Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study

Sara L Thomas, Jeremy G Wheeler, Andrew J Hall

Summary

Background Whether exogenous exposure to varicella-zoster-virus protects individuals with latent varicella-zoster virus infection against herpes zoster by boosting immunity is not known. To test the hypothesis that contacts with children increase exposure to varicella-zoster virus and protect latently infected adults against zoster, we did a case-control study in south London, UK.

Methods From 22 general practices, we identified patients with recently diagnosed zoster, and control individuals with no history of zoster, matched to patients by age, sex, and practice. Participants were asked about contacts with people with varicella or zoster in the past 10 years, and social and occupational contacts with children as proxies for varicella contacts. Odds ratios were estimated with conditional logistic regression.

Findings Data from 244 patients and 485 controls were analysed. On multivariable analysis, protection associated with contacts with a few children in the household or via childcare seemed to be largely mediated by increased access to children outside the household. Social contacts with many children outside the household and occupational contacts with ill children were associated with graded protection against zoster, with less than a fifth the risk in the most heavily exposed groups compared with the least exposed. The strength of protection diminished after controlling for known varicella contacts; the latter remained significantly protective (odds ratio 0·29 [95% CI 0·10–0·84] for those with five contacts or more).

Interpretation Re-exposure to varicella-zoster virus via contact with children seems to protect latently infected individuals against zoster. Reduction of childhood varicella by vaccination might lead to increased incidence of adult zoster. Vaccination of the elderly (if effective) should be considered in countries with childhood varicella vaccination programmes.

Lancet 2002; **360:** 678–82. Published online July 2, 2002
http://image.thelancet.com/extras/01art6088web.pdf

Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
(S L Thomas MSc, J G Wheeler MSc, A J Hall FRCP)

Correspondence to: Dr Sara L Thomas
(e-mail: Sara.Thomas@lshtm.ac.uk)

Introduction

Primary infection with varicella-zoster virus causes varicella, after which the virus establishes latency in dorsal root ganglia.[1–3] Reactivation of latent infection is thought to result from declining specific cell-mediated immunity, and leads to herpes zoster.[4–6] Zoster occurs frequently in ageing populations and causes substantial acute and chronic morbidity, the commonest long-term complication being persistent pain (post-herpetic neuralgia).[7]

Hope-Simpson postulated that exogenous exposure to people with varicella or zoster might boost specific immunity and therefore decrease the risk of zoster in latently infected individuals.[8] Mothers of children with varicella have cell-mediated immune boosting, and children with leukaemia seem to be protected against zoster by household exposure to varicella.[9,10] However, whether exogenous exposure protects against zoster in immunocompetent adults is unclear. In one study, paediatricians had more contacts with patients infected with varicella-zoster virus than dermatologists or psychiatrists, and were significantly less likely to have developed zoster, but the results could have been influenced by very low response rates to the survey.[11]

The role of immune boosting is an important issue for varicella vaccination programmes, since a reduction in childhood varicella will result in fewer exogenous exposures to varicella-zoster virus, which could lead to increased incidence of zoster among unvaccinated adults.[12] Varicella vaccination has already been introduced in countries such as the USA and Japan, and is being considered by many European countries. We therefore set up a study to test the hypothesis that exogenous exposure to varicella-zoster virus protects against zoster.

Methods

Patients and controls

This investigation was one objective of a community-based case-control study of risk factors for zoster in immunocompetent adults in south London, UK, between September, 1997, and December, 1998. A reporting system was set up among 22 general practices to identify individuals who had recently been diagnosed with zoster by their family physician. For each patient with zoster, two controls with no history of zoster were sought by searching practice registers for individuals who were nearest in age to the patient, and matched for sex and practice. Patients and potential controls were approached and invited to take part in the study. Those who agreed and were eligible were interviewed at home. Ethics approval was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee, and from four local research ethics committees. All participants gave written informed consent.

