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■ Review Article ■

Epidemiology of Shigellosis in Korea

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Shigellosis is an acute diarrheal disease caused by bacteria of the genus *Shigella*. Following the occurrence of a large outbreak of shigellosis as well as sporadic cases since 1998, shigellosis has been a major health problem in Korea. There have been major changes in epidemiology during the last five decades concerning shigellosis in terms of total incidence of shigellosis, prevalence of certain serogroups, selection of specific clones, and introduction of new *Shigella* clones. *S. dysenteriae* was the most prevalent species until the early twentieth century, *S. flexneri* was the most prevalent until the late 1980s, and *S. sonnei* has been the most prevalent since 1990. Diverse serotypes of *S. dysenteriae* (4 serotypes), *S. flexneri* (8 serotypes), and *S. boydii* (4 serotypes) were found during the Korean War and many of these Korean endemic *Shigella* strains circulated in the community until the late 1970s. However, the endemic strains of *S. dysenteriae*, *S. boydii*, and *S. sonnei* disappeared in the late 1980s. A new clone of *S. sonnei* that was introduced between the late 1980s and the early 1990s was responsible for a large proportion of shigellosis in recent years. *S. flexneri* serotype 4a was the most frequently found during the Korean War and then the incidence of *S. flexneri* 2a gradually increased with time. *S. flexneri* isolates detected from 1991 to 1997 were all serotype 2a. However, the diverse clones of *S. flexneri* reemerged in Korea since 1999. It has not been determined whether the *S. flexneri* strains from the 2000s were the descendants of the Korean endemic strains or imported new strains, but the PFGE patterns were different between *S. flexneri* strains from the 1980s and 2000s. The widespread of new *S. sonnei* strains and the persistence of *S. flexneri* strains are responsible for the endemicity of shigellosis in Korea.

Key Words: *Shigella*, Clone, Serotype, Korean endemic strain, PFGE

SHIGELLOSIS

Organisms of the genus *Shigella* are small non-motile Gram-negative facultative anaerobic bacilli. Four *Shigella* species, *S. dysenteriae* (serogroup A), *S. flexneri* (serogroup B), *S. boydii* (serogroup C), and *S. sonnei* (serogroup D), cause shigellosis in humans (5,17). *S. dysenteriae*, which was initially termed *Bacillus dysenterie*, was the first *Shigella* species isolated by Kiyoshi Shiga in 1896 (40). Subsequently, three additional groups of related organisms, designated *S. flexneri*, *S. boydii*, and *S. sonnei*, were taxonomically placed in the genus *Shigella* (16). However, DNA hybridization studies showed that with the exception of *S. boydii* serotype 13, *Escherichia coli* and *Shigella* belongs to the same genetic species (6,7). Enteroinvasive *E. coli* (EIEC) and *Shigella* species exhibit very similar genetic backgrounds (33,42).

Shigellosis, an acute diarrheal disease caused by bacteria of the genus *Shigella*, is a major public health problem in both developing and industrialized countries (5,43). Epidemic and endemic shigellosis are most frequently caused by *S. dysenteriae* and *S. flexneri* in developing countries, whereas *S. sonnei* causes epidemic shigellosis in industrialized countries (13,32).

Humans are the only natural host for *Shigella*; therefore, transmission of *Shigella* is usually from human to human through the fecal-oral route, or the intake of contaminated food or drinking water (15,24). The carriers are important to maintain the transmission of *Shigella*. The carriers usually shed the organism in their feces for 1 to 4 weeks, but excretion of the organism may last for more than one year in

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long-term carriers (20,24). *Shigella* organisms are highly contagious, with infectious doses of as low as 10 to 100 viable bacteria. Shigellosis is usually confined to the colonic mucosa, but sometimes it can cause extraintestinal complications, including bacteremia, urogenital symptoms, and neurological manifestations (4). The annual incidence of shigellosis is estimated at 164.7 million cases in the world and 1.1 million of those infected die. Seventy percent of all shigellosis and 60% of shigellosis-related deaths involve children younger than 5 years old due to their oral habits (3).

