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# Understanding the immunology of Shingrix, a recombinant glycoprotein E adjuvanted herpes zoster vaccine

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## Abstract

Herpes zoster is common in older and immune suppressed persons due to diminished VZV-specific cellular immunity. A recombinant herpes zoster vaccine (RZV) consisting of a single VZV glycoprotein and an adjuvant system stimulates robust and persistent VZV-specific antibody and CD4+ T cell responses in these high-risk populations. VZV-specific immune responses induced by RZV, including the generation of polyfunctional T cells, are driven by the synergistic actions of the components of the vaccine adjuvant system. RZV provides unprecedented protection against herpes zoster in older adults regardless of age at vaccination and is efficacious in immune suppressed populations. Adjuvanted subunit antigens may represent a general strategy for vaccines in the elderly and other individuals typically considered immunologically resistant to vaccination.

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## Background

Primary infection with varicella-zoster virus (VZV), resulting in chickenpox, is followed by life-long residence of the VZV genome in the dorsal-root or cranial-nerve ganglia [1]. Viral reactivation later in life can result in herpes zoster (HZ), a painful, unilateral dermatomal rash. Almost all adults worldwide have been infected with VZV and are at risk for HZ, which occurs with an incidence of approximately 0.5−>1%/year in people 60 years and older [2–5]. In addition, a substantial proportion of HZ cases are followed by complications, most commonly postherpetic neuralgia (PHN), an often-devastating chronic pain syndrome [6].

HZ occurs when VZV-specific cell-mediated immunity (CMI) fails to contain viral reactivation, presumably by falling below an as yet undefined protection threshold, and the reactivated VZV continues to propagate [1,7]. Natural immunity to HZ, which is first acquired during chickenpox, can be maintained through either intrinsic or extrinsic boosting, the former in response to subclinical reactivation of VZV and the latter from asymptomatic exposure to VZV in the community. HZ risk increases in people 50 years and older due to the effects of immunosenescence on VZV-specific CMI or in people of any age with immunity compromised by disease or medication [8••,9].

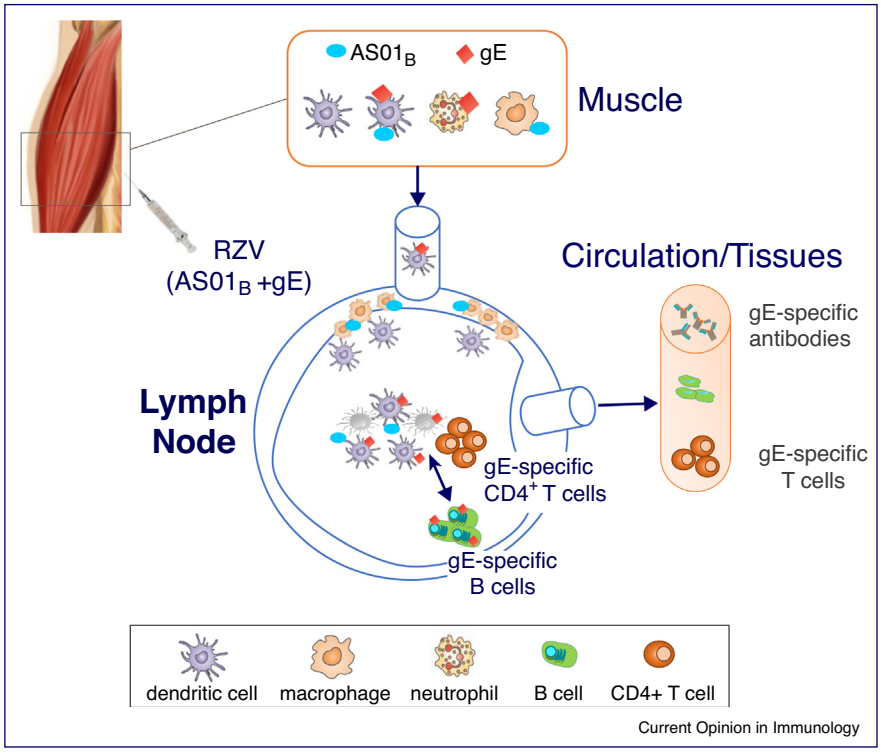
Initial HZ vaccine development focused on producing a live, attenuated VZV vaccine that could elicit CMI responses to a broad spectrum of viral antigens. This approach led to development of the groundbreaking Zostavax vaccine (ZVL; Merck). ZVL provides older adults with substantial protection against HZ and its complications (51% efficacy against HZ and 67% protection against PHN in adults 60 years and older) [4], although efficacy declines with age of the vaccinee (70% versus 37% HZ efficacy, respectively, in adults 50–59 and ≥70 years) [4,10]. ZVL efficacy also markedly declines by 6–8 years after vaccination [11].

