A Phase 1/2 Clinical Trial Evaluating Safety and Immunogenicity of a Varicella Zoster Glycoprotein E Subunit Vaccine Candidate in Young and Older Adults

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Background. An adjuvanted recombinant varicella zoster virus (VZV) subunit vaccine is being developed for the prevention of herpes zoster and its complications.

Methods. In a phase I/II, open-label, randomized, parallel-group study, older adults (50–70 years) received 2 doses 2 months apart of an adjuvanted recombinant glycoprotein E vaccine (HZ/su; n = 45), a live attenuated Oka strain VZV vaccine (OKA; n = 45), or HZ/su and OKA administered concomitantly (n = 45). To evaluate safety prior to administration in older adults, young adults (18–30 years) were vaccinated with 2 doses 2 months apart of HZ/su (n = 10) or OKA (n = 10). Safety and immunogenicity were assessed up to 42 months for older adults immunized with HZ/su and up to 12 months for all others.

Results. Few grade 3 events and no severe adverse events were reported. Fatigue, myalgia, headache, and injection site pain were the most common solicited reactions for HZ/su and occurred more frequently than with OKA. CD4+ T-cell and humoral immune responses were much higher with HZ/su than with OKA and remained elevated until 42 months. Addition of OKA to HZ/su did not increase immunogenicity.

Conclusions. In this study, HZ/su adjuvanted subunit vaccine was well tolerated and more immunogenic than a live attenuated VZV vaccine.

Clinical Trial registration. NCT00492648 and NCT00492648

Herpes zoster (HZ), also known as shingles, is a common and often debilitating disease that occurs primarily in older or immunocompromised individuals. HZ is caused by the symptomatic reactivation of latent varicella zoster virus (VZV) in the dorsal root and cranial ganglia. The virus is usually acquired during childhood as chickenpox [1]. The incidence of HZ increases with age and is most common in adults over 50 years of age [1]. The estimated lifetime risk of developing HZ is 10%–30% [2, 3]. A recent study in the United States found a population-based recurrence rate of 6.2% after 8 years of follow-up, with recurrence significantly more likely in immunocompromised people and people who had previously suffered from HZ-associated pain lasting ≥30 days [4].

Cell-mediated immunity (CMI) plays the main role in controlling VZV reactivation and appears to be a reliable correlate of protection against symptomatic HZ [5, 6]. The higher incidence of HZ in older individuals appears to be due to the decline in CMI as a result of immunosenescence [7]. Accordingly, the ability to elicit VZV-specific CMI is a key attribute of HZ vaccines [8, 9]. The Shingles Prevention Study showed that immunization of adults ≥60 years of age with a high-dose (median, 24 600 pfu/dose) of a live
attenuated Oka VZV vaccine (Zostavax, Merck & Co., Inc) reduced the incidence of HZ by 51% and the incidence of PHN by 67% [10]. This result was supported by a recent analysis of postlicensure data in the United States collected between 2007 and 2009, which showed that vaccination with Zostavax reduced the risk of HZ in adults ≥60 years of age by 51% [11]. However, in the Shingles Prevention Study, vaccine efficacy against HZ was lower in subjects ≥70 years of age (38%) than in subjects aged between 60 and 69 years (64%), a finding that was mirrored by a significantly lower VZV-specific CMI response in subjects ≥70 years [12].

Recombinant subunit vaccines are an alternative to live vaccines and have the potential advantages of strong immunogenicity, safety in immunocompromised individuals, and ease of production [13]. VZV glycoprotein E (gE) is an attractive candidate as the subunit antigen in an HZ vaccine because it is the most abundant glycoprotein in VZV virions and in VZV-infected cells and because it is the principal target of VZV-specific CD4+ T-cell responses [14–17]. In a study in mice, recombinant gE-induced potent CD4+ T-cell responses when adjuvaned with AS01 [18]. AS01, a liposome-based adjuvant system containing 3-O-desacyl-4′-monophosphoryl lipid A (MPL) and the saponin QS21 [19, 20], enhances immune responses by activating Toll-like receptor 4 and by increasing antigen uptake and retention by dendritic cells [21]. Clinical studies of other subunit vaccines have shown that AS01 has an acceptable safety profile and promotes strong CD4+ T-cell responses to recombinant proteins [20, 22, 23].