The major therapeutic intervention for shigellosis consists of fluid and electrolyte therapy. Antimicrobial therapy shortens the duration of clinical symptoms and fecal excretion of the organism (20). Selection of specific antimicrobial agents should be made based on susceptibility of the organism or information on local susceptibility patterns. However, because *Shigella* isolates with resistance to first-line antibiotics have been reported throughout world, third generation cephalosporins and quinolones are the mainstay of treatment. Extended-spectrum β-lactamases (ESBL) such as TEM-, SHV-, and CTX-M-types have been detected in *Shigella* strains (19,22,35). Innovative therapeutic approaches to shigellosis and new generations of vaccine candidates have been challenged.

EPIDEMIOLOGY OF SHIGELLOSIS IN KOREA

Epidemiological studies of bacterial diseases reveal the distribution and determinants of diseases. One of the main goals of the epidemiological study of shigellosis is to generate data that can be used to prevent the spread of shigellosis and implement interventions. Korean microbiologists and clinicians recognize changes in epidemiology of shigellosis such as overall incidence of shigellosis and prevalence of the serogroup. However, the epidemiology of shigellosis in Korea is not fully understood because of the non-consecutive study or the limited data on local areas, although there have been many reports or publications dealing with shigellosis. We reviewed the epidemiology of shigellosis during the last five decades to understand the evolutionary changes of *Shigella* strains in Korea.

1. Shigellosis before the Korean War

No valuable reports on the bacteriological study of shigellosis appeared until the Korean War on account of poor laboratory facilities, lack of public health system, and lack of skilled bacteriologists. Most cases of shigellosis would have been identified as diarrheal diseases. Chun D (13) and other microbiologists suggested that *S. dysenteriae* was the most prevalent species until the early twentieth century and then *S. flexneri* gradually became more prevalent. A considerable number of cases of *S. dysenteriae* were also detected in Korea before 1945.

2. Shigellosis during the Korean War

Bacteriological studies were mainly conducted by the U.N. Forces (44,45) and related Korean laboratories during the Korean War. A total of 3,732 *Shigella* species were isolated from military personnel, war refugees, prisoners of war, and Koreans who worked in the U.N. Forces during the periods of 1952 to 1953 (10) (Table 1). *S. flexneri* was the most prevalent species, being found in 3,392 isolates (90.9%), followed by *S. dysenteriae* in 236 isolates (6.3%), *S. sonnei* in 44 isolates (2.3%), and *S. boydii* in 20 isolates (0.5%). On the basis of the serotype of *S. flexneri*, serotype 4 (1,003 strains) and serotype 5 (849 strains) accounted for 49.6% of all *Shigella* isolates. Another report about shigellosis appeared during the Korean War (18). Bacteriologists who worked in the Korean Armed Forces Central Medical Research Institute (formally the Korean Army Medical General Laboratory) and Chunnam National University College of Medicine collected 133 *Shigella* isolates from stool samples from 1952 to 1954. *S. flexneri* was the most prevalent species, being found in 120 isolates (90.2%), followed by *S. dysenteriae* in 11 (8.3%). In contrast to the prevalence of *S. flexneri* serotype 4 in the data of *Shigella* isolates from 1952 to 1953, *S. flexneri* serotype 3 was the most prevalent (38 isolates) among the *Shigella* isolates tested.

