

# What does epidemiology tell us about risk factors for herpes zoster?

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Reactivation of latent varicella zoster virus as herpes zoster is thought to result from waning of specific cell-mediated immunity, but little is known about its determinants in individuals with no underlying immunosuppression. We systematically reviewed studies of zoster epidemiology in adults and analysed data from a large morbidity study to identify factors that might be modulated to reduce the risk of zoster. Annual zoster incidence in population-based studies varied from 3.6–14.2/10<sup>3</sup> in the oldest individuals. Risk factors identified in analytical studies that could explain this variation included age, sex, ethnicity, genetic susceptibility, exogenous boosting of immunity from varicella contacts, underlying cell-mediated immune disorders, mechanical trauma, psychological stress, and immunotoxin exposure. Our review highlights the lack of information about risk factors for zoster. We suggest areas of research that could lead to interventions to limit the incidence of zoster. Such research might also help to identify risk factors for age-related immune decline.

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Herpes zoster (shingles) results from reactivation of latent varicella zoster virus (VZV). The lifetime risk of zoster is estimated to be 10–30% and incidence increases markedly with age, affecting up to 50% of people who live to 85 years.<sup>1–3</sup> It is characterised by a painful vesicular dermatomal rash and can result in chronic pain (post-herpetic neuralgia), particularly in older individuals. This pain can be reduced by prompt administration of antivirals, but not all patients with zoster present in time to benefit from therapy, and 20% of people older than 50 years who receive treatment still experience pain 6 months after rash onset.<sup>4</sup> Therefore, zoster represents a significant cause of morbidity in older populations.

The virus is thought to be maintained in its latent form by VZV-specific cell-mediated immunity. Therefore, people with cell-mediated immunosuppression are at increased risk of zoster.<sup>5–7</sup> However, these individuals only constitute a minority of zoster cases in population-based studies, and the precise determinants of VZV reactivation in people without underlying immunosuppression are unknown. The increased risk of zoster among older individuals may be due to waning of specific immunity with increasing time since primary infection (varicella), or may occur as part of the generalised decay in cell-mediated immunity that occurs with age (immunosenescence), an important factor in the increased susceptibility to infections, malignancies, and autoimmune

disorders in the elderly.<sup>8</sup> Little is known about the determinants of either generalised or VZV-specific immune decay. We therefore systematically reviewed the descriptive and analytical epidemiology of zoster in adults (focusing on older populations) to identify factors that might be modulated to reduce the risk of zoster.

## Methods

Published articles on the descriptive and analytical epidemiology of zoster were identified using the methods outlined in the search strategy (see page 32), and reports from two large study programmes of morbidity seen in general practice in England and Wales were also examined: (1) the four Morbidity Statistics from General Practice (MSGP) studies, done in 1955–56, 1971–72, 1981–82, and 1991–92, the last comprising a total study population of 502 493 patients,<sup>9–12</sup> and (2) the continuing Royal College of General Practitioners (RCGP) weekly returns service, which currently comprises a population of 650 000 patients.<sup>13</sup> Inclusion and exclusion criteria for studies are detailed below.

Standardised extraction tables were used to extract information from each study. For incidence studies this information included the study date, setting, population, sample size, method of ascertaining zoster cases, zoster diagnostic criteria used, overall incidence with 95% confidence intervals (95% CI), and (where available) incidence by age, sex, and geographical area, and evidence of seasonality. Exact 95% CI for incidence estimates were calculated if 95% CI were not provided but the necessary raw data were available. Additional data extracted from analytical studies included participation rates (in case-control or cross-sectional studies) or loss to follow-up (in cohort studies), exposure measurement, univariable and multivariable relative risks (RR), or odds ratios (OR) with 95% CI, and adjusted for confounders.

