Title: Herpes zoster in severely immunocompromised individuals: what are the options for prevention?

Authors: Charlotte Warren-Gash[1], Judith Breuer[2]

Affiliations:

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

Corresponding author: Dr Charlotte Warren-Gash

Email: charlotte.warren-gash1@lshtm.ac.uk. Tel: 020 7927 2796.

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"Of all the classical precipitants of zoster, two – leukaemia and Xrays – are at present the most important"

R.E.Hope-Simpson (1965)[1]

The link between compromised immunity and herpes zoster (HZ) has been recognised for more than half a century. Individuals who are severely immunocompromised due to immunosuppressive conditions or therapies experience HZ with greater frequency and severity. HZ incidence rates of 43.03, 17.04 and 17.43 per 1,000 person years at risk (PYAR) are reported in adults with bone marrow or stem cell transplants, solid organ transplants and HIV respectively, compared to 4.82 per 1,000 PYAR in a general population[2]. Complications of HZ are also roughly 3-fold higher among people with HIV compared to an age-matched general population[3]. Furthermore, severe immunocompromise is a contraindication to receiving live attenuated vaccine against varicella zoster virus (VZV), due to the potential risk of vaccine virus replicating to cause disease[4]. Preventing HZ and its complications in severely immunocompromised individuals therefore remains an important public health goal.

In this issue of the *Lancet Infectious Diseases*, Kathleen Mullane and colleagues report promising efficacy and safety of a gamma irradiation-inactivated VZV vaccine (vOka strain) in patients with solid tumour malignancies receiving chemotherapies[5]. In the randomised double-blind, placebo-controlled phase III trial conducted across 40 countries, the primary endpoint – HZ incidence – was markedly reduced among those receiving vaccine compared to placebo (22 versus 61 cases; vaccine efficacy (VE) 63.6% [97.5% CI 36.4%-79.1%]). These results came from 2,678 patients with solid tumour malignancies on chemotherapy followed for an average of 2.45 years who each received at least one vaccination (a modified-intention-to-treat population). The vaccine did not, however, reduce HZ incidence among 2,552 patients with haematological malignancies who received at least one vaccine dose (VE 16.8% [97.5% CI -17.8%-41.3%]).

Well-tolerated in patients with solid tumour malignancies receiving chemotherapy, the vaccine was not associated with differences in rates of serious adverse events (SAEs) or vaccine-related SAEs up to 28 days post-inoculation. Vaccine-related adverse events, typically mild injection-site reactions, were, however, more common in those receiving the gamma irradiation-inactivated vaccine compared to placebo (36.2% versus 14.1%). Similar patterns were seen among patients with haematological malignancies.

Non-live vaccines are likely to hold the key to preventing HZ among severely immunocompromised individuals. However, questions remain about which vaccine to use for which patient groups. The study by Mullane and colleagues highlights the heterogeneity of vaccine responses between patients with different immunocompromising conditions. It also raises an important issue about the validity of immunogenicity endpoints in vaccine trials. While individuals with haematological malignancies in this trial appeared to mount an effective immune response to the gamma-irradiated vaccine, this did not translate into clinical efficacy[5].

Another non-live adjuvanted recombinant zoster vaccine (RZV, Shingrix, GlaxoSmithKline) is also undergoing clinical trials among immunocompromised patients. Licensed to prevent HZ and PHN among adults aged ≥50 years, RZV is highly efficacious in immunocompetent older adults (VE ~90% in all age groups from 50 years[6]). Its safety and immunogenicity have been established in phase I/II trials among recipients of autologous haemopoietic stem-cell transplants (HSCT)[7] and people with HIV[3], as well as phase III trials among renal transplant patients[8]. Early trial results suggest a VE against incident HZ of 87% among patients with haematological malignancies[9], 68% in those with autologous HSCT[10] and 68% for renal transplant patients[11]. This compares to a VE of 64% for the gamma irradiation-inactivated vaccine among autologous HSCT recipients[12].

However, the duration of protection conferred by non-live vaccines among those with severe immunocompromise remains unclear. Despite four vaccine doses each a month apart, response to the gamma irradiation-inactivated vaccine waned markedly over time (VE ~80% months 0-12; VE 43.8% months ≥13). Duration of immunity has not yet been reported for RZV in immunocompromised individuals, although VE remains >88% against incident HZ at four years for immunocompetent older adults[6].

In summary, non-live vaccines offer new hope for preventing HZ and its costly complications among immunocompromised individuals. While implementation plans have yet to be finalised, some countries such as the UK are likely to recommend RZV for immunocompromised patients aged ≥50 years shortly. Large studies with clinically meaningful endpoints will provide further insights into the relative efficacies, duration of protection, long-term safety and cost effectiveness of non-live zoster vaccines for different immunocompromised groups.

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Declaration of interests

We report no conflicts of interest.

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