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Serotyping of *Streptococcus pyogenes* isolated from common and severe invasive infections in Japan, 1990–5: implication of the T3 serotype strain-expansion in TSLS

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SUMMARY

To clarify the relationship between the epidemics of severe invasive group A streptococcal infections (streptococcal Toxic Shock-Like Syndrome; TSLS) and common group A streptococcal infections in Japan, we examined the T serotypes of *S. pyogenes* strains (group A streptococci) isolated from clinical specimens of the streptococcal infections (17999 cases) in the period 1990–5, including the severe infections (TSLS) (29 cases) in the period 1992–5. Characteristic points of the analyses were: (1) dominant serotypes of the infections in these periods were T12, T4, T1, T28 and TB3264, which were consistently isolated; (2) isolates of T3 rapidly increased through 1990 to 1994 while T6 decreased in the period 1990–3; (3) when Japanese area was divided into three parts, T3 serotype tended to spread out from the north-eastern to the south-western area; (4) strains of T3 and T1 serotypes were dominant in the TSLS. Dominant-serotype strains of streptococcal infections did not always induce severe infections and dominance of T3 serotype in the TSLS seemed to be correlated with the increase of T3 in streptococcal infections. These results may indicate that certain clones of *S. pyogenes* are involved in the pathogenesis of the TSLS.

INTRODUCTION

Streptococcus pyogenes (group A streptococcus) is one of the most common and dispersible of human pathogens. It causes a wide array of infections, the most frequent of which are acute pharyngitis (strep throat) and impetigo (pyoderma). Other typical symptoms of its infection include sinusitis, otitis, peritonsillar and retropharyngeal abscess, pneumonia, scarlet fever, erysipelas, cellulitis, lymphangitis, pu-

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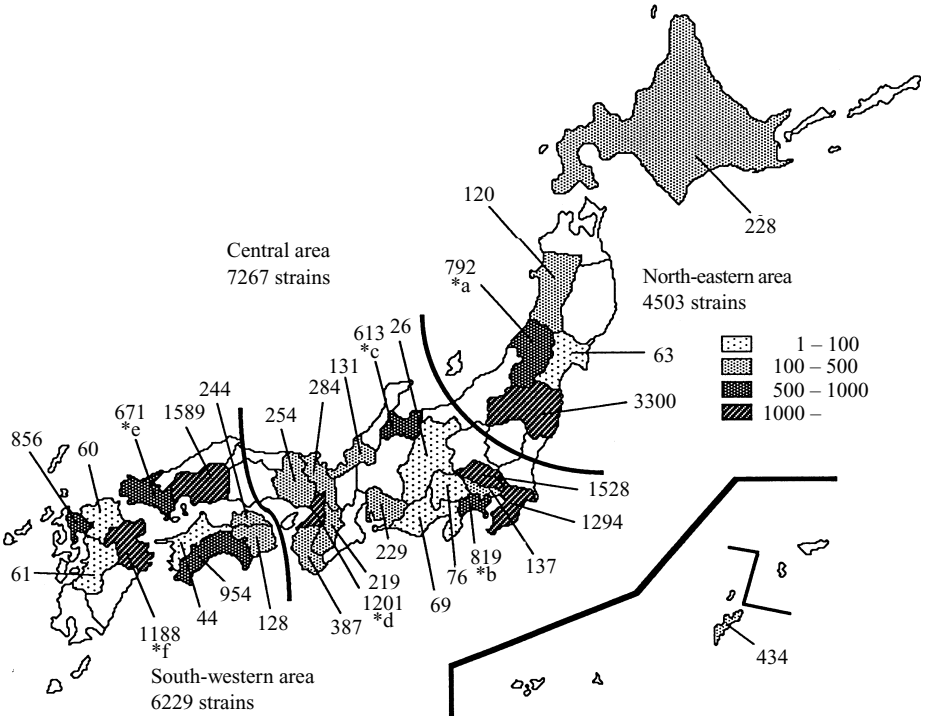

Fig. 1. Number of *S. pyogenes* isolates in each prefecture used in this study in the period 1990–5. The six branches of reference centre in Japan are in the prefectural Institute of Public Health of (a) Yamagata, (b) Kanagawa, (c) Toyama, (d) Osaka, (e) Yamaguchi, and (f) Oita. The number shown in each prefecture indicates the number of isolates of *S. pyogenes* in 1990–5. We classified the number of isolates into the four steps by the amount of 'dot' as shown in the figure. Prefecture shown by the blank did not report the number. We divided Japan into the three parts, north-eastern, central and south-western areas.

erperal sepsis, vaginitis, myositis, gangrene and perianal cellulitis. In addition, rheumatic heart disease or acute glomerulonephritis sometimes develops after a streptococcal infection. In this way, many varieties of symptoms have resulted from infections of *S. pyogenes* [1–3].