Descriptive studies were summarised in tabular and graphical forms. The fourth MSGP study collected additional social data from participants, allowing investigation of these factors as potential determinants of zoster. Data from the study were obtained and analysed by Poisson regression to

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## Zoster incidence in population-based studies that include adults

Country	Date	Population	Case ascertainment	Diagnosis	Cases (n)	Incidence per 10 <sup>3</sup> population per yr (95% CI)
USA <sup>28</sup>	1945–59	Inhabitants of Rochester Ages: <14–>75 yrs	Computerised records from OPD, hospitals, housecalls, nursing homes	Review of medical records	590	1.2 (1.1–1.4)*
USA <sup>29</sup>	1983–92	Family practice in New Hampshire Ages: 0–>90 yrs	Records of all cases	Single GP	124	3.3†
USA <sup>30</sup>	1989–90	3206 independently living older individuals in North Carolina Mean age: 73.6 yrs (65–104)	Interview: zoster in past 3 yrs	Self-reported	69	7.2 (5.6–9.1)*
USA <sup>31</sup>	1990–92	250 204 members of Harvard Community Health Plan Ages: 0–>75 yrs	Computer records from emergency departments, ambulatory settings, hospitals, telephone consultations	Individual clinicians	1075	2.2 (1.9–2.4)
Scotland <sup>32</sup>	1947–48	Individuals attending selected GPs/hospitals in Edinburgh Ages: NR	Notified by GPs/hospital doctors	NR	246	2.0‡
Scotland <sup>33</sup>	1948–55	General practice in Hawick (2/3 suburban, 1/3 rural) Ages: 0–>65 yrs	Records of all cases	NR	81	4.8 (3.8–6.0)*
Scotland <sup>34</sup>	1972–73	8 general practices in Glasgow About 36 000 individuals Ages: NR	Notified by GPs	a) Individual GPs b) Paired sera	87	a) 2.4 (1.9–3.0)* b) 2.2 (1.7–2.7)*
Scotland <sup>35</sup>	1955–85	General practice in Dumfriesshire 1850 patients Ages: 0–>80 yrs	Records of all cases	NR	151	2.6* (2.2–3.1)*
England <sup>3,36</sup>	1947–62	General practice in Cirencester About 3500 patients Ages: 0–>90 yrs	Records of all cases	NR	192	3.4 (3.0–3.9)*
England/Wales <sup>12</sup>	1991–92	60 general practices (88% urban) 502 493 patients (MSGP4) Ages: 0–109 yrs (14% ≥65yrs)	Reporting of all diagnoses in face-to-face contacts	Individual GPs	1645	3.5§ (3.3–3.7)*
England/Wales <sup>37</sup>	1967–89	Up to 91 general practices (RCGP) 161 729–239 984 patients Ages: 0–>65 yrs	Weekly returns of all diagnoses	Individual GPs	NR	3.2
England/Wales <sup>13</sup>	1994–2001	Up to 85 general practices (RCGP) Currently 650 000 patients Ages: 0–>65 yrs	Weekly returns of all diagnoses	Individual GPs	NR	4.0
Germany <sup>38</sup>	1992–93	Population of Ansbach (about 40 000) Ages: NR	All cases seen by GPs, dermatologists, paediatricians	Individual clinicians	152	2.3
France <sup>39</sup>	1997–98	4635 general practices and 513 dermatologists throughout France Ages: 0–≥75 yrs	Notified by GPs	Individual clinicians	8103	4.8
France <sup>40</sup>	1998	744 general practices (mostly urban) Ages: NR	Postal survey of GPs—cases seen in previous year	Individual GPs	605	3.2 (3.0–3.4)
Italy <sup>41</sup>	1995	71 general practices throughout Italy 98 508 patients Ages: >15 yrs	Reporting by GPs: all cases seen in previous year	Individual GPs	408	4.1 (3.8–4.6)
Iceland <sup>42</sup>	1990–95	62 general practices (58% urban) Ages: 0–>80 yrs (26% <20 yrs)	Notified by GPs and searches of computerised records	Individual GPs: researchers excluded “wrong diagnoses”	457	2.0 (1.8–2.2)*
Netherlands <sup>43</sup>	1994–99	22 general practices in six areas About 49 000 patients Ages: 0–>75 yrs	Searches of computerised records	Individual GPs	837	3.4 (2.9–3.9)

\*Recalculated from data presented. †Incidence calculated assuming 1/3 town serviced by practice. ‡Incidence calculated assuming practices saw 15–20% of all cases.

§Minimum estimate, calculated using “first ever” episodes of zoster OPD=outpatient departments. NR=not recorded. py=person years. MSGP=Morbidity Statistics from General Practice. RCGP=Royal College of General Practitioners' Weekly Returns Service.

look at the independent effects of age, sex, geographical area, occupation, socioeconomic status, social contacts with children, smoking, ethnicity, and country of birth on risk of zoster. These analyses were restricted to adults who developed a “first ever episode” of zoster during the study year (n=1474) and to adults with no mention of a zoster diagnosis

(n=39 431). People with “new” zoster episodes were excluded because these cases were originally defined as zoster consultations occurring more than 28 days after a previous consultation—recurrent episodes of zoster are uncommon, so many “new” zoster episodes may have been continuing consultations for an existing episode.