Cases of zoster were confirmed where possible by use of PCR to detect varicella-zoster virus DNA in vesicular fluid or crust samples obtained at interview.[13] Unconfirmed cases were divided into "probable" and "other" groups with standardised diagnostic criteria applied at interview. Probable cases had a unilateral vesicular or maculopapular rash with a dermatomal distribution where either rash or pain covered at least half the dermatome, or rash and pain were less extensive, but pain lasted at least 1 month after rash onset. Patients with a history of a similar dermatomal rash at any site within the past 10 years were excluded from the probable group. In this study, only data from confirmed and probable cases and their matched controls were analysed.

Patients and controls were excluded if they were younger than 16 years; had a cell-mediated immunosuppressive disorder or therapy in the past 6 months or a history of active cancer in the past 5 years; were of African ethnic origin (a group at higher risk of undiagnosed HIV infection in this population);[14] were temporarily registered with the practice; or were incapable of answering questions. Patients were also excluded if they were identified more than 8 weeks after rash onset. Controls were excluded if they had a history of zoster.

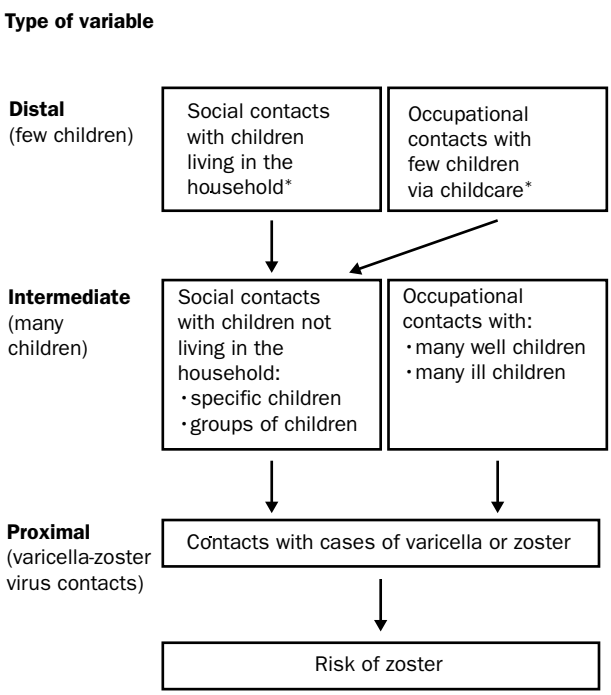
Data collection

Participants were asked about contacts with people with varicella or zoster in the past 10 years. Because varicella is mostly acquired before the age of 10 years in the UK,[15] additional data were sought on contacts with children aged 1–10 years as surrogates for exogenous varicella exposures. We asked questions about social contacts with children in the past 10 years, including (1) specific children living in the household, (2) specific children not living in the household (such as grandchildren and neighbours), or (3) a range of different children in groups with changing membership (such as at school playgrounds or parties). For each child, we sought information on the average frequency (per week or per month) and duration (in years) of contact. We also asked about the duration of occupational exposure to children, either with (4) a few specific children through childcare (eg, through childminding, full-time parenting), (5) with many well children (eg, through teaching), or (6) with many ill children (eg, through being a doctor). These data were used to create three types of exposure: exposure to people with varicella or zoster, exposure to a few children (1 and 4, above), or exposure to many children (2, 3, 5, and 6). Information on potential confounders included ethnic origin, lifetime country of residence, and socioeconomic factors (household tenure and car ownership).

We calculated the total number of social contacts with children in the past 10 years by multiplying the average frequency of contact by duration of contact for each child, and summing the results. Social contacts were then grouped into "none" and into two, three, or five "exposed" groups, each of which contained an equal number of controls (quantiles of exposure). Duration of occupational exposure was divided into "none", "up to 5 years", and "more than 5 years" of exposure.