Here we describe the results of the first clinical study examining the immunogenicity and safety of an adjuvanted gE subunit candidate vaccine (HZ/su). In this study, young (18–30 years) and older (50–70 years) adults were randomized to receive 2 doses of vaccine at months 0 and 1, respectively. Safety was assessed and monitored by an internal safety committee 4 weeks after vaccination. The young adults (18–30 years) were randomized to receive an equal ratio with HZ/su alone or HZ/su in combination with Oka. The older adults (50–70 years) were randomized to receive an equal ratio with Oka alone, HZ/su alone, or both Oka and HZ/su (Figure 1). Initially, 20 young adults received a first dose of vaccine on day 0. Once the safety of the first dose in young adults had been confirmed by an internal safety committee 4 weeks after vaccination, dose 2 in the 2 young adult groups and dose 1 in the 3 older adult groups were administered. Dose 2 in the 3 older adult groups was injected only after the safety of dose 2 in the young adult groups was confirmed. Safety was assessed and blood samples were taken for analysis of cellular and humoral immunity at months 0 (prevaccination), 1, 2, 3, and 12.

Older adults who were vaccinated with HZ/su alone and who successfully completed the 12-month primary trial were eligible for inclusion in an extension study. Subjects were excluded from the extension study if they were receiving immunomodulatory treatments; previously received a vaccine against HZ; previously received a vaccine containing MPL or QS21; or had an immunosuppressive or immunodeficient condition. Subjects received no additional treatment during the extension study. Blood samples were taken for analysis of cellular and humoral immunity at months 30 and 42, and severe adverse events (SAEs) and suspected HZ episodes were recorded up to month 42.

Materials and Methods

Study Design and Subjects

The first part of this study was a 12-month, phase I/II, open-label, randomized, parallel-group trial with staggered enrolment (ClinicalTrials.gov identifier NCT00492648) conducted between 14 December 2004 and 27 May 2005 at the Center for Vaccinology, Ghent University and Hospital, Belgium. Between 25 June 2007 and 23 June 2008, older adults vaccinated with HZ/su who completed the 12-month primary study were followed up in an exploratory, open-label, phase I/II extension study (ClinicalTrials.gov identifier NCT00492648). Both studies were approved by the ethics committee of the Ghent University Hospital and were conducted in accordance with Good Clinical Practice, all applicable local rules and regulatory requirements of Belgium, and the Declaration of Helsinki. All subjects gave written informed consent before being included in the trials.

Healthy men and women not previously vaccinated for VZV who were between 18 and 30 years of age or between 50 and 70 years of age were eligible for inclusion. Subjects were excluded if they received chronic administration (>14 days) of immunosuppressants or other immune-modifying drugs within 6 months (for corticosteroids, ≥0.5 mg/kg/day prednisone or equivalent); received immunoglobulins or blood products within 3 months; received a vaccine other than influenza vaccine within 30 days before the first dose of study vaccine(s); had previously received a VZV vaccine or a vaccine containing MPL or QS21; had a history of HZ within the previous 5 years; had known exposure to VZV within the previous 2 years; had any contraindications to vaccination, such as allergy; or had acute disease at enrollment. Women had to be surgically sterilized, at least 1 year postmenopausal, or if of childbearing potential, abstinent or using adequate contraception for 30 days prior to vaccination and have a negative pregnancy test.

