

REVIEW ARTICLE

Genital Herpes Infection: A Review

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Genital herpes infection is life-long and may result in painful and recurrent genital lesions, systemic complications, serious psychosocial morbidity, and rare but serious outcomes in neonates born to infected women, including permanent neurological handicap and death. Herpes simplex virus (HSV)-2 is the principal cause, with an increasing proportion of first-episode disease caused by HSV-1. Genital HSV transmission is usually due to asymptomatic viral shedding by people who are unaware that they are infected and clinical screening fails to detect most infections. Type-specific serological assays can distinguish the two viral subtypes, but these are expensive and currently restricted to a few research settings. Most infections are asymptomatic, or cause a mild illness which does not lead to health service attendance; but the limited evidence suggests a rise in disease incidence, perhaps related to a fall in HSV-1 age-specific prevalences. The prevalences of HSV genital infections increase with age and numbers of sexual partners, with higher rates in specific ethnic and low socioeconomic groups. However, infection is not restricted to high-risk populations. Antiviral agents, such as acyclovir, can reduce disease severity, prevent recurrences and shorten periods of viral shedding, but currently there are no effective population control measures. This may change with the advent of HSV vaccines, if their safety and long-term efficacy are confirmed. Possible applications for vaccines may include the suppression of disease and recurrences in patients with genital infections (immunotherapy), the prevention of viral transmission to their seronegative partners, and immunoprevention through vaccinating the latter. Economic evaluations of existing and potential control strategies, age-specific population HSV-1 and 2 seroprevalence studies for targeting future interventions, and cohort studies to elucidate the natural history of HSV-2 infections are needed.

Keywords: genital herpes; herpes simplex virus, HSV-1, HSV-2, epidemiology

Herpes simplex virus (HSV), types 1 and 2, is the commonest infective cause of genital ulceration in developed countries.¹ Genital herpes disease is of public health importance due to its morbidity, frequency of recurrence and the rare but serious neonatal disease which may occur following intrapartum transmission of HSV.² A range of antiviral agents has become available since the early 1980s which can reduce disease severity,^{2–7} but HSV infection is life-long⁸ and, once established, there is no treatment which will eliminate it.¹ This paper reviews the natural history of genital herpes infection and its epidemiology, focusing on the problems of estimating disease incidence and assessing its public health importance, symptomatic and asymptomatic viral transmission, and the prevalence of genital herpes infections. Current and potential new interventions

for controlling HSV genital disease are discussed, and research and development priorities for underpinning future disease control programmes are outlined.

NATURAL HISTORY

Viral Subtypes 1 and 2

Herpesviruses which are endemic in all human populations include: herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus and human herpesvirus-6, 7 and 8.^{8–10} The subtypes HSV-1 and 2 are closely related and share many common epitopes,^{8,11} resulting in cross-reactive responses in serological assays.^{12,13} Although HSV-1 and 2 genital disease is clinically indistinguishable,¹⁴ there are important differences in the epidemiology and natural history of the disease caused by the two viral subtypes.¹⁵ Herpes simplex virus-1 usually causes orolabial disease, but has been reported in 20–60% of cases of genital disease in the UK,¹⁵ while HSV-2 disease is almost always genital.¹³ The identification of antigenic subtype differences,^{16,17} principally the glycoproteins gG-1 and gG-2, has allowed the development of a wide range of tests for typing

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clinical isolates, and more recently of type-specific serological assays which indicate previous exposure to HSV-1 or 2 infection.¹⁸

Pathogenesis of Genital Herpes Infection

Genital infection is caused by inoculation of the virus onto a mucosal surface or through cracks in the skin, usually through close sexual contact.^{19–21} Disease is caused by a direct cytopathic effect of the replicating virus, destroying tissue.¹¹ At primary infection, the virus ascends peripheral sensory nerves and becomes established in sensory or autonomic nerve root ganglia, evading immune attack.¹⁹ Recurrent genital disease is generally due to reactivation of the initial strain of virus from latently infected sacral nerve root ganglia.^{2,13}

