Review

Varicella and herpes zoster vaccine development: lessons learned

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ABSTRACT

Introduction Before vaccination, varicella zoster virus (VZV), which is endemic worldwide, led to almost universal infection. This neurotropic virus persists lifelong by establishing latency in sensory ganglia, where its reactivation is controlled by VZV-specific T-cell immunity. Lifetime risk of VZV reactivation (zoster) is around 30%. Vaccine development was galvanised by the economic and societal burden of VZV, including debilitating zoster complications that largely affect older individuals.

Areas covered We describe the story of development, licensing and implementation of live attenuated vaccines against varicella and zoster. We consider the complex backdrop of VZV virology, pathogenesis and immune responses in the absence of suitable animal models and examine the changing epidemiology of VZV disease. We review the vaccines' efficacy, safety, effectiveness and coverage using evidence from trials, observational studies from large routine health datasets and clinical post-marketing surveillance studies and outline newer developments in subunit and inactivated vaccines.

Expert commentary Safe and effective, varicella and zoster vaccines have already made major inroads into reducing the burden of VZV disease globally. As these live vaccines have the potential to reactivate and cause clinical disease, developing alternatives that do not establish latency is an attractive prospect but will require better understanding of latency mechanisms.

Keywords: Varicella; herpes zoster; live attenuated vaccine; subunit vaccine; vaccine safety; vaccine efficacy; vaccine effectiveness; post-marketing surveillance

1. Introduction: Varicella zoster virus: structure, pathogenesis and immune response

Varicella zoster virus (VZV) is a ubiquitous neurotropic human herpesvirus that causes two distinct diseases. These are primary varicella infection (chickenpox) and herpes zoster (shingles), a vesicular dermatomal rash that results from reactivation of the latent virus. Along with herpes simplex virus types 1 and 2, VZV is part of the alpha herpesvirus family of DNA viruses. Its linear 125kb double-stranded DNA genome encodes at least 71 unique open reading frames (ORFs)[1], with approximately 40 conserved genes shared with other human herpesviruses[2]. The genome is located within an icosahedral capsid, surrounded by a protein tegument and encapsulated by a polyamine, lipid and glycoprotein envelope[3]. Glycoproteins located within the envelope facilitate viral entry into cells[4].

After transmission to a susceptible host, VZV proliferates in the oropharynx[5]. During an initial viraemic phase, infected T cells transport the virus to skin and possibly other organs, although the lack of suitable animal models of infection limits understanding of the precise mechanisms of VZV pathogenesis[6]. Epidermal replication of the virus to produce cell-free VZV occurs; when local antiviral responses have been overcome, the characteristic lesions of varicella appear[6]. The incubation period ranges from 10 to 21 days.

Viral replication during infection is controlled by both innate and adaptive immune responses, with initial host defences mediated through natural killer cells and type 1 interferons[2]. VZV-specific T cells, which are essential to terminate the viraemic phase and enable recovery from varicella, become detectable one to three days after the skin rash appears[7]. These VZV-specific T cells target antigens that include VZV glycoprotein gE, immediate early (IE) 62 protein and other viral proteins[8]. Severity of infection is inversely correlated with the rapidity of T-cell proliferation and the magnitude of this response[7,9]. Individuals with T-cell deficiencies such as patients with

haematological malignancies, those on chemotherapy or people with HIV typically experience severe varicella[10,11]. VZV-specific T-cell immunity is primarily a T helper type 1 (Th1) response, which produces characteristic cytokines such as interleukin (IL)-2, IL-12, tumour necrosis factor (TNF)-a and IFN-gamma[12].

In addition, IgM, IgA and IgG antibodies directed against a range of VZV proteins are detectable within 3 days of the appearance of the varicella rash[8]. However, unlike for VZV-specific T-cells, early production of antibodies is not associated with reduced clinical severity of infection[7]. Patients with agammaglobulinaemia have similar levels of protection against a second episode of varicella as individuals with normal B-cell responses[13], again suggesting that antibodies are not crucial to VZV control. This is supported by studies using the simian varicella virus model – the only animal model that approximates human varicella infection. In this model, CD4 T-cell immunity was more critical for controlling varicella than CD8 T-cell responses and antibodies[14].

After resolution of initial infection, VZV establishes latency in sensory ganglia, where it persists lifelong. During latency, the VZV genome is maintained in a non-integrated circular concatemeric form, with a very restricted pattern of viral gene expression[3]. The absence of an animal model of VZV natural history has hampered understanding of the precise pattern of gene expression during latency, although low-level transcription of the immediate early gene ORF 63 has been repeatedly detected in human ganglia from autopsy samples taken as close to death as possible[15]. Recent evidence suggests that latency of both VZV and herpes simplex virus type-1 may be epigenetically regulated[15]. VZV-specific memory T-cells, with a mixed central and effector phenotype, are important for maintaining VZV latency, with immunity boosted periodically by endogenous (subclinical) reactivation and exogenous re-exposure to VZV[16]. Latent virus retains its ability to resume replication and cause recurrent clinical disease[3].