The young adults (18–30 years) were randomized to be vaccinated in an equal ratio with HZ/su alone or HZ/su in combination with Oka. The older adults (50–70 years) were randomized to be vaccinated in an equal ratio with Oka alone, HZ/su alone, or both Oka and HZ/su (Figure 1). Initially, 20 young adults received a first dose of vaccine on day 0. Once the safety of the first dose in young adults had been confirmed by an internal safety committee 4 weeks after vaccination, dose 2 in the 2 young adult groups and dose 1 in the 3 older adult groups were administered. Dose 2 in the 3 older adult groups was injected only after the safety of dose 2 in the young adult groups was confirmed. Safety was assessed and blood samples were taken for analysis of cellular and humoral immunity at months 0 (prevaccination), 1, 2, 3, and 12.

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Study Vaccines and Administration

All groups received one dose of vaccine at month 0 and a second dose 2 months later. Oka (Varilrix, approximately 10^4 pfu per dose of attenuated VZV in 0.5 mL diluent) was administered by subcutaneous injection in the right deltoid area. The recombinant adjuvanted vaccine, HZ/su (50 µg recombinant VZV gE
Figure 1. Study design and subject disposition. Initially, 20 young adult (18–30 y) subjects were randomized to receive a first dose of vaccine (HZ/su alone or HZ/su + OKA). The first dose of vaccine for the 135 older adult (50–70 y) subjects and the second dose of vaccine for the young adults were administered after the safety of the first vaccination in young adults had been confirmed by the internal safety committee. The second dose of vaccine for the older adults was administered after the safety of the second dose in young adults had been confirmed by the internal safety committee. Dotted arrows indicate where vaccination with the dose in older adults was dependent on establishment of safety of that dose in young adults. Abbreviations: TVC, total vaccinated cohort; ATP, according to protocol cohort; HZ/su, AS01B-adjuvanted glycoprotein E vaccine; OKA, live attenuated Oka vaccine.
antigen [24] in 0.2 mL mixed with 0.5 mL of AS01B adjuvant [a liposome-based adjuvant system containing 50 µg MPL and 50 µg QS21; GlaxoSmithKline Biologicals] was administered by intramuscular injection into the left deltoid area. Subjects receiving both HZ/su and OKA were injected with the 2 vaccines simultaneously into the deltoid areas of opposite arms.

Safety
Solicited local reactions (pain, redness, and swelling at injection site) and solicited general reactions (fatigue, fever, myalgia, gastrointestinal symptoms, and headache) were recorded by subjects on diary cards for up to 6 days after vaccination. Investigators recorded all unsolicited adverse events (AEs) until 30 days after each vaccination and all severe SAEs for the duration of the study. Causality was assessed by the study physician except for solicited local reactions, which were always considered treatment-related. Blood hematology (complete blood count) and biochemistry (renal and hepatic function tests) were monitored throughout the study (up to month 12). For subjects with varicella-like rash (papulo-vesicular or vesicular rash), samples of fluid in the vesicles/blisters were collected for VZV-polymerase chain reaction testing.

Intracellular Cytokine Staining
Intracellular cytokine staining (ICS) was performed essentially as described elsewhere [25] except using a pool of 64 20-mer peptides (overlapping by 10 amino acids), at 1.25 µg/mL for each peptide, covering the entire gE sequence (Eurogentec) or with VZV lysate (1:25 dilution; GlaxoSmithKline Biologicals) for stimulation and using antibodies to CD40 ligand (CD40L), interleukin 2 (IL-2), interferon-γ (IFNγ), and tumor necrosis factor α (TNF-α) for detection.

Serum anti-VZV and anti-gE titers
Serum anti-VZV levels were measured by using Enzygnost anti-VZV/immunoglobulin G enzyme-linked immunosorbent assay (ELISA) from Dade Behring (Siemens Healthcare Diagnostics). Serum anti-gE levels were measured by ELISA (Henogen). Seropositivity was defined as a titer above the detection limit of the ELISA (50 international units/mL for anti-VZV, 195 ELISA units/mL for anti-gE).

