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The burden of Herpes Zoster: A prospective population based study

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Abstract

We analysed prospectively the medical, societal and economic burden among patients from 18 general practices in East London, serving 158,716 patients who presented to their general practitioners with acute Herpes Zoster over an 8-month period. One hundred and eighty-six patients with HZ were seen by GPs during the study period, of whom 96 were referred, 70 enrolled and 65 completed. PHN occurred in 13.4% of patients. The average overall cost of HZ in the first 6 months was calculated at £524 per patient. Medical costs were highest in those aged over 65 and societal costs highest in those aged under 65 years.
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1. Introduction

Varicella zoster virus (VZV) causes chickenpox (Varicella), a generally mild infection of childhood and shingles (Herpes Zoster), a painful unilateral vesicular rash which follows reactivation of virus latent in dorsal root and some cranial nerve ganglia [1]. The incidence of Herpes Zoster (HZ) increases with age, particularly in those over 50 years, and is higher in conditions associated with impaired cell mediated immunity, including HIV, steroid therapy and bone marrow or solid organ transplantation [1]. Between 13 and 26% of patients with Herpes Zoster develop complications [2–4], the most common of which is persistent neuropathic pain known as post herpetic neuralgia (PHN) [2–7]. PHN, also increases with age occurring in 50% of those aged 70 years and above [4,7]. Early administration of acyclovir and analogues to those most at risk has been shown to reduce the duration and severity of PHN but not to prevent it [8].

A multi-centred US study evaluated the efficacy of vaccine utilizing the Oka virus strain and placebo in preventing HZ and PHN in almost 39,000 subjects aged 60 years or greater. Incidence of postherpetic neuralgia was reduced by 66.5% and of HZ by 63.9% in the vaccine group [9]. Although a number of studies have estimated the medical [10,11,13] as well as societal [12,13] costs of HZ, to our knowledge there have been no community-based prospective studies of the associated health and economic burden. Better data are now needed on the savings that might accrue from immunisation to prevent acute zoster as well as PHN, particularly in relation to age as this affects both medical and societal costs.

2. Materials and methods

2.1. Design and setting

This was a prospective observational study conducted in general practices in Tower Hamlets and Hackney over 8 months. Using figures from Hope-Simpson, of 2–3 cases of shingles per 1000 population [4], and assuming an incidence of PHN at three months of 15% [4], we calculated that

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a population of 150,000 would produce 2–300 cases of shingles in 8 months and up to 45 cases of PHN. Following ethical approval, we approached 45 local GP practices who had previously participated in a shingles research study, were associated with the Academic Department of General Practice or had attended our educational meeting about HZ. Eighteen practices, covering a population of 158,716 patients, agreed to participate. Leaflets outlining best management practice for acute shingles and associated pain were distributed [14]. Briefly, zoster-level doses of acyclovir or analogues were recommended for patients over the age of 50 years who presented within 72 h of the onset of rash. Paracetamol or opiate analgesics were recommended for the acute pain with the addition of amitriptyline or gabapentin if necessary. GPs were alerted, at their discretion, to other treatments including capsaicin and referral to a specialist pain clinic for pain lasting longer than 6 weeks.

2.2. Recruitment

A Read Code-linked computer 'flag' was programmed into 11 out of 15 practices that used the EMIS patient record system, to remind GPs to refer patients within 7 days of rash onset or with active vesicles. The remaining practices (4) could not be programmed or did not have EMIS (3). Age, gender, ethnicity, and duration of rash of cases who were not eligible for inclusion, or who did not wish to be included, were recorded anonymously. Cases were confirmed by PCR of vesicle fluid for VZV [15].

Age, gender, self reported ethnicity and marital status were documented. Details of the patient's and carer's employment status and occupation and days of work lost to HZ were noted. Immunosuppressive conditions and drugs which might predispose to HZ were also documented, as were previous and current medication, including complementary and self-prescribed therapies. The nature, duration and severity of prodromal pain was recorded. The Zoster Brief Pain Inventory (ZBPI) [16] was used to assess level of pain and interference with activities of daily living caused by pain. In addition, abnormal sensations which are not normally classified as pain including itching, tingling, loss of sensation, allodynia, loss of vision (ophthalmic cases) were assessed using unambiguous objective questions devised by the authors for this study [9] Reduction in health-related quality of life was assessed by the EQ-5D (www.euroqol.org) [17] and anxiety and depression by the hospital anxiety and depression (HAD) score [18]. Patients were further assessed using all three questionnaires, at 4, 12 and 26 weeks following enrolment. In addition the duration of pain and abnormal sensations, the number of medical visits, the duration of use of each zoster related medication, and days off work were recorded.

