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## Risk Assessment for Streptococcal Toxic Shock Syndrome (STSS) in Japan

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### ■ Background

Streptococcal toxic shock syndrome (STSS) is a highly fatal infectious disease characterized by rapid and dramatic disease progression. Based on the Infectious Diseases Control Law, STSS is designated as a Category V Infectious Disease (notifiable diseases) in the National Epidemiological Surveillance of Infectious Diseases (NESID) Program. The patient is eligible for notification if he or she is diagnosed as meeting the following criteria: 1) at least two of the following symptoms are present in addition to shock symptoms: liver failure, renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation syndrome, soft tissue inflammation, generalized erythematous rash, and central nervous system symptoms. 2)  $\beta$ -hemolytic *Streptococcus* spp. are detected in normally sterile sites (e.g., blood). STSS is caused by group A *Streptococcus* (GAS: Group A *Streptococcus*, *Streptococcus pyogenes*), as well as group B, C, and G Streptococci.

For clinical manifestations of STSS due to GAS and its related surveillance, please refer to the January 2024 Infectious Agents Surveillance Report (IASR) bulletin rapid report article<sup>[1]</sup>.

The number of reported STSS and GAS pharyngitis cases caused by GAS is increasing in Japan. In addition, since the summer of 2023, a cluster of *S. pyogenes* M1UK sublineage, which was prevalent in the United Kingdom in the 2010s, and considered to be highly pathogenic and transmissible, has been confirmed in Japan for the first time.

We reported the situation of STSS up to December 2023 in the January 2024 IASR rapid report article.

This article is to provide an update on the domestic situation since then and to conduct another risk assessment of the domestic situation.

### ■ Trends of invasive group A streptococcal infections outside of Japan

It should be noted that while Japan designates STSS as a notifiable disease in the NESID Program, in many other countries, invasive Group A *Streptococcus* (iGAS) infection (only requires GAS detection at a sterile site) is designated as a notifiable disease, and thus the case definitions differ [iii]. The United States counts STSS cases, but unlike Japan, only those caused by group A *Streptococcus* are included [iii].

An increase in iGAS infections was reported in the UK, France, Ireland, the Netherlands, and Sweden in late 2022 and early 2023, particularly in children under 10 years of age, with an increase in the number of reported M1UK sublineages of GAS reported at this time [iv]. Outbreaks of iGAS infections in these countries have calmed down around April 2023, but the situation after that time varies from country to country. In the United Kingdom, there have been no abnormalities in surveillance of iGAS infections and scarlet fever since February 2023, when the trend returned to normal [v]. In Sweden, on the other hand, the number of reported iGAS infections has increased again since late 2023 predominantly among people aged 70 years or older [vi].

In the U.S., STSS is further tabulated separately among iGAS infections. iGAS infections in children increased in December 2022, as in Europe, and the Centers for Disease Control and Prevention (CDC) issued an advisory, but there have been no reports of an increase in iGAS infections or STSS since then. STSS surveillance according to the general GAS infections has not seen a major epidemic wave [vii] although slightly increased than before the COVID-19 pandemic.

In Canada, although there are no reports of a national outbreak, British Columbia has reported an increase in iGAS infections among those under 20 years of age since December 2023, and the number of iGAS infections reported in that province has been on the rise since 2016 [viii].

In Australia, iGAS infections have not been designated as a surveillance disease until 2021, but the number of reported cases has been gradually increasing since the start of the surveillance; as of March 21, 2024, the number of reported cases is at the same level as that of 2023 [ix].

In Argentina, while there was no increase in the number of reported cases at the end of 2022, there was an increase in the number of reported cases and deaths from iGAS infections in 2023 mainly in children. Most of the lineages analyzed were M1-type strains, of which 9.1% were M1UK sublineages [x].