The increase in VZV reactivation observed with age is largely attributed to declining T-cell, rather than humoral, immunity[17]. It remains unclear whether this effect is mediated through a reduction in the quantity or quality of circulating T-cells[16]. As with varicella, the magnitude of VZV-specific T-cell immunity in shingles is inversely correlated with disease severity and the risk of serious consequences such as post-herpetic neuralgia[16]. A single episode of herpes zoster results in a rapid marked T-cell response and typically protects individuals from repeated zoster episodes[16], although recurrence is observed in around 6% of immunocompetent herpes zoster patients in both Japan and the US[18,19].

2. Epidemiology of varicella and herpes zoster

Varicella is present worldwide. It has a distinct seasonal pattern in temperate climates where the highest incidence occurs in winter and spring[5]. Before the introduction of varicella vaccine, almost universal infection with VZV occurred, with the annual incidence of varicella in many countries corresponding approximately to the birth cohort[20]. There are some geographic differences, e.g. infection typically occurs in early childhood in temperate settings such as the U.S. where more than 90% of people are infected before the age of 15 years[5,21], in contrast to tropical countries where primary VZV infection may be more common among adolescents and adults[9].

Varicella is highly infectious, with a secondary attack rate of around 90% among susceptible household contacts[22]. It is transmitted from person to person through inhalation of virus-containing droplets and from direct contact with or aerosol transmission from infectious vesicular fluid[2,21,23]. Patients with varicella remain infectious from 1 to 2 days before the onset of rash, until around 4 to 5 days after rash onset when all of the lesions have formed crusts[22].

Clinical varicella is usually a mild self-limiting illness, characterised by a widespread vesicular rash frequently accompanied by fever and malaise, but complications affect around 2 to 4% of cases. In developed countries, there are around 3 to 6 hospitalisations for every 1,000 cases of varicella and around 3 deaths per 100,000 cases[24]. Complications are more common at the extremes of age, among people with cellular immune deficiencies and pregnant women but can also occur among previously healthy people[21,24]. These include secondary bacterial infections of skin and soft tissue, pneumonia, sepsis, neurological complications such as encephalitis and haemorrhages. The risk of congenital varicella syndrome is around 1 to 2% for pregnancies affected up to 20 weeks[24]. Even among those with mild illness, varicella causes a substantial societal burden, resulting in school absenteeism and necessitating time off work for caregivers[25].

Clinical VZV reactivation, or zoster, is experienced by around 25 to 35% of people over their lifetime[26]. In many developed countries, there has been a gradual increase in zoster incidence over time that predates the introduction of varicella vaccine and may relate to changing social or environmental conditions. Overall zoster incidence is 2.0 to 4.6 cases per 1,000 person years rising to 10.0-12.8 cases per 1,000 person years in people aged 80 years or over[27,28]. Both the incidence and severity of zoster increase with age, with complications occurring in almost half of older people with zoster[29]. Post-herpetic neuralgia, a debilitating neuropathic pain syndrome, is the commonest complication, increasing notably with age – typically rates start to rise from around age 50 years – and among people with severe immunosuppression[30]. Other possible sequelae of zoster include ophthalmic involvement, a range of neurological complications including cranial nerve palsies and meningoencephalitis[21], exacerbations of underlying cardiovascular disease causing stroke and myocardial infarction[31,32] as well as the possibility of disseminated disease, predominantly among immunocompromised populations[21].

For varicella among immunocompetent individuals, treatment is usually symptomatic. Antiviral treatment with oral aciclovir in healthy children initiated within 24 hours of rash onset can reduce the number of lesions, the duration of systemic signs and symptoms and promote earlier healing of cutaneous lesions[33,34]. Administration of varicella zoster immunoglobulin (VZIG) as post-exposure prophylaxis is recommended for individuals with a significant exposure to varicella or zoster, who have a clinical condition that increases their risk of severe varicella and are seronegative for VZV[22]. Use of antiviral agents such as aciclovir, valaciclovir and famciclovir to treat zoster reduces the severity and duration of illness[35,36] but may not be associated with a reduction in post-herpetic neuralgia[37]. Developing vaccines to reduce the population burden of VZV disease has therefore been an important goal.

3. Story of varicella vaccine development

The first live attenuated vaccine, known as vOka, was developed in Japan in 1974 to reduce severe or fatal complications of varicella among immunocompromised children[38]. Derived from wild type VZV isolated from a child with typical varicella, vOka was produced through serial passage of the wild type virus in human embryo fibroblast cells and guinea pig embryo fibroblasts with additional propagation in human diploid cells (WI-38)[1,39]. The vOka is attenuated for replication in skin but less so in other target tissues such as T cells and trigeminal ganglia[40,41]. It comprises a mixture of VZV genotypes and, by deep sequencing of multiple batches, has been shown to differ from wild type Oka strains by at least 224 single nucleotide polymorphisms[42]. Which of these is primarily responsible for attenuating the virulence of VZV in live vaccines remains unclear, but fixed mutations at positions 106262, 107252 and 108111 in ORF62 are believed to play key roles[43]. A further 11 positions have been shown to be significantly more likely to be wild type in vaccine viruses recovered from post immunisation rashes, encephalitis and retinitis, suggesting a role for the vaccine allele in attenuating replication in tissue[42]. Of these, a stop codon at position 560 in ORF0

has been shown to reduce VZV replication in epithelial xenografts in scid hu mice[44], while a substitution of lysine for proline at position 446 in a transactivating region of ORF 62 is always wild type in rashes (p 7.25 x 10^{-11}) suggesting a critical role in recovery of replicative ability in skin[42,45].

