

## Herpes Simplex Virus Type 2 Seroprevalence in Korea: Rapid Increase of HSV-2 Seroprevalence in the 30s in the Southern Part

To determine the characteristics of seroprevalence of herpes simplex virus type 2 (HSV-2) infection among Korean people, a cross-sectional study was conducted on three groups in 2004. The three groups consisted of the general public who visited public health centers, commercial sex workers (CSWs), and human immunodeficiency virus (HIV)-infected persons. Among the general public, HSV-2 seroprevalence rates for age under the 20s, in the 20s, 30s, 40s and the above 22.6%, 32.7% and 32.3%, respectively, which showed rapid increase of the rate in the 30s ( $p < 0.0001$ ). In case of the above of 19 yr old, women (28.0%) was higher than men (21.7%) ( $p < 0.0001$ ). The rate of CSWs (81.6%) was about 10 times higher than that of general women. In case of HIV-infected men (47.6%), the figure was about 2-3 times higher than that of general men. The low rate in the teens and the 20s proved that it is essential to develop sexually transmitted infections (STIs) prevention programs of education and publicity for them as a precaution measure. This study is the first major study of its kind on HSV-2 and would provide basic data for prevention of STIs including information about target groups subject to vaccination program.

**Key Words :** HSV-2; HIV; Herpes Genitalis; Sexually Transmitted Diseases; Seroprevalence

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## INTRODUCTION

Herpes simplex virus type 2 (HSV-2) can be transmitted without any symptoms during the viral revival period through genital mucus membrane by sexual contact. It can also be transmitted vertically from an infected mother to the fetus (1-4). Once infected, it is impossible to cure completely: it is hidden in the neural system and revitalized with the weakening of immune system or by a stimulus such as UVs to secrete infectious HSV-2 (5, 6). Most of infected persons do not know information about the transmission mode or the fact that continuing sexual contacts could trigger transmission of HSV-2, eventually increasing the cumulative number of infected persons (3, 7). Sexually transmitted infections (STIs) should be reported to the related authority in Korea within 7 days when verified by public health centers or clinics of any kind. STIs can be classified according to its cause or the type of infected bacteria and virus: syphilis, gonorrhea, chlamydia, non-gonococcal urethritis, condyloma acuminata, and genital herpes. Although HSV-2 infection is detected, it is not required to report its occurrence to health authorities in most countries, so that it is difficult to figure out the magnitude of its incidence. Korea designated HSV-2 as a surveillance factor concerning commu-

nicable diseases in 2001. Each year 600-700 HSV-2 infected persons or pseudo-infected persons are reported but information on the magnitude of infection and the transmission rate is insufficient (8). Since HSV-2 infection itself is not fatal, prevention and treatment can be neglected, which increases the risk of other STIs and the possibility of its transition to other fatal diseases. For human papilloma virus (HPV)-infected women with HSV-2, the incidence rate of cervical cancer is 2 to 3 times higher than that of women infected with HPV only. Furthermore, it is reported that ulcer incurrence by HSV-2 increases human immunodeficiency virus (HIV) infection rate by 3 to 9 times (9-11). The aims of this study were to investigate the magnitude in HSV-2 infection in the general public in Korea and to compare it with the magnitude of infection of risk groups for STIs.

## MATERIALS AND METHODS

In 2004, we selected 1,768 persons from the public health centers in the region P, a big harbor city, and 882 in the region J, an inner rural area, both of which are located in the southern part of Korea and conducted HSV-2 IgG antibody

test for physical examination. All of them were visitors to public health centers.

In order to verify whether the seroprevalence data of the southern part in Korea represents generality, we used the stratified random sampling to select 455 sera from 40,000 samples obtained by the project of "National Survey of Health and Nutrition (NSHN)" conducted between 6 April 2005 and 30 June 2005. The NSHN was a nationwide big project to analyze the state of health and nutrition on a regular basis under the supervision of the Ministry of Health and Welfare in Korea. The 455 samples' power was 80%.

We also investigated 304 commercial sex workers (CSWs), a high-risk group of STIs, who were to make regular visits to health centers in two big cities, S and P, for a periodical STIs examination. Furthermore, we examined HSV-2 seroprevalence in 196 persons infected with HIV by sexual contact in 2003.

