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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 suspected to have STSS based on signs and symptoms, and 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) β -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 *Streptococcus*.

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[i]. For clinical management of STSS, please refer to the Clinical Management Guidance of STSS published by Disease Control and Prevention Center, National Center for Global Health and Medicine[ii].

The number of reported STSS caused by GAS and GAS pharyngitis cases are 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, and published a risk assessment based on the domestic situation for the time being on March 29th 2024. This article is to provide an update on the overall situation since then.

■ 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 [iv].

An increase in iGAS infections was reported in the UK, France, Ireland, the Netherlands, Sweden, etc. 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 [v]. 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 [vi]. In Sweden, the number of reported iGAS infections has increased again since late 2023 predominantly among people aged 70 years or older, but the overall number of reports peaked in February 2024 and has started to decline [vii]. Norway has seen an increase in iGAS infections in early 2024, in addition to the epidemic in the first half of 2023 [viii].

In the U.S., STSS is further tabulated separately among iGAS infections. In December 2022, the Centers for Disease Control and Prevention (CDC) issued an advisory[ix] due to an increase in iGAS infections in children, as in Europe, and the levels remained high during the 2023 epidemic season (January to April), 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 [x] 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 [xi].

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 [xii].

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 [xiii].

Although the M1UK sublineage produces about 9 times more erythrotoxin 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 [xiv]. Reports from European countries during this period have also been inconsistent, with Spain reporting no association [xv], while reports from Belgium, Germany, and Argentina suggested an association. [xiii],[xvi],[xvii],[xviii].

■ Trends of group A streptococcal infections in Japan based on the National Epidemiological Surveillance of Infectious Diseases (NESID)

1) Trends of Streptococcal Toxic Shock Syndrome (STSS) (as of June 19, 2024)

The number of STSS cases diagnosed from the EW (Epidemiological week) 1 to 24 in 2024 (January 1 to June 16, 2024) and notified to the National Epidemiological Surveillance of Infectious Diseases (NESID) was 1,060, the highest number of notifications since the start of the Surveillance. The breakdown according to the Lancefield's serogroups was: group A (656 cases), group B (114 cases), group C (10 cases), group G (222 cases), and others/unknown (58 cases), with group A being the highest number of notifications. In the past six years (2018-2023), the proportion of group A *streptococcus* (GAS) cases to the total number of STSS notifications ranged from about 30% to 50%, but the proportion increased to 62% in 2024.

In 2024, 656 STSS cases caused by GAS were reported, which is the highest number reported in the past 6 years (2018-2023). Of the 656 notifications, 377 (57%) were male and 279 (43%) were female. The age breakdown was as follows: 15 cases (2%) under 10 years of age, 10s (8 cases(1%)), 20s (11 cases(2%)), 30s (55 cases(8%)), 40s (87 cases(13%)), 50s (98 cases(15%)), 60s (132 cases(20%)), 70s (140 cases(21%)), and 80s or above (110 cases(17%)). Since July 2023, the number of notifications over 30 years old is high among the total filings [Table 1]. The number of deaths reported was 149, of which 87 (58%) were males and 62 (42%) were females. The age breakdown was as follows: 0 under 10 years of age, 10s (0 cases), 20s (2 cases), 30s (12 cases), 40s (16 cases), 50s (16 cases), 60s (34 cases), 70s (36 cases), and 80s or older (33 cases). The number of notifications by prefecture was higher in Tokyo, Saitama, Aichi, Kanagawa, and Chiba prefectures, in that order, with most notifications coming from the Kanto region. It should be noted that only deaths reported at the time of notification are counted, and in principle, cases in which deaths occurred after notification are excluded.

Estimated routes of infection were reportedly: wound infection in 288 cases (44%), unknown route of infection in 227 cases (35%), droplet infection in 59 cases (9%), and contact infection in 24 cases (4%). Wound infection and unknown route of infection were the most common.

Notifications of STSS cases caused by GAS showed an increasing trend since November 2023, peaking in January 2024. Thereafter, the number of STSS cases decreased in February and remained flat until May, but the number is still high compared to previous years. [Fig.1] 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 from EW 33 (8/14-20) in 2023 to a peak (5.04 reports per sentinel site) in EW 50 (12/11-17), which was the highest in the same period in the past six years. In 2024, the number of reports remains high since EW 3 (1/15-21) compared to the same period in the past six years, peaking in EW 21 (5/20-26) (5.03 reports per sentinel site), and remains in the same level to date (4.46 reports per sentinel site in EW 24 in 2024 (6/10-16)) [xix].