Taken together with the above results of shigellosis during the Korean War, *S. flexneri* 4a was the most prevalent species during the Korean War. *S. dysenteriae*, *S. boydii*, and *S. sonnei* were only responsible for 9.1% of all shigellosis during this period. Diverse serotypes of *Shigella* were detected during this period: four serotypes of *S. dysen-*

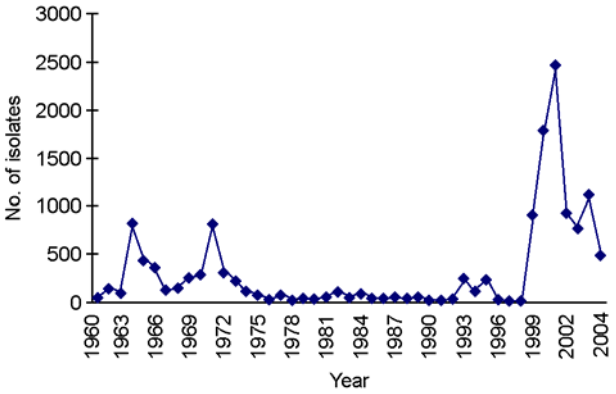

Figure 1. Incidence of shigellosis in Korea during the periods of 1960 to 2004.

teriae, eight serotypes of *S. flexneri*, and four serotypes of *S. boydii*. After the armistice agreement of the Korean War, few bacteriological studies of shigellosis were conducted due to poor laboratory resources and no valuable data was generated.

3. Shigellosis in the 1960s

The Korean National Institute of Health (KNIH) began communicable disease surveillance in 1960 (Fig. 1) (28). However, the number of reported cases of shigellosis was too small to estimate the incidence of shigellosis in Korea. They did not report the distribution of serogroups of *Shigella*. Chun and his colleges (1,11,14) collected 271 *Shigella* isolates in Daegu and Kyungpook province from 1961 to 1968 (Table 2). *S. flexneri* was the most prevalent, being found in 225 isolates (83.0%), followed by *S. dysenteriae* in 26 (9.6%), *S. sonnei* in 13 (4.8%), and *S. boydii* in 8 (3.0%). The overall distribution of serogroups was similar to that of the isolates from the 1950s (Table 1), but a slight decrease of *S. flexneri* was noticed. In contrast to the prevalence of *S. flexneri* in Korea, *S. sonnei* was the most prevalent species in so-called developed countries in the 1960s. *S. sonnei* was responsible for 72.8% of shigellosis in Japan in 1965, 55% in U.S.A. in 1968, and 23.2% in Hong Kong in 1963 (14). Although the exact reason for the shift of serogroups is still unknown, Chun D (13) suggested that hospital accessibility of patients suffering from shigellosis was an important factor in the distribution of *Shigella* species. Only patients with severe symptoms caused by *S. dysenteriae*, *S. flexneri*, and *S. boydii* visited hospitals to be treated for shigellosis, and mild cases of shigellosis caused by *S. sonnei* were treated in the home and were not subjected to the bacteriological study. Accordingly, the incidence of *S. sonnei* may be underestimated in developing countries.

Table 1. Prevalence of *Shigella* species isolated in Korea during the periods of 1952 to 1953

Species/serotype		No. of isolates in 1952		No. of isolates in 1953		Total (%)
		Korean	U.N. Forces	Korean	U.N. Forces	
S. dysenteriae	1	54	2	11	3	70
	2	141	−	10	10	161
	4	1	−	2	−	3
	6	1	−	1	−	2
S. flexneri	1	294	7	29	11	341
	2	541	67	119	57	787
	3	321	12	28	26	387
	4	867	33	88	15	1,003
	5	689	8	147	5	849
	6	4	−	−	2	6
	var. X	6	−	2	−	8
	var. Y	11	−	3	−	14
S. boydii	1	4	−	−	1	9
	2	1	−	−	−	1
	4	1	1	−	−	2
	5	6	−	2	−	8
S. sonnei		35	9	7	33	84
Total		2,977	143	449	163	3,732

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There were distinct changes in serotypes of *S. flexneri* isolates from the 1960s. The most prevalent serotypes of *S. flexneri* are 1b, 2a, 3a, 4a, and 6 in developing countries and 2a in developed countries. Although *S. flexneri* 1a, 1b, 2b, 3a, 3c, 4a, 4b, and 5 were detected in the 1960s, the most prevalent serotype of *S. flexneri* changed from serotype 4a in the isolates from the 1950s to serotype 2a in the isolate from the 1960s. Evolutionary changes such as small shift of serogroup and selection of a certain serotype occurred among the Korean endemic *Shigella* strains in the 1960s.