Blood samples were processed by centrifugation at the site

**Table 1.** Demographic characteristics of study groups

Characteristics	No. tested	%
Total	3,605	
Gender		
Men	1,719	47.7
Women	1,886	52.3
Age		
<20	1,301	36.1
20-29	841	23.3
30-39	540	15
40-49	353	9.8
50-59	291	8.1
≥60	279	7.7
Region		
P	1,870	51.9
J	882	24.4
Others*	853	23.7
Group		
General†	3,105	86.1
CSWs	304	8.5
The HIV infected	196	5.4

\*, 196 HIV infected persons and 202 CSWs from S including 455 sera from the National Survey of Health and Nutrition, 2005; †, 2,650 residents in the region P and J including 455 sera from the National Survey of Health and Nutrition, 2005. CSWs, commercial sex workers; HIV, human immunodeficiency virus.

of collection. The separated serum was aliquotted and then frozen at -20°C. We used sera for IgG antibody test. To examine a HSV-2 specific antibody, HerpeSelect 2 ELISA IgG (Focus Technologies, Memphis, TN, U.S.A.) was used according to the manufacturer's instructions.

We processed the data with Excel and used the Statistical Analysis System for Windows (Ver. 8.1, SAS institute Inc., Cary, NC, U.S.A.). The seroprevalence of the study group was defined as the number of positive persons per one of the tested persons.  $\chi^2$  test was used to assess the difference of seroprevalence by age, sex, and region. A *p* value less than 0.05 was considered statistically significant. Power was checked for selecting samples from the National Survey of Health and Nutrition. The stratified random sample selection by age and sex was used for sampling the general public who represented the Korean population.

## RESULTS

Demographic characteristics for study groups are shown in Table 1. Serological test results in child and youth in the region P are in the Table 2, which indicates that the seroprevalence of HSV-2 under the 20s was 2.8% (2.7% for men, 3.0% for women), rendering no difference in seroprevalence for age (*p*=0.4979) or for sex (*p*=0.7056). Table 3 shows that the seroprevalence of adults aged 20 and above was 24.9% and women (28.0%) were recorded higher than men (21.7%) (*p*=0.0053); 7.4% for aged 20-29 (men 6.8% and women 8.0%, *p*=0.6817), 22.6% for aged 30-39 (men 13.8% and women 30.9%, *p*=0.0004), 29.6-34.9% for aged 40 and above. Overall, the seroprevalence in the 30s (22.6%) significantly increased compared with that of the 20s (7.4%) (*p*<0.0001), and in the 40s (32.7%) than the 30s (*p*=0.0066), respectively. Women's seroprevalence greatly increased in the 30s (30.9%) than in the 20s (8.0%) (*p*<0.001), while men's increasing rate of seroprevalence in the 20s (6.8%) compared to the 30s (13.8%) and the 30s to the 40s (31.0%) was significantly higher in the older groups (*p*=0.0497 and *p*=0.0005, respectively). Women's seroprevalence was higher than that of men in the 30s, while the other age groups showed no difference among the groups or gender (*p*=0.0004). The comparison by region showed a contradictory difference in the 20s and the 60s (*p*=0.0012, *p*=0.0209),

**Table 2.** HSV-2 seroprevalence of the general public (<20 yr old) in the region P of Korea

Age	Men		Women		Total	
	No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)
≤6	198 (4)	2.0 (0.1-4.0)	199 (8)	4.0 (1.3-6.7)	397 (12)	3.0 (1.3-4.7)
7-12	200 (6)	3.0 (0.6-5.4)	198 (7)	3.5 (1.0-6.1)	398 (13)	3.3 (1.5-5.0)
13-19	202 (6)	3.0 (0.6-5.3)	197 (3)	1.5 (0.0-3.2)	399 (9)	2.3 (0.8-3.7)
Total	600 (16)	2.7 (0.1-4.0)	594 (18)	3.0 (1.7-4.4)	1,194 (34)	2.8 (1.9-3.8)

HSV-2, herpes simplex virus type 2; CI, confidence interval.

**Table 3.** HSV-2 seroprevalence of the general public (≥20 yr old) who visited public health centers in the southern part of Korea in 2004