3.1 Varicella vaccine efficacy and safety

Early studies in healthy children in Japan showed that the vaccine was safe and produced strong, persisting immunity[39,46,47]. In the US, a randomised controlled trial (RCT) of high potency varicella vaccine conducted among 914 healthy children with a mean age of 4.7 years showed a vaccine efficacy (VE) of 100% at one year and 98% at two years, or 92% in households with a case of varicella[48]. In most early dose-ranging and efficacy trials, the vaccine gave a high degree of protection against varicella, but some vaccine failures occurred, notably in very young children, children with asthma or eczema and children on corticosteroid treatment[49]. Importantly, clinical trials among children with acute leukaemia or other cancers showed that vaccination was safe for patients among whom chemotherapy was suspended who had acceptable lymphocyte counts or were in remission[50].

Varicella vaccines were first licensed in Germany and Sweden in 1984[51], Japan and Korea in 1988 and the U.S. in 1995[21]. The currently licensed monovalent vaccines – Varivax (OKA/Merck) and Varilrix (OKA/GSK) – were derived from the seed vOka by additional passaging in cell culture[49]. Two combined measles-mumps-rubella-varicella live attenuated vaccines (ProQuad/Merck, Priorix-Tetra/GSK) were also developed to enable more streamlined integration with existing childhood vaccination schedules[49]. ProQuad/Merck was licensed by the US Food and Drug Administration (FDA) in 2005 for children aged 12 months to 12 years[21] on the basis of safety and non-inferior immunogenicity compared with MMR and monovalent varicella vaccines[24].

3.2 Varicella vaccine effectiveness and coverage

Even though the vaccine was originally developed in Japan, as vaccination remained voluntary until 2014[38], much vaccine effectiveness data is derived from the United States where a universal single dose varicella vaccine programme was introduced for children aged 12 to 18 months in 1995[52]. There has been extensive post-licensing surveillance of the Varivax monovalent vaccine, which shows that it is generally well-tolerated[53], with an effectiveness of a single dose for preventing varicella of around 80 to 85%, reaching 97 to 100% for prevention of severe cases[24]. For the quadrivalent MMRV vaccine, similar studies have shown that one additional febrile convulsion occurs for every 2,300 to 2,600 children aged 12 to 23 months who receive the combined vaccine compared to separate MMR and varicella vaccines at the same visit[21].

Vaccine coverage in the US rose from 25.8% in 1997 to 87.9% in 2005[54]. Among children who were aged seven in 2012, 88% had received two doses of vaccine[55]. Active surveillance in two geographical sites showed that varicella disease had declined by around 90% in 2005, compared to rates in 1995, in areas with vaccine coverage of 94% and 92% respectively. The decline was seen in all age groups, with the highest reductions in children aged under 10 years. An 80% decline was seen among infants too young to be eligible to receive the vaccine and a 74% decline among adults, suggesting that the vaccine induced herd immunity[56]. In addition, varicella-related hospitalisations and deaths declined to a very low level in developed countries with universal childhood varicella vaccination programmes[24]. Despite this, mild breakthrough infections were commonly observed among vaccinated children in outbreaks in daycare and primary schools. This led to the Advisory Committee on Immunization Practices (ACIP) approving a routine two dose varicella vaccine schedule for children in the US in 2006[57].

Currently there is varying practice globally in the use of childhood varicella vaccines. The World Health Organization (WHO) recommends that countries in which varicella poses an important public

health problem should consider introducing varicella vaccine into the routine childhood immunisation schedule, with the first dose given at 12 to 18 months of age[51]. Conditions essential for an effective vaccine programme include having adequate disease surveillance and sufficient resources to maintain vaccine coverage at over 80%[51]. Universal childhood vaccination is recommended in some settings such as the US, Canada, Australia, New Zealand, Japan, South Korea and some parts of the Middle East and South America. In Europe, only five countries (Cyprus, Germany, Greece, Latvia and Luxembourg) recommend universal childhood varicella vaccine at national level and two at regional level (Italy and Spain)[49]. A further 17 European countries recommend nationwide vaccination only for susceptible adolescents or medical and occupational risk groups[49]. A previous review suggested that the decision made by some European countries not to implement routine varicella vaccine programmes may reflect lack of recognition of varicella as a serious disease, as well as concerns that vaccine-induced changes to the epidemiology of varicella and zoster could give rise to more complications[58]. Variable cost-effectiveness estimates and perceived difficulties in obtaining suitable vaccine coverage are also likely to contribute to reluctance to implement universal vaccination programmes.