Statistical Analysis
Safety data were analyzed on all subjects receiving at least 1 dose of vaccine. Immunogenicity was analyzed on all subjects receiving 2 doses of vaccine and following all other study procedures. ICS results were analyzed using a nonparametric test (Wilcoxon or Kruskall-Wallis test) to compare the differences between groups. Geometric mean concentration (GMC) and 95% confidence intervals (CIs) were calculated for humoral responses. All significance tests were 2-tailed. P values ≤ .05 were considered statistically significant. A humoral response was defined as a ≥4-fold increase in GMC in subjects with a detectable titer before the first dose of vaccine. Proportions of responders within each group were reported with exact 95% CIs. Statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, North Carolina) or StatXact version 5.0 (Cytel, Cambridge, Massachusetts).

RESULTS
Subjects
A total of 155 subjects were enrolled, including 20 young adults and 135 older adults (Figure 1). All subjects had anti-VZV antibodies at baseline (data not shown). All subjects completed the study up to month 12. One older subject receiving both HZ/su and OKA was excluded from the immunogenicity and safety analyses at month 12 because OKA had been administered intramuscularly instead of subcutaneously. Ages were similar between the different groups in young adults (means ranged from 22 to 23 years) and older adults (means ranged from 55 to 57 years). Men represented 50% and 70% of the subjects in the HZ/su and HZ/su + OKA young adult groups, respectively, but less than half of the subjects in the older adult groups (27% for HZ/su, 31% for OKA, 38% for HZ/su + OKA).

Safety and Reactogenicity up to Month 12
In all subjects, most solicited general and local reactions were of mild to moderate intensity (Table 1). For both older and young adults vaccinated with HZ/su alone, the most common solicited general reactions were fatigue, myalgia, and headache, and the most common solicited local reaction was injection site pain. The frequency of solicited events in young and older adults was similar between HZ/su alone and HZ/su + OKA. Similar proportions of older subjects had solicited general reactions following immunization with HZ/su and with HZ/su + OKA. Among solicited reactions, fatigue, fever, headache, and myalgia were more common in older adults vaccinated with HZ/su alone or HZ/su + OKA than in those receiving OKA alone. Injection site pain was more common in subjects vaccinated with HZ/su alone or HZ/su + OKA than in subjects vaccinated with OKA alone. In contrast, redness and swelling tended to be more common in subjects vaccinated with OKA alone or HZ/su + OKA than in subjects vaccinated with HZ/su alone.

The most common unsolicited AEs were upper respiratory infections, influenza-like illness, and chills. Most of these were of mild to moderate intensity (data not shown). The only related grade 3 unsolicited AEs were 2 cases of chills and 1 case of insomnia in older adults vaccinated with HZ/su alone. These symptoms lasted 1 day and resolved without treatment. No vaccine-related SAEs and no deaths were reported in this study.
No clinically significant changes in hematology and/or biochemistry values were observed during the course of the study. Two cases of generalized rash were reported in older adults vaccinated with HZ/su and one in an older adult vaccinated with OKA alone. The subject vaccinated with OKA alone and 1 of the 2 subjects vaccinated with HZ/su were reported as having vesicular lesions. VZV genomes could not be detected in vesicular fluid from these 2 subjects by polymerase chain reaction (data not shown).

**Cell-Mediated Immune Responses up to Month 12**

Cell-mediated immune responses were measured up to 12 months in all subjects by ICS. To increase the specificity of the assay, T cells were considered positive only if they expressed at least 2 immune markers following gE or VZV induction. In young and older adults, the frequency of CD4+ T cells was higher following immunization with 2 doses of HZ/su than following immunization with 2 doses of OKA alone (for older adults at month 3, $P < .0001$ for stimulation with gE).
and \( P < .0002 \) for stimulation with VZV lysate) (Figure 2). In both young and older adults, the frequency of CD4+ T cells expressing at least 2 immune markers was not significantly different between 2 doses of HZ/su alone and 2 doses of HZ/su + OKA. Also, the maximum CD4+ T-cell response to vaccination with HZ/su alone or HZ/su + OKA occurred after 2 doses of vaccine (ie, at month 3). Finally, in all groups, the frequency of CD4+ T cells expressing CD40L or IL-2 was higher than the frequency of cells expressing IFN\( \gamma \) or TNF\( \alpha \) (see Supplementary Table 1). In contrast, stimulation of CD8+ T cells was not detected in any of the study groups (data not shown). Analysis of lymphoproliferation gave similar results as ICS for CD4+ T cells, namely, a greater response to HZ/su than OKA alone (See Supplementary Figure 1).

