

Strapline: CNS infections

Title: A new herpes zoster subunit vaccine for older adults

Charlotte Warren-Gash¹, Judith Breuer²

Affiliations:

1. Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom
2. Division of Infection & Immunity, University College London, 90 Gower Street, London WC1E 6BT, United Kingdom

Correspondence to:

J.B. j.breuer@ucl.ac.uk

A randomized placebo-controlled phase 3 trial of adjuvanted herpes zoster subunit vaccine has shown a substantial improvement in vaccine efficacy in adults aged 70 years and over compared to the current live attenuated vaccine. The finding has profound implications for reducing illness burden, although the duration of vaccine protection needs further evaluation.

Refers to

Herpes zoster causes major morbidity among older people. The incidence of the disease rises dramatically with age, with a lifetime zoster risk for those aged ≥ 85 years approaching 50%¹.

Moreover **[Au: Addition of “moreover” here OK, to highlight that it is not only the incidence of HZ but also the increased likelihood of long term sequelae that is increased in older adults?]**, the risk of post-herpetic neuralgia — a debilitating neuropathic pain syndrome — increases markedly after the age of 50 years². Case fatality of herpes zoster is also highly age-correlated: more than 95% of deaths occur in people aged ≥ 60 years³. T-cell mediated immunity, which inhibits **[Au: OK to add “inhibit” here?]** reactivation of the varicella zoster virus (VZV) from latency and promotes recovery

after herpes zoster, declines progressively with age⁴. In addition, cell-mediated immune response to the currently licensed live attenuated zoster vaccine is lower in older age groups, and the effects of the vaccine wane over time⁴. Identification of more-effective strategies to prevent zoster among older adults is, therefore, essential.

In a GlaxoSmithKline-funded study, published recently in the *New England Journal of Medicine*, Anthony Cunningham and colleagues reported impressive efficacy of an adjuvanted herpes zoster subunit vaccine in adults aged 70 years and over⁵.

In the study, known as ZOE-70, 13,900 participants with a mean age of 75.6 years were recruited from 18 countries and randomly allocated to receive either two doses of an investigational herpes zoster subunit vaccine (HZ/su; GSK vaccines) or placebo⁵. The new vaccine **[Au: what does “su” mean? I think it could be useful to tell a bit more how it differs from the previous vaccines.]** contained 50 µg of recombinant VZV glycoprotein E and the liposome-based AS01b **[Au: Could you please briefly explain for the nonexpert reader what this is?]** adjuvant system, which enhances CD4+ T-cell and humoral immune responses to recombinant proteins. Over 3.7 years of follow up, only 23 confirmed cases of herpes zoster were observed in the vaccinated group, whereas 223 cases were confirmed in the placebo group, meaning that the vaccine efficacy (VE) for preventing herpes zoster in individuals who had received both vaccine doses was 89.8% (95% CI 84.2- 93.7).

To increase statistical power of the study, authors conducted several prespecified pooled analyses between participants from ZOE-70 and the ZOE-50 trial. The ZOE-50 trial was conducted by the same group of investigators, and used methods identical to ZOE-70 to investigate efficacy of HZ/su vaccine in adults aged ≥50 years⁶. The results of the ZOE-50 trial were published last year and showed a very marked reduction in herpes zoster among vaccinated participants in this age-group (VE 97.2% (95% C.I. 93.7- 99.0)). **[Au: Could you please briefly summarize them here?]** . Combined analysis of all 16,596 ZOE-50 and ZOE-70 trial participants aged ≥70 years showed a 91.3% (95% CI 86.8-94.5%) VE

against herpes zoster. In another prespecified pooled analysis of ZOE-50 and ZOE-70 trial participants aged ≥ 50 years, VE against post-herpetic neuralgia was 88.8% (95% CI 68.7-97.1%).

The choice of primary end point in the present study — reduction in herpes zoster incidence — is supported by a recent review of endpoints in zoster vaccine studies⁷, which concluded that use of the main alternative endpoint, burden of illness (determined by averaging pain severity and duration scores based on the Zoster Brief Pain Inventory), tends to overestimate VE⁷. Although other studies have considered the effect of zoster vaccine on activities of daily living or health-related quality of life, the main effect of zoster vaccine on these endpoints is through preventing zoster, rather than by attenuating severity or duration of illness⁷, which supports the approach Cunningham and co-investigators took.