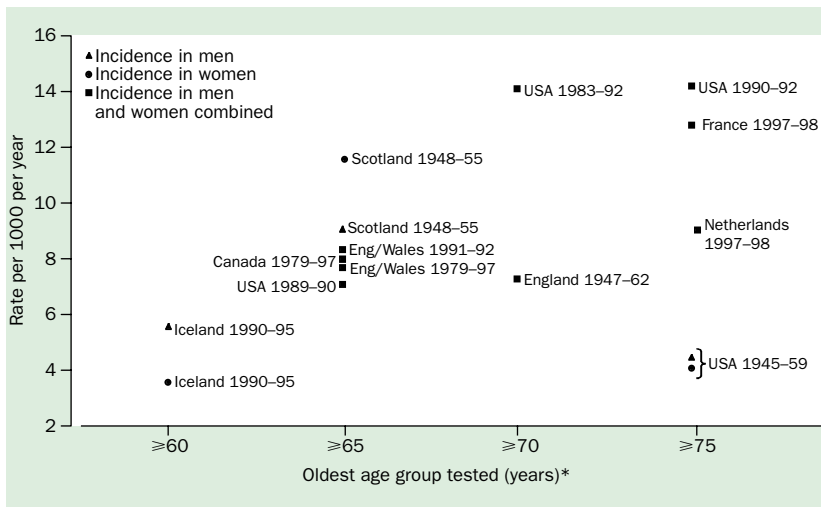


Figure 1. Incidence of zoster amongst older individuals in population-based studies.\*Incidence among all people in the study aged  $\geq$ the age stated.

Analytical studies were subdivided into three groups according to the purported mechanism by which zoster risk was altered. Studies investigated either (1) potential determinants of loss of VZV-specific immunity, (2) potential determinants of generalised loss of cell-mediated immunity, or (3) other risk factors for zoster. Studies that investigated loss of VZV-specific immunity were in turn subdivided into studies of age at varicella and studies of factors that might stimulate exogenous boosting of specific immunity. Very early age at varicella could increase risk of zoster. Acquisition of varicella in utero or in the 1st year of life has been shown to increase the risk of zoster in later childhood (perhaps because the immature immune system of the infant or fetus is less able to establish and maintain viral latency), and early infection might also increase zoster risk in adulthood.<sup>14,15</sup> Conversely, late acquisition of varicella (in adolescence or adulthood) could delay waning of VZV-

specific immunity over time and thus decrease the risk of zoster. Exogenous boosting of specific immunity has been shown in mothers of children with varicella, and in one study leukaemic children who had varicella household contacts were at lower risk of zoster.<sup>16,17</sup> Therefore, contacts with varicella might also protect latently infected adults against zoster by boosting their specific immunity.<sup>3</sup>

**Results**  
**Incidence studies**  
 31 reports that included population-based descriptive data for adults were identified, of which five had no denominator information,<sup>18-22</sup> and four contained data entirely duplicated elsewhere.<sup>23-26</sup> Published reports from the first three MSGP studies could not be used to estimate zoster incidence, because they either reported "patient consulting rates" (prevalent and new cases together) or combined first and new zoster episodes.<sup>10,11,27</sup> The 19 reports of zoster incidence from 17 studies (including additional analyses of MSGP4 data) are summarised in the table. These studies included four studies from North America,<sup>28-31</sup> eight from the UK (with two RCGP summaries for different time periods),<sup>3,12,13,32-37</sup> and six studies from elsewhere in Europe.<sup>38-43</sup> All except one study included both old and young people, with overall annual incidences ranging from 1.2-4.8/10<sup>3</sup>. Within all these populations, there was a steep rise in zoster incidence with age; incidences among the oldest age groups in 11 studies (three of which only reported sex-specific incidences) are summarised in figure 1. There was variation in incidence within each oldest age group examined. Limited data on 95% CI suggested that some of the differences in incidence were significant for example, the 1997-98 Netherlands study reported an annual incidence of 9.1/10<sup>3</sup> (8.1-10.2) in people aged 75 years or older, compared with 14.2/10<sup>3</sup> (10.8-18.4) in the 1990-92 US study.