**Humoral Immune Responses up to Month 12**

GMCs were maximal after the first dose of HZ/su in young adults and after the second dose in all other groups (Figure 3). For all groups, GMCs decreased by approximately two-thirds (range, 56%–68%) between months 3 and 12. In the young

![Figure 3. Antibody response. Serum samples were collected at the indicated time points and antiglycoprotein E (gE; upper panel) and anti-varicella zoster virus (VZV; lower panel) antibody concentrations were measured by enzyme-linked immunosorbent assay. Values are geometric mean concentrations (GMCs).](image-url)
Table 1. Percentage of Subjects Experiencing Local and General Solicited Reactions During the 7-day Postvaccination Period Following Any Vaccine Dose

<table>
<thead>
<tr>
<th>Event</th>
<th>Severity</th>
<th>Young adults</th>
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<th>Older adults</th>
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<td>HZ/su (N = 10)</td>
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<td>OKA (N = 45)</td>
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<td>Fatiguea</td>
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<td>9 (90.0) 55.5–99.7</td>
<td>10 (100) 69.2–100.0</td>
<td>6 (13.3) 5.1–26.8</td>
<td>28 (62.2) 46.5–76.2</td>
<td>25 (55.6) 40.0–70.4</td>
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<td></td>
<td>Grade 3</td>
<td>0 (0.0) 0.0–30.8</td>
<td>1 (10.0) 0.3–44.5</td>
<td>0 (0.0) 0.0–7.9</td>
<td>3 (6.7) 1.4–18.3</td>
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<td>Feverb</td>
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<td>5 (50) 18.7–81.3</td>
<td>0 (0) 0.0–7.9</td>
<td>9 (20) 9.6–34.6</td>
<td>7 (15.6) 6.5–29.5</td>
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<td>5 (50) 18.7–81.3</td>
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<td>8 (17.8) 8.0–32.1</td>
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<td>0 (0) 0.0–30.8</td>
<td>1 (10) 0.3–44.5</td>
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<td>11 (24.4) 12.9–39.5</td>
<td>27 (60) 44.3–74.3</td>
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<td>9 (90) 55.5–99.7</td>
<td>7 (15.6) 6.5–29.5</td>
<td>30 (66.7) 51.0–80.0</td>
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<td>10 (100) 69.2–100.0</td>
<td>23 (51.1) 35.8–66.3</td>
<td>40 (88.9) 75.9–96.3</td>
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<td>28 (62.2) 46.5–76.2</td>
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<td>20 (44.4) 29.6–60.0</td>
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Abbreviations: CI, confidence interval; HZ/su, AS01B-adjuvanted glycoprotein E vaccine; N, no. of subjects enrolled in each group; no., number of subjects reporting the symptom; OKA, live attenuated Oka vaccine.

a Scored as grade 1 (mild) for axillary temperature 37.5°C to 38.0°C, grade 2 (moderate) for axillary temperature 38.1°C to 39.0°C, or grade 3 (severe) for axillary temperature >39°C.

b Scored as grade 1 for easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities; grade 2 for sufficiently discomforting to interfere with normal everyday activities, or grade 3 for events preventing normal daily activities.

c Scored as grade 1 for a diameter >0 to ≤20 mm, grade 2 for a diameter >20 to ≤50 mm, or grade 3 for diameter >50 mm.
and older adults, anti-gE and anti-VZV GMCs were higher for subjects immunized with HZ/su alone or HZ/su + OKA than for subjects immunized with OKA alone. In both young and older adults, GMCs were similar in subjects immunized with HZ/su or with HZ/su + OKA. In older adults, administration of OKA alone induced a relatively small increase in the anti-gE and anti-VZV GMCs. Assessment of humoral immune responses by VZV neutralization yielded similar results, namely, a greater response to HZ/su than OKA and no enhancement by the addition of OKA to HZ/su (see Supplementary Information).