Table 1. Chronological changes in the age and proportion of cases due to group A *Streptococcus* (GAS) among cases reported as Streptococcal Toxic Shock Syndrome (STSS) in Japan (as of June 19, 2024)

		2018年 (n=312)		2019年 (n=415)		2020年 (n=265)		2021年 (n=177)		2022年 (n=209)		2023年1-6月 (n=132)		2023年7-12月 (n=277)		2024年1-6月* (n=656)	
		届出数	割合	届出数	割合	届出数	割合	届出数	割合	届出数	割合	届出数	割合	届出数	割合	届出数	割合
年代	10歳未満	6	2%	8	2%	6	2%	3	2%	2	1%	2	2%	10	4%	15	2%
	10代	4	1%	5	1%	3	1%	0	0%	2	1%	1	1%	0	0%	8	1%
	20代	9	3%	11	3%	3	1%	2	1%	5	2%	3	2%	5	2%	11	2%
	30代	31	10%	20	5%	13	5%	6	3%	9	4%	7	5%	27	10%	55	8%
	40代	26	8%	39	9%	14	5%	11	6%	15	7%	13	10%	45	16%	87	13%
	50代	31	10%	64	15%	39	15%	27	15%	34	16%	19	14%	35	13%	98	15%
	60代	81	26%	90	22%	62	23%	37	21%	62	30%	22	17%	64	23%	132	20%
	70代	62	20%	95	23%	58	22%	49	28%	35	17%	32	24%	54	19%	140	21%
	80代以上	62	20%	83	20%	67	25%	42	24%	45	22%	33	25%	37	13%	110	17%

（感染症発生動向調査：2024年6月19日現在届出数*）

*2024年は1月1日～6月16日(疫学週第1週～第24週診断)の集計(2024年6月19日時点)