4. Shigellosis in the 1970s

There are three distinct changes in the epidemiology of *Shigella* in the 1970s. First, the overall incidence of shigellosis decreased in the late 1970s in accordance with the general improvement of national socioeconomic status, the establishment of a public health system, and the improvement of private hygiene. Second, the prevalence of *Shigella* species changed in the 1970s. *S. flexneri* was still the most prevalent species in the 1970s, which accounted for 83.5% of *Shigella* isolates, but the incidence of *S. sonnei* rapidly increased from 4.8% of the isolates from the 1960s to 14.7% of the isolates from the 1970s (Table 3). The incidence of *S. dysenteriae* and *S. boydii* dramatically decreased to 1.5% and 0.3%, respectively. Third, the isolation rate of *S. flexneri* 2a rapidly increased from 41.3% of the isolates from the 1960s to 93.2% of the isolates from the 1970s (2,14) (Table 4).

The increase of *S. sonnei* and decrease of *S. dysenteriae* and *S. boydii* can be partly explained by the hospital accessibility of the patients and the use of antibiotics to treat shigellosis. Limited antimicrobial therapy such as sulfonamides was available to treat shigellosis in the 1960s. Korean pharmatheutical companies actively produced the first-line

Table 2. Prevalence of *Shigella* species isolated in Daegu and Kyungpook province during the periods of 1961 to 1968

Species/serotype		No. of isolates from 1961 to 1964	No. of isolates from 1965 to 1968	Total (%)
S. dysenteriae	1	11	1	12 (4.4)
	2	4	4	8 (3.0)
	3	3	1	4 (1.1)
	4	1	1	2 (0.7)
S. flexneri	1a	4	16	20 (7.4)
	1b	2	0	2 (0.7)
	2a	73	40	112 (41.3)
	2b	16	0	16 (5.9)
	3a	11	8	19 (7.0)
	4a	18	18	36 (13.3)
	4b	10	3	13 (4.8)
	5	3	4	7 (2.6)
S. boydii	1	2	0	3 (1.1)
	2	4	0	4 (1.5)
	4	1	0	1 (0.4)
S. sonnei		11	2	13 (4.8)
Total		174	97	271 (100)

Table 4. Prevalence of serotype of *S. flexneri* isolates in Korea during the last five decades

Serotype	Incidence of *S. flexneri* [a]				
	1952~1954	1961~1969	1970~1979	1991~1997	1998~2004
1a	11.7%	9.0%	1.1%	−	−
1b	−	0.9%	0.7%	−	−
2a	26.8%	50.2%	93.2%	100%	84.8%
2b	−	6.3%	−	−	3.0%
3a,c	14.0%	8.5%	0.2%	−	6.0%
4a	34.2%	16.1%	0.2%	−	−
4b	−	5.8%	−	−	−
5	12.3%	3.1%	−	−	3.0%
Others (X, Y)	1.0%	0%	4.6%	−	3.0%

[a], Data of *S. flexneri* isolated from 1980 to 1989 were not available

Table 3. Prevalence of *Shigella* species in Korea during the last five decades

Serogroup	Incidence of shigellosis					
	1952~1954	1961~1968	1970~1979	1980~1987	1991~1997	1998~2004
S. dysenteriae	6.4%	9.6%	1.5%	0.5%	−	−
S. flexneri	90.9%	83.0%	83.5%	75.7%	13.5%	3.6~20%
S. boydii	0.5%	3.0%	0.3%	0.2%	1.3%	0.2~1%
S. sonnei	2.2%	4.8%	14.7%	23.6%	77.1%	79~96.2%
Total No. of isolates	3,865	271	713	2,223	617	8,448

