15)	0.765		
Connective tissue disease	3/13 (23.1)	1.54 (0.41-5.78)	0.520		
Immunocompromised	21/96 (21.9)	1.64 (0.91-2.98)	0.101	2.33 (1.07-5.09)	0.034
Malignancy	18/81 (22.2)	1.64 (0.88-3.04)	0.119		
Immunosuppressant use	3/11 (27.3)	1.94 (0.5-7.55)	0.338		
Influenza within 30 days	3/13 (23.1)	1.54 (0.41-5.78)	0.520		
Preceding pharyngitis	1/20 (5.0)	0.26 (0.03-2.01)	0.198		
Preceding skin breakage	15/107 (14.0)	0.72 (0.37-1.38)	0.320		



B

Characteristic	No. of death/ total (%)	Univariate analysis, OR (95% CI)	*p* value
Male	6/46 (13.0)	2.10 (0.39-11.17)	0.384
Post-COVID-19 period	2/20 (10.0)	0.91 (0.17-4.91)	0.910
STSS	5/9 (44.4)	26.67 (4.63-153.73)	<0.001
Bacteremia without focus	3/18 (16.7)	2.54 (0.54-12.00)	0.240
OAI	1/15 (6.7)	0.55 (0.06-4.86)	0.591
Necrotizing fasciitis	1/8 (12.5)	1.24 (0.13-11.65)	0.848
Underlying medical condition	3/10 (30.0)	5.23 (1.02-26.72)	0.047
Chronic medical condition	1/7 (14.3)	1.48 (0.15-14.10)	0.735
Immunocompromised	3/5 (60.0)	19.80 (2.66-147.32)	0.004
Influenza within 30 days	1/6 (16.7)	1.80 (0.18-17.68)	0.614
Preceding pharyngitis	2/13 (15.4)	1.71 (0.29-10.00)	0.552
Preceding skin breakage	1/11 (9.1)	0.68 (0.08-6.06)	0.726

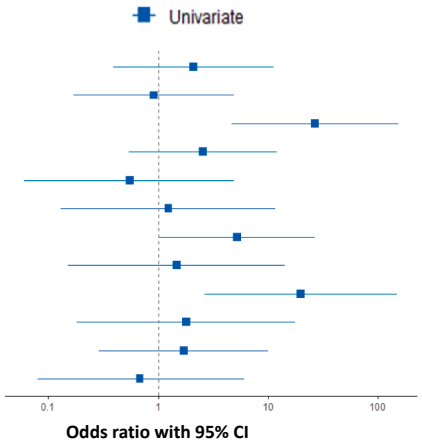


Fig. 2: **Factors associated with mortality in invasive group A streptococcal infection among adults (A) and children (B).** Forest plots show odds ratios (ORs) with 95% CIs from univariate (blue) and multivariable (orange) logistic regression analyses. Squares represent point estimates of ORs, and horizontal lines represent 95% CIs. The vertical dashed line at OR = 1.0 indicates no association. CNS, central nervous system; CI, confidence intervals; COVID-19, coronavirus disease 2019; OAI, osteoarticular infection; SSTI, skin and soft tissue infection; SSTS, streptococcal toxic shock syndrome.

(aOR 2.33, 95% CI 1.07–5.09) (all p < 0.05) among adults. Among children, STSS (OR 26.67, 95% CI 4.63–153.73; p < 0.001) and immunocompromised condition (OR 19.80, 95% CI 2.66–147.32; p = 0.004) were significantly associated with mortality on univariate analysis. Due to the limited number of deaths (n = 8), multivariable analysis was not performed in the paediatric cohort.

Streptococcal toxic shock syndrome

Among 433 cases, 89 (89/433, 20.6%) had STSS, including nine children (9/76, 11.8%) and 80 adults (80/357, 22.4%). The annual incidence of STSS remained stable in 2015–2019 (0.68–1.28 per 100,000 inpatients in children; 1.57–2.21 in adults), declined markedly in 2020–2022, then increased post-pandemic, particularly in children (2.93 per 100,000 inpatients in 2024) (Appendix p 5). STSS was more common in younger adults (39/202, 19.3%) and older adults (41/155, 26.5%) than in children (9/76, 11.8%) (p = 0.030, Table 1). Compared with non-STSS, patients with STSS were more likely to present with necrotising fasciitis and respiratory tract infection, and have an underlying history of disease or alcohol use (p < 0.05 for all) (Table 2). OAI and deep-seated abscesses were less common in STSS cases (p < 0.05 for both). Among 17 isolates obtained from STSS cases, *emm*1 (8/17, 47.1%) and *emm*28 (4/17, 23.5%) were predominant.