Natural History of Genital Herpes Infection

Genital herpes presents clinically as first-episode and recurrent episode disease. First-episode disease may be primary genital herpes infection in a person with no previous exposure to HSV-1 or 2, or may be non-primary.²⁰ Non-primary first-episode disease occurs in a person with previous exposure to HSV-1 or 2 infection and may be due to reactivation of an asymptomatic genital infection, or a genital infection in someone with previous orolabial HSV-1 infection.²⁰ Primary HSV-1 and 2 genital diseases are of similar severity and duration resulting in painful genital and extra-genital lesions. A review of published studies has reported high complication rates for primary HSV-2 infections including meningism (28%), pharyngitis (10%), hospitalization for aseptic meningitis (5%) and autonomic nervous system sacral radiculopathy (1%).² High rates for headache or photophobia alone (c. 40%), due to primary HSV-1 or 2 infection, have also been reported.²⁰ Systemic symptoms are more common in primary than in non-primary first-episode disease, and the mean duration of viral shedding from genital lesions is longer (11.4 days compared with 6.8 days).² The median age of first-episode disease presenting to the health services is 20–24 years for both men and women.^{15,22} Recurrent disease is common, especially in the first 18 months after first episodes, after severe first episodes (duration >35 days), after clinically manifest HSV-2 primary infections (up to 95%) in men, and after early age of first-episode disease.^{15,20,22,23} Recurrent disease is milder, with shorter mean duration of viral shedding (4.3 days).²

Large scale retrospective studies have estimated that only about 20% of people who have been infected with HSV-2, as defined by the presence of HSV-2 antibodies, report a history of genital herpes disease.^{25–28} But small-scale prospective studies have elicited symptoms

in up to 50%,²⁹ and symptoms or culture-confirmation of infection in 75%,¹³ of HSV-2 antibody positive women who were initially asymptomatic. Recall and ascertainment biases in retrospective studies, where histories of symptoms are elicited in large structured questionnaires, may result in underestimates of past disease. Study samples are often not representative, although estimates of the proportions of antibody positives who have experienced symptoms among university students (17%)²⁶ and sexually transmitted disease (STD) clinic attenders (18%²⁵ and 22%²⁸) have been similar. The high rate of symptom-recognition in one of the prospective studies was associated with intensive counselling, at a level which might not be found in a normal therapeutic encounter.²⁹ The 50% recognition rate may also have been partly due to selection biases, such as high rates of refusal to participate (108/276 gynaecology clinic attenders), losses to follow-up (73/140), being in a relationship with a symptomatic partner, socioeconomic status and ethnic status of the subjects. These studies illustrate the difficulties of estimating disease incidence because the spectrum of genital herpes infection ranges from truly asymptomatic to severe disease; and disease incidence estimates partly depend on health care-seeking behaviour and the efforts made to ascertain symptoms in health care settings. Clinical disease due to HSV-2 infection is also less common in people with previous HSV-1 infections than in those with HSV-2 infection alone.¹³

Disease Burden

The intrapartum transmission of HSV from the mother to the neonate results in skin, eye or oral infections (35% of cases), encephalitis (33%), or the dissemination of infection to the visceral organs (32%).³⁰ Regardless of treatment, a mortality rate from the latter of 60%, and permanent neurological sequelae in 50% of survivors of encephalitis and disseminated infection, has been reported.³⁰ The psychosocial morbidity associated with a diagnosis of genital herpes infection in the adult is often more debilitating than the physical features.^{1,31,32} Significantly greater levels of non-psychotic psychiatric morbidity, as measured by the General Health Questionnaire, have been reported in patients with first-episode disease, compared with a control group of STD clinic attenders without genital herpes,³³ and in patients with recurrent disease, compared with a control group with first-episode disease.³⁴

Human Immunodeficiency Virus (HIV) and HSV Infections

Population subgroups at high risk of HIV infection, e.g. homosexuals and injecting drug users, are usually already infected with HSV, with HSV-1 antibody

prevalence rates of 80–95%, at the time HIV infection was first diagnosed.⁹ Therefore, disease due to primary genital herpes infection is currently rare in HIV-infected people. However, it is likely to increase in frequency as individuals with congenitally acquired HIV infection survive into adult life. Being HIV seropositive has been shown to be a strong risk factor for subsequent first-episode and recurrent-episode genital herpes disease in those who are also HSV-2 positive, independently of other known behavioural risk and protective factors.³⁵ As immunosuppression progresses, more extensive mucocutaneous ulceration occurs than in normally immune patients, with a sharp rise in the proportion of genital ulcers which are HSV infected when CD4 counts fall below 50 cells \times 10⁶/l.³⁶ The presence of chronic slow healing herpetic ulcers in HIV positive people has been included among the Centers for Disease Control (CDC) and Prevention AIDS case definitions.³⁷ Asymptomatic HSV-2 shedding is four times more common in HIV positive than in HIV negative women, and increases as CD4 cell counts fall.³⁸