Statistical analysis

Sample-size calculations for the entire study were derived from standard equations for matched case-control studies, adjusted for our choice of two controls per case.[16] Taking an odds ratio of 2·0, a minimum 10% prevalence of exposure in controls, 90% power at 5% significance (two-sided), and a 20% increase to accommodate multivariable analyses, we needed to assess 244 confirmed and probable cases, and 488 controls.



Conceptual framework for modelling effect of contacts with children or with patients with varicella or zoster on risk of zoster

*Parents who stayed at home to look after children full-time appear in both distal groups.

We set out to test the hypothesis that contacts with children protected latently infected adults against zoster, and that this protection resulted from increased exposure to varicella-zoster virus. Analyses were done with Stata statistical software, version 6.0 (StataCorp, College Station, TX, USA). Odds ratios were estimated by conditional logistic regression, with zoster as the outcome variable. The significance of associations between exposure variables and risk of zoster was calculated with likelihood ratio tests of heterogeneity and of linear trend; 95% CIs were calculated with Wald-based SEs. Univariable analyses identified variables associated with zoster to the significance level of $p \leq 0{\cdot}2$ for initial inclusion in multivariable models.

Variables were classified as distal, intermediate, or proximal, according to their position in the proposed chain of causation as outlined in the figure.[17] In this conceptual framework, varicella or zoster exposures had a direct effect on the risk of zoster, and were categorised as proximal variables. Social or occupational contacts with many children that were likely to result in varicella exposures were categorised as intermediate variables. Contacts with a few children living in the household or via childcare work were categorised as distal variables because some of their effect might be mediated through contacts with a wider range of children outside the household (the intermediate variables). Distal variables were added first to the multivariable model, and retained as long as they remained significantly associated with zoster ($p \leq 0{\cdot}1$). Intermediate variables

Distal variables	Patients (n=244)	Controls (n=485)	Univariable odds ratio (95% CI)	p	Adjusted for intermediate social child contacts	p
Childcare work with a few specific children						
None	233 (95·5%)	436 (89·9%)	1·00		1·00	
⩽5 years' duration	10 (4·1%)	28 (5·8%)	0·37 (0·13–1·06)		0·94 (0·27–2·99)	
>5 years' duration	1 (0·4%)	21 (4·3%)	0·06 (0·01–0·50)	0·0004	0·19 (0·02–1·79)	0·214 0·169 (trend)
Number of child-day contacts with children living in household						
None	202 (82·8%)	355 (73·2%)	1·00		1·00	
7–2550*	27 (11·1%)	65 (13·4%)	0·62 (0·37–1·05)		0·96 (0·54–1·69)	
2551–14 901	15 (6·1%)	65 (13·4%)	0·34 (0·18–0·64)	0·001	0·71 (0·34–1·47)	0·638 0·403 (trend)

*Quantiles of exposure, see methods.

Table 1: **Effects on risk of zoster of contacts with limited numbers of children living in household and via childcare work in past 10 years**

were added second, to demonstrate the extent to which they explained the effect of distal variables, then proximal variables were added to determine whether they explained distal and intermediate factors. Variables excluded at the univariable or distal stages of analysis were added again at the proximal stage to assess whether they became significantly associated with zoster in the presence of other variables. Confounding variables were added to the model if they changed any of the effect estimates of interest by 10% or more.[18] Interactions between contact variables and age were investigated in the final model.

Role of the funding source

Neither funder of this study was involved in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

Results

During the study period, 436 patients were identified, of whom 139 were ineligible (46 were younger than 16 years, 37 had recent immunosuppression, 18 were African, 11 were temporarily registered, four were incapable of answering questions, and 23 were identified more than 8 weeks after rash onset). Of the remaining 297 patients, 16 (5·4%) were not enrolled: 12 refused and four were away from London or repeatedly unavailable for more than 8 weeks. The eligibility of these patients was not ascertained. The remaining 281 patients were categorised as confirmed (92), probable (152), or other (37) cases. Of the confirmed and probable cases, 107 (43·9%) were men, and the median age was 57·2 years (range 16·5–91·2).

