

*Scientific Report*

# The Changing Epidemiology of Herpes Simplex Virus Type 1 Infection: The Associated Effects on the Incidence of Ocular Herpes

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Received 20 January 2014; accepted 13 February 2015  
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## ABSTRACT

Herpes simplex virus type 1 (HSV-1) with a worldwide distribution has been reported in all human populations, resulting in a clinical spectrum of infections. Although HSV type 2 (HSV-2) is known as the most common cause of genital herpes, an increasing number of cases with genital herpes are caused by HSV-1. The present study aimed to discuss the changes in the epidemiology of HSV-1 infection including the decline in the general incidence of HSV-1 infection in childhood and the increased rate of genital herpes, caused by HSV-1. Moreover, changes in the epidemiology of ocular herpes, i.e., the reduced rate of primary ocular herpes in children and increased incidence of ocular HSV infection in adults, were discussed.

**Keywords:** Herpes simplex virus type 1 (HSV-1), Ocular herpes, Genital herpes, Epidemiology

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## INTRODUCTION

Herpes simplex virus (HSV), as a member of the *Herpesviridae* family and *Alphaherpesvirinae* subfamily, has a worldwide distribution. The term “herpes” is derived from a Greek word meaning “to creep” or “to crawl”, which describes the way the virus spreads across the skin, as defined by Greek scholars (Beswick, 1962). HSV is divided into two types, i.e., type 1 (HSV-1) and type 2 (HSV-2). Both types contain a large double-stranded DNA molecule and share extensive nucleic acid sequence homology (50%) (Kieff *et al.*, 1972). In general, HSV is a human

pathogen, capable of causing a variety of clinical diseases. The virus persists in neuronal cells, especially in trigeminal and sacral ganglia, and is frequently reactivated to cause symptomatic or asymptomatic recurrent infections (Pereira *et al.*, 1996). HSV has been associated with the infections of oral mucous membranes (e.g., gingivostomatitis, herpes labialis, and pharyngitis) and genital membranes (e.g., genital herpes), neonatal and congenital infections, visceral HSV infection in immunocompromised hosts, encephalitis, erythema multiforme, ocular complications, and eczema herpeticum in patients with underlying diseases such as atopic dermatitis, Darier's

disease, or Sézary syndrome (Safrin, 1992, Stewart *et al.*, 1995). According to a research at King Abdulaziz University Hospital in Saudi Arabia, sexually transmitted infections (STIs) are relatively common among HSV-positive patients (Fageeh *et al.*, 2013, Caldeira *et al.*, 2013). Generally, HSV-1 causes orofacial lesions, while HSV-2 is responsible for genital lesions. However, such associations are not absolute, and both viruses (HSV-1 and HSV-2) can cause infections in a wide variety of ocular structures.

HSV-1 transmission occurs as a result of direct contact with infected mucocutaneous secretions or lesions between a susceptible individual and a human carrier excreting the virus symptomatically or asymptotically. Factors such as crowding, poor hygiene, and age, which affect the level of exposure to sources of infection, influence the prevalence and incidence of virus transmission. In general, asymptomatic shedding of HSV-1 is recognized as the most common mode of virus transmission. Individuals with herpes labialis shed the virus on 5-10% of asymptomatic days (Douglas *et al.*, 1970). Asymptomatic shedding of HSV-1 occurs intermittently in oropharyngeal secretions of nearly 80% of infected patients; shedding in a single episode occurs on 0.5% and 1% of asymptomatic days (Umene *et al.*, 1999). Although in traditional and developing societies, HSV-1 is most commonly acquired as an oral infection in early years of life, in Western countries, reduced childhood exposure has shifted the epidemiology of the virus, and a second peak of infection, caused by sexual contact, is often reported during adolescence or later (Cowan *et al.*, 2000). The present study aimed to evaluate the epidemiological trend of HSV-1 infection, with a focus on changes in the epidemiology of HSV-1 virus and ocular herpes.