Characteristics of isolates

emm typing data were available for 98 isolates: 36 from children (36/97, 37.1%) and 62 from adults (65/357, 17.4%). *emm*1 was the most common (32/98, 32.7%), followed by *emm*12 (13/98, 13.3%), *emm*28 (11/98, 11.2%), and *emm*89 (8/98, 8.2%); *emm*3, *emm*4, and *emm*90 accounted for 5.1% each (Fig. 3, Appendix p 8, 14). Before the pandemic (n = 71), *emm*1 predominated (28/71, 39.4%), followed by *emm*28 (10/71, 14.1%), *emm*89 (8/71, 11.3%), and *emm*3 and *emm*12 (5/71, 7.0% each). In the post-pandemic period (n = 21), *emm*12 was the most common (7/21, 33.3%), followed by *emm*1 (3/21, 14.3%). Among 32 *emm*1 isolates, two

Characteristics	Total, N (%)			Children, N (%)			Adults, N (%)		
	STSS (N = 89)	non-STSS (N = 344)	p value	STSS (N = 9)	non-STSS (N = 67)	p value	STSS (N = 80)	non-STSS (N = 277)	p value
Sex, male	61 (68.5)	196 (57.0)	0.063	6 (66.7)	40 (59.7)	0.970	55 (68.8)	156 (56.3)	0.062
Period			0.316			0.405			0.182
Pre-COVID-19	71 (79.8)	253 (73.5)		0 (0.0)	1 (1.5)		6 (7.5)	41 (14.8)	
During-COVID-19	6 (6.7)	42 (12.2)		4 (44.4)	16 (23.9)		8 (10.0)	33 (11.9)	
Post-COVID-19	12 (13.5)	49 (14.2)		5 (55.6)	50 (74.6)		66 (82.5)	203 (73.3)	
Clinical diagnosis									
SSTI	21 (23.6)	81 (23.5)	1	1 (11.1)	10 (14.9)	1	20 (25.0)	71 (25.6)	1
Bacteremia without focus	11 (12.4)	60 (17.4)	0.320	1 (11.1)	17 (25.4)	0.598	10 (12.5)	43 (15.5)	0.623
Deep-seated abscess	6 (6.7)	62 (18.0)	0.015	1 (11.1)	14 (20.9)	0.805	5 (6.2)	48 (17.3)	0.023
OAI	6 (6.7)	54 (15.7)	0.045	2 (22.2)	13 (19.4)	1	4 (5.0)	41 (14.8)	0.033
Respiratory tract infection	21 (23.6)	45 (13.1)	0.022	1 (11.1)	7 (10.4)	1	20 (25.0)	38 (13.7)	0.025
Necrotizing fasciitis	25 (28.1)	35 (10.2)	<0.001	3 (33.3)	5 (7.5)	0.072	22 (27.5)	30 (10.8)	<0.001
Intra-abdominal infection	3 (3.4)	25 (7.3)	0.275	0 (0.0)	3 (4.5)	1	3 (3.8)	22 (7.9)	0.296
Carditis	2 (2.2)	7 (2.0)	1	.	.	.	2 (2.5)	7 (2.5)	1
Pelvic inflammatory disease	0 (0.0)	5 (1.5)	0.557	.	.	.	0 (0.0)	5 (1.8)	0.503
Pregnancy-related infection	2 (2.2)	1 (0.3)	0.205	.	.	.	2 (2.5)	1 (0.4)	0.25
Others	0 (0.0)	8 (2.3)	0.312	0 (0.0)	2 (3.0)	1	0 (0.0)	6 (2.2)	0.404
Underlying disease	59 (66.3)	182 (52.9)	0.032	2 (22.2)	8 (11.9)	0.74	57 (71.2)	174 (62.8)	0.209
Chronic medical condition	43 (48.3)	141 (41.0)	0.260	1 (11.1)	6 (9.0)	1	42 (52.5)	135 (48.7)	0.641
Immunocompromised	21 (23.6)	80 (23.3)	1	1 (11.1)	4 (6.0)	1	20 (25.0)	76 (27.4)	0.772
Social history									
Smoking	11 (14.7)	39 (13.0)	0.849	.	.	.	11 (16.7)	39 (16.7)	1
Alcohol use	15 (19.5)	22 (7.4)	0.003	.	.	.	15 (22.1)	22 (9.5)	0.011
IV drug user	4 (6.8)	6 (2.3)	0.168	.	.	.	4 (8.0)	6 (3.0)	0.233
Outcome									
Death	47 (52.8)	20 (5.8)	<0.001	5 (55.6)	3 (4.5)	<0.001	42 (52.5)	17 (6.1)	<0.001
Disability	19 (21.3)	31 (9.0)	0.002	2 (22.2)	4 (6.0)	0.299	17 (21.2)	27 (9.7)	0.01