488 controls were needed for the 244 confirmed and probable cases. Letters were sent to 895 individuals, of whom 162 were ineligible (118 had a history of zoster, 22 had recent immunosuppression, 11 were African, one was temporarily registered, and 10 were incapable of answering questions). A further 145 were unsuitable (106 no longer lived in London, 22 were living away for extended periods, 11 were dead, and six had an incorrect date of birth on practice records). Of the remaining 588 potentially eligible individuals, 103 (17·5%) were not included in the study (75 refused, nine twice cancelled interviews, three were in hospital, one had a non-existent address, and 15 could not be contacted after more than four attempts). The remaining 485 controls were enrolled; for three of the enrolled patients only one matched control was obtained. The mean difference in age between patients and their matched controls was 4·7 days. Controls were interviewed a median of 35 days after patients.

Contact with a few children living in the household or via childcare work in the past 10 years was strongly associated with protection against zoster on univariable analysis, with evidence of a dose-response effect. However, neither distal variable remained significantly associated with risk of zoster after adjusting for the effects of social contacts with specific children not living in the household and children in groups (table 1). Childcare and household contact variables were therefore dropped from the model.

Table 2 lists univariable effect estimates for the intermediate child contact variables, in the 10 years before interview, that were associated with zoster. Protection increased with longer duration of occupational exposure to many ill children, and with greater numbers of social contacts with specific children not living in the household or children in groups. There was no significant association between duration of occupational exposure to many well children in the past 10 years and risk of zoster, even after analyses were restricted to individuals working in primary-school or nursery settings (odds ratio 0·94 [95% CI 0·47–1·87]). Intermediate child contact variables remained significantly associated with protection against zoster after adjusting for each other and for ethnic origin, with little change to the effect estimates (data not shown). However, the strength of associations between intermediate child contacts and zoster decreased after adjusting for contact with known cases of varicella (table 2), remaining most strongly significant for contacts with children in groups.

Contact with people with varicella in the past 10 years was strongly associated with protection against zoster on univariable analysis (table 2), and this association remained after adjusting for occupational and social child contacts. Contact with people with zoster was weakly associated with protection against zoster on univariable analysis, but not significantly associated with zoster in the final model (table 2). Ethnic origin slightly confounded the effect of occupational exposure to ill children, and was added to all models. After adding ethnic origin, childhood residence in the tropics and socioeconomic variables made little difference to effect estimates for the variables of interest. The effect of the contact variables did not vary with participants' age (p for interaction >0·3 for all).

We could not test study participants for HIV infection, and so could not confirm that all cases and controls were HIV-negative. The effect of child contacts might be confounded by undiagnosed HIV infection in patients. Homosexual men in London are a group at high risk of HIV infection (which increases their chance of developing zoster), and could have relatively few child