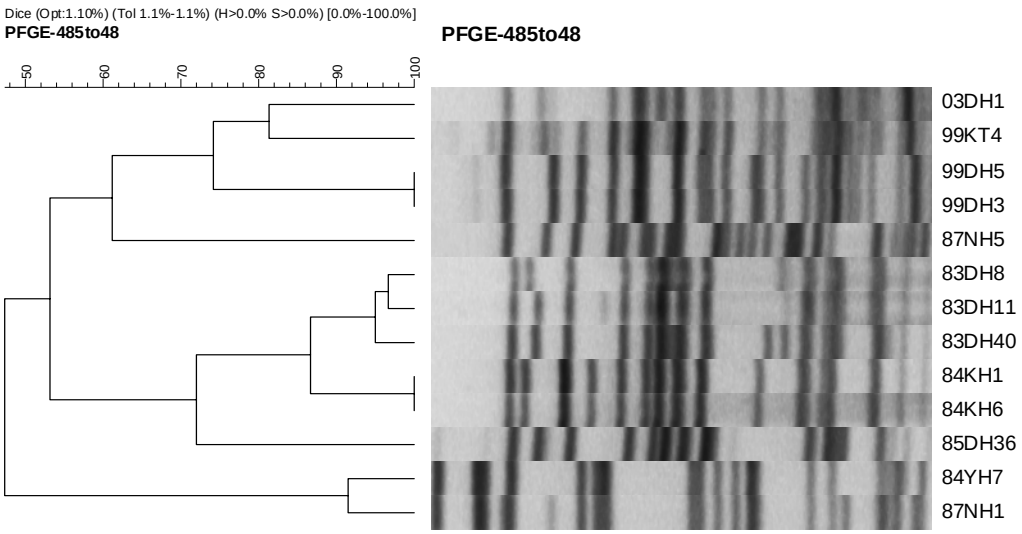

Figure 2. The representative of PFGE patterns of *S. flexneri* isolates in Korea. *S. flexneri* isolates during the periods of 1983 to 2003 were selected based on antimicrobial susceptibility, transferability of antimicrobial resistance, and biochemical profiles.

antibiotics for shigellosis such as trimethoprim/sulfamethoxazole (co-trimoxazole) in the early 1970s. Accordingly, highly virulent strains of *S. dysenteriae*, *S. flexneri*, and *S. boydii* were gradually eradicated by antimicrobial therapy, whereas the detection rate for *S. sonnei* was increased by increased accessibility to hospitals due to the improvement of economic status and public health control. Many Korean endemic strains of *S. dysenteriae* and *S. boydii* were not detected in the 1970s.

5. Shigellosis in the 1980s

According to the communicable disease surveillance from KNIH, the total incidence of shigellosis in Korea was not high in the 1980s compared with other developed countries (28). Of the 2,223 *Shigella* isolates from the 1980s, *S. flexneri* and *S. sonnei* were responsible for 75.7% and 23.6% of shigellosis, respectively (Table 3). The isolation rate of *S. sonnei* gradually increased during the 1980s. The incidence of *S. dysenteriae* and *S. boydii* was very low, which accounted for only 0.5% and 0.2% of shigellosis, respectively (36). Shin and Oh (41) isolated 197 *Shigella* isolates from one hospital located in Seoul during the periods of 1974 to 1986. They reported that the incidence of *S. flexneri*, *S. Sonnei*, and *S. boydii* was 81.0%, 17.0%, and 1.1%, respectively. Accordingly, the local data on shigellosis were also similar to the overall incidence of shigellosis in Korea as a whole.