Herpes simplex virus genital ulcerative disease may facilitate the transmission and acquisition of HIV.^{15,39–44} and it is biologically plausible that this is contributing to the high rates of HIV transmission in Africa. A high prevalence of HSV-1 and 2 in the genital ulcers of STD clinic attenders in Uganda (36/98 tested)⁴⁵ may mean that mass bactericidal treatment for STD, as a strategy for controlling HIV transmission, may have limited effectiveness. In people with latent HIV infection, HSV reactivation or primary infection may also stimulate HIV replication, accelerating immunosuppression and progression to AIDS.⁴⁶ Reciprocal enhancement of HSV and HIV viral replication, in the presence of concurrent infection, has been described,⁴⁷ suggesting the importance of HSV suppressive treatment to prolong the survival of AIDS patients.

Transmission of HSV

Herpes simplex virus is transmitted by symptomatic lesions and through asymptomatic viral shedding, the former being more efficient because lesions have higher viral titres.^{13,15} Transmission of HSV-2 may be more efficient from men to women (4/13 women in steady relationships with HSV-2 positive men seroconverted over 3 years, compared with no seroconversions among 16 seronegative men with HSV-2 positive female partners).⁴⁸ This may partly be due to the higher rate of disease recurrences in men which may make them more infectious.²³ Asymptomatic shedding occurs in both men and women but is more easily detected in women, mainly from the cervix and vulva. It is more common in the first year after first-episode disease, in HSV-2

infections, and for one week after symptomatic recurrences.^{12,15,49–51} The contribution of asymptomatic viral shedding to the genital transmission of HSV in the population has not been quantified, but is believed to account for most transmissions.¹³ In 50–90% of transmissions, the source contact is unaware of being infected.^{19,25,28,52–58} Therefore effective control of genital herpes transmission at the population level will not be possible through interventions targeted only at those with known disease.

Where HSV-2 infected people have been educated about the signs and symptoms of genital herpes, and counselled to avoid exposing a seronegative partner to contact with active lesions (i.e. HSV-2 discordant couples), the risk of transmission has been reduced from as high as 30% to around 10% annually.^{12,43,48,59,60} Studies of such discordant couples suggest that asymptomatic shedding is responsible for 50–80% of cases of genital HSV transmission.^{19,59} Daily administration of acyclovir, an antiviral agent, has been shown to reduce symptomatic viral shedding.^{51,61,62} Its effectiveness at reducing asymptomatic shedding, though promising,⁶² is less certain and the results of larger studies are awaited.⁵¹ Concern has been expressed about the possibility of patient demand for long-term maintenance on a yet-to-be proven regime, uncertainty about how long it should be continued, and the danger of increasing psychosocial morbidity, given current uncertainty about asymptomatic transmission.⁵¹ Surprisingly, the use of condoms has not been shown to be effective at reducing transmission, but continues to be indicated on grounds of plausibility and the absence of any single method which has been shown to be effective at preventing transmission.^{51,62}

Transmission of infection from mother to baby usually occurs during vaginal delivery (85% of transmissions) and is dependent on the prevalence of genital viral shedding at the time of delivery.⁶³ Intrauterine (5%) and postnatal transmissions (10%) are rarer.⁶³ Intrapartum transmission is rare in recurrent maternal infections (3–5%), but rises to between 33% and 50% where the mother has a first episode genital infection, with the greatest neonatal morbidity following late gestation primary infections.^{55,57,64–66} In one study, almost 10% of 190 pregnant women were seronegative and at risk of acquiring HSV from their seropositive partners,⁵⁵ and a first episode of genital herpes has been reported in 3% of pregnant women.⁶⁷ Despite the higher risk of transmission from women experiencing first-episode disease, asymptomatic viral shedding and undiagnosed disease are responsible for a higher proportion of transmissions; and most mothers (70%) are unaware of being infected until the neonatal infection has been diagnosed.³⁰

DIAGNOSIS OF HSV GENITAL INFECTION

Clinical Presentation

Clinical screening (history and examination), although more sensitive than history alone, has a low sensitivity for detecting genital herpes infection, ranging from 19% to 39% of women in published studies.^{28,53,64,68,69} Intensive counselling, as already stated, may increase the detection rate to 50% in prospective studies.²⁹ Genitourinary HSV infections present with a diverse clinical spectrum but, although many patients show the classical, vesicular, ulcerative lesions of genital herpes disease, atypical presentations are increasingly being recognized.^{28,29,43}

