Antibody to herpes simplex virus type 2 as serological marker of sexual lifestyle in populations

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Abstract

***Objectives*—To examine the epidemiology of antibody to herpes simplex virus type 2 and to assess its suitability as a serological marker of sexual behaviour in populations with high and low prevalences.**

***Design*—Cross sectional survey.**

***Setting*—Department of genitourinary medicine and blood donation centre in central London.**

***Subjects*—Representative sample of 869 patients attending department between November 1990 and December 1991, and 1494 consecutive blood donors attending for donation between February and April 1992.**

***Method*—Participants had a blood sample taken for antibody testing with a novel type specific assay and completed a questionnaire.**

***Results*—Prevalence of antibody differed significantly between the two groups (188/833 (22·7%) clinic attenders; 102/1347 (7·6%) blood donors). In both populations antibody was strongly associated with sex, sexual orientation, years of sexual activity, number of lifetime sexual partners, and past infection with sexually transmitted diseases after other factors were controlled for. Only 130 (45%) of all those with antibody had symptoms suggestive of genital herpes, and 79 (27·4%) had had genital herpes diagnosed. Of those without antibody to herpes simplex viruses type 1 and 2, 8·0% reported genital blisters or sores and 1·1% had had genital herpes diagnosed by a doctor.**

***Conclusions*—The strong relation between herpes simplex virus type 2 and sexual lifestyle suggests that the presence of antibody to the virus may be suitable for use as an objective, serological marker of patterns of sexual behaviour in different populations. These data show that only a minority of those infected with herpes simplex virus type 2 have a diagnosis of genital herpes or express clinical symptoms, making serological determinants of infection essential for epidemiological studies.**

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Introduction

There has been increasing interest in measuring sexual behaviour to aid understanding of the transmission dynamics of sexually transmitted diseases, including HIV infection. In particular there is a need for a simple measure to assess differences in behaviour between societies and changes over time. The most commonly used method for assessing sexual lifestyle has been by questionnaire, but this approach is expensive, time consuming, and subject to measurement error.[1] If a serological marker were available which could be used as a proxy marker of past sexual behaviour it could be used to monitor changes in behaviour in populations, measure differences in levels of high risk sexual activity between populations, and control for the confounding effect of sexual lifestyle in epidemiological studies. Nahmius *et al* have suggested that antibody to herpes simplex virus type 2 might prove to be such a marker.[2]

Epidemiological studies of people with clinically apparent genital herpes indicate that herpes simplex virus type 2 is almost always sexually transmitted.[2] Studies of transmission of genital herpes confirm that asymptomatic, unrecognised infection with herpes simplex virus type 2 is common.[3,4] Although infection results in lifelong persistence of antibody, determining the extent and epidemiology of asymptomatic infection has been hampered by the absence of a serological test which could accurately detect the antibodies. Such assays have now been developed.

We report the results of a cross sectional seroepidemiological study of herpes simplex virus among attenders of genitourinary medicine clinics and blood donors performed by using a new type specific test for antibody to herpes simplex virus.[5] We examined the relation between infection, symptomatology, demographic variables, and lifetime sexual behaviour to assess the suitability of antibody to herpes simplex virus type 2 as a serological marker of sexual lifestyle.

Methods

STUDY POPULATION

Eligible patients were all those presenting to systematically selected routine sessions at a genitourinary medicine clinic in a central London hospital with a new clinical problem and who were having a blood sample taken for other reasons. All eligible patients were invited to participate. Study clinics were selected so that each of the three daily clinical sessions were equally represented.

Participants gave written consent, completed a structured questionnaire, and had a serum sample taken for testing for antibody to herpes simplex virus. The questionnaire included demographic details and sexual history (sexual orientation, age at first sexual intercourse, number of lifetime sexual partners, and history of sexually transmitted disease). Participants were also asked if they had genital herpes and or symptoms suggestive of genital herpes.

Consecutive blood donors attending a session in central London were also recruited to the study. They gave verbal consent and had a blood sample taken for testing for antibody to herpes simplex virus. To maximise the response rate a shortened version of the genitourinary medicine questionnaire was administered. The questions used in the present analysis were identical in both versions. Donors were assured that none of the information collected on individual donors would be made available to the Blood Transfusion Service.