	Patients (n=244)	Controls (n=485)	Univariable odds ratio (95% CI)	p	Adjusted for other intermediate variables and varicella contacts*	p
Intermediate variables						
Number of social contacts with specific children not living in household						
None	30 (12·3%)	49 (10·1%)	1·00		1·00	
2–107†	60 (24·6%)	87 (17·9%)	1·02 (0·59–1·81)		1·03 (0·57–1·85)	
108–420	53 (21·7%)	88 (18·1%)	0·91 (0·51–1·62)		0·94 (0·52–1·73)	
421–1334	52 (21·3%)	87 (18·9%)	0·89 (0·49–1·63)		0·90 (0·48–1·70)	
1335–3457	30 (12·3%)	87 (18·9%)	0·53 (0·28–0·98)		0·60 (0·30–1·17)	
3458–32 631	19 (7·8%)	87 (17·9%)	0·30 (0·14–0·63)	0·0003	0·43 (0·19–0·94)	0·079 0·007 (trend)
Number of social contacts with children in groups						
None	197 (80·7%)	308 (63·5%)	1·00		1·00	
6–550†	24 (9·8%)	59 (12·2%)	0·63 (0·38–1·06)		0·72 (0·41–1·27)	
551–3652	16 (6·6%)	59 (12·1%)	0·32 (0·17–0·62)		0·44 (0·22–0·89)	
3653–45 023	7 (2·9%)	59 (12·2%)	0·12 (0·06–0·35)	<0·0001	0·19 (0·07–0·50)	0·001 0·0001 (trend)
Occupational contact with many ill children						
None	241 (98·8%)	460 (94·8%)	1·00		1·00	
≤5 years' duration	2 (0·8%)	14 (2·9%)	0·26 (0·06–1·17)		0·25 (0·05–1·20)	
>5 years' duration	1 (0·4%)	11 (2·3%)	0·17 (0·02–1·29)	0·015	0·27 (0·03–2·51)	0·062 0·025 (trend)
Proximal variables						
Number of known varicella contacts						
None	179 (73·4%)	283 (58·4%)	1·00		1·00‡	
1	34 (13·9%)	74 (15·3%)	0·67 (0·42–1·08)		0·90 (0·54–1·52) ‡	
2	20 (8·2%)	45 (9·3%)	0·61 (0·34–1·09)		0·83 (0·45–1·56) ‡	
3–4	6 (2·5%)	44 (9·1%)	0·15 (0·06–0·39)		0·26 (0·10–0·72) ‡	
≥5	5 (2·0%)	39 (8·0%)	0·14 (0·05–0·39)	0·0001	0·29 (0·10–0·84) ‡	0·016 0·003 (trend)
Number of known zoster contacts						
None	189 (77·5%)	338 (69·7%)	1·00		1·00§	
1	44 (18·0%)	110 (22·7%)	0·71 (0·48–1·05)		0·79 (0·51–1·23)§	
≥2	11 (4·5%)	37 (7·6%)	0·51 (0·25–1·04)	0·052	0·92 (0·42–2·03)§	0·581

*Also adjusted for ethnic origin. †Quantiles of exposure, see methods. ‡Adjusted for intermediate variables and ethnic origin. §Adjusted for intermediate variables, varicella contacts, and ethnic origin.

Table 2: **Effects on risk of zoster of contacts with many children and exgenous exposure to varicella-zoster virus in the past 10 years**

contacts.[14,19] Multivariable analyses were therefore repeated in two subgroups of individuals at low risk of HIV infection: first women and then all individuals older than 60 years. Statistical power was reduced, but protective trends associated with social and occupational child contacts were similar to those shown in the whole dataset (data available on request). The effect of imperfect specificity of the probable zoster case definition was also investigated by repeating analyses in the subset of confirmed cases and their matched controls. Similar protective patterns were shown.

Discussion

The findings from this study suggest that continued exogenous exposure to varicella is protective against zoster in latently infected adults. This result is consistent with those of Gershon and colleagues,[10] who found that vaccinated children with leukaemia were at significantly lower risk of zoster if they had household exposure to varicella, and that many of these children had evidence of immunological boosting. In our study, there were dose-response effects associated with a range of occupational and social exposures to children and with varicella contacts. Results of analyses using a hierarchical model-building strategy (figure) show that living with children seems to protect against zoster largely by increasing access to a range of other children outside the household, and that the protection afforded by contacts with many children seems to be largely explained by exposure to varicella-zoster virus. The latter conclusion is supported by analyses showing that protection against zoster is strongest when contacts are with children in groups of changing membership in occupational or social settings (increasing the likelihood of contacting a case of varicella).