In older adults, the gE-specific humoral response rate was >95% for a single dose and 100% for 2 doses of HZ/su alone or HZ/su + OKA, whereas the response rate was <40% for 1 or 2 doses of OKA alone (Figure 4). The VZV-specific humoral response rates were slightly lower, with rates of >65% for a single dose and >75% for 2 doses of HZ/su alone or HZ/su + OKA and <30% for 1 or 2 doses of OKA alone. Response rates were similar in younger and older adults.

**Long-Term Follow-up of Safety and Immunogenicity in Older Adults Vaccinated with HZ/su Alone**

For older adults vaccinated with HZ/su alone, SAEs were recorded up to month 42, and immunogenicity was assessed at month 30 (n = 29) and month 42 (n = 20). The frequency of gE-specific CD4+ T cells secreting at least 2 cytokines decreased from month 12 to month 42, although the median frequency remained higher at month 42 than at baseline (median [interquartile range], 511 [342–1152] vs 104 [1–292] per 10^6 CD4+ T cells) (Table 2). Similarly, the frequency of VZV-specific CD4+ T cells secreting at least 2 cytokines decreased from month 12 to month 42, with median frequencies higher at month 30 than at baseline (644 [348–885] vs 395 [82–930] per 10^6 CD4+ T cells). The median frequency at month 42 (361 [301–862] per 10^6 CD4+ T cells) was not higher than at baseline. Humoral responses also decreased from month 12 to month 42 but remained higher at month 42 than at baseline for both anti-gE (GMC [95% CI], 2413 [1899–3429] vs 179 [231–299] EU/mL) and anti-VZV (2683 [1991–3615] vs 744 [940–1188] EU/mL). No SAEs and no cases of HZ were reported between months 12 and 42.

**DISCUSSION**

This is the first report to our knowledge on the safety and immunogenicity in humans of an adjuvanted VZV gE subunit vaccine, HZ/su. HZ/su was well tolerated and highly immunogenic: 2 doses of HZ/su induced significantly stronger gE and VZV-specific CD4+ T-cell and antibody responses than 2 doses of a live attenuated Oka strain VZV vaccine. In contrast, neither HZ/su nor the live Oka strain VZV vaccine induced detectable CD8+ T-cell responses, a finding consistent with the immune response pattern reported in a previous study of a similar live Oka strain VZV vaccine [26]. Of the immune responses stimulated by HZ/su, the strong induction of CD4+ T cells is perhaps most relevant for its potential to prevent HZ, because previous studies established a correlation between vaccine-induced CD4+ T-cell responder frequency, but not humoral immunity, and reduced HZ morbidity [27].

HZ/su was well tolerated. Injection site reactions were more common in the groups that received HZ/su, but they were transient and generally mild to moderate in intensity, and no subjects withdrew consent due to an AE. These findings are consistent with previous clinical studies of subunit vaccines adjuvanted with AS01B, which also demonstrated acceptable safety profiles (reviewed in [20, 22, 23]).

Two doses of HZ/su induced substantially higher humoral and CD4+ T-cell responses than a single dose. Although the