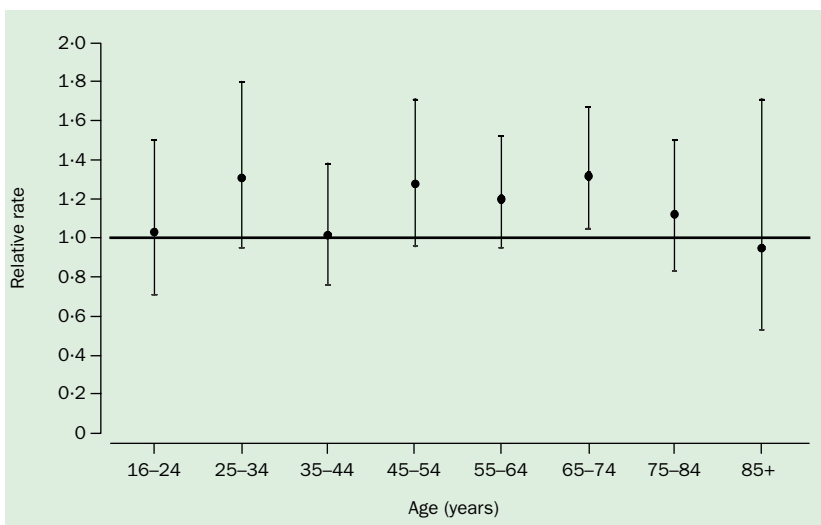


Figure 2. Relative rate (95% CI) of zoster amongst women compared with men, by age (MSGP4 data).

11 studies reported sex-specific zoster incidence, with four reporting no overall difference in incidence between men and women on crude<sup>35</sup> or age-adjusted analysis,<sup>28,30,31</sup> three reporting a slight male excess,<sup>3,33,38</sup> and four an overall female<sup>13,29,34,39</sup> excess on crude analysis. Further analysis of MSGP4 showed that women had a significantly higher age-adjusted rate of zoster than men, although the magnitude of increased risk was not great (adjusted RR 1.19, 95% CI 1.07-1.32, p=0.0009). Eight studies examined male/female differences in incidence within age groups among

the oldest individuals studied, two studies reported no significant differences<sup>28,31</sup> and five reported a female excess,<sup>13,33,35,39,42</sup> although only one of these reported that this difference was significant.<sup>35</sup> Patterns of excess female risk in younger age groups were less consistent. For example, one French and one UK study reported excess female risk within all age groups except the youngest (without reporting statistical significance),<sup>13,39</sup> the 1992–93 US study reported no significant differences within any age group,<sup>31</sup> and the US Rochester study reported a significantly lower incidence among women than men aged 35–44 years.<sup>28</sup> The age-specific effects of female sex on risk of zoster within MSGP4 are summarised in figure 2: women were at significantly or near-significant increased risk of zoster in four of the eight adult age groups examined, but not among youngest adults, those aged 35–44 years, and those older than 75 years.

Seasonality of zoster incidence was not seen in most studies,<sup>2,19,20,28,29,32,38,42</sup> or in two long-term analyses of the UK RCGP data,<sup>13,37</sup> although one Scottish and one English study reported higher incidence of zoster in summer and autumn.<sup>35,36</sup> Urban/rural residence was investigated in two studies and population density/household crowding in one study, none of which saw a significant effect,<sup>30,32,33</sup> and rural residence was not associated with significant risk of zoster in MSGP4 (RR 1.00, 95% CI 0.85–1.16,  $p=0.969$ ). The risk of zoster also did not vary significantly with socioeconomic status (adjusted  $p=0.935$ ). There was conflicting evidence of secular changes in incidence. In the US Rochester study, there was a 41% age-adjusted rise in men and a 28% rise in women in 1955–59 compared with 1945–49.<sup>28</sup> The 1990–92 study of a similar US population showed a 64% rise in zoster incidence compared with the Rochester study after standardising for age to the same 1970 US white population.<sup>31</sup> In the UK RCGP study, increase in zoster incidence was not seen in the aggregated data of the first 23 years of reporting or within the past 8 years of available data.<sup>13,37</sup> However, the mean annual incidence was greater for the latter period ( $3.95/10^3$  compared with  $3.2/10^3$ ), and there was a slight increase in the number of cases in 1998 among those aged 65 years or older compared with the previous 10-year average.<sup>44</sup>