Improvement of socioeconomic status, establishment of medical insurance and public health control, and improvement of general hygiene could affect the incidence of shigellosis. In addition to socioeconomic factors, the Korean government tried to eradicate endemic infectious diseases caused by *Salmonella*, *Shigella*, *Vibrio cholerae*, and other bacterial species. All these efforts to eradicate endemic infectious diseases are responsible for low incidence of shigellosis in Korea.

The overall distribution of serotypes of *S. flexneri* was not known, but it has been shown that the prevalent serotypes of *S. flexneri* were different according to isolation areas. Of the 164 *S. flexneri* isolates collected from all parts of Korea in 1985, serotype 1b was the most prevalent, which accounted for 84 (51.2%) isolates (9). However, approximately 90% of *S. flexneri* isolates detected in Daegu and Kyungpook province in the 1980s were serotype 2a (8, 12,37,38,39). Some selected *S. flexneri* isolates from the 1980s showed different pulsed field-gel electrophoresis (PFGE) patterns (Fig. 2), suggesting that they were genetically unrelated. PFGE also identified diverse clones of *S. sonnei* in the 1980s (Fig. 3). These findings indicate that diverse clones of *S. flexneri* and *S. sonnei* were circulating in Korea in the 1980s.

6. Shigellosis during the periods of 1990 to 1997

The annual incidence of shigellosis was estimated to less

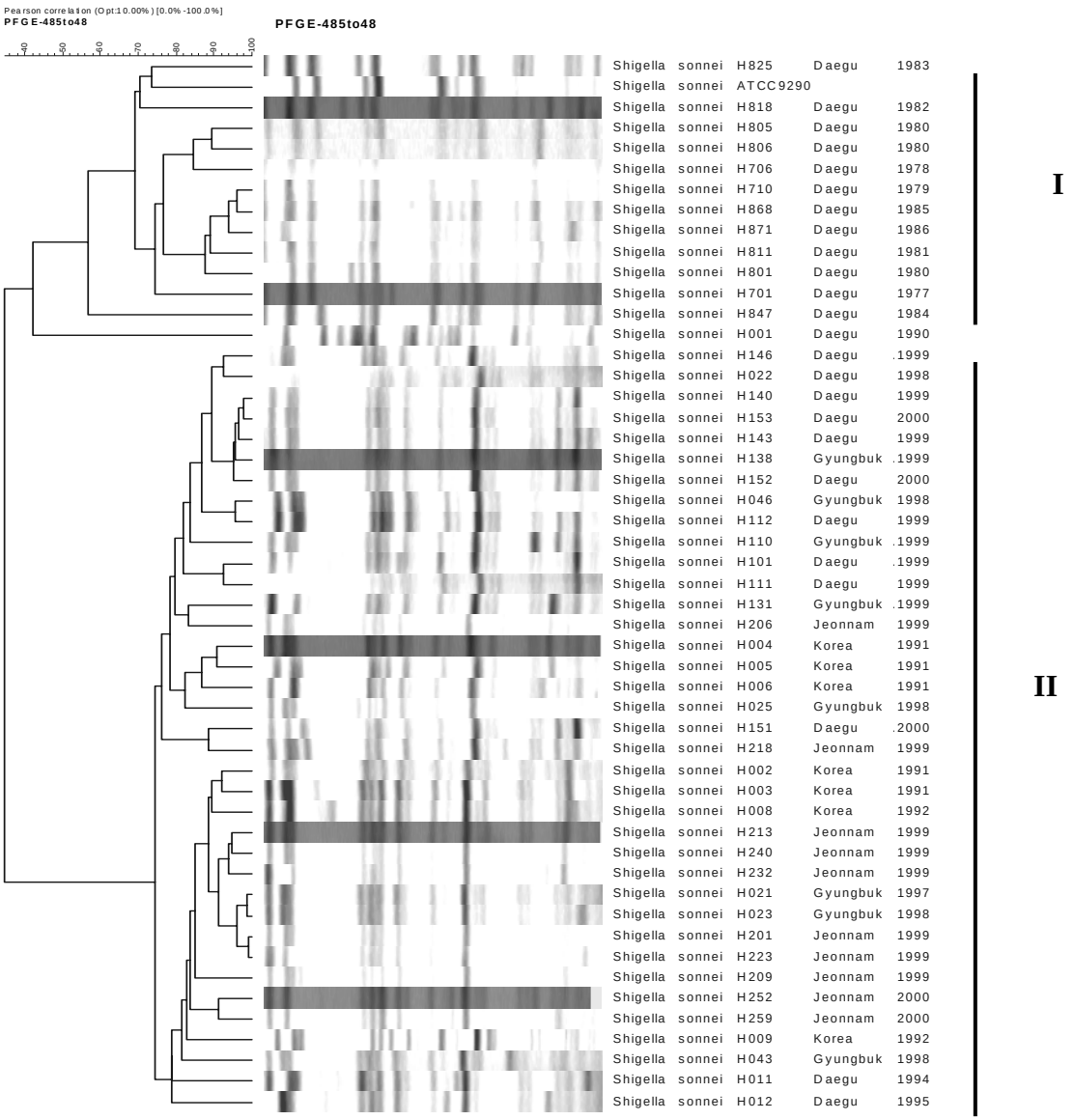

Figure 3. The representative of PFGE patterns of *S. sonnei* isolates in Korea. *S. sonnei* isolates during the periods of 1977 to 2000 were selected based on antimicrobial susceptibility, transferability of antimicrobial resistance, and resistant mechanisms of antimicrobial agents.