3.3 Unanswered questions about varicella vaccine

Optimal dose schedule

When varicella vaccine is included as part of the universal childhood immunization schedule, it is unclear whether one or two doses is preferable. A one-dose schedule has been shown to be highly effective in reducing severe disease, but breakthrough cases of mild varicella occur. Studies comparing immune responses following a one- or two-dose regime have shown that higher seroconversion rates and a higher antibody titre are achieved among subjects who receive two vaccine doses, regardless of the time interval between doses[59-62]. Nevertheless, cost-effectiveness modelling of two- versus one-dose schedules, suggesting that addition of a second

dose demonstrates unfavourable incremental cost-effectiveness, has been instrumental in informing Australia's decision to implement a one-dose schedule[55,63]. More recent modelling suggests that improving vaccine coverage, e.g. from 83% to 95% by age 24 months, results in the incremental benefit of a second dose falling by 70%[64]. As well as being cheaper to implement, potential advantages to a one-dose schedule include the persistence of low levels of circulating wild type varicella, which would prevent a shift of varicella into older age groups who are at greater risk of complications. Persisting varicella circulation would also provide exogenous boosting to maintain levels of immunity in older people, and theoretically prevent a rise in the incidence of zoster cases[65,66].

Incidence of varicella complications to inform models

Models of the cost-effectiveness of varicella vaccination programmes are highly dependent upon assumptions about complex immunological processes, and may be hampered by a lack of robust studies to guide parameterisation. In the UK, lack of data on some serious complications of varicella such as invasive group A streptococcus, have been noted as a limitation to cost-effectiveness modelling[66]. Other areas of limited knowledge, highlighted by a recent report on varicella vaccine in the EU, include the duration of vaccine-induced immunity, the optimal timing of second and subsequent doses of vaccine, whether breakthrough varicella increases in severity with time from vaccination, and the effect of different levels of vaccine coverage on long-term VZV epidemiology including zoster incidence[49].

Effect of varicella vaccine on zoster incidence

VZV vaccine could affect zoster incidence in two ways. First, direct reactivation of the vOka strain can cause zoster among vaccinated individuals. However, in vitro studies of a VZV latency model using induced pluripotent stem cell neurones show that, while both vOka and wild type VZV are equally capable of establishing latency, vOka is less able to reactivate[67]. This is supported by studies

among both immunocompetent and immunocompromised individuals, which show significantly lower rates of zoster among vaccinated children than among those infected naturally with wild type virus[1,68].

Second, the dramatic decline in varicella incidence associated with universal vaccination programmes reduces the probability of exogenous immune boosting through contact with varicella cases in the community[69]. A seminal paper by Brisson et al, that modelled the impact of mass vaccination of 12 month old Canadian children, suggested that the most effective programmes for reducing varicella incidence also resulted in the biggest increase in zoster cases[65]. This finding was extended in a transmission dynamic model using a similar approach, which concluded that implementing an infant vaccination programme in the UK was likely to result in an increase in zoster cases for up to 30 to 50 years[70]. Authors concluded that vaccinating older people against zoster would only partly offset this rise, as most new zoster cases were predicted to occur among people too young to be vaccinated[70]. In the US, however, there has not been a rapid rise in zoster incidence following introduction of universal varicella vaccine[55]. This might be explained through the initial one-dose schedule and low early vaccine coverage allowing continued VZV transmission, although some US commentators consider that the effect of exogenous boosting might be less than previously estimated. While it is clear that both endogenous and exogenous boosting contribute to maintaining VZV-specific T-cell immunity[69,71], the relative contribution of these mechanisms remains controversial. Knowledge of the magnitude and duration of an immune boost conferred by an exogenous varicella contact, as well as the population and situations in which such boosting occurs, is critical to inform accurate mathematical models of VZV transmission[72].

4. Development of a vaccine against zoster, efficacy and safety

The varicella vaccine provided an important opportunity to explore whether boosting VZV-specific T-cell immunity in older adults reduced the risk of VZV reactivation. Early research using the varicella vaccine found that it successfully increased levels of VZV T-cell immunity among healthy, older adults[73-76], and decreased the incidence and severity of zoster in bone marrow transplant recipients[77,78].

Thirty years after development of the live-attenuated Oka vaccine to prevent varicella, the same vaccine was trialled at a much higher concentration for zoster prevention. This vaccine had a minimum potency of 19,400 plaque-forming units (PFUs) per dose compared to Varivax, where the equivalent figure is 1,350 PFU/dose[21]. The Shingles Prevention Study (SPS) was the first trial to demonstrate zoster vaccine efficacy: in this randomised, double-blind, placebo-controlled trial of 38,546 participants aged 60 years and over in the US, the vaccine reduced the incidence of zoster by 51% and PHN by 67%[79]. A later double-blind, placebo controlled clinical trial, the ZOSTAVAX Efficacy and Safety Trial (ZEST), which was carried out among 22,439 people aged 50-59 years from North America and Europe, demonstrated a VE for preventing zoster of 69.8%[80]. Recently, a Cochrane review including 10 RCTs of live attenuated zoster vaccine found that the pooled risk ratio for incident zoster up to three years post vaccination was 0.49 (95% C.I. 0.43 to 0.56)[81]. The zoster vaccine has not demonstrated major safety concerns. In the SPS, which assessed vaccine side effects in 97% of study participants, serious adverse events within 42 days of inoculation were reported in the same proportion of vaccinated (1.4%) and unvaccinated participants (1.4%)[79]. A more detailed sub-study of 6616 SPS participants found local side effects, such as erythema, pain, swelling, rash and pruritus, at the inoculation site were more frequently reported in the vaccinated (48%) than the placebo group (16%). However, events were rarely long-lasting or severe. Longer term follow-up showed rates of hospitalization and death were similar between the vaccinated and unvaccinated