Age	Sex	Region P		Region J		Total	
		No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)
20-29	M	100 (2)	2.0 (0.0-4.7)	48 (8)	16.7 (6.1-27.2)	148 (10)	6.8 (2.7-10.8)
	F	118 (7)	5.9 (1.7-10.2)	58 (7)	12.1 (3.7-20.5)	176 (14)	8.0 (4.0-12.0)
	Subtotal	218 (9)	4.1 (1.5-6.8)	106 (15)	14.2 (7.5-20.8)	324 (24)	7.4 (4.6-10.3)
30-39	M	53 (10)	18.9 (8.3-29.4)	85 (9)	10.6 (4.0-17.1)	138 (19)	13.8 (8.0-19.5)
	F	52 (15)	28.8 (16.5-41.2)	97 (31)	32.0 (22.7-41.2)	149 (46)	30.9 (23.5-38.3)
	Subtotal	105 (25)	23.8 (15.7-32.0)	182 (40)	22.0 (16.0-28.0)	287 (65)	22.6 (17.8-27.5)
40-49	M	56 (15)	26.8 (15.2-38.4)	99 (33)	33.3 (24.0-42.6)	155 (48)	31.0 (23.7-38.2)
	F	49 (15)	30.6 (17.7-43.5)	99 (36)	36.4 (26.9-45.8)	148 (51)	34.5 (26.8-42.1)
	Subtotal	105 (30)	28.6 (19.9-37.2)	198 (69)	34.8 (28.2-41.5)	303 (99)	32.7 (27.4-38.0)
50-59	M	34 (11)	32.4 (16.6-48.1)	100 (31)	31.0 (21.9-40.1)	134 (42)	31.3 (23.5-39.2)
	F	40 (18)	45.0 (29.6-60.4)	98 (35)	35.7 (26.2-45.2)	138 (53)	38.4 (30.3-46.5)
	Subtotal	74 (29)	39.2 (28.1-50.3)	198 (66)	33.3 (26.8-39.9)	272 (95)	34.9 (29.3-40.6)
≥60	M	32 (12)	37.5 (20.7-54.3)	99 (22)	22.2 (14.0-30.4)	131 (34)	26.0 (18.4-33.5)
	F	40 (17)	42.5 (27.2-57.8)	99 (29)	29.3 (20.3-31.3)	139 (46)	33.1 (25.3-40.9)
	Subtotal	72 (29)	40.3 (28.9-51.6)	198 (51)	25.8 (19.7-31.8)	270 (80)	29.6 (24.2-35.1)
Total	M	275 (50)	18.2 (13.6-22.7)	431 (103)	23.9 (19.9-27.9)	706 (153)	21.7 (18.6-24.7)
	F	299 (72)	24.1 (19.2-28.9)	451 (138)	30.6 (26.3-34.9)	750 (210)	28.0 (24.8-31.2)
	Total	574 (122)	21.3 (17.9-24.6)	882 (241)	27.3 (24.4-30.3)	1,456 (363)	24.9 (22.7-27.2)

HSV-2, herpes simplex virus type-2; CI, confidence interval; M, male; F, female.

**Table 4.** HSV-2 seroprevalence rate of the general public from the National Survey of Health and Nutrition in Korea in 2005

Age	Men		Women		Total	
	No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)
10-19	57 (2)	3.5 (2.6-4.5)	50 (3)	6.0 (0.0-12.6)	107 (5)	4.7 (0.7-8.7)
20-24	59 (1)	1.7 (0.0-5.0)	61 (8)	13.1 (4.6-21.6)	120 (9)	7.5 (2.8-12.2)
25-29	57 (4)	7.0 (0.4-13.6)	59 (11)	18.6 (8.7-28.6)	116 (15)	12.9 (6.8-19.0)
30-34	54 (4)	7.4 (0.4-14.4)	58 (7)	12.1 (10.4-13.7)	112 (11)	9.8 (4.3-15.3)
Total	227 (11)	4.8 (2.1-7.6)	228 (29)	12.7 (8.4-17.0)	455 (40)	8.8 (6.2-11.4)

HSV-2, herpes simplex virus type-2; CI, confidence interval.

but there was no difference after adjusted by age. Seroprevalence of in the 20s and above was not significant by region under the standardized age ( $p=0.3949$ ).

We selected samples from the national pool to verify whether the age-specific HSV-2 seroprevalence of sexually active age group in the southern part of Korea represents generality. The HSV-2 seroprevalence among 455 adults aged between 10 and 35 in the NSHN was 8.8%; 4.7% for aged 10-19, 7.5% for aged 20-24, 12.9% for aged 25-29, and 9.8% for aged 30-34. There was no significant difference among age groups ( $p=0.1681$ ). The women's seroprevalence was 12.7% and showed a significant difference compared with the seroprevalence in men, 4.8% (Table 4,  $p<0.0001$ ).