2.3. Data entry

Questionnaires were completed by hand and the data for each visit entered into a password protected, SPSS database, in accordance with data protection requirements.

2.4. Missed cases

Missed cases of patients registered with the study practices were identified from Accident and Emergency and the Walk-In Clinic computerised data for the period of the study. Databases from the GP practices were searched for Read Coded cases of HZ that had not been referred.

2.5. Additional data sources

Population census data was obtained from National Census 2001(www.statistics.gov.uk/census2001/default.asp) for the calculation of age specific population rates of zoster and the analysis of ethnicity data.

2.6. Outcome and economic measures

Health related quality of life (QoL) was estimated from EQ-5D questionnaire data using time trade-off tariffs [18]. Pain interference estimates were derived by summation of the specific questions. Effect on mood was assessed with the Hospital Anxiety and Depression Scale (HAD) score, which was derived by simple summation of the separate anxiety and depression scores.

Unit costs for prescribed pharmaceuticals were taken from the British National Formulary [19]. The average unit costs for a GP consultation, outpatient consultations, and booked and emergency ambulance journeys were taken from standard sources [20]. The average cost of an inpatient stay was taken from NHS Reference Costs (www.dh.gov.uk), based on a Healthcare Resource Group of J45. Costs to wider society from work-loss by either the patient or carer were calculated using average age and sex-specific daily wages for part and full-time workers (www.statistics.gov.uk). Costs to the patients included self-reported travel and out-of-pocket expenses, such as prescription charges consultations with complementary medical practitioners. All costs were zoster-related and recorded in 2003 pounds sterling (UK£).

2.7. Statistical analysis

Demographic data were analysed in SSPS [21]. Multiple linear regression was used to assess the impact of explanatory variables on the baseline QoL estimate and the logarithm of costs to the patient, NHS and society (logarithms were taken as the costs were highly skewed). The explanatory variables assessed were age, sex (male = 0), whether the patient received antivirals, whether the patient had a history of zoster (1 = yes), a medical history of diabetes (1 = yes), whether the patient was receiving concomitant medication (1 = yes), had any immunocompromising conditions (1 = yes), the number of days of rash prior to presentation, whether the patient was married or cohabiting (1 = yes, 0 otherwise), was employed

(1 = yes, (part-time or full-time), 0 = otherwise, including homemakers, students, and retired individuals), and the ethnicity (1 = Caucasian, 0 = otherwise). Backward stepwise regressions were conducted in which explanatory variables with the least significant coefficients were sequentially omitted until all coefficients were significant at the 10% level. Results of the full and parsimonious models were compared to assess overall model fit and the robustness of estimated coefficients to alternative model specifications.

3. Results

Ninety-six cases of shingles were referred to the study (Fig. 1). Of these, 70 cases were confirmed as shingles by PCR, 22 were old, healing rashes which could not be confirmed, herpes simplex was found in three, and one case was eczema. During the study two patients died, and three withdrew consent to participate, leaving 65 cases who were followed up for the full 6 months. A further 94 cases were found from GP records after the study ended (Fig. 1). No previously unknown cases were found. Recruitment to the study was lower than expected, partly as a result of poor referral rates by some practices (Fig. 2). Eight practices referred 50% or more of HZ cases during the study period, and two of these referred all their recorded cases (Fig. 1). A significantly higher proportion of patients were referred from practices with EMIS prompts ($p \leq 0.001$; χ^2 11.34). The time from rash onset to GP consultation was shorter for those patients not referred (mean 4.3 days versus 5.9 days; Table 1) confirming that poor referral rates were not due to late clinical presentation. There were no significant differences in age, gender or ethnicity between the patients referred to the study and those not referred (Table 1) so the data were pooled to give a total of 186 patients with HZ as compared with 255–318 expected for this period [4] (Fig. 2). The annual incidence of HZ per 1000 patients for each practice ranged from 0.6 to 4.3 (mean 1.85; S.D. 0.92).