Laboratory Detection of Clinical Isolates

The detection of HSV in cell culture, with HSV-1 and 2 typing, has been the gold standard diagnostic test for early stage genital HSV infection but becomes less reliable as lesions progress to ulceration and crusting,¹ and in reactivations.¹³ Most laboratories subtype isolates by using monoclonal antibodies directed to type-specific antigens in enzyme immunoassay (EIA) and fluorescence immunoassay formats.¹⁸ Recent advances include the development of HSV antigen DNA detection tests, including HSV polymerase chain reaction (PCR) and DNA hybridization techniques.^{18,43} These are more sensitive in reactivations but are expensive and are not commercially available for routine diagnostic use.¹³

Serological Assays

Dual infections with HSV-1 and 2 are common, with a seroprevalence in a study of family planning clinic attenders of 12.3%, compared to 9.3% for HSV-2 alone.²⁵ Commercially available EIA, complement-fixation and neutralizing antibody assays are not reliably type-specific and may fail to detect HSV-2 serological markers due to anamnestic HSV-1 antibody production in those with prior HSV-1 infection.^{58,70,71} Type-specific serological assays, developed in the mid 1980s, allow reliable discrimination of exposure to these closely related viral subtypes. These assays can provide estimates of the population prevalence of HSV-2 genital infection, given the assumptions that all HSV-2 seropositives are infected and HSV-2 primarily causes genital infection,^{13,15} although oral HSV-2 infections occasionally occur.²⁴ But they cannot reveal the prevalence of inapparent HSV-1 genital infection, in that HSV-1 seropositivity may indicate either orolabial or genital infection.

Highly sensitive and specific type-specific serological assays include immunodot enzyme assays (IEA), based on a type-specific protein, glycoprotein G,^{17,18} and western immunoblot (WBA) assays which detect antibodies

to a range of viral proteins.⁷² Validation studies, using blinded sera, have shown a high concordance in the results obtained by these two tests.⁷² A monoclonal antibody blocking radioimmunoassay has recently been reported to be as reliable as the WBA at detecting HSV-1 antibodies in first-episode and HSV-1 and 2 antibodies in recurrent genital infections.⁷³ Type-specific serological tests can be used in the investigation and management of patients and their partners, and in screening pregnant women to identify those at risk of transmitting HSV-2 during childbirth.¹⁵ But they are time consuming and expensive and not yet widely available.

TREATMENT

No treatment to eliminate HSV infection is currently available. Patient management includes the provision of information, counselling, expert psychosexual support, and antiviral therapy.⁷⁴ Acyclovir was introduced in the early 1980s and has been shown to produce a clinical benefit in primary genital herpes, when administered either intravenously^{3,4} or orally.^{5-7,75} Other therapeutic antiviral agents include famciclovir, valaciclovir, penciclovir, topical trifluridine and intravenous foscarnet.⁷⁶ Acyclovir reduces the clinical severity of the disease episode, shortens its duration, prevents complications and reduces symptomatic viral shedding, but does not eliminate the infection.^{1,12,62,76,77}

Early patient-initiation of oral acyclovir, which requires individual patient counselling to facilitate the prompt recognition of prodromal symptoms,¹ has been shown to be beneficial in recurrent disease.⁷⁸⁻⁸⁰ A recent randomized trial of oral acyclovir in 1100 immunocompetent individuals showed a greatly reduced frequency of recurrences, with 70% on long-term suppressive acyclovir symptom-free in the first year, compared with less than 10% of a control group receiving episodic treatment.⁸¹ After 5 years of suppressive therapy, 80% were recurrence-free. The decision to institute suppressive treatment is governed by the frequency and severity of recurrences, but also takes psychosocial factors into account.⁷⁶ Valaciclovir may be more effective than acyclovir at aborting lesions, if taken early in the prodromal period of a recurrence.⁷⁶

Resistance to acyclovir is not yet a significant problem in clinical practice,^{81,82} and continues to be the mainstay of treatment.⁴³ However, case reports of acyclovir and foscarnet-resistant HSV strains are emerging, especially in the immunocompromised, although transmission of resistant strains does not appear to occur.^{76,83-85} Intravenous acyclovir and vidarabine have performed equally well in reducing neonatal mortality due to encephalitis to 18%, and from disseminated infection to

55%.³⁰ The safety of acyclovir in pregnancy has not yet been established.^{86,87} The results of clinical trials of the efficacy of topical acyclovir cream or ointment have been equivocal.^{1,76}