#### **Potential determinants of loss of VZV-specific immunity**

None of the identified published studies directly investigated the effect of age at varicella on risk of zoster. However, country of birth (or country of residence or ethnicity as proxies for country of birth) has been suggested as a proxy for age at varicella, because the average age at varicella is delayed to adolescence or adulthood in some tropical countries.<sup>45–51</sup> In the North Carolina cohort of older individuals, black people were at approximately one-third the risk of zoster on multivariable analysis compared with white people (RR 0.35, 95% CI 0.24–0.51).<sup>52</sup> VZV-specific immunity was not measured. In MSGP4 only 1.4% (4373) of individuals with available information were born in a tropical country, and they were not at significantly lower risk of zoster in the year of the study (age-adjusted and sex-adjusted RR 0.64, 95% CI 0.30–1.20,  $p=0.133$ ). However, there was a near-significant reduced risk of zoster in people

born in countries with stronger evidence of late-onset varicella (the Caribbean, Central America, India, Pakistan, Sri Lanka, Bangladesh, Singapore, and Malaysia; age-adjusted and sex-adjusted RR 0.56, 95% CI 0.28–1.12,  $p=0.072$ ). Similarly, black people were at less than half the risk of zoster after adjusting for age and sex (RR 0.42, 95% CI 0.22–0.81). This reduced risk remained after additionally controlling for country of birth (0.46, 0.21–0.97).

Five studies were identified that directly or indirectly examined the effect of contacts with varicella on risk of zoster in adults. Garnett and Grenfell<sup>53</sup> used time-series analysis of RCGP data and saw no association between the two diseases at the weekly level, indicating that varicella incidence had no immediate effect on zoster incidence. However, at the annual level an increase in varicella incidence in children under 5 years old was accompanied by a significant decrease in zoster incidence among individuals aged 15–44 years, suggesting that increased varicella in young children could exert a protective effect against zoster in the young adults exposed to them. In our community-based case-control study we investigated both the effect of varicella contacts in the past 10 years and the effect of social child contacts (as a proxy for varicella contacts) on risk of zoster.<sup>54</sup> We showed that contacts with varicella cases were associated with a strong protective effect against zoster (OR=0.14, 0.05–0.39 for those with  $\geq 5$  contacts). Living with a child in the household was significantly associated with reduced risk of zoster, and this protection seemed to be largely mediated through increased contacts with multiple children outside the household. In turn, people with the most contacts with multiple children were at approximately one-fifth the risk of zoster on multivariable analyses, and this seemed to be at least partly explained by increased varicella contacts. An analysis of MSGP4 data by Brisson et al<sup>55</sup> also showed that people living with a child were at significantly lower risk of developing zoster in the year of the study (RR=0.75, 0.63–0.89), and that younger adults who lived with children had a higher varicella incidence rate (suggesting that they were more heavily exposed to cases of varicella). Further analysis of MSGP4 for this review showed that the protection against zoster associated with black ethnicity was not explained by increased household child contacts (multivariable RR=0.47, 0.22–1.00,  $p=0.032$ ).

Our study also examined occupational exposure to children as a potential protective factor against zoster.<sup>54</sup> Contact with multiple ill children (for example, general practitioners) was associated with significantly lower zoster risk (adjusted OR=0.20, 0.06–0.73 for those with occupational contacts in the past 10 years) but contact with multiple well children (for example, teachers) was not associated with significant protection. Two other published studies of occupational exposures to children and risk of zoster were identified. A US postal survey showed that 1109 paediatricians had more contacts with VZV-infected patients compared with 1984 dermatologists and 462 psychiatrists, and were significantly less likely to report a history of zoster. However, fewer than 40% of physicians responded to the questionnaire.<sup>56</sup> Similarly, 34 (9.1%) of 352 Japanese paediatricians and family practitioners responding

to a questionnaire reported a history of zoster, which was estimated to be 50–87% lower than the age-specific incidences in the general population.<sup>57</sup> In MSGP4, we saw that individuals who reported working with young children (primary school teachers, nursery nurses, playgroup leaders, or “other child care”) were significantly less likely to develop zoster in the year of the study after adjusting for age, sex, ethnicity, and a child living in the household (RR=0.70, 0.58–0.85). Unfortunately, MSGP4 occupational codes were insufficiently detailed to investigate the effect of working with ill children.