LABORATORY METHODS

Type specific antibodies to herpes simplex virus types 1 and 2 were detected by means of a modified western blot technique. The laboratory methods have been described in detail elsewhere.[5] Briefly, serum samples from patients were incubated overnight with cell proteins from both types of the virus which had been separated by electrophoresis and transferred on to nitrocellulose strips. Bound antibodies were detected by antihuman antibody and 4-chloronaphthol. Each run included four serum controls (positive for antibody to herpes simplex virus type 1; positive for antibody to herpes simplex virus type 2; positive to antibody to herpes simplex virus type 1 and herpes simplex virus type 2 and negative to herpes simplex virus). Results were expressed as positive or negative for herpes simplex virus type 1 and herpes simplex virus type 2 by using previously published criteria.[5] As antibody titres are not related to degree or frequency of exposure to herpes simplex virus, they were not measured. This assay has been shown to be sensitive and specific for identifying subjects with past herpes simplex virus type 1 and herpes simplex virus type 2 or coinfected with both agents.[5]

STATISTICAL ANALYSIS

The data were analysed by using SPSS[6] and EGRET.[7] Duration of sexual activity and lifetime number of sexual partners were divided into five categories. Early age at first sexual intercourse was defined as first intercourse before 16 years.

Multiple logistic regression with seropositivity for herpes simplex virus as the dependent variable was used to examine the independent effect of demographic variables, sexual behaviour, and past sexually transmitted diseases. Only variables found to be significantly associated with the presence of antibody on univariate analysis were included in the model. As age and years of sexual activity were strongly correlated and any effect attributable to age was likely to reflect years of sexual activity, age was not included in the model. The distribution of number of lifetime sexual partners was highly skewed and therefore $\log_{10}$ (lifetime number of sexual partners) was included in the model rather than the actual number of partners. The results are expressed as the odds of seropositivity for herpes simplex virus after controlling for confounders.

The relation between antibody to herpes simplex virus, symptoms, and a diagnosis of herpes was examined (χ^2 for difference in proportions).

Results

Eight hundred and sixty nine of 887 (98%) attenders at genitourinary medicine clinics and 1494 of 1524 (98%) blood donors who were eligible to participate agreed to do so.

CLINIC ATTENDERS

Among clinic attenders, sufficient serum was available for antibody testing in 347 women, 294 heterosexual men, and 192 homosexual men. The median (range) age of women was 25 (17-68) years, of heterosexual men was 29 (17-69) years and of homosexual men was 29 (19-69) years. Of the 833 participants, 535 (64·2%) were single and 789 (84·6%) were white. The prevalence of antibody to herpes simplex virus type 2 was 188/833 (22·7%; 95% confidence interval 19·9 to 25·5%). Table I shows the prevalence of herpes simplex virus type 2 by sex and sexual orientation.

BLOOD DONORS

Serum samples were available for antibody testing in 639 women and 708 men. Men who have sex with other men are asked not to donate blood. The median (range) age of women was 30 (18-68) years and of men was 36 (18-68) years. Two hundred and forty eight (35%) men and 326 (51%) women were single, and overall 1266 (94%) were white. The overall prevalence of antibody to herpes simplex virus type 2 was 102/1347 (7·6%; 95% confidence interval 6·2% to 9·0%). Table I shows the prevalence of antibody to herpes simplex virus type 2 by sex.

TABLE I—*Prevalence of antibodies to herpes simplex virus type 2 among attenders of genitourinary medicine clinics and blood donors*

Subjects	No tested	No (%) positive for antibody to herpes simplex virus type 2
Clinic attenders:		
Heterosexual men	294	51 (17·3)
Homosexual men	192	52 (27·1)
Women	347	85 (24·5)
Blood donors:		
Men	708	23 (3·2)
Women	639	79 (12·4)
Total	2180	290 (13·3)

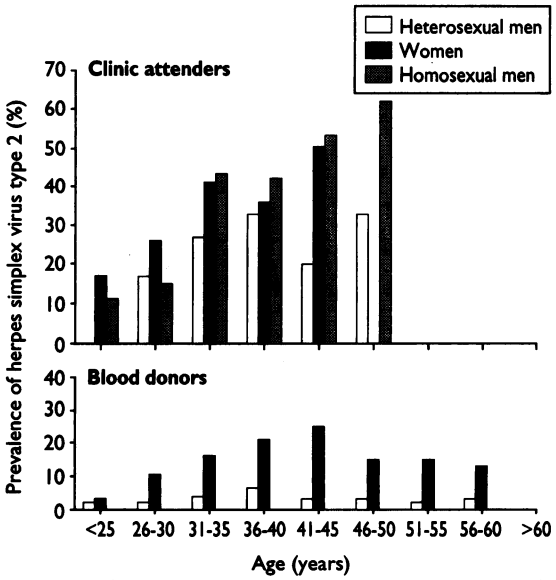
COMPARATIVE RESULTS

The prevalence of antibody to herpes simplex virus type 2 was significantly higher in clinic attenders than blood donors (odds ratio 3·6; 95% confidence interval 2·8 to 4·6) and among women and homosexual men than among heterosexual men.