CNS, central nervous system; COVID-19, coronavirus disease 2019; OAI, osteoarticular infection; SSTI, skin and soft tissue infection; IV, intravenous.

Table 2: **Clinical characteristics of patients with and without streptococcal toxic shock syndrome in children and adults.**

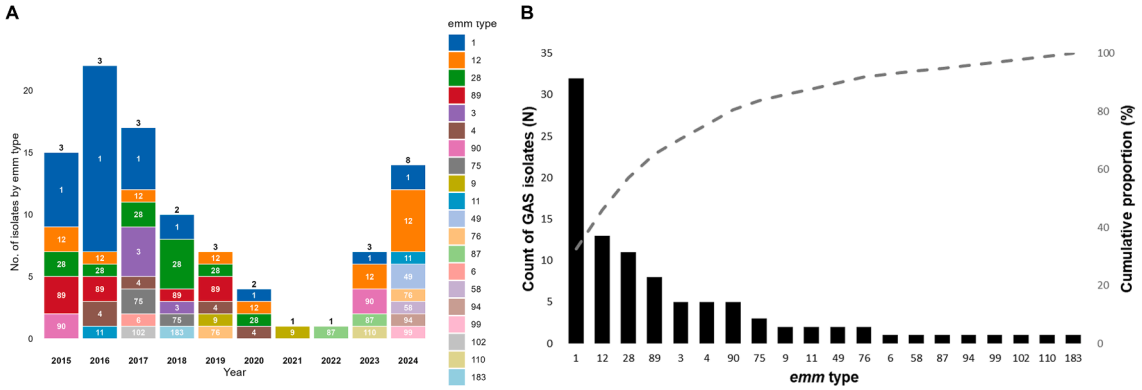


Fig. 3: **Distribution of *emm* types among 98 invasive group A streptococcal infection isolates in the Republic of Korea, 2015–2024.** (A) Annual distribution of *emm* types shown as stacked bars. Each colour represents a different *emm* type, with numbers indicating the *emm* type. The number above each bar indicates the number of hospitals contributing isolates in that year. During the retrospective period (2015–2023), isolates were predominantly contributed by 4 hospitals located in Seoul and Gyeonggi-do. During the prospective period (June–December 2024), isolates were contributed by 8 hospitals across 5 geographically diverse regions (Seoul, Gyeonggi, Gyeongnam, Jeonnam, and Chungnam). (B) Isolate count and cumulative proportion by *emm* type. Bars represent the number of isolates for each *emm* type (left y-axis), and the line represents the cumulative proportion (right y-axis).

were identified as the M1UK lineage: an adult case of brain abscess in 2020 and one paediatric case with STSS and necrotising fasciitis requiring amputation in 2024. Two *emm*49 isolates newly emerged in 2024 without fatality. Compared to non-*emm*1 cases, *emm*1 cases demonstrated higher mortality (28.6% [6/21] vs. 10.5% [6/57], p = 0.075) and a higher disability rate (19.0% [4/21] vs. 3.5% [2/57], p = 0.042), although the number of typed isolates was limited (Appendix p 8).