groups[82]. The vaccine was also well-tolerated in the ZEST trial, with serious adverse event rates similar in both groups [80].

4.1 Zoster vaccine use, effectiveness and uptake

The currently available zoster vaccine – Zostavax (Merck) – was first licensed in 2006 by the FDA and is now approved for use in over 60 countries worldwide[83]. However, indications for zoster vaccination vary by setting and WHO does not currently offer any recommendation concerning routine use of zoster vaccine, due to uncertainty about the burden of disease in many countries[51]. In the US, zoster vaccine is recommended by ACIP for immunocompetent adults aged 60 years and over[21] whereas in the UK, where a zoster vaccine programme was introduced in 2013/14, it is recommended for immunocompetent individuals at the age of 70 years, with a catch up campaign for older cohorts aged up to 79 years[84]. Other countries including Australia and France also recommend routine zoster vaccine for older adults.

Research suggests the zoster vaccine has already impacted on zoster burden. A cohort study, using routinely collected claims data from Kaiser Permanente health plan in the US, identified 75,761 vaccinated individuals over 60 years and matched them to three unvaccinated controls; the incidence of zoster was reduced by 55% in those vaccinated[85]. Unpublished data from the Clinical Practice Research Datalink, a routinely collected primary care database of almost 13 million patients in the UK, suggests that among patients in England aged between 65 and 84 years, there has been a 22% decline in consultations for zoster among those eligible for vaccination, compared to those ineligible[66].

Despite the well-established efficacy and real-world effectiveness of the vaccine, its uptake has varied considerably worldwide. In England, where the zoster vaccine was offered to patients alongside influenza vaccine, coverage in the first year of the programme was 61.8% for the 70-year

old routine cohort and 59.6% for the 79 year old catch-up cohort[86] (although uptake has declined a little since[87]). In contrast, uptake in the US was initially very low, though has shown improvement in recent years; claims data from over 6 million US adults aged 60 years and above, suggest zoster vaccine coverage increased from 1.3% in 2007 to 19.5% by 2013[88]. Coverage in Canada, where the vaccine is not publicly funded, has been similarly low; in the region of Alberta in Canada, 8.4% of patients age 60 years and over were vaccinated between 2009-2013[89]. Both patient and provider barriers have been suggested to explain the poor uptake of the zoster vaccine in the US, such as high vaccine cost, complex methods for reimbursement and requirement for freezer storage[90,91]. A survey of public attitudes to zoster vaccine in South Korea found that high vaccine cost and low perceived risk of zoster were the main obstacles to vaccination, although a physician recommending the vaccine could reverse around 70% of vaccine refusals[92].

Administration of the zoster vaccine with another routinely given vaccine may improve uptake. Concomitant administration of the zoster vaccine with inactivated influenza vaccine does not alter the immunogenicity of either vaccine[93]. Although the FDA initially prohibited concurrent use of the zoster and pneumococcal vaccine after an RCT suggested that this may result in lower VZV antibody levels[94], this guidance has now been revised. A US-based retrospective cohort study compared incidence rates of zoster, rather than antibody levels, over a three year period among individuals receiving both vaccines either concomitantly (n=7187) or with at least a 30 day gap (n=7179). The study found no difference between the groups (HR 1.19, 95% CI 0.81-1.74)[95].

4.2 Cost-effectiveness of zoster vaccine

A range of studies from different settings have demonstrated that zoster and its complications place a substantial economic burden on health-care system[96]. In a review of 15 studies from North America and Europe, most concluded the zoster vaccine was cost-effective, assuming that protection

lasted an average of 10 years following immunization; the main cost benefits were via reducing morbidity associated with PHN, rather than zoster[97].

As for varicella vaccine, establishing zoster vaccine cost-effectiveness through modelling studies relies upon a number of assumptions, particularly related to the duration of protection induced by vaccine. The original SPS had a relatively short follow up period (mean 3.4 years) so the duration of vaccine-induced protection was unclear. Most cost-effectiveness studies assumed life-long vaccine protection, some studies modelled a more conservative 7.5 to 10 years protection and others incorporated a waning effect of the vaccine over time[97]. Longer term follow-up of SPS participants, in the Short and Long Term Persistence Study (STPS and LTPS respectively), demonstrates a waning of VE over time. Clinical efficacy of zoster vaccine becomes increasingly limited beyond 5-8 years;[98,99] the LTPS study showed that during the years 5 to 11 post-vaccination, the estimated VE for zoster was 21.1% (95% CI 10.9–30.4) (compared to 51.3% in years 0-5) and the estimated VE for the prevention of PHN was 35.4% (95% CI 8.8-55.8) (down from 66.5% in years 0-5)[98].