Table II shows the univariate relation between antibodies to herpes simplex virus, demographic characteristics, and sexual lifestyle for clinic attenders and blood donors. There was a strong association between the presence of antibody to herpes simplex virus type 2 and sexual lifestyle. For all groups the prevalence of positive results increased with increasing duration of sexual activity, increasing number of lifetime sexual partners, and increasing number of past infections with other sexually transmitted diseases. Early age at first sexual intercourse was not associated with presence of antibodies in any of the groups studied.

Among clinic attenders antibodies to herpes simplex virus type 2 were associated with increasing age (figure). While this relation was also observed in younger blood donors, there was a decline in prevalence of antibody to herpes simplex virus type 2 with age among older donors.

Table III shows the association between antibody to herpes simplex virus type 2 and demographic and



Prevalence of antibody to herpes simplex virus type 2 by age in attenders at genitourinary medicine clinic and blood donors

TABLE II—*Association between prevalence of antibody to herpes simplex virus type 2, demographic characteristics, and sexual behaviour in attenders of genitourinary medicine clinics and blood donors*

Variable	Proportion (%) of clinic attenders positive for antibody to herpes simplex virus type 2 (No of subjects*)						Proportion (%) of blood donors positive for antibody to herpes simplex virus type 2 (No of subjects*)			
	Heterosexual men		Women		Homosexual men		Men		Women	
Marital status†:										
Married	20·5 (34)		25·0 (24)		100 (1)		2·9 (384)		18·1 (155)	
Single	14·8 (223)	P=0·13	24·4 (287)	P>0·9	27·7 (177)	P=0·63	2·8 (245)	P=0·02	11·8 (364)	P=0·03
Widowed/separated/divorced	23·3 (30)	P>0·9	33·3 (27)	P=0·73	20·0 (5)	P=0·15	10·6 (47)	P=0·93	14·3 (110)	P=0·51
Age at first sexual intercourse (years):										
<16	16·0 (75)		25·5 (51)		27·0 (37)		5·1 (78)		15·7 (51)	
≥16	16·3 (214)	P>0·9	25·1 (287)	P>0·9	28·6 (147)	P>0·9	3·1 (603)	P=0·49	13·6 (579)	P=0·72
Race†:										
White	15·0 (246)		25·9 (277)		28·9 (159)		3·1 (642)		14·0 (590)	
Asian	9·1 (11)	P=0·59	9·1 (11)	P=0·21	0 (7)	P=0·01	0 (10)	P=0·57	12·5 (16)	P=0·86
Black	29·6 (27)	P=0·05	24·4 (41)	P=0·84	41·7 (12)	P=0·35	12·5 (24)	P=0·01	8·7 (23)	P=0·47
Years of sexual activity:										
<5	0 (26)		10·8 (65)		5·8 (17)		0 (36)		3·2 (62)	
5-9	2·8 (77)		21·6 (134)		13·6 (44)		0·9 (117)		6·7 (164)	
10-14	16·5 (79)		29·9 (77)		17·5 (57)		1·9 (106)		13·2 (152)	
15-19	30·2 (53)		41·1 (34)		47·2 (35)		7·1 (127)		18·7 (75)	
≥20	29·6 (54)	P<0·001	42·9 (28)	P<0·001	56·3 (32)	P<0·001	3·7 (294)	P=0·02	22·6 (177)	P<0·001
No of lifetime partners‡:										
<5							1·1 (338)		6·7 (314)	
5-9							0·7 (152)		15·3 (196)	
10-14							8·2 (73)		20·0 (60)	
15-19							5·0 (20)		50·0 (14)	
≥20							11·8 (76)	P<0·001	37·5 (40)	P<0·001
<10	4·0 (75)		19·6 (179)		4·5 (20)					
10-19	17·3 (49)		24·2 (99)		0 (21)					
20-29	12·2 (49)		46·4 (28)		29·1 (23)					
30-39	28·1 (32)		45·5 (11)		8·3 (10)					
≥40	28·0 (50)	P<0·001	42·9 (14)	P<0·001	40·9 (88)	P<0·001				
No of past sexually transmitted diseases:										
None	8·5 (118)		20·4 (161)		13·8 (36)		2·5 (590)		10·6 (529)	
1	14·8 (108)		24·8 (109)		12·5 (40)		8·5 (71)		31·1 (77)	
≥2	33·9 (62)	P<0·001	36·8 (68)	P=0·01	39·3 (107)	P<0·001	12·5 (16)	P<0·001	30·4 (23)	P<0·001