Many streptococcal virulence factors that relate to symptoms, have been reported, including pyrogenic exotoxins (Spe-A, -B, -C), M protein, hyaluronic acid capsule, streptolysins, various enzymes like nuclease and proteinase, etc. Among these virulence factors, the pyrogenic exotoxins are believed to play an important role in infections.

The pyrogenic exotoxins are responsible for the rash of scarlet fever, and are known as erythrogenic toxins or scarlet fever toxins. Genes of *speA* and *speC* are located in lysogenic bacteriophage [4–6]. A *speB* gene that is on bacterial chromosome, encodes cysteine proteinase [7]. M protein, which is also an important virulence factor of *S. pyogenes*, protects *S. pyogenes* from phagocytosis by polymorphonuclear leukocytes [8, 9], and has immunoglobulin(Ig)-binding activity with affinity for IgG and/or IgA [10–12].

In recent years, a new type of severe infectious disease (severe invasive group A streptococcal infections, or streptococcal Toxic Shock-Like Syndrome; TSLS) caused by this pathogen has spread [13, 14], although the incidence of severe infectious diseases by *S. pyogenes* has decreased greatly with the use of antibiotics. There is a current concept by Stevens that the interaction between known virulence factors (pyrogenic exotoxins, etc.) of *S. pyogenes* and host's defence mechanisms cause this pathogenesis of the TSLS [14].

However, the Centers for Disease Control and Prevention (CDC) have lately reported that M1 and M3 isolates caused 81% of the cases of bacteraemia examined in 1989–90 in the USA [15]. In addition, the TSLS-associated M1 and M3 isolates are closely related to each other, perhaps clonally derived [16]. These reports show the possibility that unknown virulence factors are involved in the TSLS and/or *S. pyogenes* had changed the pathogenesis of the bacterial virulence factors.

In this paper, to clarify the relationship between the TSLS and the epidemic of *S. pyogenes* in Japan, we examined the epidemic of *S. pyogenes* in the period 1990–5, and we deduced the relationship between some dominant isolates from the general clinical specimens and the isolates which cause the TSLS.

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Table 1. *T-serotype and number of isolates from* S. pyogenes *infections, 1990–5*

	Number of isolates in each year (%, each number/total in the year)													
T-serotype	1990	(%)	1991	(%)	1992	(%)	1993	(%)	1994	(%)	1995	(%)	Total	(%)
T1	380	(19·3)	496	(18·7)	713	(25·4)	491	(11·5)	464	(11·5)	283	(8·7)	2827	(15·7)
T2	1		3		13		21		11		9		58	
T3	11	(0·6)	9	(0·3)	104	(3·7)	263	(8·0)	421	(10·4)	152	(4·7)	960	(5·3)
T4	569	(28·0)	691	(26·0)	714	(25·4)	775	(23·6)	808	(20·0)	617	(19·0)	4174	(23·2)
T6	149		59		23		6		17		21		275	
T8	13		10		7		8		6		6		50	
T9	7		9		10		22		7		9		64	
T11	51		66		59		144		135		96		551	
T12	395	(20·1)	746	(28·1)	377	(13·4)	588	(17·9)	1074	(26·6)	1067	(32·8)	4247	(23·6)
T13	31		34		31		64		29		26		215	
T18	8		8		18		71		156		49		310	
T22	55		130		105		100		103		93		586	
T23	1		4		0		0		0		1		6	
T25	1		7		5		5		13		9		40	
T28	121	(6·2)	133	(5·0)	102	(3·6)	176	(5·4)	290	(7·2)	275	(11·5)	1197	(6·7)
TB3264	66	(3·4)	129	(4·9)	234	(8·3)	301	(9·2)	304	(7·5)	257	(7·9)	1291	(7·2)
TImp.19	1		1		21		0		0		3		26	
T5/27/44	1		5		3		9		8		6		32	
T14/49	3		6		1		0		1		7		18	
N.D.	103		109		270		240		184		166		1072	
Total	1967	(100)	2655	(100)	2810	(100)	3284	(100)	4031	(100)	3252	(100)	17999	(100)

N.D., not determined.