#### **Potential determinants of generalised loss of cell-mediated immunity**

Several studies have shown that people with suppressed cell-mediated immunity from immunosuppressive disorders or therapies are at higher risk of zoster, with incidences ranging from 25.0–91.5/10<sup>3</sup> person-years.<sup>5–7,58–69</sup> In three studies that compared zoster incidence in HIV-positive and HIV-negative people, the former were at 12–17-fold greater risk of developing zoster.<sup>65,67,70</sup> In areas of high HIV prevalence, zoster has been shown to have an 85–95% positive predictive value for underlying HIV infection.<sup>71–75</sup> By contrast, two US studies showed that incident zoster may not be a good indicator of underlying cancer. In the Rochester study, cancer incidence was similar among individuals with zoster after 9389 person-years of follow-up compared with local residents without zoster (RR=1.1, 0.9–1.3),<sup>76</sup> and people in the North Carolina cohort with a history of cancer were not at increased risk of zoster after 8 years of follow-up (adjusted RR=1.03, 0.58–1.80). However, in the latter study people who reported their health as “excellent” were at half the risk of subsequent zoster (adjusted RR=0.51, 0.27–0.95).<sup>52</sup>

Three publications examined the effect of psychological stress and/or lack of social support. These factors can cause generalised cell-mediated immunosuppression, and a recent study has indicated that long-term stress may result in premature ageing of the immune system.<sup>77,78</sup> Irwin et al<sup>79</sup> showed that 11 adults with major depression had lower VZV-specific cellular immunity compared with age/sex-matched controls without depression, but did not examine subsequent risk of zoster. The other reports were of two separate studies on the North Carolina cohort. In the first, 101 individuals with recent zoster reported a significantly higher number of stressful life events in the 6 months before rash onset compared with 101 age-matched controls (mean 2.64 vs 1.82 events,  $p=0.008$ ), and a significantly higher number of events in the 2 months before rash that they perceived as “negative” (OR=2.60, 1.13–6.27).<sup>80</sup> In the second, negatively perceived life events were weakly associated with risk of subsequent zoster on multivariable analysis after 8 years of follow-up among 2568 individuals (RR=1.38, 0.96–1.97,  $p=0.078$ ), but social support variables (such as presence of a confidant or being married) were not associated with zoster risk.<sup>52</sup> In MSGP4, individuals who were not cohabiting (either single or separated/divorced) were at slightly increased risk of zoster compared with individuals who were married or cohabiting (RR adjusted for age, sex, and household child contacts=1.17, 1.01–1.37,

$p=0.04$ ), but individuals who were widowed were not at increased zoster risk.

Some metals, pesticides, and volatile organic substances can also suppress cell-mediated immunity, and early reports referred to arsenic as a risk factor for zoster.<sup>3,81,82</sup> One US cross-sectional study reported that 900 individuals aged between 18 and 40 years who lived within 2.5 miles of pesticide dump sites were twice as likely to report a history of zoster at telephone interview compared with individuals from neighbouring communities (multivariable RR=2.1, 1.0–4.3).<sup>83</sup> The temporal sequence of residence in the area and zoster was not ascertained. Older individuals in the study were not at increased risk of zoster the authors suggested that they could have had lower exposure rates, due to fewer outdoor recreational activities than younger individuals.

Cigarette smoking and alcohol can also have a harmful effect on cell-mediated immune functioning.<sup>84,85</sup> None of the studies identified was set up to look specifically at smoking or alcohol consumption, but cigarette smoking was associated with significant protection against zoster in the North Carolina cohort (adjusted RR=0.47, 0.25–0.89).<sup>52</sup> In MSGP4, smoking was not associated with risk of zoster after adjusting for age and sex (RR=1.03, 0.91–1.17).

#### **Other risk factors**

Case reports and case series have suggested that mechanical trauma precipitates zoster in the affected dermatome, perhaps because stimulation of the nerve triggers reactivation of virus in the dorsal root ganglion.<sup>86–88</sup> However, trauma can be common in older populations, and none of these studies compared the frequency of trauma in individuals with and without zoster. In our study, recent trauma was reported significantly more often in cases compared with matched controls.<sup>89</sup>

A recent study investigated genetic susceptibility to zoster, studying polymorphisms at the promoter region of the gene for interleukin 10 (a cytokine that can downregulate cell-mediated immunity).<sup>90</sup> A significantly higher proportion (53%) of 60 immunocompetent patients with zoster carried the ATA haplotype at this region of the gene compared with 152 (38%) of 400 blood donors.