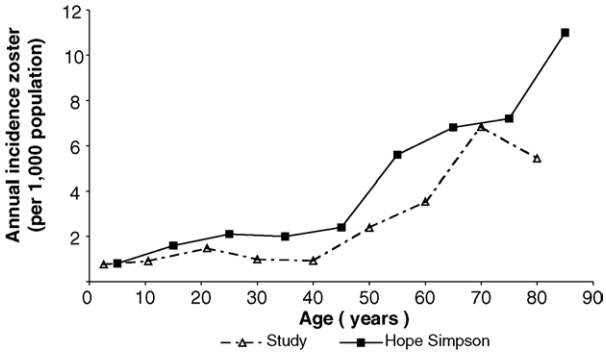

Fig. 2. Comparison of Hope-Simpson and study incidence of PHN.

3.1. Health outcome

The numbers of patients with pain at 3 months (by definition PHN) [22,23] as assessed by the ZBPI was 13.4% and at 6 months 5.4% (Fig. 3). Also shown in Fig. 3 are the numbers of patients who had pain (pain score of >0) and/or abnormal sensations (the presence of one or more of the abnormal sensations listed) as assessed by the questionnaire. This is in line (although at the lower end) with findings from other cohort studies of PHN [2–7]. The median duration of pain was 2 weeks. 79% of subjects age over 50 received antivirals and in 63% of cases the drugs were started within the recommended 72 h. Ninety-four percent (66/70) of patients received other prescribed drugs. Seventeen patients received amitriptyline (tricyclic) during the period of the study and two of these also received gabapentin (alpha-2 delta ligand). Ten of the 17 patients (58.8%) were prescribed amitriptyline at their first visit. The baseline QoL scores varied widely. Of the 69 patients with confirmed herpes zoster who filled

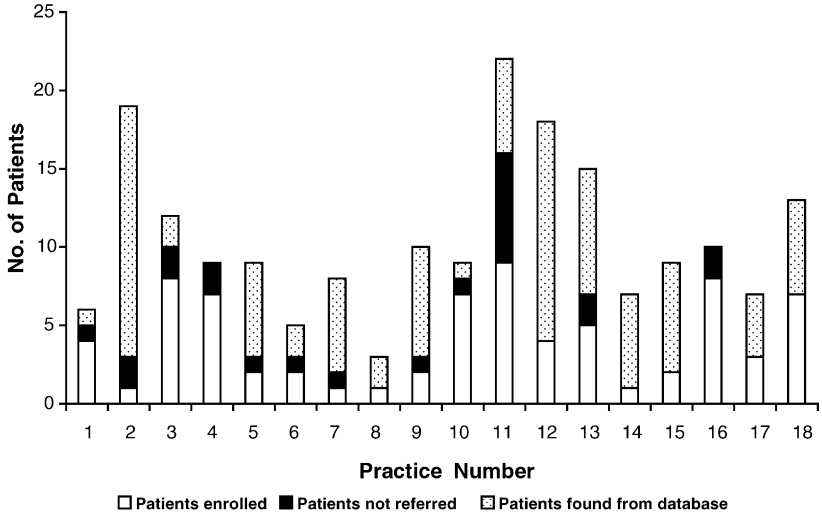

Fig. 1. Number of patients enrolled from 18 general practices.

Table 1
Characteristics of patients with herpes zoster

	Mean age (years)	Male	Caucasian	Mean no days from rash to GP consultation
Patients referred to study[a] ($n = 96$)	49.9	48 (50.0%)	76 (79.2%)	5.9 ± 0.49 (S.E.) 95% C.I. = 5.0–6.9
Patients with HZ ascertained from practice records ($n = 94$)	44.1	48 (51.1%)	63 (67.0%)	4.3 ± 0.26 (S.E.) 95% C.I. = 3.8–4.8
Patients recruited to study with confirmed HZ ($n = 70$)	50.7	37 (52.9%)	56 (80.0%)	4.9 ± 0.34 (S.E.) 95% C.I. = 4.3–5.6

[a] Ninety-two with HZ, four with other diagnoses.