MATERIALS AND METHODS

Bacterial isolates

A total of 17999 *S. pyogenes* strains (group A streptococci) for T serotyping were isolated from clinical specimens in fixed co-operative hospitals in Japan in the period 1990–5 (Fig. 1) and serotyped in the Prefectural Institutes of Public Health. The information was collected into the National Institute of Health (reference centre) through branch offices of *S. pyogenes* reference centre (six branch offices are in the Prefectural Institutes of Public Health of Yamagata, Kanagawa, Toyama, Osaka, Yamaguchi and Oita; see Fig. 1). Almost all of 17999 T-serotypes strains were isolated from the throat-swabs of paediatric patients (children under 14 years old) who suffered from the typical symptoms of pharyngitis (strep throat) or tonsillitis, and others from respiratory secretions (sputum, tracheal aspirates, specimen of the lower respiratory tract) and blood of mainly adults [17].

The information on streptococcal TSLS, and T and M serotypes of the pathogenes in the period 1992–5 was also collected into the National Institute of Health from the branch offices of reference centre and co-operative hospitals. The *S. pyogenes* strains were cultured from the blood of TSLS-patients. We included TSLS criteria into the surveillance system from 1992. The diagnostic criteria of TSLS were principally based on those described by the working group on severe streptococcal infections of the Centers for Disease Control and Prevention (CDC) [18].

Dividing Japanese areas

We divided Japanese areas into the three parts for the analysis on the distribution of the pathogens; the north-eastern area, the central area and the south-western area (Fig. 1). The north-eastern area comprises Hokkaido-island and north-eastern Honshu-island. The central area indicates central Honshu-island including Tokyo and Osaka. The south-western area comprises south-western Honshu-island, Shikoku-island and Kyushu-island including Okinawa. There are 1–3 local branch(es) of reference centre for *S. pyogenes* in each area (see Fig. 1).

M and T serotyping

Group A streptococci have been identified by the serological differences between the two antigens, M

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Table 2. *Serotype of* S. pyogenes *strains isolated from the blood of TSLS-patients in Japan, 1992–5*

Case	Prefecture	Age	Sex	Date	Serotype	*spe* genotype	NIH#	Disease*
1	Chiba	44	M	4/6/92	M3,T3	*AB*	1	TSLS,NF,PH
2	Chiba	6	F	12/7/92	M4,T4	*BC*	2	TSLS,PH
3	Hiroshima	37	M	28/8/92	T22	*B*	32	TSLS,NF
4	Chiba	28	F	7/3/93	M3,T3	*AB*	3	TSLS,PH
5	Chiba	37	M	23/6/93	T22	*BC*	4	TSLS,NF
6	Hiroshima	34	F	29/10/93	M1,T1	*AB*	17	TSLS
7	Chiba	57	F	20/11/93	T11	*B*	5	TSLS,PH
8	Chiba	69	F	31/12/93	M4,T4	*BC*	6	TSLS
9	Chiba	70	M	31/12/93	M3,T3	*AB*	7	TSLS
10	Chiba	45	M	31/12/93	M3,T3	*AB*	8	TSLS,SA
11	Chiba	34	M	11/1/94	M3,T3	*AB*	9	TSLS
12	Hiroshima	46	M	19/3/94	M3,T3	*AB*	18	TSLS
13	Tottori	83	M	18/4/94	M3,T3	*AB*	16	TSLS,NF
14	Chiba	42	F	22/4/94	M1,T1	*AB*	11	TSLS
15	Kochi	75	M	7/5/94	M3,T3	*AB*	34	TSLS,NF
16	Kanagawa	71	M	27/5/94	M3,T3	*AB*	15	TSLS
17	Shizuoka	53	M	6/4/94	M1,T1	*ABC*	19	TSLS,NF
18	Oita	37	F	28/10/94	M3,T3	*AB*	12	TSLS,OS,NF
19	Hiroshima	37	F	7/12/94	M3,T3	*AB*	33	TSLS
20	Chiba	61	M	1/1/95	M12,T12	*BC*	30	TSLS
21	Shizuoka	63	M	14/1/95	M3,T3	*AB*	21	TSLS,NF
22	Shizuoka	60	F	26/1/95	M1,T1	*AB*	22	TSLS
23	Tokushima	43	M	21/4/95	M1,T1	*AB*	27	TSLS,CE,NF
24	Tokushima	8	M	27/4/95	M1,T1	*AB*	28	TSLS
25	Kochi	14	M	19/6/95	T28	*BC*	35	TSLS
26	Saga	64	M	27/7/95	M1,T1	*AB*	36	TSLS,NF
27	Miyazaki	78	M	5/9/95	T28	*B*	37	TSLS,NF
28	Akita	59	M	16/10/95	M1,T1	*AB*	39	TSLS,ER,SA
29	Nara	38	M	27/12/95	M12,T12	*BC*	42	TSLS,NF