than 100 cases from 1989 to 1991 (Fig. 1). Most shigellosis occurred as sporadic cases. Thereafter, the incidence of shigellosis slightly increased to 284 and 164 cases in 1992 and 1993, respectively (28). The annual incidence of shigellosis from 1994 to 1997 was the lowest in Korea since the Korean War. Only 8 cases of shigellosis were reported in all parts of Korea in 1997. *S. sonnei* was the most predominant species in Korea during this period. Of the 54 *Shigella* isolates from 1991, 43 (79.6%) isolates were *S. sonnei* and 10 (18.5%) isolates were *S. flexneri*. This is the first reversion of prevalence of *S. flexneri* to *S. sonnei* in Korea. The total isolation rate of *S. sonnei* (77.1%) was higher than that of *S. flexneri* (13.5%) during this period. The serotype of all *S. flexneri* isolates was 2a. Only 8 *S. boydii* strains were isolated. No *S. dysenteriae* was isolated.

There were significant differences in phenotypic and genotypic markers between *S. sonnei* isolates from the 1980s and 1990s. Based on the biotype (27), *S. sonnei* isolates from the 1980s fermented rhamnose (biotype a), whereas the isolates from the 1990s did not ferment rhamnose (biotype g) (19,23,34). *S. sonnei* isolates from 1977 to 2000 were distributed into two groups by PFGE, arbitrarily designated

as patterns I and II (Fig. 3). PFGE pattern I included *S. sonnei* isolates from the 1977 to 1987 and was divided into two subgroups by 70% of similarity value, indicating that they originated from two different clones. PFGE pattern II consisted of one large group of *S. sonnei* isolates from the 1990s and 2000s by 82% of similarity value, except one isolate from 1990 (21,34). This PFGE finding suggests that a new *S. sonnei* clone emerged in 1990 and that a second clone was introduced in 1991. After the disappearance of the Korean endemic *S. sonnei* strains, a new clone of *S. sonnei* strains, which was first detected in 1991, was responsible for sporadic cases of shigellosis from 1991 to 1997. The genetic relatedness of *S. flexneri* isolates in the 1980s and from 1990 to 1997 is not known.