### Table 2. Cellular and Humoral Responses up to Month 42 in Older Adults Vaccinated with HZ/su Alone

<table>
<thead>
<tr>
<th>Measure</th>
<th>Antigen</th>
<th>Value</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 12</th>
<th>Month 30</th>
<th>Month 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>gE</td>
<td>Median</td>
<td>104</td>
<td>540</td>
<td>402</td>
<td>2323</td>
<td>988</td>
<td>864</td>
<td>511</td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>Median</td>
<td>395</td>
<td>591</td>
<td>543</td>
<td>1862</td>
<td>904</td>
<td>644</td>
<td>361</td>
<td></td>
</tr>
<tr>
<td>Serum antibody concentration (EU/mL)</td>
<td>gE</td>
<td>GMC</td>
<td>179</td>
<td>4402</td>
<td>3406</td>
<td>12122</td>
<td>4170</td>
<td>3390</td>
<td>2413</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>231–299</td>
<td>6099–8451</td>
<td>4844–6889</td>
<td>14817–18110</td>
<td>5111–6312</td>
<td>2684–4281</td>
<td>1899–3428</td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>GMC</td>
<td>744</td>
<td>4596</td>
<td>3571</td>
<td>7438</td>
<td>4038</td>
<td>4049</td>
<td>2683</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; gE, varicella zoster virus glycoprotein E; GMC, geometric mean concentration; Q1, first quartile; Q3, third quartile; VZV, varicella zoster virus.
impact of the second dose was especially prominent in older adults, the peak cellular and humoral immune responses elicited by 2 doses of HZ/su were comparable between young and older adults. After the second HZ/su vaccination, a high frequency of activated CD4$^+$ T cells was detected not only upon stimulation with gE antigen but also upon stimulation with whole VZV lysate containing a full complement of virus-encoded proteins. Similarly, HZ/su vaccination elicited high concentrations of antibodies directed against a mixture of whole VZV antigens. Together, these data indicate the prominence of gE as a target of both cellular and humoral VZV-specific immune responses.

Not only were the immune responses to the Oka strain VZV vaccine substantially lower than the responses to HZ/su, but a second dose of the live vaccine failed to boost either the cellular or humoral immune responses beyond those elicited by the initial dose. This is consistent with the finding that a second dose of Zostavax 6 weeks after the first similarly failed to boost CMI and humoral responses in older adults [28]. The magnitude of the CMI response to the Oka strain VZV

Figure 4. Antibody response rates. Shown are the humoral response rates against glycoprotein E (gE; upper panel) and varicella zoster virus (VZV; lower panel). A humoral response was defined as a ≥4-fold increase in GMC initially in subjects with a detectable titer before the first dose of vaccine. Bars indicate means, and error bars indicate 95% confidence intervals.
vaccine used in the current study (1.71-fold peak increase in mean CD4⁺ T-cell frequency over prevaccination level) was comparable to that induced by Zostavax in the Shingles Prevention Study (1.85-fold peak increase) [12]. However, caution must be used in comparing the CMI results between studies; moreover, CMI responses to Oka vaccines do not correlate with vaccine efficacy in the prevention of HZ [29], so these results cannot be used to predict the efficacy of HZ/su.

The greater immune response to HZ/su compared to the live attenuated vaccine in this study might be due to the action of the adjuvant, AS01. This adjuvant has been shown in previous clinical trials to elicit strong cellular and humoral immune responses to other subunit antigens, including hepatitis B surface antigen, RTS,S malaria antigens, human immunodeficiency virus gp120, and tuberculosis antigens [30–32].

The possibility that a live VZV vaccine given with HZ/su would further enhance the immune responses was investigated by concomitantly administering both vaccines at different sites. However, coadministration of the live Oka strain VZV vaccine with HZ/su did not result in substantially higher cellular or humoral immune responses compared to those elicited by HZ/su alone.

Certain limitations need to be considered in the interpretation and application of this study’s results. First, this was a phase I/II study focused primarily on older adults, as these persons are at higher risk of HZ. Therefore, although the number of older adults was sufficient to provide robust immunogenicity data and to assess the incidence of AEs, the ability to evaluate and compare immune responses and AEs in young adults was limited by the small numbers enrolled. Second, this study did not assess safety, reactogenicity, or immunogenicity of HZ/su in persons over 70 years of age, an important group given their high incidence of HZ [33].

Additional studies are needed to further evaluate the safety and immunogenicity of HZ/su, in particular, its ability to elicit durable immune responses in people 70 years and older and in persons with compromised immune systems due to disease or immunosuppressive therapies. Such individuals have a particularly high risk for HZ, and a vaccine that can overcome their intrinsic resistance to vaccine-induced immunity may provide substantial benefit.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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