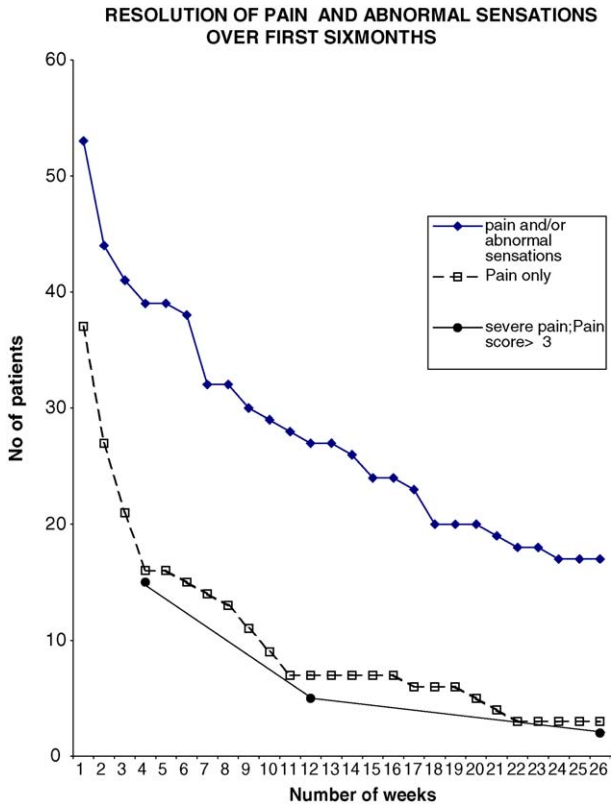

Fig. 3. Resolution of pain (pain score > 0), abnormal with or without abnormal sensations and severe pain (pain score > 3) over first 6 months.

out the EQ-5D questionnaire (one infant was excluded), the mean score was 0.43 (range −0.32 to 1; interquartile range 0.06–0.69). Female sex was associated with a lower QoL score at baseline assessment (average reduction in score = −0.31, $p = 0.0001$). No other variables, including age, previous history of zoster, presence of immunocompromising conditions, etc. was significantly associated with QoL score (Table 2). Pain and Anxiety were the dimensions of EQ-5D that were most affected by HZ. At baseline only four patients (6%) reported no pain or discomfort, and two thirds reported that they were moderately or extremely anxious or depressed. Although wide variability also occurred in self-reported HAD scores (mean 10.2; range 0–28) and pain interference (mean at baseline 23; range 0–66), they showed significant correlation with overall EQ-5D score (correlation coefficient = −0.73 and −0.47, respectively at baseline).

Fifty-seven of 66 patients who filled out the EQ-5D at 4 weeks, reported an improvement in self-assessed health related QoL at 4 weeks, five did not improve, and four had reported full health at baseline. The mean QoL score at 4 weeks was 0.87 (inter-quartile range 0.78–1). All five patients who failed to improve at 4 weeks, developed PHN. One died before completing the study and two were in pain with the remaining two still experiencing abnormal sensations at 6 months when the study ended (Fig. 4).

3.2. Economic outcomes

Among the 70 zoster patients with detailed follow-up information, there was a total of 146 zoster-related GP consultations, seven hospital consultations, three booked and six

Table 2
Results of regression of initial QoL score against explanatory variables

Explanatory variable	Full model				Parsimonious model			
	Coefficient	S.E.	t Stat	p-Value	Coefficient	S.E.	t Stat	p-Value
Intercept	**0.580**	**0.186**	**3.114**	**0.003**	**0.585**	**0.056**	**10.519**	**1×10^{-17}**
Age	0.000	0.002	−0.072	0.943	–	–	–	–
Sex	**−0.335**	**0.092**	**−3.662**	**0.001**	**−0.315**	**0.080**	**−3.943**	**2×10^{-4}**
Antiviral	0.032	0.066	0.479	0.634	–	–	–	–
Previous HZ	−0.059	0.256	−0.231	0.818	–	–	–	–
History diabetes	0.110	0.086	1.291	0.202	–	–	–	–
Concomitant medication	−0.013	0.110	−0.115	0.909	–	–	–	–
Immunocompromised	−0.151	0.139	−1.090	0.281	–	–	–	–
Days of rash before presentation	−0.004	0.016	−0.249	0.804	–	–	–	–
Married or cohabiting	−0.083	0.097	−0.857	0.395	–	–	–	–
Employed	−0.088	0.102	−0.859	0.394	–	–	–	–
Ethnicity	0.135	0.096	1.397	0.168	–	–	–	–
	F-test = 0.04, $r^2 = 0.28$, adjusted $r^2 = 0.14$				F-test = 0.0001, $r^2 = 0.19$, adjusted $r^2 = 0.18$			

Significant variables are shown in bold.