7. Shigellosis from 1998 to present

A total of 906 cases of shigellosis were reported in 1998 in all parts of Korea, except Daejoen and Jeju (28). The incidence of shigellosis increased annually, peaking at 2,462 cases in 2000, and then gradually decreasing to 487 cases in 2004. Two *Shigella* species, *S. sonnei* (92.0%) and *S. flexneri* (8.0%), were isolated in 1998. *S. sonnei* was the most prevalent species during this epidemic period, but there were some fluctuations in the distribution of *Shigella* species due to the size of outbreak caused by *S. flexneri*. Outbreaks of shigellosis were mainly caused by *S. sonnei*, but outbreaks caused by *S. flexneri* occurred in every year. Outbreaks of *S. sonnei* infection in 1998 and 1999 were highly associated with school meals for children.

S. flexneri 2a was only detected in the isolates from 1990 to 1997, whereas five different serotypes such as 2a, 2b, 3, 5, and others were found in the isolates from 1998 to 2004, indicating the possibility of introduction of new *S. flexneri* strains or the reemergence of the Korean endemic *S. flexneri* strains. PFGE patterns of four selected *S. flexneri* isolates from 1999 and 2003 were different from those of *S. flexneri* isolates from the 1980s (Fig. 2). This finding suggests that *S. flexneri* isolates during the epidemic periods may be imported and spread in Korea, but the possibility of the Korean endemic strains can not be excluded. The imported cases of *S. flexneri*, *S. sonnei*, and *S. boydii* were detected in the national surveillance system (29~31). Introduction of new *Shigella* strains from foreign countries by travelers, foreign workers, or illegal immigrants may contribute to the maintenance of clonal diversity of *Shigella* in Korea.

The characteristics of the Korean epidemic *S. sonnei* clone from 1998 to 2004 are defined by biotype g, arbitrarily PFGE pattern II (Fig. 3), and commonly resistant to tetracycline, streptomycin, sulfonamide, and trimethoprim. *S. sonnei* isolates from 1998 to 2004 were closely related to *S. sonnei* isolates from the early 1990s (23,34,37). However, *S. sonnei* isolated from Australia, Italy, Ireland, U. S. A., and African countries during the same period exhibited biotype g and very similar PFGE patterns with the Korean *S. sonnei* isolates (25,26), suggesting the existence of pandemic *S. sonnei* clone worldwide. The imported cases of this *S. sonnei* clone cannot be easily differentiated from the Korean epidemic *S. sonnei* clone. Accordingly, epidemiological markers are necessary to differentiate the imported cases of *S. sonnei* and the Korean epidemic strains. The widespread of *S. sonnei* strains and the persistence of *S. flexneri* strains are responsible for the endemicity of shigellosis in Korea.

SUMMARY

Clonal evolution was occurred in the Korean endemic *Shigella* strains during the last five decades. The Korean endemic *Shigella* strains that were first detected during the Korean War circulated until the late 1970s. Some specific Korean endemic *Shigella* strains were selected by combinations of the socioeconomic status and the use of first-line antibiotics. Virulence of *Shigella* strains and clinical manifestations of shigellosis also has affected the persistence of certain *Shigella* species. The Korean endemic strains of *S. dysenteriae*, *S. boydii*, and *S. sonnei* disappeared in the late 1980s, but the persistence of the Korean endemic *S. flexneri* strains was not known. New clones of *S. sonnei* were introduced in Korea from the late 1980s to the early 1990s. A new *S. sonnei* strain was responsible for the high incidence of shigellosis and outbreaks in all parts of Korea in recent years. New *S. flexneri* strains that were not genetically related to the isolates from the 1980s have emerged and circulated in Korea since 1998. The imported cases of *S. flexneri*, *S. sonnei*, and *S. boydii* were detected by monitoring of the national surveillance system. Accordingly, an active surveillance system and effective control strategy are necessary to prevent the emergence of new *Shigella* clones

and the spread of the epidemic *Shigella* clones in Korea.

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