* PH, pharyngitis; NF, necrotizing fasciitis; SA, septic arthritis; OS, osteomyelitis; ER, erysipeas; CE, cellulitis.

protein and T protein. We classified only the isolates which caused the TSLS using the anti-M rabbit sera which have been made by ourselves; M-typing sera for 1, 3, 4, 6, 12 and 18 were available. M serotyping was performed as described by Swift and Lancefield [19–21].

T protein is a trypsin- and pepsin-resistant molecule on the surface of group A streptococci and has been proven very useful as an epidemiological tool for the differentiation of group A streptococci [19, 22]. Twenty-five different T serotypes are reported [17, 23, 24]. Nineteen groups of T serotypes (1, 2, 3, 4, 6, 8, 9, 11, 12, 13, 18, 22, 23, 25, B3264, Imp.19, 5/27/44 and 14/49) (DENKA-SEIKEN Co., Tokyo, Japan) were distinguishable in our system. By the T agglutination technique, trypsinized suspensions of streptococci were tested on slides for agglutination by diluted absorbed anti-sera [19, 22].

Generally speaking, the number of T serotype corresponds to the same number of M serotype; for example, almost of T1, 3, 4 and 5 serotypes strains have each M1, 3, 4 and 5 antigen [19]. In fact, as far as we examined, T1, 3, 4 and 12 serotype strains showed M1, 3, 4 and 12 serotypes, respectively (Table 2).

RESULTS

Dominant T serotypes of the total isolates, 1990–5

We have determined the T serotypes of a total of 17999 strains of *S. pyogenes* (group A streptococci) in Japan in the period 1990–5 (see Table 1 and 'Materials and Methods'). The sum of six serotype (T12, T4, T1, TB3264, T28 and T3) strains occupied 81·7% of the total strains (see Table 1). Dominant serotypes were T4, T12 and T1 in 1990; T12, T4 and T1 in 1991; T4, T1 and T12 in 1992; T4, T12 and T1 in 1993; T12, T4 and T1 in 1994; T12, T4 and T28 in 1995 (Table 1). In

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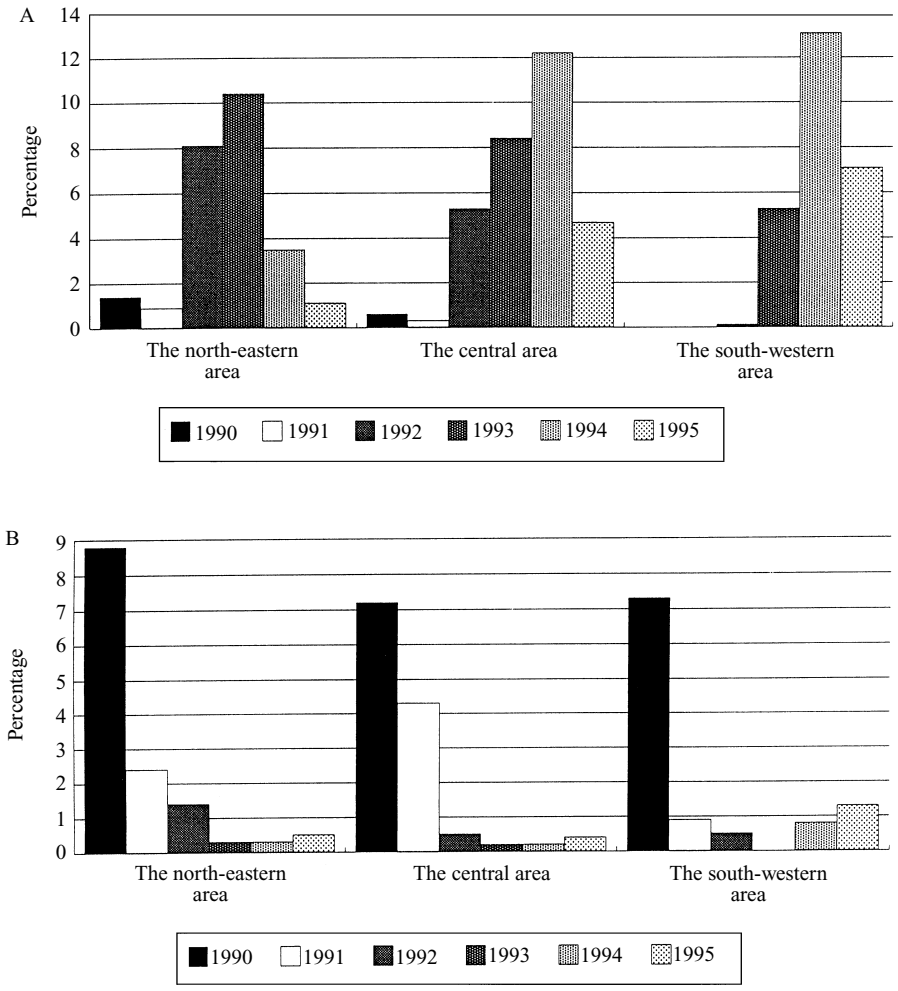