Although the M1UK sublineage produces about 9 times more erythrogenic toxin than other M1-type strains and is more transmissible, no epidemiological association was reported between the increase in iGAS infections and the increase in M1UK sublineage in Europe between 2022 and 2023 [xi]. Reports from

European countries during this period have also been inconsistent, with Spain reporting no association, while reports from Belgium, Germany, and Argentina suggested an association. [x],[xiii],[xiv],[xv].

## ■ Trends of group A streptococcal infections in Japan based on the NESID Program (as at March 25, 2024)

### 1) Trends of Streptococcal Toxic Shock Syndrome (STSS)

From epidemiological week (EW) 1 (January 1-7) to EW 11 (March 11-17) of 2024, 521 STSS cases were diagnosed and notified to the NESID Program, with the highest number of serogroup A (335 cases) followed by other serogroups (group B, group C, group G, and others/unknown) (56, 7, 93, and 30, respectively). In the past 6 years (2018-2023), the proportion of group A cases to the total number of STSS notifications ranged from 30% to 50%, but the proportion increased to 64% in 2024.

There were 409 STSS cases caused by GAS for the entire year 2023 and 335 for EW 1-11 in 2024. The average number of notifications during EW 1 through 11 of each of the past 6 years was 77.5 (range: 39-106), but in 2024, 335 cases (EW 1 through 11, 2024) were notified, the highest number to date.

Of the 335 notifications, 192 (57%) were male and 143 (43%) were female, with 13 cases under 20 years of age, 6 cases in their 20s, 22 cases in their 30s, 46 cases in their 40s, 44 cases in their 50s, 68 cases in their 60s, 76 cases in their 70s, and 60 cases in their 80s or older. Of these, 77 cases were deceased at the time of notification (with 44 males and 33 females), and the age breakdown was as follows: 0 were under 20 years old, 1 was in his 20s, 5 were in their 30s, 6 were in their 40s, 11 were in their 50s, 16 were in their 60s, 20 were in their 70s, and 18 were in their 80s or older. In the under-50 age group, the ratio of deaths at the time of notification to the number of notifications was 13.8%, similar to the previous level (2018-2022: 9.1%-24.1%).

The number of reported STSS cases caused by GAS has increased since July 2023, especially among those under 50 years of age<sup>[1]</sup>. Subsequently, the overall number of STSS cases caused by GAS also increased in November, reaching its peak in January 2024 (165 cases). Although the number of notifications of STSS cases under 50 years of age increased noticeably since July, the number of notifications of cases over 50 years of age also increased since November, and the ratio of notifications of cases over 50 years of age to all notifications was the same as before (2018-2022: 76%-88%).

As of March 25, 2024, the number of STSS cases caused by GAS is decreasing (3/1-17: 60 cases), but the number is still high compared to previous years. Since the most recent notifications are compiled late, the trend should continue to be monitored carefully.

## 2) Trends in outbreaks of group A streptococcal pharyngitis (Pediatric sentinel sites)

The number of GAS pharyngitis cases reported per pediatric sentinel sites increased rapidly from EW 33 (August 14-20) in 2023 to its peak (5.04 cases per sentinel site) in EW 50 (December 11-17). This was the highest value compared to the same period in the past six years. The number of reports per sentinel site during EW 11 in 2024 was 4.48 and remained high<sup>[xvii]</sup>.

### ■ Bacteriological trends of group A *Streptococcus* in Japan

By March 15, 2024, 126 isolates in 126 cases of STSS patients with onset on or after January 1, 2024, have been sent to the National Institute of Infectious Diseases from 38 prefectures. Of these, GAS from 92 cases (73.0%) [Table 1], group B *Streptococcus* from 10 cases (7.9%), and group G *Streptococcus* from 24 cases (19.0%) were isolated, respectively.

Of the 92 GAS isolates from 92 cases, 54 (58.7%, 54/92) were M1-serotype strains, of which 43 (79.6%) were M1UK sublineages.