It has been suggested that antiviral drugs could reduce health care costs, through shortening genital herpes disease episodes, reducing recurrences and possibly reducing the transmission of HSV.⁸⁸ There are also potential indirect savings through reduced absence from work, as well as improvements in the quality of life. But antiviral agents are expensive and acyclovir was introduced in an era when cost-effectiveness and cost-benefit analyses were not included in clinical trials and there is a paucity of such data.^{84,88} More frequent prophylactic use of acyclovir to prevent disease recurrence, and possibly to prevent transmission of infection, will increase the treatment costs although these may be partly offset by increased competition following the expiry of drug patents.⁸⁹ A review of the costs of the antiviral treatment of neonatal infection, which measured both the direct and indirect costs of long-term care of the child with HSV disease, postulated a small potential cost saving in the US, by reducing estimated national costs from \$250 million to \$215 million.³⁰

EPIDEMIOLOGY

Estimates of Genital and Neonatal Herpes Disease Incidence

A doubling in the annual rate of first-episode attendances reported from some US studies, during the 1960s and 1970s,^{2,90,91} does not necessarily reflect national trends. In the UK, where data describing attendances at genitourinary medicine (GUM) clinics are aggregated at the national level, there was a threefold rise in attendance rates for genital herpes (first-episode disease and recurrences) in women between 1981 and 1994, rising from 32 to 98/100 000,²² and a 24% rise in first-episode attendances between 1989 and 1994.⁹² However, while population prevalences for HSV-2 genital herpes infection can be accurately estimated through representative surveys,⁵² the incidence of adult genital herpes disease remains uncertain, as stated earlier, because an unknown proportion of cases does not present to the health services. Differences in disease incidence rates and trends between countries may be partly due to differences in health care awareness and expectations, in patterns of health service utilization, in diagnostic efforts and capacity, as well as to true differences or trends in population incidence rates.

A recent report provides the first firm evidence of a true rise in population HSV-2 seroprevalences in the US, rising from 16.4% (1976–1980) to 21.7%

(1989–1991).⁹³ However, possible changes in the proportions of HSV-2 infections which manifest as clinical disease, which may be partly due to a fall in age-specific HSV-1 prevalence rates and resultant reduced humoral immunity leading to a rise in the proportion of HSV-2 infections which cause disease, may confound attempts to derive estimates of disease incidence and trends from antibody prevalence studies. Changes in health service referral and utilization patterns may partly account for the UK trend. However, there was also an upward trend in GUM clinic attendances for other viral STD, along with a downward trend for bacterial STD, which suggest that UK GUM clinic data do reflect a true increase in genital herpes disease incidence.⁹²

Neonatal HSV disease incidence rates are relatively low but vary considerably between countries. A 1987–1988 survey reported a UK annual estimate of 3 per 100 000 births.⁹⁴ There was a fourfold rise from 3.6 (1962–1965) to 15.4 per 100 000 (1982–1985) reported in one US state,² with current US estimates of between 20 and 40 cases per 100 000 births.³⁰ This apparent rise may be due to an increase in case ascertainment, a rise in the incidence of adult genital herpes infection, and/or a rise in the intrapartum transmission of asymptomatic maternal HSV infection. Maternal HSV-1 antibodies may transplacentally confer humoral immunity on the fetus³⁰ and a failure to acquire HSV-1 early in life, associated with rising socioeconomic levels, and delayed pregnancies, may partly account for the rising incidence of neonatal herpes disease.²⁵ Delayed acquisition of HSV-1 may also contribute to the higher rates of physician visits for genital herpes among US whites, compared to blacks, as whites have lower age-specific HSV-1 prevalence rates.^{52,95,96}

HSV-1 and 2 Type-Specific Trends

In US studies, most genital infections are caused by HSV-2, but 20–40% of first episodes are due to HSV-1.^{14,18} In the UK, studies of GUM clinic attenders have reported an increasing proportion of HSV-1 genital infections during the 1980s and early 1990s, where they now account for most first-episode disease among women (Table 1). This distribution and trend has not been reported in other European countries where HSV-2 genital infections still predominate.^{97–99} Almost all HSV infections before the age of 10 are due to HSV-1, and by the age of 60 years 60–85% of US populations are HSV-1 seropositive.¹⁰⁰ Prior HSV-1 infection reduces the risk of acquiring HSV-2 infection, is associated with a higher proportion of subclinical HSV-2 infections, and shortens its clinical course.^{25,48,49,53,59}

The reason for the increasing proportion of HSV-1 genital disease in the UK is not yet known. Possible