All isolates were susceptible to penicillin, cefotaxime, and vancomycin (Appendix p 9). Susceptibility rates were 88.6% (396/447) for erythromycin, 89.5% (400/447) for clindamycin, and 89.7% (339/378) for levofloxacin. Erythromycin and clindamycin susceptibility rates were higher in children (96.8% [91/94] and 95.7% [90/94], respectively) than in adults (86.4% [305/353] and 87.1% [310/356], respectively).

Discussion

This study is the first to systematically investigate the epidemiologic and clinical characteristics of iGAS infections in both paediatric and adult populations over a decade-long period in the ROK. The incidence sharply declined during the COVID-19 pandemic but rebounded thereafter, particularly among children, whose incidence returned to pre-pandemic levels by 2024. This pattern is consistent with the post-pandemic resurgence observed in multiple countries, underscoring the global vulnerability of paediatric populations to iGAS following periods of reduced pathogen exposure.[16] We also documented the first GAS isolate of the M1UK lineage in the ROK, identified in 2020, highlighting the emergence of internationally circulating hypervirulent strains within the country. Despite contemporary advances in clinical care, overall mortality remained high at 15.5%, with STSS being the strongest independent predictor of death across all age groups.

Consistent with global observations, iGAS incidence markedly declined during the COVID-19 pandemic and subsequently rebounded, particularly among children in the ROK.[5–8,17] Interestingly, a declining trend in incidence was already observed in the pre-pandemic period, which may reflect secular epidemiological fluctuations or changes in healthcare utilisation and diagnostic practices. This temporal pattern is consistent with multiple contributing factors. First, public health measures applied to combat COVID-19 may have reduced *S. pyogenes* transmission. Their relaxation may have facilitated its spread, particularly in crowded settings such as schools and childcare facilities. A similar pattern was observed with other respiratory pathogens, including influenza and respiratory syncytial virus.[18,19] Second, the return of viral infections that predispose children to secondary bacterial infections, such as influenza and varicella, may have increased the risk for iGAS.[19,20] Third, reduced exposure to GAS during the pandemic might have caused an immunity debt, particularly in children who lacked previous exposure.[16,20–22] This is supported by our age-specific recovery pattern: paediatric incidence returned to pre-pandemic levels by 2024, while adult incidence remained suppressed. Similar disproportionate paediatric increases in iGAS have been reported globally.[23–25]

The population-based incidence of iGAS in our study appears considerably lower than that reported in Western countries, where pre-pandemic incidence ranged from 1.8 to 7.9 per 100,000 population, declined to 0.5–1.2 per 100,000 during the COVID-19 pandemic, and subsequently increased to 5.2–8.2 per 100,000 in the

post-pandemic period.[5,6,22,23] In contrast, the population-based incidence observed in our study was substantially lower, despite the hospital admission-based incidence showing a similar temporal trend to international reports. Several factors may explain this discrepancy. Under-ascertainment is a major concern, as the retrospective design may have led to incomplete case identification. Although the participating tertiary university hospitals covered regions representing over 90% of the national population, iGAS cases presenting to secondary or community-level hospitals would not have been included in this study, as iGAS is not a nationally notifiable disease in the ROK. Moreover, the historically high rates of antibiotic prescribing in the ROK, particularly for upper respiratory tract infections,[26] may have prevented progression to invasive disease in some patients, thereby reducing the observed incidence of iGAS. Furthermore, in the Korean healthcare system, patients are frequently prescribed antibiotics at primary or secondary care facilities before being referred to tertiary centers for invasive infections. As a result, blood cultures and sterile site cultures obtained upon tertiary hospital admission are likely to yield negative results in a considerable proportion of cases, leading to further underestimation of true iGAS incidence.