*Numbers do not always add up to total as some subjects did not answer all questions.
†P values for marital status derived from χ^2 test comparing single and widowed/divorced/separated groups separately with married and for race by comparing Asian and black separately with white separately; P values for all other variables derived from χ^2 test for trend.
‡Categories for clinic attenders and blood donors differ because overall clinic attenders had far more sexual partners.

TABLE III—*Multivariate analysis of association of demographic and sexual lifestyle variables with antibodies to herpes simplex virus type 2. Values are adjusted odds ratios (95% confidence intervals)*

Variable*	Attenders of genitourinary medicine clinics	Blood donors
Female sex	3·2 (2·0 to 5·2)	8·9 (4·9 to 14·8)
Black race	1·9 (1·1 to 3·4)	1·3 (0·5 to 3·8)
Single versus married	1·0 (0·5 to 2·1)	1·3 (0·7 to 2·5)
Homosexual versus heterosexual	1·3 (0·7 to 2·3)	
Years of sexual activity†:		
≤9	1·0	1·0
10-14	1·7 (1·0 to 2·9)	1·9 (0·9 to 4·0)
15-19	3·3 (1·9 to 5·9)	4·0 (1·8 to 8·7)
≥20	4·1 (2·1 to 7·9)	4·4 (2·2 to 8·9)
No of lifetime sexual partners:		
<5	1·0	
5-9	2·3 (1·3 to 4·1)	
10-14	3·8 (1·9 to 7·7)	
15-19	10·0 (3·6 to 27·8)	
≥20	8·3 (4·0 to 17·2)	
No of lifetime sexual partners:		
<10	1·0	
10-19	1·2 (0·7 to 2·1)	
20-29	1·9 (1·0 to 3·8)	
30-39	1·8 (0·8 to 4·1)	
≥40	2·7 (1·3 to 5·4)	
No of past sexually transmitted diseases:		
None	1·0	1·0
1	1·0 (0·6 to 1·6)	1·8 (1·1 to 3·1)
≥2	2·1 (1·2 to 3·4)	1·0 (0·5 to 2·9)

*Variables included in model are sex, $\log_{10}$ (lifetime sexual partners), marital status, sexual orientation, race, and years of sexual activity and number of past sexually transmitted diseases.
†Reference category for years of sexual activity was changed to include first two categories (that is, <9 years) as there were too few subjects positive for antibody to herpes simplex virus type 2 in category <5 years to make stable reference group.

sexual behaviour variables after we controlled for confounding by using multivariate analysis. There was a strong independent association between presence of antibody and increasing years of sexual activity, increasing number of lifetime sexual partners, and a history of sexually transmitted diseases in both blood donors and clinic attenders. Female sex was also independently associated with antibodies to herpes simplex virus type 2.

Fifty nine of 184 (32·1%) clinic attenders with antibody to herpes simplex virus type 2 detected had a history of genital herpes compared with only 19 of 100 blood donors (P<0·001). Likewise, clinic attenders with antibody to herpes simplex virus type 2 were more likely to have symptoms suggestive of genital herpes than blood donors (98 (52.0%) clinic attenders, 31 (30·0%) blood donors). In contrast, among subjects negative for antibodies to herpes simplex virus 50 (20·2%) clinic attenders and 26 (3·4%) blood donors reported genital sores or blisters, and eight (3·3%) and two (0·3%), respectively, had a clinical diagnosis of genital herpes.