TABLE 1 Proportions of, and trends in, *Herpes simplex virus-1* subtypes in genital specimens in UK. Genitourinary medicine clinic studies (1985–1995)

Author	Place	Year of study	Gender	HSV-1		Sample size	P-value for trend in women
				No.	%		
Scoular ¹¹⁹ (1990)	Glasgow	1985–1986	Male		21	2485	
			Female		41		
		1986–1987	Male		21		
			Female		47		
		1987–1988	Male		17		
Female			54				
Ross ¹²⁰ (1992)	Edinburgh	1978	Male		9	1794	<0.05
			Female		6		
		1991	Male		22		
			Female		43		
Tayal ¹²¹ (1994)	Newcastle	1983–1992	Male	526	39		<0.001
			Female	609	65		
Smith ¹²²	Edinburgh	1976	Male	11	9		
			Female	14	22		
Barton ¹²³ (1982)	Sheffield	1980		19	63		
Lavery ¹²⁴ (1986)	Northern Ireland	1982–1984	Male	19	23		
			Female	19	41		
Wooley ¹²⁵ (1990)	Sheffield	1989	Male	15	29		
			Female	38	48		
Wilson ¹²⁶ (1994)	Oxford	1993	Male	9	32		
			Female	26	62		
Edwards ¹²⁷ (1994)	Durham	1992–1994	Male	9	25		
			Female	75	68		
Rodgers ¹⁰⁸ (1995)	Chester	1993–1995	Male	15	35		
			Female	36	63		

explanations include changes in orogenital sexual behaviour and delayed exposure in life to HSV-1, associated with rising socioeconomic levels, so that the primary HSV-1 infection manifests genitally rather than orally. It may also be a particular feature of GUM clinic populations in that low grade or subclinical HSV-2 genital infections may not present in this setting, or because HSV-1 genital infection in women is more likely than HSV-2 infection to be symptomatic. Current UK trends suggest that HSV-1 is becoming the predominant cause of first-episode genital infection; however, similar studies from other countries are awaited to determine whether or not this is a more widespread trend.

Estimates of HSV-2 Seroprevalence Rates

The HSV-2 seroprevalences reported from the US, using accurate type-specific tests, have varied according to the age and population studied, ranging from low rates in young university students,^{26,53} intermediate in family planning clinic attenders²⁵ and pregnant women,⁶⁷ reaching high levels among STD clinic attenders⁵³. (Table 2)

Similar HSV-2 seroprevalences have been found in the UK, with low rates in blood donors, intermediate rates in pregnant women and high rates in GUM clinic attenders.^{101,102} The inherent biases of seroprevalence studies in geographically localized and specific health care or institutional settings make the generalization of findings to the wider population difficult, as evidenced by the differences in seroprevalences in university settings.^{26,53}

In a stratified, household survey of 3416 non-institutionalized US adults aged 15–74 years (65% white and 30% black), conducted between 1976 and 1980, the HSV-2 antibody prevalence rate was 16.4%, with 13.3% among whites and 41.0% among blacks.⁵² The 32% rise in US population seroprevalence between 1976–1980 and 1989–1991 was mainly due to a rise among whites, where the highest rates were in 30–39 year olds.⁹³ Whereas, the highest rates in blacks continued to be found in 60–74 year olds. The HSV-2 seroprevalences increase with age in all studies, with the most rapid rise in the third decade of life,^{13,103} An upward secular trend was reported for Stockholm

TABLE 2 *Herpes simplex virus-2 antibody prevalence rates in major US, UK and Swedish studies*