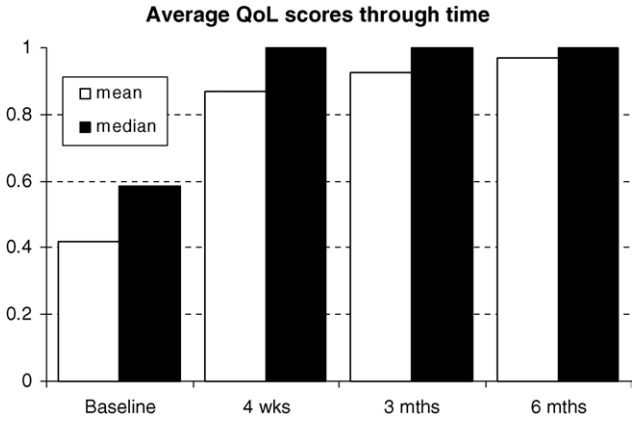

Fig. 4. Mean and median self-reported QoL scores over time, based on the EQ-5D time-trade-off tariffs.

emergency ambulance trips, four hospital admissions, and six consultations with complementary medical practitioners. A total of 307 workdays were lost by the patients, and another 52 by carers. Forty patients reported other associated expenses. The average costs to the patient, NHS and wider society over the follow-up period were £22, £198 (on average £47 was attributable to antivirals, and £23 to other prescribed drugs), and £304, respectively, giving an average overall cost of £524. However, there was considerable variation between patients and by age (Table 3). Zoster in elderly patients was associated with higher costs to the health service, but lower costs to society (fewer days of work lost). The regression analysis suggested that increasing age, the presence of immunocompromising conditions and the use of antivirals were all associated with increased costs to the health service, whereas a previous history of HZ was associated with decreased medical costs (Table 4a). Being

Table 3
Mean cost per case of HZ over 6-month follow-up period by age group of patient

Age class	Sample size	Patient (£)	NHS (£)	Society (£)	Total (£)
<65 years	45	10.8 (0, 4, 187)	85.6 (20, 68, 696)	430.0 (0, 26, 3265)	526.3 (20, 173, 3578)
65+ years	25	42.5 (0, 0, 1000)	400.9 (48, 138, 3257)	76.6 (0, 0, 957)	519.9 (48, 138, 4218)
Overall	70	22.1 (0, 1, 1000)	198.2 (20, 86, 3257)	303.8 (0, 0, 3267)	524.0 (20, 158, 4218)

The minimum, median and maximum costs are in parentheses.

Table 4
Results of regression of log costs to (a) the NHS and (b) society against explanatory variables

Explanatory variable	Full model				Parsimonious model			
	Coefficient	S.E.	*t* Stat	*p*-Value	Coefficient	S.E.	*t* Stat	*p*-Value
(a)								
Intercept	**1.282**	**0.223**	**5.758**	**3×10^{-7}**	**1.331**	**0.104**	**12.848**	**2×10^{-19}**
Age	**0.012**	**0.002**	**5.185**	**3×10^{-6}**	**0.011**	**0.002**	**5.661**	**3×10^{-7}**
Immunocompromised	**0.612**	**0.141**	**4.349**	**6×10^{-5}**	**0.581**	**0.125**	**4.660**	**2×10^{-5}**
Antiviral	**0.012**	**0.006**	**2.056**	**0.044**	**0.013**	**0.005**	**2.468**	**0.016**
Sex	0.014	0.091	0.150	0.881	–	–	–	–
Married or cohabiting	−0.149	0.098	−1.516	0.135	–	–	–	–
Previous HZ	**−0.537**	**0.261**	**−2.058**	**0.044**	**−0.687**	**0.251**	**−2.738**	**0.008**
History diabetes	0.012	0.082	0.142	0.887	–	–	–	–
Concomitant medication	−0.133	0.111	−1.196	0.237	–	–	–	–
Days of rash before presentation	−0.008	0.016	−0.482	0.632	–	–	–	–
Employed	0.102	0.104	0.984	0.329	–	–	–	–
Ethnicity	0.114	0.097	1.175	0.245	–	–	–	–
	F-test = 1×10^{-6}, $r^2 = 0.54$, adjusted $r^2 = 0.45$				F-test = 4×10^{-9}, $r^2 = 0.49$, adjusted $r^2 = 0.46$			
(b)								
Intercept	**1.871**	**0.742**	**2.522**	**0.014**	**0.978**	**0.285**	**3.434**	**0.001**
Age	−0.003	0.008	−0.354	0.725	–			–
Immunocompromised	−0.127	0.468	−0.271	0.787	–			–
Antiviral	0.016	0.019	0.847	0.400	–			–
Sex	−0.247	0.301	−0.820	0.416	–			–
Married or cohabiting	−0.040	0.327	−0.122	0.903	–			–
Previous HZ	−0.697	0.869	−0.802	0.426	–			–
History diabetes	−0.229	0.274	−0.838	0.406	–			–
Concomitant medication	0.022	0.371	0.059	0.953	–			–
Days of rash before presentation	−0.093	0.052	−1.773	0.081	−0.079	0.047	−1.688	0.096
Employed	**1.429**	**0.346**	**4.134**	**1×10^{-4}**	**1.548**	**0.294**	**5.273**	**1×10^{-6}**
Ethnicity	−0.344	0.324	−1.060	0.293	–	–	–	–
	F-test = 0.002, $r^2 = 0.38$, adjusted $r^2 = 0.26$				F-test = 1×10^{-6}, $r^2 = 0.33$, adjusted $r^2 = 0.31$			