Studies were selected among more than 80 articles published in PubMed and references cited in the selected papers, using keywords including “HSV-2”, “HSV-1”, “herpes”, “prevalence”, and “epidemiology”.

**prevalence of HSV-1 infection.** Several studies have described the prevalence of HSV-1 infection in

different populations. HSV-1 infection is acquired during childhood and adolescence and is markedly more widespread than HSV-2 (Smith, 2002). In various countries, HSV-1 infection is ubiquitous and 90% of the population becomes seropositive by the fourth decade of life (Weiss *et al.*, 2004). The prevalence of HSV-1 infection is correlated with age, socioeconomic status, and geographical location (Nahmias *et al.*, 1990, Whitley *et al.*, 1998). In less-privileged populations, approximately 33% of children show serological evidence of HSV-1 infection within the first five years of life; the frequency of infection rises to 70-80% by early adolescence (Nahmias *et al.*, 1990, Whitley *et al.*, 1998). In comparison, in more developed countries, middle- or upper-class populations are infected later on in life. Also, seroconversion occurs in 20% of children younger than five years, followed by a rising trend at the age of 20-30 years in 40-60% of the population (Whitley *et al.*, 1998, Nahmias *et al.*, 1990). In the US, race has been reported to affect HSV-1 acquisition. According to the National Health and Nutrition Examination Survey (NHANES), more than 35% of African-Americans are infected with HSV-1 by the age of five years, whereas only 18% of white children become infected within the first five years of life. In addition, according to the literature, the annual incidence of infection has been estimated at 5-10% among university students (Nahmias *et al.*, 1990, Whitley *et al.*, 1998). In the UK, a lower seroprevalence has been reported among women with a high socioeconomic status and non-manual occupations (Ades *et al.*, 1989). Various studies have suggested a decline in the age-specific prevalence of HSV-1 infection. In a previous study, 37% of the first-year college students were HSV-1 seropositive and 46% became seropositive by the fourth year of college. Predictors of HSV-1 serology were introduced as female gender, African-American race, first intercourse before the age of 15 years, total years of sexual activity, and partners with oral sores (Gibson *et al.*, 1990). In Iceland, the prevalence of HSV-1 antibodies decreased from 80% in 1979 to 74% in 1985 (Nahmias *et al.*,

1990). Moreover, a British survey of middle-class children, aged 3-15 years, found that 62% and 41% had HSV-1 antibodies in 1953 and 1965, respectively. Based on a more recent study in the UK, the prevalence of HSV-1 antibodies in birth cohorts increased from 34% in 1986-1987 to 41% in 1994-1995; also, the prevalence continued to increase in children above 15 years of age (Vyse *et al.*, 2000). In addition, the prevalence of HSV-1 antibodies in 10- to 14-year-old children declined from 34% in 1986-1987 to 24% in 1994-1995 (Vyse *et al.*, 2000). According to a previous study in the UK in the early 1990's, 44% of blood donors and 59.5% of STD clinic attendees were HSV-1 seropositive (Cowan *et al.*, 1996). Moreover, in a study on Swedish school girls (n=839), 23% were HSV-1 seropositive at the age of 15 years, whereas 50% were seropositive by the age of 30 years (Christenson *et al.*, 1992). Additionally, in a study in Africa, 80% of subjects in almost all age groups (except young children) were HSV-1 seropositive (Ghebrekidan *et al.*, 1999). In a study performed in Brazil, Estonia, India, Morocco, and Sri Lanka, the prevalence of HSV-1 varied with respect to geographical region; the prevalence rate ranged from 78.5% to 93.6% in male adults and from 75.5% to 97.8% in female adults. Additionally, according to reports from different countries, the seroprevalence of HSV-1 significantly increased with age (Cowan *et al.*, 2003). Overall, the epidemiology of HSV-1 infection is speculated to change, owing to improvements in the socioeconomic status of the general population. The reduced prevalence of HSV-1 infection during childhood is correlated with the increased incidence of HSV-1 infection in adults. Based on a study in Poland, the seroprevalence of HSV-1 was notably high, even among young female adolescents, aged 15-19 years (80%); also, the prevalence of HSV-2 seropositivity was below 12% in all age groups (Smith *et al.*, 2006). In the majority of conducted studies, the prevalence of HSV-1 infections increased in accordance with age across the age spectrum and plateaued after the age of 30 years. The US population-based NHANES III