Author	Country	Year of study	Setting	Test used	Population group	Prevalence estimate (%)	Confidence intervals	Sample size	
Johnson ⁵² (1989)	US	1976–1980	Household survey	Immunodot	Male	13.2	10.5–15.9	3416	
					Female	19.4			16.6–22.2
					15–29 yrs	6.9			
					30–44 yrs	20.2			
					60–74 yrs	23.4			
					TOTAL	16.4			
Gibson ²⁶ (1990)	US	1983–1984	University students	Immunodot	Male	1.8	1063		
					Female	2.3			
					TOTAL				
Breinig ²⁵ (1990)	US		Family Planning clinic (female)	Immunodot	17–20 yrs	10.0	1435		
					21–24 yrs	21.7	1567		
					25–28 yrs	29.9	875		
					29–32 yrs	34.4	404		
					>32 yrs	38.2	246		
					TOTAL	21.6	4527		
Frenkel ⁶⁷ (1993)	US	1985–1988	Obstetrics practice	Western blot	Pregnant women	32.4	29.9–34.9	1355	
Koutsky ⁵³ (1990)	US	1984–1986	STD clinic University	Western blot	Female	43.4	776		
					Female	8.8	636		
Ades ¹⁰² (1989)	UK	1980–1981	Antenatal clinics	ELISA (native gG2)	<20 yrs	4.4	545		
					20–24 yrs	9.5	1240		
					25–29 yrs	11.3	1027		
					30–34 yrs	13.8	515		
					>34 yrs	18.8	202		
					TOTAL	10.4	3533		
Cowan ¹⁰¹ (1994)	UK	1992	Blood donors	Western blot	Male	3.2	708		
		1990–1991	GUM clinic		Female	12.4	639		
					Male	21.2	486		
					Female	24.5	347		
Forsgren ¹⁰⁴ (1994)	Sweden	1969	Antenatal clinics	ELISA (native gG2)	1969	19	941		
		1983			1983	33	1759		
		1989			1989	33	1000		
Persson ¹⁰⁵ (1995)	Sweden	1970 + 1973	Antenatal clinics	ELISA (native gG2)	1970 + 1973	21	1198		
		1979			1979	20	294		
		1987 + 1989			1989 + 1989	23	562		
		1990–1993			1990–1993	16	1190		

between 1969 and 1983,¹⁰⁴ but a reversal of this trend occurred between 1989 and 1993 in Malmö¹⁰⁵ (Table 2). The downward trend was highly significant in women under 25 years, suggesting a declining incidence of primary infections, and perhaps the adoption of safer sex practices, by younger Swedish women.

Risk Factors for HSV-1 and 2 Seropositivity

Studies in the US and the UK, using reliable type-specific assays, have identified a range of factors which are independently associated with HSV-2 seropositivity, including: increasing age, which probably reflects

a longer period of sexual activity;^{25,52,95,101,106} ethnic status, with blacks having higher prevalences;^{25,52,95} higher numbers of sexual partners;^{25,27,52,95,101,106} early age at first intercourse;^{27,106} lower levels of education or income;^{25,95} HIV infection;^{42,95} female gender^{52,101} and a history of an STD.¹⁰¹ HSV-1 seropositivity is also associated with older age, lower level of education or income, ethnic status and a higher level of sexual activity.^{25,95} Risk factors for HSV-2 seropositivity are potential markers of population subgroups who are more likely to have acquired, or are at higher risk of acquiring, HSV-2 genital infection.

PREVENTION AND CONTROL

Primary Prevention of Genital Herpes Infection

Prevention currently relies on promoting safer sex, both among those with and without diagnosed genital infection. Using sexual or other risk factors to screen and identify individuals at higher risk of infection, so as to target interventions at them, however, may not be feasible or acceptable. In addition, as most genital infections are unrecognized or asymptomatic and infection is not restricted to high risk groups, targeted behavioural interventions may not have a major impact on the spread of infection in many populations.^{13,107,108} The possibility that behavioural changes at the population level have resulted in reduced transmission, as suggested by recent Swedish data¹⁰⁵ remains speculative in the absence of supportive data or studies confirming the effectiveness of such strategies.

It has been suggested that all HSV-2 seropositives should be considered epidemiologically contagious,¹³ but the significance for an asymptomatic person of a positive test result is uncertain, in the absence of cohort studies to estimate the proportion of seropositives who will develop clinical disease or transmit infection. Serological screening in high risk populations has been recommended as a way of targeting education strategies.¹¹ However, informing people with unrecognized or asymptomatic infection that they are seropositive, in the absence of a cheap and effective treatment for eliminating the virus, may not be ethically desirable because of the potential for causing psychosocial morbidity. Educating those with clinical disease to recognize the symptoms of recurrences and avoid unprotected sex, and perhaps the prophylactic use of antiviral agents, might reduce the risk of HSV transmission. However, the high prevalence of asymptomatic or unrecognized infection, the high proportion of infections transmitted through asymptomatic shedding, and the low sensitivity of clinical screening for the detection of genital infection, mean that case-finding will not be the basis of an effective population control programme.