Discussion

This is the first epidemiological study in Britain to use a reliable type specific antibody test for herpes simplex virus type 2. It is one of the first to include men and the only survey to include a low risk population of blood donors. The two important implications of the study are, firstly, that the presence of antibody to herpes simplex virus type 2 has a strong graded association with sexual behaviour, particularly among blood donors, and as such may be a useful serological marker of sexual experience in the general population. Secondly, most of those infected with herpes simplex virus have no symptoms or are unaware of their infection; data that relate antibody status to a history or symptoms of herpes suggest that clinical, non-serological methods of determining past infection are insensitive and poorly specific when compared with reliable serological techniques.

The weight of evidence from clinical and sero-epidemiological studies suggests that herpes simplex virus type 2 is almost always transmitted as a result of sexual contact.[2 8] This, coupled with its strong association with lifetime sexual experience in populations both at high and low risk of acquiring sexually transmitted diseases, makes it suitable for use as a

serological marker of sexual behaviour in populations. In our study the prevalence of herpes simplex virus type 2 was higher among attenders of genitourinary medicine clinics than blood donors, reflecting the clear difference in sexual lifestyle between the two groups. (Clinic attenders were younger at first sexual intercourse, had had more lifetime sexual partners (median number of lifetime partners: clinic attenders 13; blood donors four), and were more likely to have had a sexually transmitted disease in the past than blood donors.)

The prevalence of antibody to herpes simplex virus type 2 among our clinic attenders was lower than that found among attenders of clinics for sexually transmitted disease in Seattle[9]; however, users of clinics in the two countries are not comparable. A population based survey in the United States found the prevalence of antibody to herpes simplex virus type 2 to be 16·4% in adults, which is higher than among blood donors in London.[10] Studies in the United States among attenders of family planning clinics and college students have suggested a similar relation between sexual behaviour and prevalence of antibody to herpes simplex virus type 2,[11,12] while a population based study of AIDS in San Francisco has shown that antibody to herpes simplex virus type 2 was associated with risk factors for acquisition of sexually transmitted diseases.[13]

Female sex was independently associated with the presence of antibody to herpes simplex virus type 2, probably explained by the evidence of Mertz *et al*, who examined risk factors for transmission of genital herpes and found higher efficiency of transmission from male to female than from female to male.[14]

Among clinic attenders the prevalence of antibody to herpes simplex virus type 2 increased with age. In blood donors the prevalence also increased with age but only until the fifth and sixth decade, when it declined. This is consistent with changing patterns of sexual lifestyle in successive birth cohorts characterised by increasing numbers of partners and earlier age at first sexual intercourse.[15]

Both symptoms and a history of genital herpes were insensitive measures of prior exposure to herpes simplex virus type 2. (Several centres have reported a high prevalence of genital herpes due to herpes simplex virus type 1, but 16·5% of study participants with a history of genital herpes had antibodies to herpes simplex virus type 1 alone (data not shown).[16,17]) Whereas the proportion of clinic attenders positive for antibody to herpes simplex virus type 2 who gave a history of genital herpes was similar to that found in women attending clinics for sexually transmitted disease and university students in Seattle[9] the proportion of blood donors positive for antibody to herpes simplex virus type 2 with a history of genital herpes was significantly lower. This is probably explained by selection bias in those attending genitourinary medicine clinics, who are likely to present for management of symptomatic disease.

This study suggests that non-serological methods of determining past infection with herpes simplex virus type 2 have unacceptably high rates of false negative and false positive results for use in clinical and epidemiological studies when compared with reliable type specific serological assays. As commercially available enzyme immunoassays have been shown to give misleading results about herpes simplex virus subtypes and reliable type specific testing for antibody to herpes simplex virus is currently limited to a few research laboratories worldwide,[18] its use is confined to that of a research tool (for example, in vaccine trials for herpes simplex virus), but it may have wider applications in the future. At present type specific antibody testing for herpes simplex virus is not routinely available to assist in management of patients with herpes infection or their sexual partners.

Epidemiological implications

- Changes in population sexual behaviour are important in the epidemiology of sexually transmitted diseases
- So far data have been available only from the results of questionnaires
- Antibody to herpes simplex virus type 2 can be detected by a new type specific test
- Presence of antibody to herpes simplex virus type 2 correlates highly with sexual lifestyle comprising risk behaviour for sexually transmitted diseases
- This test will in the future be a useful tool in the epidemiology of sexually transmitted diseases

The presence of antibody to herpes simplex virus type 2 is objective evidence that a person has been directly or indirectly exposed to high risk sexual behaviour. It may be as good as other simple measures of sexual lifestyle in populations such as number of sexual partners. This is not specific for exposure to a sexually transmitted disease and alone does not measure other aspects of behaviour such as use of condoms or characteristics of partners. The greater specificity of antibody to herpes simplex virus type 2 for other aspects of risk behaviour is suggested by the independent association with a history of other sexually transmitted diseases after lifetime number of partners is controlled for. Antibody to herpes simplex virus type 2 may thus serve as an adjunct to behavioural surveys.