**直近の報告は遅れて届出される症例があり、表に反映されにくいため、解釈には注意が必要である

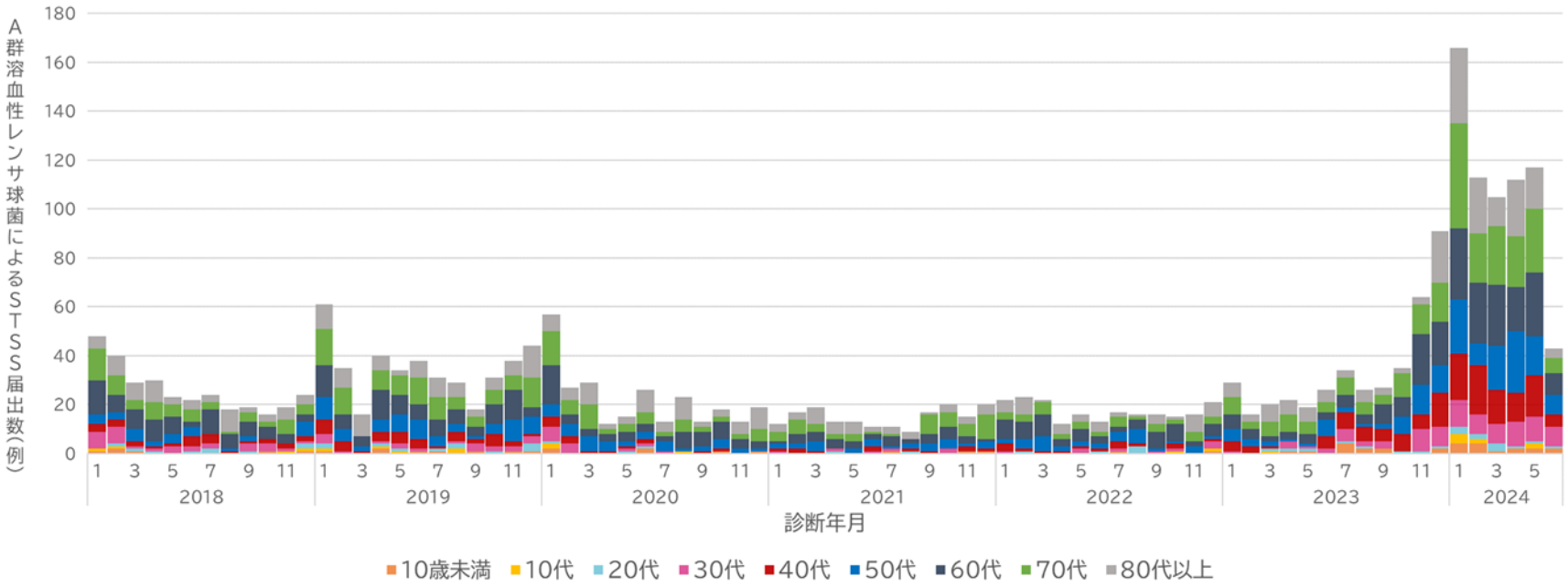

Figure 1. Number of cases due to group A *streptococcus* (GAS) among cases reported as Streptococcal Toxic Shock Syndrome (STSS) in Japan (date of diagnosis: January 1, 2018 - June 16, 2024, as of June 19, 2024)

■ Bacteriological trends of group A Streptococcus in Japan

By June 19, 2024, 532 isolates in 532 cases of STSS patients with onset on or after January 1, 2024, have been sent to the National Institute of Infectious Diseases from 43 prefectures. Of these, GAS from 377 cases (70.9%) [Table 2], group B *Streptococcus* from 42 cases (7.9%), and group G *Streptococcus* from 109 cases (20.5%) were isolated, respectively.

Of the 377 GAS isolates from 377 cases, 221 (58.6%, 221/377) were M1-serotype strains, of which 194 (87.8%) were M1UK sublineages.

The number of M1UK sublineages isolated by prefecture (M1UK sublineages/M1-type strains) was 47(47/52) in Tokyo Metropolitan, 20 (20/20) in Kanagawa Prefecture, 15 (15/15) in Chiba Prefecture, 9 (9/10) in Nagano Prefecture, 8(8/10) in Saitama Prefecture, to list some prefectures in order of most common. [Table 2, Fig. 2]

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.

Table 2. 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 June 19, 2024)

Isolation by Prefecture	GAS	M1-type strains	M1UK sublineage
National	377	221	194
Hokkaido/Tohoku/Niigata region			
Aomori	2	2	2
Akita	1	1	1
Miyagi	2	1	0
Yamagata	2	2	2
Fukushima	11	5	5
Niigata	9	6	6
Kanto/Koshinsei region			
Tochigi	3	3	3
Gunma	9	3	3
Ibaraki	8	7	7
Chiba	21	15	15
Saitama	16	10	8
Tokyo	90	52	47
Kanagawa	29	20	20

Yamanashi	5	3	3
Nagano	11	10	9
Shizuoka	6	1	1
Tokai/Hokuriku region			
Aichi	13	7	7
Gifu	6	4	3
Mie	5	0	0
Toyama	3	2	2
Fukui	2	2	2
Kinki region			
Shiga	4	4	4
Kyoto	7	4	4
Osaka	13	6	5
Nara	2	1	1
Wakayama	1	0	0
Hyogo	11	5	5
Chugoku/Shikoku region			
Okayama	11	5	5
Tottori	4	1	1
Hiroshima	7	2	2
Shimane	2	2	2
Yamaguchi	2	1	0
Tokushima	3	1	1
Kochi	1	0	0
Ehime	3	2	2
Kyushu region			
Fukuoka	15	8	2
Saga	3	2	2
Nagasaki	4	2	0
Kumamoto	4	2	2
Oita	9	6	2
Miyazaki	4	1	1
Kagoshima	4	3	3
Okinawa	9	7	6