Fig. 2. The change of prevalence of the T3 and T6 serotypes in the three-divided areas in the period 1990–5. (A) The T3 serotype. (B) The T6 serotype. Percentage was expressed as (number of isolates of each serotype in the area/total number of isolates in the area of the year) × 100.

short, the three serotype (T12, T4 and T1) strains seem to continue to spread out in Japan in the period 1990–5.

Two types of pattern in the change of epidemic

We found two types of pattern in the change of epidemic. As shown in Table 1, the isolation rate of T1, T4, T12, T28 and TB3264, which were the dominant serotypes as described above, did not change dramatically in the period 1990–5, namely a long-term change.

However, the rate of the T3 serotype isolates had increased rapidly in the period 1990–4. On the other side, the rate of the T6 serotype isolates has decreased markedly (Table 1). Both the serotypes showed a short-term change.

Change of distribution of the epidemic in Japan

To analyse distribution of the annual outbreaks of T serotypes in Japan, we divided Japan into three areas (the north-eastern area, the central area and the south-western area) and examined the epidemic of the T serotypes of each area (Fig. 1).

First, we compared the local distribution among T serotypes showing a short-term change and found a characteristic point in the change of T3-serotype. A peak rate of the T3 serotype isolates was in 1993 in the north-eastern area, in 1994 in the central area and the south-western area. The rate of T3 serotype isolates decreased markedly in 1994 in the north-eastern area, and in 1995 in the central area and the south-western area (Fig. 2A). These results may indicate that the T3 serotype isolates spread out from the north-eastern area to the south-western area. On the other side, the

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rate of the T6 serotype isolates has decreased at the same time in the three areas (Fig. 2B). The change of serotypes belonging for a long-term change was also not dramatic in the three areas (data not shown).

Dominant serotypes of *S. pyogenes* isolated from TSLS in Japan

The Centers for Disease Control and Prevention (CDC) lately reported that M1 and M3 isolates caused 81% of cases of the TSLS examined in 1989–90 in USA [15]. The first defined case of the TSLS in Japan was reported in 1992 [25]. We began to collect information on the TSLS from co-operative hospitals through prefectural Institute of Public Health from 1992. The data were summarized in Table 2. M3, T3 and M1, T1 isolates occupied 20 cases (69%; 8 cases of M1, T1, 12 cases of M3, T3) out of 29 cases of TSLS examined in the period 1992–5 in Japan. The cases in 1992 and 1993 may not always represent the total feature of TSLS in Japan because only limited prefectures, Chiba and Hiroshima, reported TSLS. However, in 1994 and 1995, 12 prefectures including north-eastern area (Akita), central areas (Chiba, Kanagawa, Shizuoka and Nara) and South-western area (Hiroshima, Tottori, Kochi, Oita, Tokushima, Saga and Miyazaki) reported cases, which may indicate that the data here were not influenced by the certain outbreak in one area. In 1994, M3,T3 was the dominant serotype (7/9 cases) followed by M1,T1 (2/9). However, in 1995, M1,T1 was the dominant (5/10) and only one case (1/10) of M3,T3 was found in TSLS patients.