While the presence of antibody to herpes simplex virus type 2 does not predict the sexual behaviour of a person, its population prevalence gives information about the pattern of sexual behaviour within that population. As a marker of sexual lifestyle, antibody to herpes simplex virus type 2 has the advantage that the prevalence in the population is not influenced by changes in provision of services or treatment (as in the case of gonorrhoea or syphilis). Though it will be a poor indictor of recent change in behaviour in older age groups who may have acquired infection long ago, secular changes in age specific prevalence of herpes simplex virus type 2 may be attributed to changes in behaviour in young sexually active populations. In addition, comparison of age specific rates between populations may give an indication of the relative levels of high risk sexual behaviour. Young people are the group at greatest risk of acquiring infection through their sexual behaviour.[19] It is in this group that there is greatest need to reduce the negative outcomes of sexual lifestyle, as was highlighted recently in targets set by the government's *Health of the Nation*.[20] Antibody to herpes simplex virus type 2 may serve as a useful new indicator of adoption of practices to reduce risk.

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1 Lee RM, Renzetti CM. The problems of researching sensitive topics. *American Behavioural Scientist* 1990;3:510-28.
2 Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl* 1990;69:19-36.
3 Mertz GJ, Schmidt O, Jourden JL, Guinan ME, Remington ML, Fahnlander A, *et al*. Frequency of acquisition of first episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985;12:33-9.

4 Mertz GJ, Coombs RW, Ashley RL, Joursden J, Remington M, Winter C, *et al.* Transmission of genital herpes in couples with one symptomatic partner and one asymptomatic partner: a prospective study. *J Infect Dis* 1988;157: 1169-77.
5 Ashley R, Militoni J, Lee FK, Nahmias A, Corey L. Comparison of western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera. *J Clin Microbiol* 1988;26:662-7.
6 SPSS. *Statistical package for the social sciences. SPSSX advanced statistic guide.* Chicago: SPSS, 1985.
7 Epidemiological Resources Incorporated. *EGRET: epidemiological graphics, estimation and testing.* Seattle, Washington: Epidemiological Resources, 1988.
8 Corey L, Spear PG. Infections with herpes simplex viruses. *N Engl J Med* 1986;314:686-91.
9 Koutsky LA, Ashley RL, Holmes KK, Stevens CE, Critchlow CW, Kiviat N, *et al.* The frequency of unrecognised type 2 herpes simplex virus infection among women. *Sex Transm Dis* 1990;17:90-4.
10 Johnson RE, Nahmias AJ, Madger LS, Lee FK, Brooks CA, Snowden CB. A seroepidemiological survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med* 1989;321:7-12.
11 Gibson JJ, Hornung CA, Alexander GR, Lee FK, Potts WA, Nahmias AJ. A cross sectional study of herpes simplex virus types 1 and 2 in college students: occurrence and determinants on infection. *J Infect Dis* 1990;162: 306-12.
12 Breinig MK, Kingsley LA, Armstrong JA, Freeman DJ, Ho M. Epidemiology of genital herpes in Pittsburgh: serological, sexual and racial correlates of apparent and inapparent herpes simplex infections. *J Infect Dis* 1990;162: 299-305.
13 Siegle D, Golden E, Washington AE, Morse SA, Fullilove MT, Catania JA, *et al.* Prevalence and correlates of herpes simplex infections: the population-based AIDS in multiethnic neighbourhoods study. *JAMA* 1992;268: 1702-8.
14 Mertz GJ, Benedetti J, Ashley R, Selke SA, Corey L. Risk factors for the sexual transmission of genital herpes. *Ann Intern Med* 1992;116:197-202.
15 Johnson AM, Wadsworth J, Wellings K, Bradshaw S, Field J. Sexual lifestyles and HIV risk. *Nature* 1992;360:410-2.
16 Scoular A, Leask BGS, Carrington D. Changing trends in genital herpes due to Herpes simplex virus type 1 in Glasgow, 1985-88. *Genitourin Med* 1990;66: 226-8.
17 Barton IG, Kinghorn GR, Najem S, Al-Omar LS, Potter CW. Incidence of herpes simplex virus types 1 and 2 isolated in patients with herpes genitalis in Sheffield. *British Journal of Venereal Disease* 1982;58:44-7.
18 Ashley R, Cent A, Maggs V, Nahmias A, Corey L. Inability of enzyme immunoassays to disciminate between infections with Herpes simplex virus types 1 and 2. *Ann Intern Med* 1991;115:520-6.
19 Cowan FM, Mindel A. Sexually transmitted diseases in children: adolescents. *Genitourin Med* 1993;69:141-7.
20 Secretary of State for Health. *The health of the nation: a strategy for health in England.* London: HMSO, 1992. (Cmnd 1986.)

