to maintain an immune response. Additional studies are needed to address the relative roles of this vaccine and antiviral prophylaxis and when best to apply different preventive strategies against varicella zoster reactivation in immunocompromised patients with haematological malignancies.

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Herpes zoster in people who are immunocompromised: what are the options for prevention?

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"Of all the classical precipitants of zoster, two—leukaemia and x-rays—are at present the most important", said R Edgar Hope-Simpson in 1965.[1] The link between compromised immunity and herpes zoster has been recognised for more than half a century. Individuals who are severely immunocompromised due to immunosuppressive conditions or therapies have herpes zoster more frequently and severely than the general immunocompetent population. Herpes zoster incidence per 1000 person-years at risk is reported to be 43·03 in adults with bone-marrow or stem-cell transplants, 17·04 in adults with solid organ transplants, and 17·43 in adults with HIV, compared with 4·82 in the general population.[2] Complications of herpes zoster are also roughly three times higher in people with HIV than in an age-matched general population.[3] Furthermore, severe immunocompromise is a contraindication to receiving live attenuated varicella zoster virus vaccine because of the potential risk of the vaccine virus replicating to cause disease.Preventing herpes zoster and its complications in individuals who are severely immunocompromised, therefore, remains an important public health goal.

In *The Lancet Infectious Diseases*, Kathleen Mullane and colleagues[4] report promising efficacy and safety of a γ irradiation-inactivated varicella zoster virus vaccine (v0ka strain) in patients with solid tumour malignancies receiving chemotherapy. In the randomised, double-blind, placebo-controlled, phase 3 trial done across 40 countries, the primary endpoint—herpes zoster incidence—was markedly reduced in patients with solid tumour malignancies receiving vaccine compared with those receiving placebo (22 *vs* 61 cases; vaccine efficacy 63·6%, 97·5% CI 36·4 to 79·1). These results came from 2678 patients with solid tumour malignancies on chemotherapy followed up for a mean of 2·45 years (SD 1·52) who each received at least one dose of the vaccine (the modified intention-to-treat population). The vaccine did not, however, reduce herpes zoster incidence in 2552 patients with haematological malignancies who received at least one vaccine dose (vaccine efficacy 16·8%, 97·5% CI –17·8 to 41·3).

The vaccine was well tolerated in patients with solid tumour malignancies receiving chemotherapy, with no differences between groups in frequencies of serious

adverse events or vaccine-related serious adverse events up to 28 days after the fourth dose. Vaccine-related adverse events, which were typically mild injection-site reactions, were, however, more common in those receiving the γ irradiation-inactivated vaccine than in those receiving placebo (36·2% *vs* 14·1%). A similar safety profile was seen in patients with haematological malignancies.

Non-live vaccines are likely to hold the key to preventing herpes zoster in individuals who are immunocompromised. However, questions remain about which vaccine to use for which patient group. 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. Although individuals with haematological malignancies in this trial appeared to mount an effective immune response to the γ-irradiated vaccine, this response did not translate into clinical efficacy.[4]

Another non-live herpes zoster vaccine (Shingrix; GlaxoSmithKline, King of Prussia, PA, USA) is also undergoing clinical trials in patients who are immunocompromised. Licensed to prevent herpes zoster and post-herpetic neuralgia in adults aged 50 years and older, this adjuvanted recombinant vaccine is highly efficacious in older adults who are immunocompetent (vaccine efficacy of around 90% in all age groups from 50 years).[5] Its safety and immunogenicity have been established in phase 1/2 trials in recipients of autologous haemopoietic stem-cell transplants[6] and people with HIV,[3] as well as in phase 3 trials in patients who have had renal transplantation.[7] Phase 3 trial data published alongside the Article of Mullane and colleagues showed safety and immunogenicity of Shingrix in patients with haematological malignancies receiving immunosuppressive therapies.[8] Early trial results suggest that efficacy of this vaccine against incident herpes zoster is 87% in patients with haematological malignancies,[9] 68% in individuals with autologous haemopoietic stem-cell transplants,[10] and 68% in patients who have had a renal transplant (NCT01610414). The efficacy of the γ irradiation-inactivated vaccine in recipients of autologous haemopoietic stem-cell transplants was 64% in a phase 3 trial.[11]