In contrast, the recombinant herpes zoster vaccine (RZV; Shingrix [GSK]) is an adjuvanted subunit vaccine consisting of a single recombinant VZV antigen, glycoprotein E (gE), and the $AS01_B$ adjuvant system [12]. RZV depends on gE alone to elicit anti-VZV immunity and on $AS01_B$ to both shape and enhance the immune response.

## RZV composition and the role of the $AS01_B$ adjuvant system

gE was the sole vaccine antigen selected for RZV because it is the most abundant glycoprotein expressed on the surface of VZV-infected cells and is a target for neutralizing antibodies and T cells during VZV infection [13,14]. However, unadjuvanted gE proved poorly immunogenic in mice [15]. Subsequent studies in mice evaluated the

**Figure 1**




$AS01_B$ induces a transient local inflammatory response in injected muscle and draining lymph nodes. This results in a high and durable VZV-specific T cell and antibody responses [Didierlaurent *et al.* [16]; Didierlaurent *et al.* [19,20].

ability of various adjuvants to enhance and shape immune responses to gE. These studies demonstrated that gE combined with the $AS01_B$ adjuvant system yielded the strongest gE-specific CD4+ T cell responses as well as strong gE-specific antibody responses [15].

$AS01_B$ consists of two immunostimulants, the saponin QS21, *Quillaja saponaria* Molina, fraction 21, and the toll-like receptor type 4 agonist, MPL (3-*O*-desacyl-4′-MPL), both delivered within liposomes. In mice, QS21 and MPL act synergistically to induce a high frequency of CD4+ T cells and additively to induce high antibody responses [[15]; Figure 1]. QS21 stimulates inflammasomes in innate immune cells, probably in injected muscle, but definitely in peripheral macrophages of draining lymph nodes. This stimulates NK cells and CD8+ T cells to release interferon-γ (IFN-γ), which in turn stimulates activation and recruitment of blood monocyte-derived and resident lymph node dendritic cells to take up and present gE to CD4+ T cells [16,17]. MPL synergizes with QS-21 to enhance the immune response to the co-administered antigen through the production of IFN-γ [18]. Furthermore, in addition to NK cells and CD8+ T cells, $AS01_B$ stimulates the release of IFN-γ from CD4+ T cells [19•]. IFN-γ generally inhibits viral replication, and it also enhances T cell responses and antibody isotype switching [16,17]. Administration of an AS01-containing vaccine in a clinical trial resulted in increased serum levels of IFN-γ indicating a similar IFN-γ response to AS01 in humans [18]. The $AS01_B$ adjuvant effect requires that the antigen and adjuvant be co-located in tissue at the same time. $AS01_B$-driven cytokine and innate-immune cell responses are transient (largely resolved by day seven) [16].

## RZV efficacy and safety in older adults

Two large clinical trials (ZOE-50 and ZOE-70) demonstrated that two doses of RZV administered intramuscularly at a two-month interval conferred unprecedented efficacy against both HZ and PHN in older adults [[21,22••]; Table 1]. In healthy adults 50 years and older, RZV efficacy against HZ was 97%, and efficacy against PHN was similarly high. Remarkably, efficacy remained above 90% in adults ≥70 and ≥80 years of age, demonstrating that RZV can overcome any deleterious effects of immunosenescence on the development of protective immunity. Importantly, these data establish that a single protein from a complex pathogen is sufficient to induce high levels of protective immunity when combined with an appropriate adjuvant. Largely according to these findings and on supportive safety data, RZV has been approved for use in the US, Canada, EU, Japan, and elsewhere.