Despite this, recent studies incorporating STPS/LTPS data on duration of VE still conclude the zoster vaccine is cost-effective[100]. Rothberg et al found the most cost-effective time for a one-dose vaccination regime was at age 70 years[101], in line with the UK vaccination policy, but not the US ACIP guidelines, prompting some commentators to suggest the ACIP guidelines be revised[96,101]. Although the US FDA expanded the licensed age range for the zoster vaccine to individuals aged 50-59 years, ACIP vaccine recommendations remain unchanged. Evidence suggests that vaccinating this age group is not cost-effective[102,103]: as protection wanes with time from vaccination, these patients would not be protected at the ages when zoster (and PHN) incidence is highest, and may in future require a booster dose.

5. Post-marketing surveillance of live attenuated varicella and zoster vaccines

A large post-licensure study of the zoster vaccine that used data from the Vaccine Safety Datalink system raised few safety concerns: among 192,000 zoster vaccine recipients ≥60 years, there was a small increased risk of allergic reactions 1-7 days following vaccination. However, no increased risk of serious adverse events including stroke, meningitis, encephalitis or Bell's palsy was seen within 42 days of vaccination[104]. Post-marketing surveillance has demonstrated the varicella vaccine is also well-tolerated, with the vaccine only being linked to a handful of cases of VZV neurological disease and single case of fatal varicella[105].

In Europe and the US, Merck have established reference laboratories where rashes and other potential complications of varicella and zoster vaccines are recorded and reviewed. One study carried out whole genome sequencing of the vaccine virus from 20 clinical samples of vesicular fluid taken from rashes induced by varicella vaccine[42]. There was no evidence that the rashes were due either to recombination between the vaccine virus and the wild type virus, or to new vaccine virus mutations. The genotypes causing immediate post vaccination rashes also did not differ from those establishing latency and reactivating, implying that all post inoculation vOka viruses are equally capable of establishing latency and there are no neurotropic vOka variants[42]. Nevertheless, continued surveillance of the molecular and phenotypic characteristics of live attenuated vOka in humans will be important to monitor any risks of virulent replication or reversion to virulence.

6. Newer developments in zoster vaccines

6.1 Herpes zoster subunit vaccine

Recent development of a new recombinant subunit vaccine, HZ/su (Shingrix), with impressive efficacy has the potential to transform current zoster vaccination policy. Application for its approval was submitted to the US FDA, the European Medicines Agency and Health Canada at the end of 2016. HZ/su consists of 50 μg of recombinant VZV antigen (glycoprotein E) which directs the immune

response to the virus itself, combined with the AS01B adjuvant system to stimulate T-cell immunity to recombinant proteins[106]. As described in detail elsewhere [106], two very large multicentre blinded RCTs reported that, among participants who had received two doses of Hz/su, VE against zoster was 97.2% (95% CI 93.7-99.0%) for adults aged ≥50 years [107] and 89.8% (95% CI 84.2-93.7%) for those aged ≥70 years[108]. In a pre-specified analysis of data pooled from both trials, the VE against PHN was 88.8% (95% CI 68.7-97.1%).

While systemic reactions were more commonly reported for the HZ/su vaccine than Zostavax (66.1%[107] versus 24.7%[79]), these adverse effects were transient and around 95% of participants receiving HZ/su in both trials received both vaccine doses. Reassuringly, serious adverse events, immune-mediated diseases and deaths across the entire study period were reported equally between the vaccinated and placebo groups in both ZOE trials. Initial results from a multi-country randomised trial among 828 adults aged ≥50 years, suggest that co-administration of HZ/su with an influenza vaccine (quadrivalent inactivated influenza vaccine, IIV4) is well-tolerated[109].

The new subunit vaccine offers some advantages to the currently licensed Zostavax vaccine. First, the VE of HZ/su against zoster is substantially higher overall (91%[108] versus 51.3%[79]). Second, theoretically HZ/su has greater potential for use in immunosuppressed patients, as it is not a live vaccine so does not pose risks of triggering varicella- or zoster-like illnesses; it has shown promise in phase I/II trials in severely immunocompromised patients[106]. Third, unlike Zostavax, the HZ/su vaccine is equally effective among older age groups; HZ/su has a VE against zoster incidence of 89.1% among those ≥80 years[108], compared to a VE of 37.6% among those aged ≥70 years for Zostavax[79].

6.2 Inactivated Zostavax vaccine

Another vaccine under investigation is the inactivated formulation of Zostavax (V212), designed to prevent zoster in immunocompromised patients. A double-blind RCT tested a four dose regimen of V212 in recipients of autologous haematopoietic stem cell transplants; early trial results showed that the inactivated vaccine reduced the incidence of zoster by 64% (95% CI 0.48-0.75) with no difference in the risk of serious adverse events between intervention and placebo groups[110].