showed a steady rise in HSV-1 prevalence with age; in fact, the prevalence increased from 44% in young adults (range: 12-19 years) to 90% among those aged 70 years (Xu F *et al.*, 2002). In contrast, based on the literature, HSV-1 seropositivity was reported to decline in older women (40 years), particularly in Uganda (Wagner *et al.*, 1994), New Mexico (Becker *et al.*, 1996), and Turkey (Arseven *et al.*, 1992).

**Genital HSV-1 infection.** Genital herpes is one of the most prevalent STDs (Stanberry *et al.*, 1999). Although HSV-2 has been historically associated with genital infections, recent reports suggest that an increasing number of cases with genital herpes are caused by HSV-1 (Ribes *et al.*, 2001, Anne Scoular *et al.*, 2002). Primary genital herpes infections, which may be asymptomatic, are usually more severe than recurrent infections. Also, primary genital HSV-1 infection is less likely to result in recurrence, compared to HSV-2 infection (Benedetti *et al.*, 1994, Engelberg *et al.*, 2003). Despite the similarity in the clinical course of primary genital herpes infections among patients with HSV-1 and HSV-2, there are differences in the epidemiology and natural history of infections, caused by the two subtypes (Kinghorn *et al.*, 1994). Genital HSV-1 infections are characterized by less asymptomatic shedding (Wald *et al.*, 1995, Kinghorn *et al.*, 1996), lower frequency of transmission to a new partner (Kinghorn *et al.*, 1996, Lafferty *et al.*, 1987, Reeves *et al.*, 1981), longer recurrence intervals, and lower rates of clinical recurrence (Mindel *et al.*, 1986, Corey *et al.*, 1985). In a recent report on 261 sexually active women, residing in the metropolitan area of Natal, Brazil, genital HSV-1 infection was four times more prevalent than HSV-2 infection. Also, the highest prevalence of infection (caused by both viruses) was reported among women, aged 31-39 years (Pereira *et al.*, 2012). On the other hand, according to a survey in the US, the rate of infection caused by HSV-1 (2.5 cases per 100 population per year) was estimated to be twice as high as HSV-2 (1.1 per 100 population per year). Moreover, HSV-1 was more common than HSV-2 as a cause of oral and genital mucosal infections in

young women (Bernstein *et al.*, 2012). Acquisition of HSV-1 infection during childhood may protect individuals against most genital HSV-1 infections in adulthood. In general, improvements in socioeconomic circumstances, increased orogenital sexual activity, and reduced age of infection acquisition may lead to changes in the epidemiology of genital HSV-1 infections. Overall, the change in the epidemiology of genital HSV-1 infection has been recognized for several years. HSV-1 is an increasingly important cause of genital herpes, and an increasing share of genital infections is attributable to HSV-1 rather than HSV-2 (Corey *et al.*, 1999, Christie *et al.*, 1997, Whitley *et al.*, 1998). Although HSV-1 is most often transmitted via non-sexual contact, recent data from some developed countries indicate that a non-negligible proportion of first-episode genital herpes is caused by HSV-1 (Brugha *et al.*, 1997).