#### **Discussion**

Zoster incidence may vary between populations, even among the oldest individuals. Some of this variation may be due to differences in the completeness of case ascertainment, accuracy of population denominators, and the diagnostic criteria used, but some is likely to be due to the frequency of risk factors for zoster. What clues do descriptive studies give about the determinants of zoster, and are these clues borne out by the findings from analytical studies?

Increasing age and cell-mediated immunosuppressive disorders are clearly risk factors for zoster, and differences between studies in zoster incidence among the oldest individuals might result from differences in their age structure or in the frequency of these disorders. We might expect increasing zoster incidence over time as populations age and immunosuppressive therapies are increasingly used,



but evidence for this is conflicting. Comparison of the two US studies that showed an apparent increase in incidence was made after adjusting for age differences.<sup>28,31</sup> In these studies, a similar proportion of individuals were documented with cancer (6.4% *vs* 6%) but 4.5% of individuals in the later study were also known to be HIV positive; the proportion of individuals on immunosuppressive therapies was not reported. The later study could also have achieved more complete case ascertainment as a result of free access to health care.

It is unclear whether the risk of zoster is increased in females, and if so what this represents. Women might be more likely to seek medical advice for their zoster compared with men or may have increased prevalence of risk factors for zoster, or there may be some biological mechanism by which women are more susceptible to VZV reactivation. An increased incidence of zoster in women is unexpected given the findings from a range of studies that strongly suggested that varicella contacts protect against zoster, because women might be expected to have more social contacts with children (and therefore with varicella) compared with men. However, the lower zoster incidence in women aged 35–44 years in the Rochester study (in the pre-HIV era) and the lower risk in the same age group in the MSGP4 analysis could indicate increased contacts with school-age children (and therefore with varicella), offsetting any increased risk in women due to other factors.<sup>28</sup>

There was little evidence of seasonality in zoster incidence from the population-based studies included in this review, although some clinic-based studies (where ascertainment may be less complete) have reported increased zoster incidence in the summer months.<sup>82,91–95</sup> Varicella incidence is seasonal, so lack of zoster seasonality suggests that any protection against zoster afforded by varicella contacts does not have an immediate effect. This inference is supported by Garnett and Grenfell's analysis, which indicated that such protection could occur over a longer timescale. The lack of seasonality in zoster incidence also does not give credence to the hypothesis that ultraviolet light exposure (a known suppressor of local and systemic cell-mediated immunity) could be a short-term risk factor for zoster, as has been recently hypothesised.<sup>95</sup> We might also expect to find lower zoster incidence in areas of high population mixing, if regular contact with varicella decreases zoster risk. Analyses from four studies showed no association with urban residence or household crowding, but these data provided no information on mixing specifically with children, who are the main source of varicella in temperate climates.

Non-whites may be at lower risk of zoster. It has been suggested that this reduced risk results from the maintenance of VZV-specific immunity in older age due to the late acquisition of varicella in people with childhood residence in late-onset varicella countries. There was no immunological evidence to support this hypothesis, and MSGP4 analyses indicated that the protection associated with ethnicity was independent of country of birth. In addition, a recent report of individuals with incident zoster participating in antiviral trials showed that being non-white

and resident in tropical countries were independently associated with significantly younger age at zoster, although this tendency could simply indicate participation bias or undiagnosed HIV infection.<sup>96</sup> In the North Carolina cohort, the protective effect of being non-white was not explained by differences in age, sex, education, health status, smoking, depression, social support, or stressful events.<sup>52</sup> One possible reason for the protective effect is that non-whites may experience exogenous boosting of specific immunity due to increased varicella contacts from multiple child contacts in extended families. In MSGP4, the protective effect of ethnicity was not explained by current household child contacts. However, this may not be an accurate indication of the range of non-household child contacts that older individuals experienced in the few years before the study. Alternatively, lower zoster risk in non-whites might result from genetic differences affecting VZV reactivation, or from differential survival—in populations with higher mortality rates, those who survive to old age may have robust immune systems (and therefore lower susceptibility to zoster).