Caesarean delivery has been recommended for primary infections in the pregnant woman,^{64,109} and in the presence of active genital lesions at the time of labour.^{94,110} But most neonatal herpes infections occur because of undiagnosed infections in the mother.^{30,63} Type-specific assays which identify infected women early in the course of primary infection, and the use of the more sensitive PCR tests to detect HSV in the birth canal,¹¹¹ could facilitate the management of childbirth in seronegative women with infected partners. But type-specific tests are expensive, and not widely available, and the cost-benefit of any general screening strategy will depend on the prevalence of neonatal

herpes in the target population. Seronegative women of child-bearing age, with seropositive partners, have been recommended as a suitable target group for a HSV preventive vaccine.⁶⁶

Vaccination

The preventive aims of vaccination programmes include: eradication (permanently removing the disease-causing pathogen), elimination (disappearance of the disease with persistence of the pathogen) and containment (control of the disease to reduce its public health impact).¹⁰⁷ Vaccines have been used to prevent infections, reduce transmission to susceptible hosts, and suppress or prevent disease expression.¹⁰⁷ Genital herpes is a suitable disease for vaccine-induced prevention because superinfection with multiple strains of the same subtype is uncommon, suggesting that subtype immunity is protective.¹³ An HSV preventive vaccine should not only prevent acute primary genital herpes disease but should also reduce or eliminate the risk of infection.^{107,112} Because genital HSV infections are not restricted to identifiable high risk groups, and because orolabial HSV-1 infection may be contributing to maintaining the genital herpes pandemic, eradication of the virus would require universal childhood vaccination with a vaccine which provided long-term or life-long immunity against HSV-1 and 2.

Vaccines have been developed, using viral surface glycoprotein gB and gD antigens, produced by recombinant DNA technology, which have completely prevented the acquisition of infection and reduced the frequency and severity of disease recurrence in guinea pigs.^{113,114} Earlier generation glycoprotein subunit vaccines showed poor immunogenicity⁵ but a recent recombinant glycoprotein vaccine for HSV-2 was shown in initial clinical trials to be safe and to induce both a specific cellular and humoral response which was equal to or greater than that induced through natural HSV-2 infection.¹¹⁵ It has been estimated that the cost-benefit of a universal national childhood HSV vaccination programme would be positive within 8 years, in terms of reduced health care costs, if the price of the hypothetical vaccine equalled the current price of the mumps vaccine.¹¹²

There is increasing interest in the immunotherapeutic potential of an HSV vaccine for suppressing HSV disease and reducing disease recurrences.^{76,113,115,116} A three to fivefold increase in gD2 and gB2 antibodies, and an increase in HSV-2 neutralizing antibodies, through a single immunization of people with naturally acquired HSV-2 infection, has been reported.¹¹⁵ A recent small double-blind randomized controlled trial demonstrated that a gD2 vaccine significantly reduced the number of

disease recurrences in the intervention group.¹¹⁷ If its safety and efficacy were shown to be equal to or superior to acyclovir, and of long duration, such a treatment could be more cost-effective as well as more acceptable than a daily acyclovir regimen.¹¹⁸ The availability of a safe and effective vaccine which reduces or prevents HSV transmission by those infected, in addition to preventing infection in those at risk, would facilitate the implementation of a limited containment strategy. Vaccination of people with genital herpes disease, and their seronegative partners, could then be implemented, pending further long-term evaluation of its efficacy and potential cost-effectiveness as a population control measure. An additional potential benefit of an immunotherapeutic HSV vaccine could lie in its contributing to a reduction in the transmission of HIV in the population. However, a vaccine which provides immunity or disease suppression of limited duration and only moderate efficacy, and which results in individuals choosing not to use other risk reduction measures, could result in them being at higher risk of contracting or transmitting infection.

RESEARCH AND DEVELOPMENT (R&D) PRIORITIES

A population HSV vaccination programme may still be a distant possibility. Nevertheless, with the preventive and immunotherapeutic potential of such vaccines, certain R&D priorities can be identified for underpinning the development of future disease control programmes. There is a need for cost-effectiveness and cost-benefit analyses of current genital herpes disease treatment strategies. Cohort studies of HSV-2 antibody positives, including population samples if possible, would improve our understanding of the natural history of genital HSV infection. Testing for type-specific antibody in stored serum samples from patients who present to STD clinics with first-episode genital herpes disease may provide some insight into disease incidence, and the factors which predispose to disease in seropositive individuals. Where the safety and efficacy of vaccines have been demonstrated, randomized controlled trials (RCT) are needed to test their effectiveness at preventing the acquisition of HSV-2 and HSV-1 infections, at preventing their transmission, and at treating/controlling genital herpes disease. Randomized controlled trials should include cost-effectiveness and cost-benefit analyses, comparing vaccines with existing interventions. Age-stratified HSV-1 and 2 seroprevalence studies in population representative groups would identify potential target (including age) groups for future interventions.

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