**Table 1**

**Shingrix efficacy by age group and year after vaccination**

| Age group | % Efficacy (95% CI) |
|---|---|
| 50–59 years | 96.6 (89.6–99.4) |
| 60–69 years | 97.4 (90.1–99.7) |
| 70–79 years | 91.3 (86.0–94.9) |
| ≥80 years | 91.4 (80.2–97.0) |

| Year after vaccination | % Efficacy (95% CI) |
|---|---|
| 1 | 97.6 (90.9–99.8) |
| 2 | 92.0 (82.8–96.9) |
| 3 | 84.7 (69.0–93.4) |
| 4 | 87.9 (73.3–95.4) |

Shingrix efficacy against HZ remains high regardless of the age at vaccination and is well-preserved during the first four years after vaccination.
[From Lal *et al.* [21] and Cunningham *et al.* [22••]].

No safety concerns were identified during the development of RZV, although the large majority of people who receive RZV experience transient injection-site reactions (most commonly pain) and frequently experience systemic symptoms (e.g. fatigue, myalgia, headache). The hypothetical risk that adjuvanted vaccines may stimulate autoimmunity was raised during development of RZV. No evidence of an increased risk of immune-mediated diseases was observed in >35 000 subjects immunized so far in clinical trials, perhaps because the adjuvant is limited to a local application for a limited exposure time. More than three million doses of RZV were administered during the first year of licensure without any signal of an increased risk of such events.

## RZV immunogenicity in older adults

### Lessons from early phase studies

Before initiating pivotal efficacy studies, the immunogenicity of RZV was evaluated in a series of phase I/II clinical trials. In these and subsequent clinical trials, gE-specific CMI was measured by flow cytometry of PBMCs stimulated *ex vivo* with overlapping peptides representing the entire gE sequence. Responding CD4+ and CD8+ cells were detected by staining for intracellular cytokines (CD40 ligand, IFN-γ, interleukin 2 (IL2) and TNF-α). A positive responding cell was defined by the expression of 2 or more of these biomarkers (designated $CD4^{2+}$) [8••].

In the first human trial, RZV proved highly immunogenic in both young (18–30 years) and older (50–70 years) adults and elicited a substantial gE-specific CMI response that was much greater than responses observed after administration of a live, attenuated VZV vaccine [23]. RZV vaccination also induced strong gE-specific humoral responses (binding antibodies, measured by gE-ELISA, and neutralizing antibodies). Notably, simultaneous administration of the live, attenuated varicella vaccine with RZV did not enhance immune responses compared to RZV alone. In that study, RZV-induced antigen-specific CD8+ T-cell frequencies in the peripheral blood were low and expressed few cytokines. However, in a subsequent study, both gE-specific CD4+ and CD8+ T cell responses, measured by a proliferation assay, were 10-fold greater than those induced by ZVL [24•].

Early RZV clinical trials contributed other key observations that shaped the ultimate development of the vaccine. First, they established that a second RZV dose given after an interval of two months maximized gE-specific CMI responses by increasing them approximately fourfold over a single dose [23,25]. Second, they established the absence of a significant effect of vaccinee age on immune responses to RZV. Two doses of RZV stimulated CD4+ T cell frequencies and antibody responses that were similar between the age groups 50–59, 60–69 and ≥70 years. Interestingly, both cellular and antibody responses to unadjuvanted gE declined substantially with age confirming the importance of the adjuvant in overcoming immunosenescence [26]. Long-term follow-up studies showed that both T cell-mediated and humoral immune responses to RZV persisted for at least nine years following vaccination [25,27]. Phase II clinical studies also established the critical role of the $AS01_B$ adjuvant system in augmenting gE-specific immune responses to RZV. RZV recipients developed a fivefold higher $CD4^{2+}$ T cell response compared to gE alone and a 15-fold increase over baseline [26]. Similar increases in gE-specific antibodies were also observed.