The number of M1UK sublineages isolated by prefecture (M1UK sublineages/M1-type strains) was 8 (8/8) in Chiba Prefecture, 7 (7/7) in Kanagawa Prefecture, 4 (4/4) in Ibaraki Prefecture, 4 (4/6) in Saitama Prefecture, 4 (4/5) in Nagano Prefecture, 3 (3/3) in Tochigi Prefecture, 2 (2/2) in Yamagata Prefecture, 2 (2/2) in Gunma Prefecture, 2 (2/2) in Kagoshima Prefecture, 1 (1/1) in Yamanashi Prefecture, 1 (1/1) in Toyama Prefecture, 1 (1/1) in Shimane Prefecture, 1 (1/1) in Ehime Prefecture, 1 (1/3) in Fukuoka Prefecture, 1 (1/1) in Kumamoto Prefecture and 1 (1/4) in Oita Prefecture. No M1UK sublineages were isolated from Miyagi (0/1), Osaka (0/1), and Nagasaki (0/1) prefectures [Table 1, Fig. 1]

Note that careful interpretation is necessary as strain analysis was performed only for a subset of STSS cases due to GAS reported in the NESID Program.

### ■ Risk assessment

- As at March 2024, the number of STSS cases caused by GAS remained high compared to previous years, although there is a declining trend. The number of GAS pharyngitis cases reported per sentinel site also remained high, although it has decreased since the end of 2023.
- The number of detected M1UK sublineage in M1-type strains increased mainly in the Kanto region and surrounding areas, and the detection rate of this strain also increased from previous reports<sup>[1]</sup>. However, the relationship between the increase in the number of STSS cases reported due to GAS, the increase in the number of GAS pharyngitis cases reported per sentinel site, and the emergence of M1UK sublineage is unknown.
- There has been an increase in the number of reported iGAS infections in children in Europe and the United States from the end of 2022 to early 2023, and some countries have seen an increase in the number of reported cases from 2023 to 2024. However, of these countries, some report a case count consistent with typical years after 2023, others experience ongoing infections above typical years, and

yet others note a rise in cases at the end of 2023. In some countries, many cases have been reported not only among children but also among the elderly.

- Further accumulation of knowledge is needed on the association between the M1UK sublineage, which is considered highly pathogenic and transmissible, and the increase in STSS cases due to GAS. It is necessary to monitor the outbreak situation and epidemiological characteristics in Japan continuously, thus an active collection of strains and epidemiological information is required.

- As a public health response, it is considered necessary to advise clinicians on appropriate diagnosis, treatment, and reporting; ensure standard precautions at medical institutions and elderly care facilities; educate the general public about infection prevention measures (hand hygiene, cough etiquette, clean treatment of wounds such as abrasions, etc.); and recommend early consultation when symptoms are present<sup>[xvii],[xviii],[xix]</sup>.

Table 1. Number of isolates of group A *Streptococcus* (GAS) from STSS patients sent to the Department of Bacteriology I, National Institute of Infectious Diseases by prefecture (onset on or after January 1, 2024) (as of March 25, 2024)

Isolation by Prefecture	GAS	M1-type strains	M1UK sublineage
National	92	54	43
Hokkaido/Tohoku/Niigata region			
Miyagi	1	1	0
Yamagata	2	2	2
Fukushima	3	0	0
Niigata	1	0	0
Kanto/Koshinsei region			
Tochigi	3	3	3
Gunma	4	2	2
Ibaraki	5	4	4
Chiba	10	8	8
Saitama	9	6	4
Kanagawa	8	7	7
Yamanashi	1	1	1
Nagano	5	5	4

Tokai/Hokuriku region			
Aichi	1	0	0
Gifu	1	0	0
Mie	3	0	0
Toyama	1	1	1
Kinki region			
Kyoto	1	0	0
Osaka	2	1	0
Hyogo	2	0	0
Chugoku/Shikoku region			
Okayama	1	0	0
Tottori	1	0	0
Hiroshima	5	0	0
Shimane	1	1	1
Yamaguchi	1	0	0
Tokushima	1	0	0
Ehime	1	1	1
Kyushu region			
Fukuoka	4	3	1
Nagasaki	3	1	0
Kumamoto	2	1	1
Oita	4	4	1
Miyazaki	3	0	0
Kagoshima	2	2	2