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Effect of homoeopathic medicines on daily burden of symptoms in children with recurrent upper respiratory tract infections

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Abstract

***Objective*—To investigate the intrinsic effects of individually prescribed homoeopathic medicines.**

***Design*—Randomised double blind placebo controlled study.**

***Setting*—Paediatric outpatient department of university hospital.**

***Patients*—175 children with frequently recurring upper respiratory tract infections. Of the 170 children evaluable, 86 were randomised to homoeopathic medicines (47 boys, 39 girls; median age at start 4·2 years; median number of episodes in past year 4) and 84 to placebo (43 boys, 41 girls; median age at start 3·6 years; median number of episodes in past year 4).**

***Main outcome measures*—Mean score for daily symptoms, number of antibiotic courses, and number of adenoidectomies and tonsillectomies over one year of follow up.**

***Results*—The mean daily symptom score was 2·61 in the placebo group and 2·21 in the treatment group (difference 0·41; 95% confidence interval −0·02 to 0·83). In both groups the use of antibiotics was greatly reduced compared with that in the year before entering the trial (from 73 to 33 in the treatment group and from 69 to 43 in the placebo group). The proportion of children in the treatment group having adenoidectomies was lower in the treatment group (16%, 8/50) than in the placebo group (21%, 9/42). The proportion having tonsillectomies was the same in both groups (5%).**

***Conclusion*—Individually prescribed homoeopathic medicines seem to add little to careful counselling of children with recurrent upper respiratory tract infection in reducing the daily burden of symptoms, use of antibiotics, and need for adenoidectomy and tonsillectomy.**

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Introduction

Some children get more upper respiratory tract infections such as acute otitis media, pharyngotonsillitis, and nasosinusitis than their peers.[1,2] Often no specific cause for increased susceptibility to upper respiratory tract infection can be found, and most children outgrow their susceptibility after the age of 6 years.

Homoeopathic doctors claim good results in treating children with recurrent upper respiratory tract infection.[3,4] The aim of homoeopathic treatment is to improve general health and reduce susceptibility. We conducted a randomised double blind placebo controlled clinical trial to study the effects of homoeopathic medicines on the frequency, duration, and severity of upper respiratory tract infections and the well being of children with recurrent upper respiratory tract infections. Individually chosen homoeopathic medicines were compared with appropriate placebos in two parallel groups. We report here the results for daily symptoms, numbers of antibiotic courses, and surgical interventions.

Patients and methods

Children aged between 1½ and 10 years were eligible for participation in the trial if they had had at least three upper respiratory tract infections in the past year or had had two such episodes and had otitis media with effusion at the time of the entry examination. We excluded children who had had adenoidectomy, tonsillectomy, or a "constitutional" homoeopathic treatment in the past six months; regular medical care for any other chronic condition including chronic non-specific lung disease; untreated dental caries; congenital malformation of the respiratory tract or the heart; mental handicap; neurological disorder; height outside the third centile; or a history of rheumatic fever, endocarditis, myocarditis, or nephritis. We also excluded children for whom no suitable homoeopathic constitutional medicine could be chosen at the entry examination because they did not have at least three symptoms relevant for the choice of a matching homoeopathic medicine, and children whose parents were not fluent enough in Dutch to answer the questionnaires.

Patients were recruited by their general practitioners and by articles in the popular press. The parents of 358 children responded, and we excluded 183. Reasons for exclusion were too few episodes of upper respiratory tract infection in the past year, refusal of informed consent, the presence of another chronic disease.