#### **The changing trend of genital HSV-1 infection.**

Several studies have reported a notable change in the epidemiology of genital herpes in developed countries. In the US, an increase has been reported in the prevalence of genital HSV-1 infection. According to a study by Ashley, 20-40% of first-episode genital infections were caused by HSV-1 (Ashley *et al.*, 1993). Also, based on a study by Lafferty, HSV-1 accounted for 20% of viral isolates, obtained from first-episode genital infections. In this study, the rate of HSV-1 infection was higher in homosexual men (46.9%), compared to heterosexual women (21.4%) or men (14.6%). Only 9.9% of the isolates from recurrent infections were HSV-1, and the partner's mouth, rather than the genital area, was the source of HSV-1 infection (Lafferty *et al.*, 2000). Based on a study by Solomon, among HSV-positive cultures, 4.2% were positive for HSV-1. HSV-1 was most prevalent among whites (6.5%), individuals with 0-2 recurrent infections over the past 12 months, and men with rectal/perirectal lesions (13.2%) (Solomon *et al.*, 2003). The observed differences may be attributed to the higher frequency of receptive oral sex in white people or lower risk of oral HSV-1 acquisition at an early age. In the UK, studies

on genitourinary medicine (GUM) clinic attendees reported an increase in the prevalence of genital HSV-1 infections during 1980's and early 1990's. A previous study on Kirkcaldy GUM clinic attendees reported the high prevalence of first-episode genital HSV-1 infection (71%) (Thompson *et al.*, 2000). Also, in Scotland, the prevalence of GUM clinic attendees with genital herpes (caused by HSV-1) increased from 20% in 1978 to 41% in 1991 (Ross *et al.*, 1993). In a study performed in another GUM clinic in Scotland, a progressive increase was reported in the prevalence of first-episode HSV-1 infections from 65% in 1995-1996 to 88.2% in 1998-1999 among women (Thompson *et al.*, 2000). Besides, in some areas in the UK, 50% of cases with primary genital HSV infections were caused by HSV-1 (Ross *et al.*, 1993, Tayal *et al.*, 1994). Furthermore, based on a study in England and Wales, the prevalence of HSV-1 antibodies in adults increased with age and was higher among females than males (54% in females aged 25-30 years). As revealed by these findings, the reduced rate of HSV-1 infection in childhood may be one of the factors contributing to the increasing incidence of genital HSV-1 infections (Vyse *et al.*, 2000). In a previous study, the majority of patients with positive HSV-1 swabs presented with herpetic symptoms, explaining the high prevalence of symptomatic HSV-1 infections (Langenberg *et al.*, 1999). More recently, the presence of HSV was detected in swabs obtained from different sites, and HSV-1 was detected in one-fourth of male and female cases with genital herpes (20% of males and 25% of females) (Buxbaum *et al.*, 2003). In a study in Sweden during 1995-1999, 64% of primary infections were caused by HSV-1, based on type-specific serological tests on 108 STD clinic patients. Also, 84% of primary HSV-1 infections and 64% of primary episodes were reported in women. This study suggested an association between orogenital sex and genital HSV-1 infection. Moreover, in a study in Norway, HSV-1 was detected in almost 90% of cases with genital herpes (Nilsen *et al.*, 2000). Coyle in a study in Northern Ireland revealed that recurrent HSV-1 infection was more