7. Zoster vaccine - unresolved questions

7.1 Zostavax

Strategies to tackle the decline in zoster vaccine-induced immunity over time[98] are being investigated. There remains debate about the extent to which VZV-specific antibody titres can predict protection against zoster, which is largely cell-mediated[5]. Nevertheless, two-dose vaccination strategies (compared to the current single-dose regimen), with doses separated by up to 12 months, seem to show little promise; there is no difference between the VZV antibody responses 4 weeks after the first or second dose[111,112]. However, a booster dose holds potential for reversing this decline in protection. A clinical trial found a booster dose of Zostavax, given ≥10 years after the first dose among adults ≥70 years, elicited a VZV antibody response similar to that of a first dose among age-matched subjects[113]. This booster dose was safe and some initial modelling work suggests such a vaccination strategy would be cost-effective[101]. This initial study supports the investigation of further work on revaccinating older individuals with Zostavax sometime after initial vaccination[114].

7.2 Newer vaccines

Given the limited duration, efficacy and use of the Zostavax vaccine, the newer vaccines hold tremendous promise. There are, however, a number of unresolved questions relating to the HZ/su vaccine.

Direct comparison of the HZ/su and the Zostavax vaccine based on existing research is difficult due to differences in study designs and populations. Therefore a head to head trial is underway to compare the immunogenicity and safety of these vaccines in immunocompetent older adults (ClinicalTrials.gov Identifier: NCT02114333). As the ZOE trials were not able to establish the duration of protection provided by HZ/su, trials are in progress to assess the immunogenicity and safety of the vaccine 10 years following vaccination, as well as after a booster dose of the vaccine (NCT02735915). As persons with a history of zoster vaccination were excluded from the ZOE trials, and considering the numbers already vaccinated with Zostavax, the safety and efficacy of an HZ/su booster for those who have received the live Zostavax vaccine is being investigated (NCT02581410). Other trials are underway to assess the impact of HZ/su on quality of life (NCT02979639) and its efficacy when co-administrated with other vaccines (NCT02052596).

Although the ZOE trials reported no serious safety concerns with the HZ/su vaccine, some highlight the need to better understand less common serious side effects, particularly given the new adjuvant included in HZ/su[115]. Further questions also remain about patient compliance; considering the high proportion of HZ/su side effects, albeit transient, it is unclear whether patients will adhere to the two-dose regimen in a real-world setting. Experience from other vaccines with two-dose regimens in older individuals, for example hepatitis A vaccine where around 60% of patients ≥65 years complete the course[116], suggests compliance may not be as high as the ZOE trials. The effectiveness of a single-dose regimen may therefore be worth investigating through post-marketing surveys. An additional area of uncertainty is whether the issues around Zostavax uptake in some countries, will also be relevant to HZ/su vaccine uptake; work on barriers to uptake are therefore needed[115]. Finally, researchers have questioned whether the HZ/su vaccine might be appropriate to prevent varicella among immunosuppressed children currently unable to receive the varicella vaccine[106], although it is unclear whether Hz/su would be effective for immune priming rather than stimulating a memory T-cell response.

7.3 Immunosuppressed patients

Zostavax is currently contraindicated for severely immunosuppressed groups, including patients with primary or acquired immunodeficiency states e.g. due to lymphoma, leukaemia, cellular immune deficiencies and HIV/AIDS as well as patients on immunosuppressive or immunomodulating therapies[84,117]. This recommendation is based largely upon expert opinion rather than clinical data[118]. It is recognised that patients with moderate immunosuppression, such as those with chronic inflammatory conditions on low dose corticosteroid therapy either alone or in combination with low dose non-biological oral immune modulating drugs can receive the vaccine[21,84]. An observational cohort study using Medicare data, estimated the effectiveness of Zostavax against zoster as 37% (95% C.I. 6% to 58%) among immunosuppressed individuals[31]. Some evidence from observational studies of patients with autoimmune conditions receiving anti-TNF biologics and non-TNF biologics suggests there is no increase in zoster risk in the 42 days following *Zostavax* vaccination[119]. The need for further research to assess the safety of Zostavax among immunosuppressed patients may however be superseded by the development of HZ/su and V212.

The safety and efficacy of the HZ/su vaccine within immunocompromised groups has been investigated in two Phase 1/2 single blind randomised trials among autologous hematopoietic cell transplant recipients with haematologic malignancies[120] and among antiretroviral treated or naïve HIV-infected adults with CD4 T-cell counts ranging from 50 to >500 cells/ml[121]. Both trials showed immunogenicity similar to that in healthy patients and no vaccination-related serious adverse effects were reported. Results from further phase 1/2 trials in other immunocompromised groups as well as phase III trials are awaited. Trials on HZ/su immunogenicity and safety in specific immunocompromised groups, such as renal transplant patients (NCT02058589) and adults with solid tumours undergoing chemotherapy (NCT01798056) and V212 efficacy in patients with solid tumour or hematologic malignancy (NCT01254630) are ongoing. Data from these trials will help to refine vaccine policy among high-risk immunosuppressed groups.