Some protective effect of child contacts remained after adjustment for known varicella contacts. This effect might represent unrecognised or forgotten contacts with children with varicella, since varicella is infectious before rash onset, and this is especially likely for social contacts with children in groups of changing membership.[20] If this explanation is correct, the total protective effect of (known and unknown) varicella contacts will be greater than that estimated in the final model, which represents only the effect of known varicella contacts independent of the effect of unknown contacts. Interestingly, occupational contact with many well children (eg, through teaching) was not protective against zoster. Perhaps varicella contacts are more distant in these settings than in social settings, and are more limited in duration if children with varicella are absent from school while experiencing rash. Contact with zoster cases was not associated with protection against zoster. This finding is less surprising, since zoster is less infectious than varicella and most zoster contacts had rash on non-exposed areas of the body.

Other explanations for the protective effect of child contacts should be considered. First, ethnic origin is a potential confounder of the effect of child contacts on risk of zoster, since some ethnic groups could be at lower risk of zoster than others and have greater contacts with children via extended families.[21] However, neither ethnic origin nor country of residence in childhood accounted for the protective effect of child contacts in this study.

Second, subgroup analyses indicated that the protective effect of child contacts was unlikely to result from undetermined HIV infection or misdiagnosis of zoster cases. Incomplete reporting of cases by practices might introduce bias if general practitioners were more likely to report cases with fewer child contacts. This situation is unlikely, since the overall study was investigating various risk factors for zoster, and investigation of a limited number of unreported cases showed that failure to be reported was due to general under-reporting by some practices or by specific practitioners, rather than selective reporting of cases. Participation by controls was high (82·5%), but some bias might have been introduced if those who refused or could not be contacted were eligible for inclusion and had fewer contacts with children.

Recall bias occurs in case-control studies if patients remember past exposures differently from controls. In this study, recall bias might have led to underestimation of the protective effects of child and varicella contacts. Many patients believed that zoster resulted from contact with cases of varicella or zoster, and had spent time trying to remember any contacts that might have infected them. Another concern in case-control studies is that having the disease affects exposure—in this situation, contact with children. However, reverse causality is unlikely to explain the findings. First, most patients were interviewed within 2 weeks of rash onset. Second, the number of child contacts was calculated from the average frequency before onset of rash, not the frequency in the past few days. For example, a patient who saw her grandchild on average once a week in the past year would be assigned 52 child contacts, even if she had not seen the child since onset of rash.

Children who are vaccinated against varicella might be at lower risk of later developing zoster.[22] Therefore, widespread varicella vaccination programmes might eventually decrease the incidence of zoster. However, the results of this study suggest that vaccination of children against varicella could lead to a prolonged period of increased incidence of zoster among unvaccinated adults, as a result of fewer exogenous exposures to varicella-zoster virus. This increase in incidence might have started already in countries such as the USA, but could be unrecognised due to limited surveillance of zoster. In view of this possibility, we should consider whether childhood varicella vaccination programmes should be expanded to include vaccination of older adults, to protect them against zoster. The results of the current US multicentre trial of varicella vaccination in elderly individuals will indicate whether this is a feasible approach.[23]

Contributors

Andrew Hall conceived and co-designed the study, and participated in the statistical analyses, interpretation of findings, and writing of the paper. Sara Thomas co-designed and ran the study, did the interviews, managed the data, designed and carried out the statistical analyses, interpreted the findings, and wrote the paper. Jeremy Wheeler participated in the design of the study, the statistical analyses and interpretation of the findings, and the writing of the paper.

Conflict of interest statement

Andrew Hall has received a contribution towards research funding from Merck, Sharp and Dohme (a vaccine manufacturer).

Acknowledgments

We thank all the individuals who agreed to take part in the study, and the participating general practices: Albion Street Health Centre; Aylesbury Partnership (all three sites); Belmont Hill Surgery; Brixton Hill Group Practice; Camberwell Green Surgery; Crown Dale Medical Centre; Grange Road Practice; Downham Way Surgery; Forest Hill Group Practice; Isidore Crown Health Centre; Jenner Health Centre; Lee Road Surgery; Mawbey Brough Health Centre; New Surgery, Clapham; Paxton Green Health Centre; Queens Road Partnership (both sites); Sternhall Lane Surgery; Sydenham Green Group Practice; and Torridon Road Surgery. We also thank Judy Breuer for helpful discussions on the diagnosis of zoster, and for doing the PCR analyses. Sara Thomas was funded initially by a research studentship from the Medical Research Council (UK), and then by the Research Foundation for Microbial Diseases, Osaka University, Japan.