Psychological stress was identified as a potential risk factor for zoster that might operate by suppressing cell-mediated immunity. Separate analyses of the same elderly US population provided some evidence that stress increases the risk of zoster, although the case-control findings might have resulted from recall bias and the cohort analysis had weak power to detect a significant effect. A second possible determinant of generalised cell-mediated immune suppression, and therefore of zoster, is exposure to immunotoxic chemicals. Immunotoxic chemicals were implicated in zoster incidence in one study, although the temporal sequence of environmental exposure and zoster was unclear and the increased zoster risk was only seen in younger residents.

Other potential risk factors for zoster identified in this review included mechanical trauma and genetic susceptibility. It is feasible that genes coding for interleukin-10 promotion or for other specific cytokines could increase zoster risk by affecting cell-mediated immunity, but these polymorphisms could be associated with general susceptibility to infections or to other immune-mediated disorders in addition to VZV reactivation, in which case voluntary blood donors (who are essentially healthy) may not have been a suitable control group.

It is surprising that we know so little about the determinants of zoster given that it is relatively common in older individuals and causes significant morbidity, and that so few studies made any immunological measurements. Some of the factors identified in this review could affect the risk of zoster at any age by boosting VZV-specific immunity or by temporarily diminishing cell-mediated immune functioning in general, although further evidence is needed to show that these are the underlying mechanisms by which risk is altered. Older people may be more susceptible to the effects of temporary immunosuppression because these occur against a background of age-related immune decline. However, older individuals vary widely in their age at onset of immunosenescence, and some have immune responses similar to those of much younger individuals.<sup>97,98</sup> Therefore,

### Search strategy and selection criteria

Data for this review (published up to the end of April 2003 in any language) were identified by searches of Medline and Embase. The search was carried out in two phases. Articles published up to mid-1998 were retrieved by searching for herpes zoster as a thesaurus term, with either "epidemiology", "aetiology", or "transmission" as subheadings, or with "inciden\*", "risk", "rate", "cohort", "case-control", or "cross-sectional" (with and without hyphens) as free-text terms. Review articles on zoster were identified using a separate search. From mid-1998 onwards, we did monthly searches of the two databases, looking at all articles that indexed herpes zoster as a thesaurus term (all subheadings) or included "zoster" as a free-text term. Books on herpes viruses were identified from the catalogues of the London School of Hygiene and the British Library. Reference lists of all retrieved articles were examined. Reports were also sought from the four Morbidity Statistics in General Practice studies and from the ongoing Royal College of General Practitioners Weekly Returns Service (see text). Zoster incidence studies were included in the review if they were population-based (for example studies of general practice populations or inhabitants of a defined geographical area), but excluded if they were restricted to selected groups such as dermatology or physiotherapy clinic attenders. Analytical studies were included if they used a cohort, case-control, or cross-sectional design, and if they examined the odds or risks of zoster for the exposures of interest. Both descriptive and analytical studies were excluded if they only provided information on child populations, or if the data were entirely duplicated in other publications.

It is possible that some of the factors identified (such as stress and immunotoxin exposure) are determinants of immunosenescence itself, in which case immunosenescence may lie on the causal pathway between these factors and risk of zoster. In other words, the factors increase the risk of immunosenescence, which in turn increases the risk of zoster. If this is so, then investigation of determinants

of zoster may also help to identify the determinants of immune dysregulation with age.

What other factors might determine the rate of immunosenescence and increase the risk of zoster? One candidate is micronutrient intake, because micronutrients are essential for cell-mediated immune function and multiple micronutrient deficiencies occur increasingly with age, causing diminished cell-mediated immunity and increased susceptibility to infections in older individuals.<sup>99-101</sup> Variation in micronutrient intake could also partially explain differences in zoster incidence by ethnicity. However, the lack of association between zoster and social class seen in MSGP4 does not provide support for this hypothesis, since micronutrient status is likely to vary with social class.

In conclusion, the descriptive epidemiology of zoster provides limited clues about its determinants, and there have been few analytical studies. More focused studies are needed to test specific hypotheses and to confirm findings. For example, it is important to clarify whether contacts with varicella protect older individuals against zoster, because widespread introduction of varicella vaccination could result in increased zoster incidence in latently infected people who no longer receive exogenous boosting. Elucidation of risk factors for zoster may lead to public-health interventions to limit the future incidence of this disease, and could also inform future research about the determinants of immunosenescence.

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### Conflicts of interest

There are no potential conflicts of interest in connection with this paper, except that SLT was invited to speak at a 1-day research meeting in 2002 with expenses partly paid by a vaccine manufacturer.

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