8. Expert commentary

Before the development of varicella vaccine, there was almost universal infection with varicella zoster virus (VZV). Although varicella is typically mild, it causes a substantial economic and social burden, and complications such as secondary bacterial infections, viral pneumonia and encephalitis affect a small proportion of those infected. After primary infection, VZV establishes latency in sensory ganglia, with VZV-specific T-cell mediated immunity largely responsible for controlling virus reactivation. Natural boosting of the immune response follows both external contact with the virus and endogenous sub-clinical reactivation. Nevertheless, with age, the risk of clinical VZV reactivation (herpes zoster) and debilitating sequelae such as post-herpetic neuralgia rises rapidly.

Understanding of the pathogenesis of VZV latency and reactivation has been informed in the absence of tractable animal models by studies using molecular epidemiology and genome sequencing including of the live attenuated vaccine and associated post immunisation varicella and zoster rashes[42,122,123]. In the early 1970s in Japan, a live attenuated varicella vaccine was developed by serial passage of a wild type VZV isolate to prevent severe or fatal varicella among immunocompromised children. Shown to be safe and effective, especially against severe disease, this vaccine is now used in routine childhood immunisation schedules in some settings worldwide. Elsewhere, concerns about vaccine-induced changes to the epidemiology of varicella and herpes zoster, leading to variable cost-effectiveness estimates from modelling studies, have underpinned decisions not to implement universal childhood varicella vaccine. Thirty years later, a more concentrated live attenuated vaccine (Zostavax) was developed. In trials, this well-tolerated vaccine reduced zoster incidence by around half and led to a two thirds reduction in the incidence of PHN. Recent introduction of Zostavax for immunocompetent older adults has already had a positive impact on zoster burden in the US and UK. Although there are unanswered questions about the long-term trajectory of vaccine-induced immunity and use of live attenuated vaccine in immunosuppressed groups, these may be superseded by the development of HZ/su. In recent RCTs,

this subunit vaccine had a very high (~90%) efficacy against both zoster incidence and PHN including among the oldest age groups and thus has the potential for major impact on zoster disease burden. VZV is the first human herpesvirus for which prevention is now largely possible.

9. Five-year view

In coming years, with good coverage of vOka for primary varicella prevention and use of the highly efficacious HZ/su to prevent VZV reactivation, there will be the potential to prevent the majority of VZV disease. Although there is strong evidence for the existence of exogenous boosting of VZV-specific T-cell immunity by exposure to circulating VZV, the impact of implementing universal varicella vaccine schedules on zoster incidence is still not fully clear. Continued evaluation of developing evidence will be essential to inform updated models of varicella vaccine cost-effectiveness in settings where routine vaccination is not currently recommended. In addition, there may in future be pressure to move to using alternative killed, subunit or non-latent live vaccines for primary immunisation in countries where wild type VZV is no longer circulating. A similar situation has occurred with poliomyelitis: most countries worldwide have transitioned from using a live attenuated oral polio vaccine, which carries a risk of vaccine-associated paralytic polio, to an inactivated vaccine. Unlike oral polio vaccine, vOka establishes latency and has the potential to reactivate and cause clinical disease. This gives added impetus to find alternatives that do not establish latency and thus obviate the need for continued vaccination against zoster. A further option would be to develop antiviral drugs that can eradicate the latent virus, thus eliminating the risk of reactivation, although these approaches will require a better understanding of VZV latency as well as appropriate models for drug testing.

10. Key issues:

- The neurotropic varicella zoster virus (VZV) causes two common diseases – varicella, due to primary infection, and zoster due to virus reactivation from latency; both place substantial economic burden on countries worldwide.
- A live attenuated varicella vaccine, based on the Oka strain, was developed in Japan in the 1970s through serial passage of a wild type VZV isolate.
- Safe and effective, vOka has markedly reduced the incidence of varicella in countries such as the US that have implemented and achieved a high coverage of universal childhood vaccine.
- In other countries, particularly in Northern Europe, decisions not to implement a universal varicella vaccine have been informed by models showing uncertain cost-effectiveness, with further evidence needed of the effect of vaccine on zoster epidemiology.
- A more concentrated live attenuated vaccine against zoster (Zostavax), first licensed in 2006, has been introduced into a number of countries for older immunocompetent individuals. Although in trials, Zostavax halved zoster incidence and reduced PHN by two thirds, it is contraindicated in immunosuppressed groups. Other limitations include its lack of life-long protection and poorer vaccine efficacy in older individuals.
- These issues may be circumvented by the recent development of a new subunit vaccine (HZ/su) which shows extremely high vaccine efficacy (around 90% against zoster and PHN).
- In the absence of an animal model, insights into the pathogenesis of VZV latency and reactivation have been advanced by molecular epidemiology and genome sequencing; the live attenuated vaccines have contributed to this knowledge.
- Recent developments in varicella and zoster vaccines now offer the potential to prevent the majority of VZV disease.

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Reference annotations

* Of interest

** Of considerable interest

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