The duration of protection conferred by non-live vaccines in individuals who are severely immunocompromised remains unclear. Despite administration of four vaccine doses each a month apart in the study by Mullane and colleagues, response to the γ irradiation-inactivated vaccine waned markedly over time (vaccine efficacy of around 80% for months 0–12 *vs* 44% beyond 1 year). Duration of immunity has not yet been reported for the attenuated recombinant vaccine in individuals who are immunocompromised, although vaccine efficacy remains higher than 88% against incident herpes zoster at 4 years in older adults who are immunocompetent.[5]

In summary, non-live vaccines offer new hope for preventing herpes zoster and its costly complications in individuals who are immunocompromised. Although implementation plans have yet to be finalised, some countries such as the UK are likely to recommend the recombinant herpes zoster vaccine for patients who are immunocompromised and aged 50 years or older in the coming months. 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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First clinical trial of a MERS coronavirus DNA vaccine

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Middle East respiratory syndrome (MERS) coronavirus is an emerging pathogen with pandemic potential that continues to cause sporadic human disease 7 years after the first case in a human was detected in 2012.[1] Zoonotic transmission with consequent risk of human epidemics will probably continue into the future, given that MERS coronavirus appears to be highly endemic among dromedary camels from geographically widespread areas of the Middle East and Africa.[2] In light of this potential threat to global public health, WHO along with the Coalition for Epidemic Preparedness Innovations have prioritised research and development of countermeasures against MERS coronavirus,[3,4] and WHO has developed a target product profile for both preventive and reactive use of MERS coronavirus vaccines.[5]

In *The Lancet Infectious Diseases*, Kayvon Modjarrad and colleagues[6] report results from their phase 1, open-label, dose-ranging study of GLS-5300, the first DNA vaccine candidate against MERS coronavirus to enter clinical trials. In the study, 75 adults aged 18–50 years at one site in the USA were enrolled sequentially using a dose-escalation protocol to receive 0·67 mg, 2 mg, or 6 mg GLS-5300 intramuscular injection at baseline, week 4, and week 12 followed immediately by co-localised intramuscular electroporation. The primary outcome of the study was safety, assessed during the vaccination period up to 48 weeks after dose 3.

There were no vaccine-associated serious adverse events. The most common adverse events were injection-site reactions (in 93% of participants), the most common solicited symptom was administration-site pain (92%), and the most common unsolicited adverse events were infections (36%). Seroconversion measured by MERS coronavirus spike glycoprotein subunit 1 (S1)-ELISA was detected in 66% and 86% of participants after the first and second injections, respectively, and in 79% at week 60. Neutralising antibodies were detected in 27 (43%) of 63 participants at week 14, 25 (39%) of 65 at week 24, and two (3%) of 66 at week 60. MERS coronavirus S-specific IFNγ-ELISPOT responses were detected in 47 (71%) of 66 participants after the second injection and in 44 (76%) of 58 after the third vaccination.

No licensed MERS coronavirus vaccine is currently available, and substantial challenges exist to the development of such a vaccine. These include: (1) available animal models (eg, transduced mice, and transgenic mice, rabbits, rhesus macaques, marmosets, alpacas, and camels) might not mimic human disease;[7] (2) an immune correlate of protection has not been defined, and the protective immune response in natural infection is poorly understood, although both humoral and cellular responses are probably necessary for viral clearance;[8] (3) there is a theoretical risk of immune enhancement during MERS coronavirus infection after vaccination, possibly leading to immunopathological pulmonary eosinophilic infiltration;[9] (4) demonstration of efficacy in the field will probably not be possible, necessitating alternative regulatory pathways for licensure; and (5) if MERS shifts from a pattern of sporadic outbreaks to pandemic spread, it is not known whether vaccines based on current MERS coronavirus isolates will offer protection against pandemic strains.

The results of Modjarrad and colleagues' study illustrate the challenges and promise in developing a vaccine against a novel pathogen with episodic outbreaks and little available knowledge. Despite preclinical demonstration of protection by GLS-5300