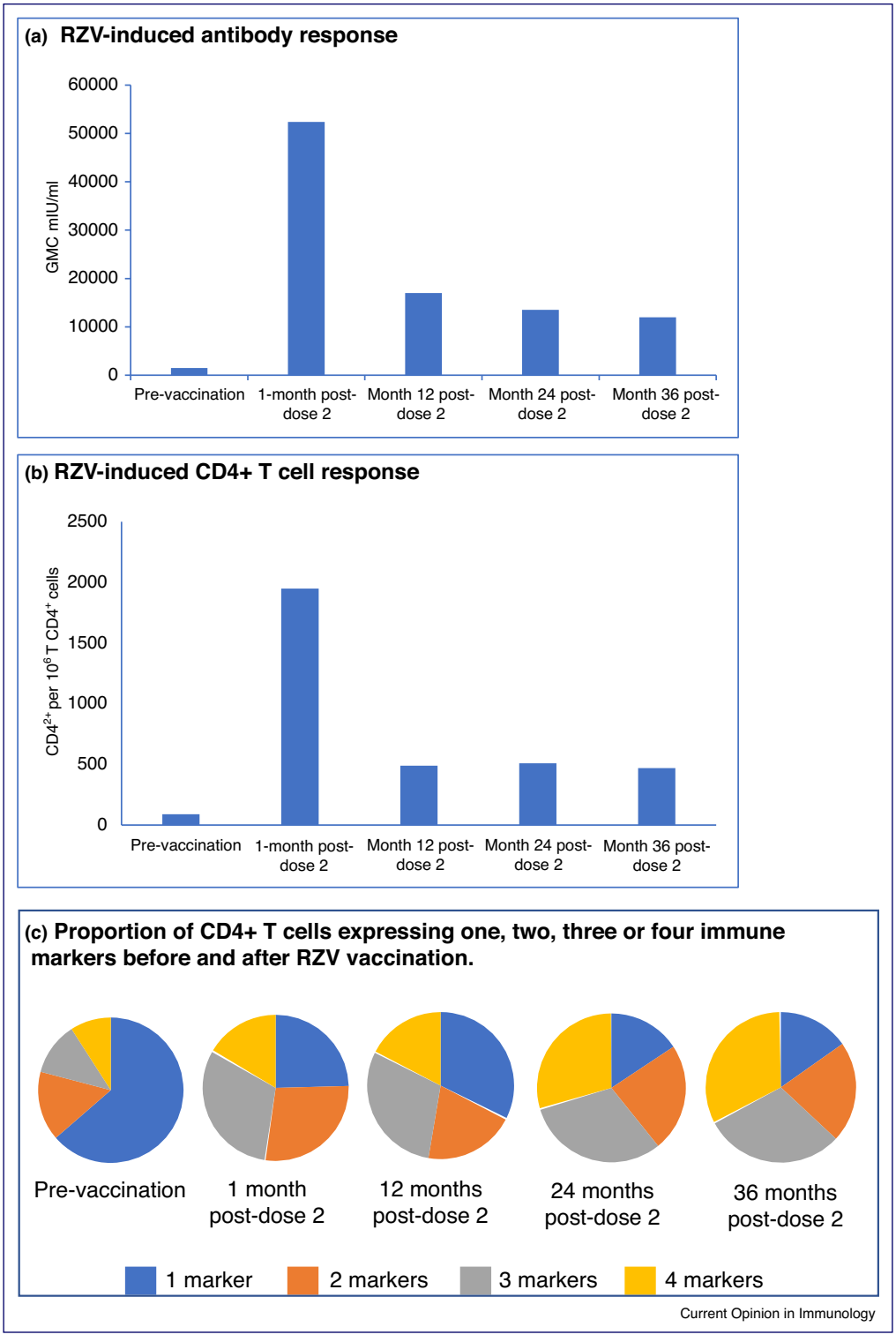
### Immunogenicity in the phase 3 efficacy studies

A subset of 3293 subjects were prospectively selected from ZOE-50 and ZOE-70 for a three-year post-vaccination immunogenicity substudy that measured gE-specific antibody responses; of these, gE-specific CMI responses were assessed in 466 participants [8••].

One month after the second RZV dose (peak response), 98% of RZV-recipients had a gE antibody response above the responder threshold compared to 2% in placebo-recipients, and the geometric mean peak gE antibody titer was 39-fold higher than in placebo-recipients [8••] (Figure 2a). Three years later, 77% of RZV-recipients remained above the responder threshold and the mean antibody level was 8.3-fold above baseline. There was no significant age effect on vaccine response rate, peak fold-rise, or response duration.