common than the recurrent HSV-2 infection in women, thus suggesting HSV-1 as the most common cause of recurrent genital ulcers in women (Coyle *et al.*, 2003). According to a study in Thailand in 1998-2004, 207 out of 1,125 samples were HSV-positive. The prevalence of genital HSV-1 infection in Thai patients increased from 106% in 1985 to 65.91% in 2004, suggesting the impact of changes in sexual behavior on the increased incidence of genital HSV infections (Bhattarakosol *et al.*, 2005). Tran and colleagues reported the results of a retrospective case series, examining the relative prevalence of genital HSV-1 and HSV-2 infections in patients living in Melbourne, Australia in 1980-2003 (Tran *et al.*, 2004). In their study, the incidence of genital HSV-1 infection increased from 15.8% in 1980 to 34.9% in 2003. Also, in 2003, HSV-1 was detected in 77% of patients, aged below 20 years. Except for females over the age of 40 years, a rising trend was detected in HSV-1 in all age groups. According to the literature, improved socioeconomic conditions, resulting in the reduced seroprevalence of HSV-1 in childhood, increase the number of susceptible adults to genital HSV-1 infection, since prior history of oral infections provides a high level of protection against HSV-1 infections (Nahmias *et al.*, 1990). Furthermore, the changing trend of sexual activities towards an increase in orogenital contact between the partners is associated with the shifting epidemiology of genital HSV-1 infection (Lafferty *et al.*, 2000b, Löwhagen *et al.*, 2000, Lafferty *et al.*, 1997). In a survey in UK, 23 cases of genital HSV-1 infection were identified. Of 16 virologically confirmed cases, 12 were female, 11 were below five years of age, and 14 had HSV-1 (Reading *et al.*, 2011). Moreover, a recent research in British Columbia showed that among 48,183 viral identifications, 56.8% were genital, 10.0% were perioral, 9.1% were cutaneous, and 22.9% were unknown. Among genital identifications, risk of HSV-1 infection was higher among females, younger age groups, and adolescents. In this study, the prevalence of genital herpes due to HSV-1 increased over time from 31.4% to 42.8% (Gilbert *et al.*, 2011). Furthermore, in a

recent study in 2005-2010, the seroprevalence of HSV-1 and HSV-2 was 53.9% and 15.7%, respectively. In fact, from 1999-2004 to 2005-2010, the seroprevalence of HSV-1 declined by nearly 7%, whereas the seroprevalence of HSV-2 did not significantly alter; therefore, it was deduced that adolescents lack HSV-1 antibodies. Also, no decline was reported in HSV-2 infections, which could cause an increase in the prevalence of genital herpes (Bradley *et al.*, 2013).

**Ocular HSV infection.** Both HSV-1 and HSV-2 can infect the eye and cause diseases in a wide variety of ocular structures. Typically, ocular diseases, which may be classified as primary or recurrent, are caused by HSV-1. Primary infection often remains unrecognized and the subclinical type usually occurs during childhood. The primary infection may result from being kissed as a child and typically manifests as acute buccal mucosa infection, spreading through the neurons in the trigeminal ganglion. Latent HSV infection is probably established in the trigeminal ganglion and the connected neural tissues; the cornea has been suggested to support the latency phase of HSV-1 (Perng *et al.*, 1994). Latency provides a viral reservoir which allows for spontaneous and recurrent reactivation of the disease (Liesegang *et al.*, 1989). Also, ocular infection caused by HSV-1 can lead to diseases including blepharitis, conjunctivitis, epithelial keratitis, and stromal keratitis (Dawson *et al.*, 1984, Liesegang *et al.*, 1999). Ocular HSV-1 infection is recognized as a major cause of blindness and a serious viral eye infection in the US (Dawson *et al.*, 1984, Liesegang *et al.* 1989, Barron *et al.*, 1994, Liesegang *et al.*, 2001). Ocular HSV-1 infection is estimated to occur in up to 20.7 cases per 100,000 population each year in different countries (Liesegang *et al.*, 1989, Darougar *et al.*, 1989, Elnifro *et al.*, 1999). Patterson and Jones reported a decline in the incidence of primary HSV ocular infection from 29% to 7% in patients under the age of five years (Patterson *et al.*, 1967). Moreover, in 1970, Norn studied all cases of dendritic keratitis from 1958 to 1964. The incidence of herpetic keratitis was estimated at 5.8 cases per 100,000 population per year