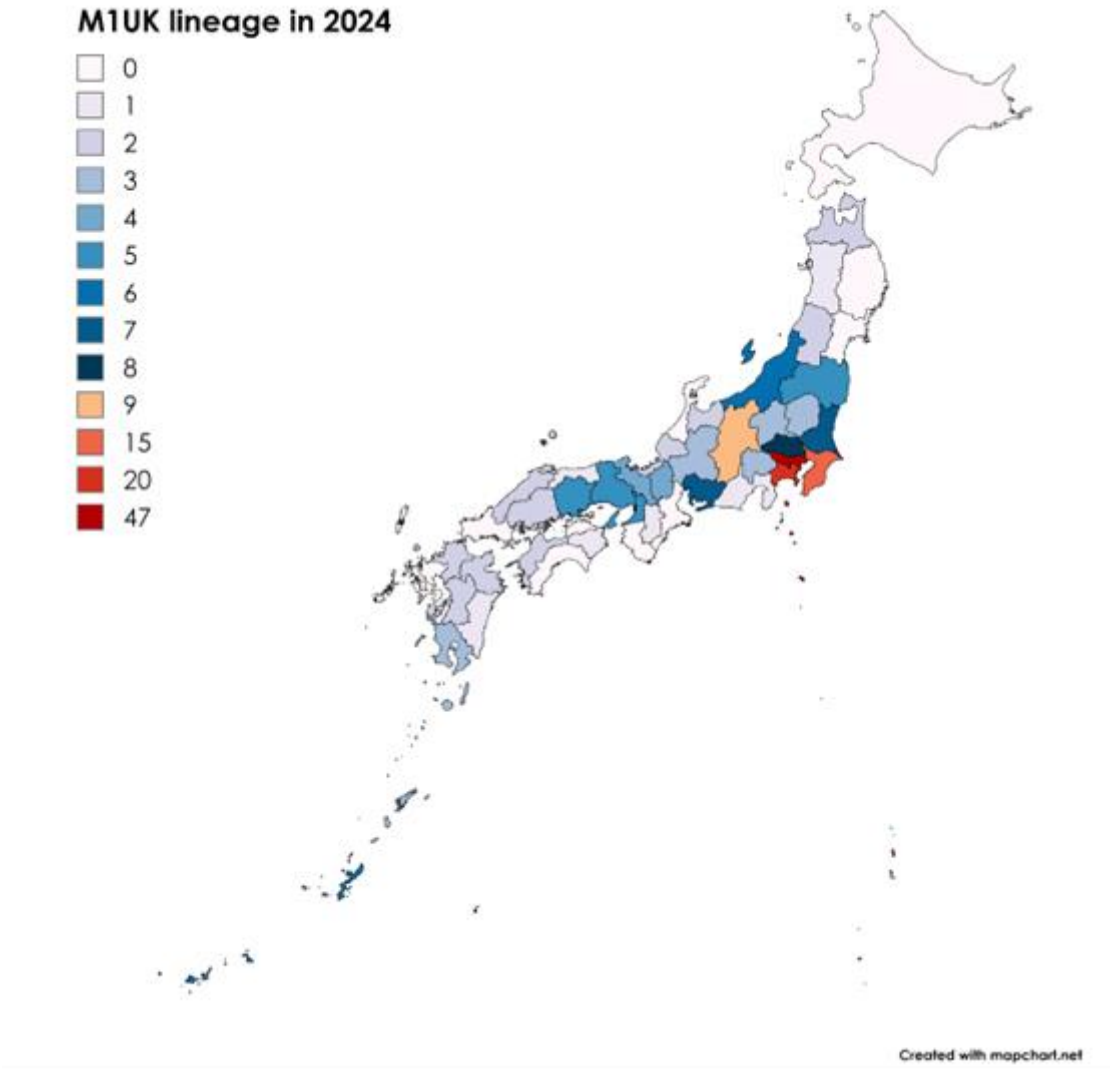

Figure 2. Number of M1UK sublineages isolated from specimens derived from STSS patients sent to the Department of Bacteriology I, National Institute of Infectious Diseases, by prefecture (onset on or after January 1, 2024) (as of June 19, 2024)

■ Risk assessment

・As of June 2024, the number of STSS cases caused by GAS remained high compared to previous years. Since July 2023, the number of notifications among persons over 30 years old has been continuously high. Wound infection and unknown route of infection are the most common estimated routes of infection. The number of GAS pharyngitis reports per pediatric sentinel site continues to be high compared to the same period in the past 6 years.

・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[i]. 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 visiting family healthcare providers when feeling sick[xx],[xxi],[xxii].

■ 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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