The results of ZOE-70 [Au: ZOE-50 and ZOE-70 combined? It was not clear which results were being referred to.] are noteworthy for several reasons: first, they demonstrate a marked increase in efficacy over the current vaccine, which is licensed for adults aged 50 years and over. This is a live attenuated Oka/Merck VZV vaccine (Zostavax), shown in the landmark Shingles Prevention Study to reduce herpes zoster incidence by 51.1%, burden of illness attributed to shingles by 61.1%, and post herpetic neuralgia by 66.5%⁸. Second, efficacy of the new subunit vaccine did not diminish with advancing age: VE was 90.0% in those aged 70-79 years and 89.1% in participants aged 80 years or older. This compares favourably to age-stratified [Au: Correct? How did the older vaccine differ from the new one?] VE estimates for the current live attenuated vaccine of 69.8% in participants aged 50 to 59 years⁹, 63.9% among subjects aged 60-69 years and 37.6% among those aged 70 years and over⁸ for reducing herpes zoster incidence.

Establishing an adequate immune response to vaccines in older people is challenging: in general, the size [Au: What does size of response mean in this context?], duration and quality of response,

regardless of vaccine type, is lower than in younger people [Au: Edited sentence OK?] ⁴. The high efficacy of the new HZ/su vaccine suggests that the vaccine is able to overcome some of the processes associated with senescence of adaptive immunity, notably the high background inflammatory state implicated in age-related alterations to T-cell immunity¹⁰, which can [Au: Edit OK?] inhibit T-cell activation following vaccination in older people. Better understanding of the biology underlying the findings from ZOE-70 could, therefore, have more general implications for improving vaccine efficacy in the elderly

Besides older people, the HZ/su vaccine could benefit other groups with impaired cell-mediated immunity— such as those individuals on immunosuppressive therapies or with various haematological malignancies — who may be at high risk of herpes zoster but in whom live vaccine is contraindicated. HZ/su vaccine is not a live vaccine and as such, the virus [Au: Edit OK?] cannot replicate. The vaccine can, therefore, theoretically be used in immunocompromised people, although this was not tested in the trial, and safety and efficacy in this group would require further investigation.

One potential disadvantage of the HZ/su vaccine is the higher frequency of solicited injection-site and systemic reactions, most frequently fatigue, reported within 7 days of the vaccine compared with placebo (79.0% versus 29.5%). These adverse reactions tended to be transient, mild to moderate reactions, with a median duration of 2-3 days for injection site reactions and 1-2 days for systemic reactions. Systemic reactions were more frequently reported in HZ/su vaccine recipients (53.0%)⁵ than in recipients of live attenuated vaccine (25%)⁸. Importantly, rates of serious adverse events, immune-mediated disease and deaths did not differ between HZ/su vaccine and placebo groups. Another potential issue is compliance: the subunit vaccine requires two doses given 2 months apart, rather than one dose as is the case for live attenuated vaccine. Encouragingly, VE

results for the total vaccinated cohort (including people who received only one vaccine) remained high, with VE of 87.7% (95% CI 82.0-92.0%).

The duration of protection provided by the HZ/su vaccine remains an open question. Efficacy of the live attenuated vaccine declines markedly over the post-vaccination years 3 to 11. Although waning of HZ/su vaccine-induced immunity will start from a higher baseline, accurate assessment of the likely duration of protection is of key importance to inform cost-effectiveness estimates and, ultimately, the design of effective public health programmes. The HZ/su vaccine offers the exciting prospect of seriously reducing the population burden of zoster complications, especially in settings that already achieve a relatively high vaccine uptake.

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Competing interests statement

No competing interests declared. [Au: Please fill in any competing interests, or declare “no competing interests”.]

Author biographies

Dr Judy Breuer is Director of Infection and Immunity and Professor of Virology at University College London and Lead for Clinical Virology at Great Ormond Street Hospital for Children. Her research has focussed for many years on varicella zoster virus pathogenesis, molecular epidemiology and vaccines.

Dr Charlotte Warren-Gash holds a Wellcome Trust Intermediate Clinical Fellowship to investigate the role of neurotropic herpes viruses in neurological disorders of ageing. Her research focusses on using linked electronic health records and biological datasets to understand infectious determinants of chronic diseases and inform targeting of personalised preventive interventions. She is an honorary consultant in public health medicine.

[Au: We need a brief (just 50 words or so) biography for each author, detailing your current job title, careers and interests. This will be an online-only feature of the journal.]