In the ROK, scarlet fever is a nationally notifiable disease; however, iGAS infections and STSS remain outside the mandatory and sentinel surveillance framework. This gap has limited the capacity to systematically assess temporal epidemiological trends and disease burden. Notably, comparison with national scarlet fever surveillance data revealed that iGAS cases preceded rises in scarlet fever notifications across multiple epidemic cycles, suggesting that scarlet fever trends alone may not serve as a reliable early warning signal for iGAS activity. This pattern may reflect delayed ascertainment of scarlet fever at the primary care level, where empirical antibiotic treatment without microbiological confirmation is common during the early phase of a GAS upsurge. Meanwhile, countries such as the United States, United Kingdom, and Australia have established population- or laboratory-based surveillance networks, which promptly detected an unusual surge in iGAS cases and fatalities in 2022.[13,22] Following post-pandemic resurgence of iGAS, the World Health Organisation and CDC issued alerts and provided guidance addressing clinical management and antibiotic shortages.[5] Japan, a neighbouring country, also reported a marked increase in STSS cases beginning May 2023, linked to the spread of the hypervirulent M1UK lineage.[8] These observations, together with the complementary value of iGAS surveillance, underscore the importance of nationwide surveillance systems that integrate clinical and microbiological data to enhance situational awareness, inform timely guideline updates, and enable early detection of emerging strains.

Notably, 86.8% of paediatric iGAS cases occurred in previously healthy children. In a recent 10-year United States study, 69.9% of children with iGAS had no underlying conditions, compared with only 7.0% of adults.[17] Lenglart et al. reported similar findings in a study involving 15 European countries, demonstrating that most children with iGAS were previously healthy.[25] These findings indicate that although mortality was higher in children with comorbidities, the burden of iGAS extends across the entire paediatric population, not limited to those with underlying medical conditions, emphasising the need for high clinical suspicion and ongoing surveillance.

Older age, underlying chronic medical conditions, and immunocompromised status were independently associated with increased mortality. STSS was associated with the highest risk of mortality in both children and adults.[27–29] In this study, patients with STSS were more likely to present with necrotising fasciitis, respiratory tract infections, underlying medical conditions, and a history of alcohol use. These associations likely reflect, in part, the diagnostic criteria for STSS.[13] These associations may partly reflect the diagnostic criteria for STSS, which inherently select for patients with more severe disease and comorbid conditions.[13] Additionally, toxin-mediated pathogenic mechanisms may contribute, as cytolytic toxins and superantigens responsible for necrotising fasciitis are also involved in the pathogenesis of STSS.[30]

*emm*1 predominated in the ROK throughout the study period, followed by *emm*12, *emm*28, and *emm*89, consistent with previous findings.[10,11] Although the global expansion of the M1UK lineage among *emm*1 isolates has raised growing concern due to its hypervirulence, it has not been previously reported in the ROK until the present study, which identified two M1UK isolates in 2020 and 2024. In our study, the reversal in the predominance of *emm*1 and *emm*12, along with the unusually high proportion of other *emm* types (non-1, 3, 12, 28, 89) (52.9%) in 2023–2024 is notable. This shift in *emm* type distribution mirrors recent observations in the United States, where an increasing variety of *emm* types among iGAS isolates has been documented, underscoring the need for laboratory surveillance.[17] Notably, two *emm*49 isolates, previously unreported in the ROK, were detected in the post-pandemic period, consistent with recent increases in *emm*49 reported in the United States and Spain.[17,31,32]

In this study, the post-pandemic upsurge was observed from 2023 onwards, approximately 1–2 year later than the upsurge reported in Europe (2022–2023),[5,7,33] and more consistent with Japan (2023–2024).[8,34] This delayed upsurge is likely attributable to the prolonged use of mandatory masking in the ROK until January 2023 and extended social distancing. Notably, the pattern of circulating *emm* types in ROK also mirrors the early phase of the European upsurge;

*emm*12, which was only occasionally observed during the pre-COVID-19 period, increased in the post-pandemic period (2 in 2023 and 5 in 2024) in the ROK, consistent with reports from Portugal and England where *emm*12 was associated with the early paediatric iGAS upsurge.[7,33] However, the post-pandemic iGAS upsurge in Europe and North America has also been strongly associated with the expansion of the toxigenic M1UK lineage.[8,33,35] The detection of M1UK clones have also been reported from Asian countries including Japan,[8] China,[36] and Taiwan,[37] whereas only two M1UK isolates were identified in the present study, suggesting that the ROK may currently be in an earlier phase of the post-pandemic upsurge, or alternatively, that geographic differences in circulating strains may exist.