As shown in Table 5, the seroprevalence of HSV-2 in Korean CSWs was 81.6%, which was remarkably different with those of the 20s (8.0%) and the 30s (30.9%) in the general public of the southern part of Korea ( $p=0.0054$ ). The seroprevalence of HIV-infected Koreans was 48.5%. The age-specific

HSV-2 seroprevalence of HIV-infected men was 23.9% for the 20s, 48.6% for the 30s, 57.1% for the 40s and 69.2% for the 50s, respectively, showing an increasing trend by age ( $p<0.0001$ ). The seroprevalence of the HIV infected women (63.6%) was higher than that of the infected men (47.6%). Due to the unbalance between the sexes, there was no difference after stratified by sex ( $p=0.3002$ ). In the seroprevalence of women of age 20-39, CSWs (81.6%) were recorded remarkably higher than the general women of the southern part (18.5%) ( $p<0.0001$ ). Fig. 1 shows that the seroprevalence of 186 HIV-infected men (47.3%) was also significantly higher than that of the general men in the southern part (21.7%) ( $p<0.0001$ ).

## DISCUSSION

This is the first voluminous study in Korea which inves-

Table 5. HSV-2 seroprevalence of CSWs and HIV-infected persons in Korea

Age	CSWs		HIV-infected persons					
	No. tested (Positive)	% Positive (95% CI)	Men		Women		Total	
			No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)	No. tested (Positive)	% Positive (95% CI)
20-29	234 (183)	78.2 (72.9-83.5)	46 (11)	23.9 (11.6-36.2)	1 (1)	100 (100-100)	47 (12)	25.5 (13.1-38.0)
30-39	65 (60)	92.3 (85.8-98.8)	72 (35)	48.6 (37.1-60.2)	4 (2)	50 (1.0-99.0)	76 (37)	48.7 (37.4-51.9)
40-49	5 (5)	100 (100-100)	42 (24)	57.1 (42.2-72.1)	3 (2)	66.7 (13.3-120)	45 (26)	57.8 (43.3-72.2)
≥50	-	-	26 (18)	69.2 (51.5-87.0)	2 (2)	100 (100-100)	28 (20)	71.4 (54.7-88.2)
Total	304 (248)	81.6 (77.2-85.9)	185 (88)	47.6 (40.1-54.5)	11 (7)	63.6 (41.6-98.4)	196 (95)	48.5 (41.5-55.5)

HSV-2, herpes simplex virus type-2; CI, confidence interval; HIV, human immunodeficiency virus; CSWs, commercial sex workers.

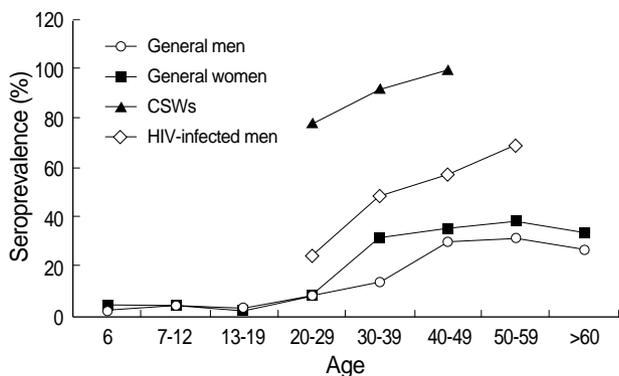


Fig. 1. Comparison of age-specific HSV-2 seroprevalence rates in four groups.

titigated the seroprevalence of HSV-2 in age close to being sexually active or in its peak in the two groups, CSWs and HIV-infected persons. In a group of the general public in Korea, the seroprevalence of the 1,855 subjects aged 13 and above in the southern part was 20.1% (20.9% for men, 22.4% for women), similar to that of the United States (12). In the United States, the seroprevalence of age 12 and above in the general public was 21.9%, 17.8% for men and 25.6% for women (12). However, Korea's seroprevalence for the aged 13-19 (2.3%) showed a significant difference with that of the United States (5.6%) and even it was lowered than 4.5% among white people in the United States. The age-specific seroprevalence of HSV-2 in the United States was 17.2% for the 20s, 27.8% for the 30s, 26.6% for the 40s, 25.1% for the 50s, and 24.3% for the 60s. As shown above the 20s, the seroprevalence of age 20-30 in Korea was lower than that of the same ages in the United States, but in the 40s and above in Korea showed a higher seroprevalence compared with the counterpart in the United States (7, 12). The seroprevalence of Koreans under the 20s was 2.8%, which was similar to that of Bangladesh (age 1-12, 2.5%) and that of the United Kingdom (16-19, 2-3%) (13, 14).