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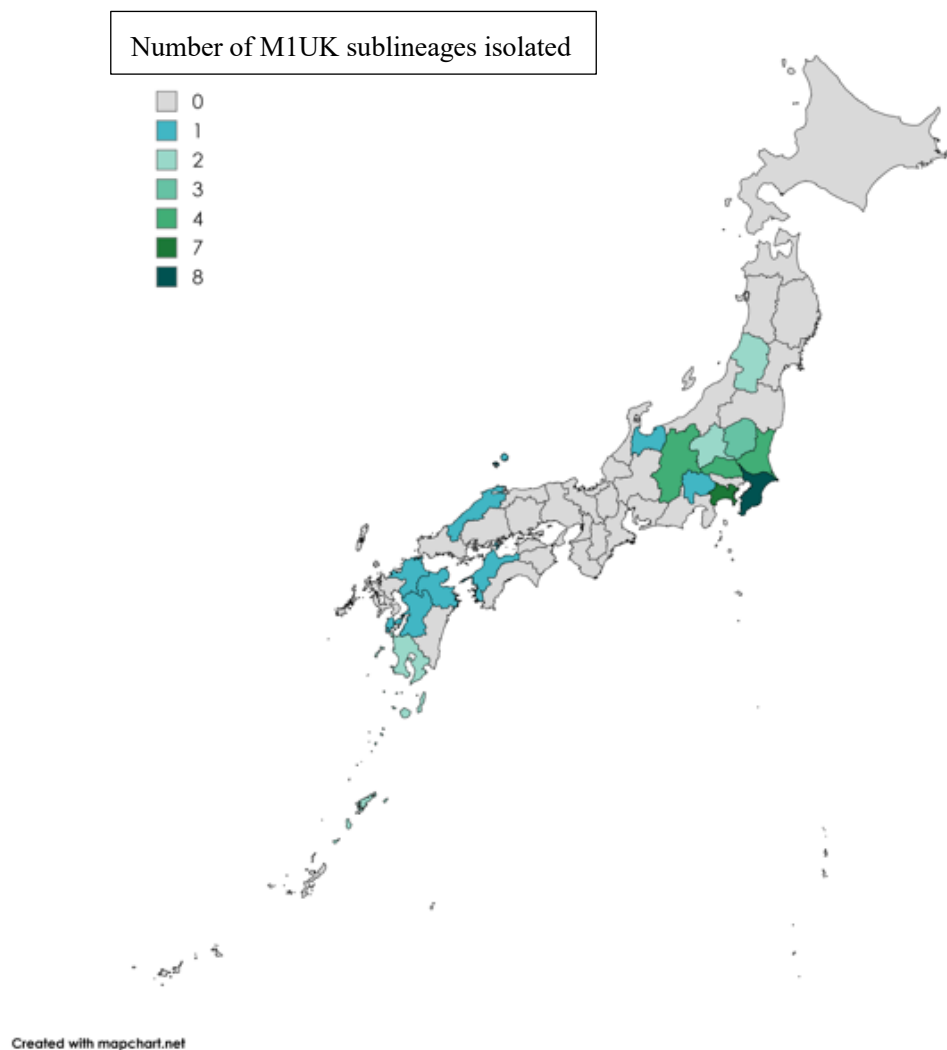


Figure. Number of M1UK sublineages isolated from specimens derived from STSS patients sent to the Department of Bacteriology I, National Institute of Infectious Diseases, by prefecture (onset on or after January 1, 2024) (as at March 25, 2024)

## ■ Precautions

This document is intended for rapid information sharing, and its contents and views are subject to change depending on the evolving situation.

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