Limitation

Several considerations should be taken into account when interpreting our findings. First, due to the retrospective nature of much of the study period, some cases may have been missed, and detailed information on epidemiologic exposures and recent infection histories may have been incomplete even among included cases. Second, *emm* typing available for a subset of isolates, which may have constrained a comprehensive assessment of molecular epidemiology and genotype-phenotype associations. Furthermore, isolates from the retrospective period were predominantly contributed by hospitals in the Seoul and Gyeonggi-do, and therefore the *emm* type distribution during this period may not fully represent the national molecular epidemiology of iGAS in the ROK. The broader geographic representation achieved during the prospective period highlights the importance of systematic nationwide isolate collection for future surveillance efforts. Third, as this was a hospital-based study conducted in the absence of a national iGAS notification system, true nationwide population-level incidence estimates could not be derived. The hospital admission-based rate (Fig. 1A) was therefore used as the primary incidence measure, with population-based incidence (Fig. 1B and C) calculated supplementarily to confirm temporal trends and facilitate approximate international comparisons; both measures demonstrated concordant patterns. Nevertheless, this study encompassed 23 university-affiliated hospitals covering regions accounting for more than 90.0% of Korean population and integrated retrospective data with prospective surveillance in 2024, enabling a robust evaluation of iGAS epidemiology and clinical characteristics across both paediatric and adult populations. In addition, changes in healthcare utilization and clinical practice patterns during the 2024 physicians' strike in the ROK may have influenced the observed iGAS incidence or fatality rates.[38] Fourth, as this study was primarily descriptive, formal power calculation was not performed, and statistical analyses were conducted in an exploratory manner. Multivariable analyses of mortality risk factors were conducted as exploratory secondary analyses, with all predictors selected a priori based on clinical rationale. Given the limited number of outcome events, the multivariable model should be interpreted with caution, as the inclusion of multiple predictors may have reduced model stability; these findings require validation in future prospective studies. In the paediatric cohort, the limited number of deaths (n = 8) precluded multivariable analysis, and univariate analyses are presented only.

Despite these considerations, this study provides the most extensive, multi-centre dataset of paediatric and adult iGAS cases in the ROK to date, covering both pre- and post-COVID-19 periods. We also demonstrate the first identification of the M1UK lineage in the ROK, collectively underscoring the need for sustained clinical and genomic surveillance. As iGAS is not currently a nationally notifiable disease in the ROK, the present study aimed to address this gap by establishing the clinical and molecular epidemiological evidence base. These findings may contribute to public awareness of iGAS and support its designation as a notifiable disease in the ROK, enabling more comprehensive and timely national surveillance.

Conclusion

In conclusion, the incidence of iGAS infection in the ROK declinded markedly during the COVID-19 pandemic, but returned to pre-pandemic levels in 2023–2024, with the earliest and most pronounced rebound observed among children. While GAS infections are commonly encountered in children, severe disease and mortality were disproportionately concentrated among adults, particularly older adults. Mortality was highest among patients with STSS and those with underlying medical conditions, underscoring the substantial clinical burden of severe iGAS disease. These findings highlight the dynamic nature of iGAS epidemiology and support the designation of iGAS as a nationally notifiable disease in the ROK, with a prospective surveillance system integrating clinical and genomic data to enable timely detection of emerging strains and inform evidence-based public health responses.

Contributors

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Y.K.K. and H.L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. H.L made the decision to submit the manuscript for publication.

Data sharing statement

Individual deidentified participant data will not be publicly available due to privacy regulations and institutional review board restrictions. Aggregated data supporting the findings of this study are available within the article and its Supplementary materials. Requests for additional data access may be directed to the corresponding author and will be considered on a case-by-case basis, subject to approval by the Korea Disease Control and Prevention Agency and relevant institutional review boards. Raw whole-genome sequencing data for emm1 isolates are publicly available in the NCBI Sequence Read Archive under BioProject accession number PRJNA1447126.

Editor note

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Declaration of interests

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2026.101885.

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