Significant variables are shown in bold.

employed was significantly associated with increased costs to society (Table 4b). None of the variables included in the analysis were significantly associated with costs to the patient (regression results not shown).

4. Discussion

Herpes Zoster is estimated to affect over 300,000 patients a year in England and Wales [24]. Our data confirm that hospitalisations, severe pain and residual neurological deficit were more likely to occur in older patients, although two thirds of zoster cases occur in those under 65 years [4,5]. Severity is lower in this age group but the costs to society tend to be higher due to absence from work. Given the relatively low incidence of PHN at three months, 13.4% as compared with other observational studies 15–30% [2–7], the overall costs calculated here might be an underestimate of the true cost in other populations. In a previous study, 17% of patients diagnosed with HZ by their GP were found to have an alternative diagnosis [25]. For this reason we excluded patients whose rashes were too old to be confirmed by laboratory tests, i.e. more than 7 days after onset. This policy may have reduced recruitment bias as patients with severe pain are more likely to visit their GPs even after rash resolution. However, this may also have contributed to the apparently low incidence of PHN in our study. Fewer cases of acute HZ were recorded than expected largely as a result of poor referral and recording. Lower than expected presentation of HZ among those aged 25–45 might reflect work pressures and milder disease. The difference in ethnic mix of our local population as compared with other studies, may also have affected the incidence of HZ. The proportions of non-Caucasians recorded by the 2001 census in Hackney and Tower Hamlets were 40.1 and 48%, respectively as compared with 8.1% nationally. By contrast, 73% of cases recorded in the study and 80% of those recruited were Caucasian. The age specific incidence of HZ in African Americans is reported as 25% that of white Americans [26] and may be similar in Afro-Caribbean and Asian populations in our area. We were unable to test this hypothesis as ethnicity data were not collected by general practices.

Over 60% of patients at baseline and 16% at 4 weeks had pain (Fig. 3), which is comparable with previously reported studies [2–7]. Fewer patients than expected had PHN, perhaps reflecting exclusion of patients with pain occurring after the acute period. In addition, high levels of early antiviral prescribing (63%) and the early use of tricyclics and gabapentin (15%) may have contributed [27]. Despite this, the medical costs associated with acute zoster were over £198 per patient, with 72% of the total cost accounted for by patients aged over 65 years, who on average cost £401. A disproportionate increase in medical costs is therefore likely if the incidence of HZ rises with population aging and the increasing use of immunosuppressive therapies.

The US Veterans Administration Study to evaluate the vOka vaccine for zoster prevention in subjects aged over 60 years, has reported (see above) [9]. A full economic evaluation of the vaccine should be performed. However, using the results of this study, and making some reasonable assumptions about vaccine price and efficacy it is possible to establish whether vaccination against HZ might be cost-effective. Taking the incidence and costs evaluated in this study (both of which may be underestimated) and assuming a 15 year life-expectancy, a discount rate of 3.5%, and a vaccine efficacy of 65% (with no waning), then vaccination of 65 year olds would be cost-saving to society at £25 per vaccine course.

Acute Herpes Zoster and its sequelae are an economic burden to the health service, society and the individual, causing severe loss of quality of life in a subset of those affected. Current therapeutic options do not alleviate completely the acute pain and fail to prevent or manage PHN.

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