DISCUSSION

Streptococcal TSLS has recently spread out in the world and certain clones of M1 and M3 serotyped strains are hypothesized to be involved in the pathogenesis of TSLS [15, 16]. There are the later analyses concerning the relation between strains causing common and severe invasive streptococcal infections [26–28]. We have collected information on TSLS-related *S. pyogenes* since a first defined case of TSLS was reported in 1992 in Japan [25]. And we also started to accumulate the information on the T serotype of common streptococcal infections about 10 years ago. In order to clarify the relationship between the severe invasive streptococcal infections (TSLS) and the epidemic of common streptococcal infections in Japan, we analysed the prevalence of T serotypes of *S. pyogenes* strains isolated from clinical specimens of streptococcal infections (17999 cases) in the period 1990–5, including TSLS (29 cases) in the period 1992–5.

We found some patterns for the change of T serotypes; dominant serotypes of common infections in these periods were T12, T4, T1, T28 and TB3264, which were constantly isolated, while T3 isolates rapidly increased through 1990 to 1994. This rapid increase of T3 serotype isolates seems to correlate with the dominancy of M3, T3 serotype isolates from TSLS patients in 1993 (3/7; 43%) and 1994 (7/9; 78%) (see Table 2). This may indicate that the T3 serotype clone is involved in the pathogenesis of TSLS, which will be also supported by correlation of the decrease of T3 serotype isolates in common infections in 1995 (Table 1) with that in TSLS (1/10; 10%) in 1995 (Table 2). We have preliminary genetic data that there is some difference in chromosomal DNA between M3, T3 serotype strains isolated from common infections in 1980s and the same serotype strains isolated from TSLS patients in 1990's (in preparation). Recent M3, T3 serotype-isolates may have acquired some genetic elements which is involved in the pathogenesis of TSLS. We do not rule out another possibility that the rapid increase of M3, T3 serotype strains causes severe infection into the people who have not acquired immunity against M3 antigen, which is one of protective antigens.

Generally speaking, common streptococcal infection causes acute pharyngitis in children. On the other hand, TSLS tends to occur in adult (average age of the patients is 48 years in our study). The exact reason is not clear. Stevens tried to explain it by the pre-existing immunity against known virulence factors of *S. pyogenes*; a person who has immunity against virulence factors, for example, M protein or pyrogenic exotoxins, does not cause severe manifestations [14]. It may be one explanation. However, even when a rapid increase of T3 or M3 serotype-streptococcal infection occurred in children in the period 1990–4, TSLS has been observed dominantly among adults but not children as shown in this study. As we did not examine the serum antibody against T3 or M3 among the population, we cannot say exactly the importance of immunity for the appearance of manifestations. However, above results may indicate that factors other than immunity, for example, new virulence factors of *S. pyogenes*, some unknown host factors in adults and etc., are involved in the occurrence of TSLS.

It is known that prevalence of the pathogens moves from one to another area. We found that the prevalence of T3 serotype tended to spread out from the north-eastern to the south-western area in Japan. We wanted to find out the correlation between the movement of T3 serotype in the area and the prevalence of TSLS in order to confirm that the T3 serotype clone is involved in the pathogenesis of TSLS. However, the number of isolates from TSLS was too small to analyse.

T12, T4 and T1 serotypes in common infections were isolated constantly in the period 1990–5. However, the isolation of M1, T1 serotype (8/29; 28%) in TSLS were larger in number than that of M12, T12 (2/29; 7%) and M4, T4 (2.29; 7%). The reason is not clear. It may be possible that the isolates of T1 serotype contain two kinds of different genotype; one causes TSLS and another causes common infections. Anyway, further investigation will be required to elucidate it.

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APPENDIX

The following are other members of the Working Group for Group A Streptococci in Japan; T. Aikawa (Hokkaido Institute of Public Health, in Sapporo), H. Sato (Akita Prefectural Institute of Public Health, in Akita), K. Otani (Yamagata Prefectural Institute of Public Health, in Yamagata), M. Sato (Fukushima Prefectural Institute of Public Health and Environmental Science, in Fukushima), M. Nakano (Sendai Institute of Public Health, in Sendai), H. Igarashi (Tokyo Metropolitan Research Laboratory of Public Health, in Tokyo), S. Kano (Kitakyusyu City Institute of Environmental Sciences), N. Sumi (Saga Prefectural Institute of Public Health, in Saga), J. Kudaka (Okinawa Prefectural Institute of Public Health, in Shimajili) and microbiologists of other Prefectural Institutes of Public Health in Japan.

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