(Norn *et al.*, 1970). Moreover, Mortensen and Sjolie (1979) in a two-year study estimated the incidence of herpetic dendritic keratitis as 12 cases per 100,000 population per year (Mortensen *et al.*, 1979). In the US, Nesburn (1983) showed that almost 500,000 individuals suffer from ocular HSV episodes each year. In addition, over 1000 corneal transplants were performed annually as a direct result of HSV scarring (Nesburn *et al.*, 1983). Only 5% of cases with ocular HSV disease had primary infections (Lee *et al.*, 1994). In addition, some studies have reported an increase in the incidence of primary HSV ocular infection from 41% to 64% in young adults (Darougar *et al.*, 1985). In a previous study performed in 1973-1980, primary HSV ocular infection was detected in 108 patients. The mean age of the patients with first-episode ocular HSV infection was 25 years; also, 64% of cases were under five years of age (Darougar *et al.*, 1985). Additionally, Liesegang reported an incidence rate of 8.4 cases per 100,000 population each year for first-episode ocular HSV infections. In total, 212 cases of ocular epithelial HSV infection were reported during 1950-1982. In the study by Liesegang, the primary episodes involved the lids or conjunctiva in 54%, the superficial cornea in 63%, the deep cornea in 6%, and the uvea in 4% of cases from 1950 to 1982. The incidence rate of all episodes was estimated at 20.7 cases per 100,000 population per year. Also, the overall prevalence of ocular HSV infection was 14.9 cases per 100,000 population per year. Also, in this 33-year study, the mean age at the onset of infection was 37.4 years, which slightly increased every ten years (Liesegang *et al.*, 1989). Additionally, Pramod and colleagues evaluated ocular HSV infection in South India from 1995 to 1997. They analyzed the prevalence of herpes stromal keratitis (HSK) among 3000 patients, attending a corneal clinic. In this study, the prevalence of HSK was estimated at 7.8% (n=234), and the mean age of the patients was 29 years (range: 9 months to 65 years). In total, 134 primary and 97 recurrent ocular episodes were reported. Also, 50% of primary episodes occurred among adolescents and young adults; cases under five

years of age accounted for only 10% of primary episodes (Pramod *et al.*, 1999). Indications for penetrating keratoplasty were observed in the UK between 1990 and 1999. Viral keratitis, including both HSV and herpes zoster, significantly decreased from 11.7% to 5.9%. Several studies have reported a decline in the number of patients requiring keratoplasty, with HSV keratitis as the main indication for surgery (Branco *et al.*, 2004). French researchers have also evaluated the incidence and clinical characteristics of keratitis. Based on the findings, the incidence of herpetic keratitis was estimated at 31.5 cases per 100,000 population per year. In this study, the most frequent ocular herpetic lesions were dendritic keratitis (56.3%), conjunctivitis (53.6%), uveitis (33.6%), lid involvement (24.8%), stromal keratitis (29.8%), and geographic keratitis (9.9%), respectively (Labetoulle *et al.*, 2005). Finally, in a survey in Suriname, ocular swabs were collected from 91 patients with presumptive ocular infections (induced by  $\alpha$ -herpes virus), attending the Academic Hospital between November 2008 and August 2010; the subjects were tested by a polymerase chain reaction-based  $\alpha$ -herpes virus assay. The ophthalmic infections were predominantly caused by HSV-1, with a prevalence of 31%. The prevalence rates of varicella zoster virus, HSV-2, and mixed HSV-1/HSV-2 infections were 4%, 3%, and 2%, respectively (Adhin *et al.*, 2012).

## CONCLUSION

According to the literature, previous history of oral HSV-1 infection can provide protection against genital HSV-1 infection later in life. The decline in the seroprevalence of oral HSV-1 infection in childhood, the age-specific reduction in the rate of HSV-1 infection, as well as the change in the prevalence of sexual behaviors, have led to an increase in the incidence of genital HSV-1 infections. Although some studies have reported a decline in primary HSV ocular infection in children, ocular herpes remains an important eye disease. Overall, the majority of studies have declared an increase in the

incidence of adult HSV ocular infection. The general decline in HSV-1 infection during childhood and the rise in genital HSV-1 infection seem to have led to changes in the epidemiology of HSV ocular infection.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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