The HSV-2 seroprevalence of women in the 20s in the southern part of Korea was 8.0%, while that of the 30s was sharply increasing to 30.9%, which consolidated the importance of a STI prevention program. Considering the average age of the

first marriage is 27 in Korea, the HSV-2 seroprevalence in the 30s can be an important indicator to trace vertical transmission as women are likely give birth to their first babies in their 20s or 30s (15). It was reported that the HSV-2 seroprevalence of pregnant women in the United States was 32% and transmission rate of birth infected by primary HSV was 30-50%, and recurred HSV was 1-4% (12). The prevalence of herpes infection for newborn babies was less than 10 per 100,000 persons in Europe, 15-48 in the United States, and more than 85% of the infection's pathogen was HSV-2.

Age-specific HSV-2 seroprevalence in the general public in Korea showed that the seroprevalence of people under the 20 was the lowest, less than 5%, despite their sexual experience rate of 7.1-31.7% in age 13-19 according to the juvenile sexual activity study, which was lower than that of the group under 13 (16). This contradiction necessitated the further study on the relation between HSV-2 seroprevalence and sexual activity. Regardless of the fact that people in the 20s are sexually active and have sexual experience (57.3%), it was found that HSV-2 seroprevalence was very low. However, the regional difference between region P and J was reported to be substantial (17, 18).

We aimed at understanding the nationwide state of age-specific HSV-2 infection notwithstanding the limited sampling region in this study, so we conducted an investigation on the HSV-2 seroprevalence of 455 sera from the NHSN as a pilot study for generalization of HSV-2 seroprevalence in Korea. We still found a low seroprevalence rate of 4.7% for age 10-19, 7.5% for 20-24, 12.9% for 25-29, and 9.8% for 30-34. However, in age 30-34, the HSV-2 prevalence of NHSN was rather lower than that of subjects of the southern part. We intended to observe a dynamic change by age and to compare data collected from the southern part of Korea as a seroprevalence study on sera from the National Survey of Health and Nutrition, but there was no difference in the 20s and in the early 30s. Since a different pattern in the southern part has known, it is necessary to study HSV-2 seroprevalence in Korea to cover more regions with a bigger sample size.

Lee et al. conducted a study for university students (age 18-25) in 2005 and showed the prevalence rate of *Chlamydia trachomatis* was 8.4% for men, 10.6% for women, and that

of *Neisseria gonorrhoea* was 0.8% for men and 0.0% women. These figures were lower than those of the Australian counterparts; 16.4% and 4.9% for subjected age 20-24, 18.2% and 5.5% for subjected age 30-34 (19, 20).

In this study, the HSV-2 seroprevalence in women was higher than in men, and that the HSV-2 prevalence rate of women in the 30s was four times higher than in the 20s. This fact could be verified the necessity of intensive STIs prevention programs and publicity to target people in the 20s in order to reduce the current 30-40% rate. Furthermore, the seroprevalence of HSV-2 of CSWs, a high-risk group of STIs, was much higher than that of the general public. Since the high seroprevalence of CSWs could accelerate transmission of sexually-transmitted virus such as HIV, it is necessary to launch education programs to prevent any transmission of STIs. The seroprevalence of CSWs in Japan, Germany, and Thailand ranges between 60% and 80% (21-23). The figure similar to Korean CSWs' 81.6%. Blood testing is encouraged to people suspected of HSV-2 infection, even though they have no symptoms. People are also persuaded to use condom for precaution and safety.

The HSV-2 seroprevalence of HIV infected persons was lower than that of CSWs, but much higher than the general public. The seroprevalence of HSV-2 in HIV-infected Brazilians was 73%, which was higher than that of Koreans, 48.5% (24). It was reported that ulcerous STIs such as HSV could increase HIV infection rate by 3 to 9 times (20). Therefore, prevention of HSV-2 infection is related to the prevention of HIV infection. According to the Fisman's study, without intervention, the prevalence of HSV-2 infection among individuals aged 15 to 39 in the United States was projected to increase up to 39% among men and 49% among women by 2025. In addition, the annual cost of new infections could be risen from \$1.8 billion in 2000 to \$2.7 billion in 2025 (25). Koreans currently have run short of the medical expenses for HSV-2 infection. The much lower seroprevalence rate of HSV-2 in teenagers and the 20s compared with the remarkably high rate in the 30s showed that it is necessary to develop a STIs prevention program of education and publicity for the 20s as well as for teenagers. This study is the first report to investigate the magnitude of HSV-2 infection in the general public as compared with a high-risk group (CSWs) and the HIV-infected group for the advanced understanding of HSV-2 infection status. It provides basic data for consistent and systematic HSV-2 studies and information about the target groups for STIs vaccine program.

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