References

1 Gilden DH, Vafai A, Shtram Y, et al. Varicella-zoster virus DNA in human sensory ganglia. *Nature* 1983; **306:** 478–80.
2 Furuta Y, Takasu T, Fukuda S, et al. Detection of varicella-zoster virus DNA in human geniculate ganglia by polymerase chain reaction. *J Infect Dis* 1992; **166:** 1157–59.
3 Kennedy PGE, Grinfeld E, Gow JW. Latent varicella-zoster virus is located predominantly in neurons in human trigeminal ganglia. *Proc Natl Acad Sci USA* 1998; **95:** 4658–62.
4 Arvin AM. Cell-mediated immunity to varicella-zoster virus. *J Infect Dis* 1992; **166** (suppl 1)**:** S35–41.
5 Burke IL, Steele RW, Beard OW, et al. Immune responses to varicella-zoster in the aged. *Arch Intern Med* 1982; **142:** 291–93.
6 Berger R, Florent G, Just M. Decrease of the lymphoproliferative response to varicella-zoster virus antigen in the aged. *Infect Immun* 1981; **32:** 24–27.
7 Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Medical progress: neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med* 2000; **342:** 635–45.
8 Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med* 1964; **58:** 9–20.
9 Arvin AM, Koropchak CM, Wittek AE. Immunological evidence of re-infection with varicella zoster virus. *J Infect Dis* 1983; **148:** 200–05.
10 Gershon AA, LaRussa P, Steinberg S, et al. The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. *J Infect Dis* 1996; **173:** 450–53.
11 Solomon BA, Kaporis AG, Glass AT, Simon SI, Baldwin HE. Lasting immunity to varicella in doctors (L.I.V.I.D study). *J Am Acad Derm* 1998; **38:** 763–65.
12 Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus infections: the influence of varicella on the prevalence of herpes zoster. *Epidemiol Infect* 1992; **108:** 513–28.
13 Nahass GT, Goldstein BA, Zhu WY, et al. Comparison of Tzanck smear, viral culture and DNA diagnostic methods in detection of herpes simplex and varicella-zoster infection. *JAMA* 1992; **18:** 2541–44.
14 Unlinked Anonymous Surveys Steering Group. Prevalence of HIV and hepatitis infections in the United Kingdom 1999. London: Department of Health, Public Health Laboratory Service, Institute of Child Health (London), Scottish Centre for Infection and Environmental Health, 2000.
15 Fairley CK, Miller E. Varicella-zoster virus epidemiology—a changing scene? *J Infect Dis* 1996; **174** (suppl 3)**:** S314–19.
16 Schlesselman JJ. Case-control studies: design, conduct, analysis. New York: Oxford University Press, 1982.
17 Victora CG, Huttley SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. *Int J Epidemiol* 1997; **26:** 224–27.
18 Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol* 1993; **138:** 923–36.
19 Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis* 1992; **166:** 1153–56.
20 Weller TH. Varicella-herpes zoster virus. In: Evans AS, Kaslow RA, eds. Viral infections of humans: epidemiology and control, 4th edn. New York: Plenum Medical Book Co, 1997: 865–92.
21 Schmader K, George LK, Burchett BM, Hamilton JD, Pieper CF. Race and stress in the incidence of herpes zoster in older adults. *J Am Geriatr Soc* 1998; **46:** 973–77.
22 Kraus PR, Klinman DM. Efficacy, immunogenicity, safety, and use of live attenuated chickenpox vaccine. *J Pediatr* 1995; **127:** 518–25.
23 Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. *Neurology* 1995; **45** (suppl 8)**:** S41–46.