One month after the second RZV dose gE-specific CMI response rates were similarly as high as gE antibody response rates. gE-specific $CD4^{2+}$ T cells were increased in 93% of RZV-recipients with a median 25-fold rise [8••] (Figure 2b). At 1-year following vaccination, 57% of vaccinees remained above the responder threshold, which plateaued thereafter at a median fold-increase of 7.9. There was a trend toward an age effect on the

**Figure 2**




Immune responses to RZV.
RZV induces robust antibody **(a)** and CD4+ T cell responses **(b)** that peak 1-month after the second dose and then plateau above pre-vaccination levels. The proportion of CD4+ T cells expressing >1 marker **(c)** increases by 1 month following vaccination and continues to increase such that most gE-specific CD4+ T cells express at least 3 activation markers at months 24 and 36 following vaccination [8••].

proportion of CMI responders, but this did not reach statistical significance. The methods used in this study did not detect an increase in CD8+ T cells following vaccination; however, they were not optimized for this assessment. It is noteworthy that the proportion of gE-specific CMI responders declined more rapidly than the clinical efficacy observed, which through four years remained at 88%. This observation may indicate that the responder threshold was set too high. Alternatively, additional immune responses other than those measured in this substudy might contribute to RZV efficacy, including for example, a role for tissue resident T cells within the ganglia.

Before RZV administration, gE-specific CD4+ T cells were present in small numbers, and usually contained only one of the four intracellular biomarkers measured. After vaccination, the proportion of polyfunctional CD4 T cells expressing 2 or more markers greatly increased including a large complement expressing IL-2 or IL-2 and IFN-γ-expressing cells, characteristic of central and effector memory, respectively [8••] (Figure 2c). The number of polyfunctional T cells remained stable in the second and third year of the substudy, while their proportion increased to 60–70% of gE-specific CD4+ T cells. At 24 and 36 months following vaccination, more than 50% of gE-specific CD4+ cells expressed three or more markers. Polyfunctional T cells have been associated with successful vaccination against several pathogens and correlated with outcomes in some infections [28–30].

## RZV in immunocompromised adults

Immunocompromised people are at increased risk for HZ and for severe complications of HZ, underscoring the need for a safe and effective vaccine for this population. However, ZVL, a live attenuated vaccine, is contraindicated in immunosuppressed individuals due to concerns of possible vaccine-associated disseminated disease (as noted in the FDA Zostavax prescribing information). As a non-live subunit vaccine, RZV avoids this concern. To evaluate the potential of RZV to stimulate protective immunity in the face of significant immune suppression, five disease entities associated with immune compromise have been the subject of blinded, placebo-controlled trials, all conducted in adults 18 years and older. In each of these trials, the reactogenicity profiles were similar to those observed in immune competent older adults and no safety signals were identified.

### Autologous hematopoietic stem cell transplantation

Patients ($n = 1721$) received the first dose of RZV or placebo at 50–70 days after transplantation and the second dose 1 to 2 months later (presented at the BMT Tandem Meeting, Salt Lake City, February 2018). Efficacy against HZ over a 21-month median follow-up was 68%, and there was no effect of age on efficacy. Immune responses from this study have not been reported. However, in an earlier study in this population [31], all subjects who received two doses of RZV on the same vaccination schedule developed a gE-specific CMI response to vaccination. Following the second vaccination, the geometric mean frequency of gE-specific CD4+ T cells was 20-fold higher compared to an unvaccinated control, and gE-specific antibodies increased 27-fold.

### Hematologic malignancies

Patients ($n = 562$) received two doses of RZV or placebo separated by 1 or 2 months, with vaccine administration ~10 days before or after chemotherapy or at 10 days to 6 months after cessation of therapy. A post-hoc analysis demonstrated that RZV provided 87% efficacy for the prevention of HZ with a median follow-up of 11 months [32]. Vaccine-specific antibody responses occurred in 65–80% of participants, depending on the type of malignancy and treatment; the mean peak fold-rise was 16. gE-specific CMI responses were present in 84% of RZV recipients with a 30-fold increase in median gE-specific CD4+ T cell frequencies.

### HIV-infected adults

Patients ($n = 124$), in three cohorts based on CD4+ T cell count and treatment status, received 3 doses of RZV at 0, 2 and 6 months [33]. gE-specific CMI and antibody responses were stimulated in 88% and 92% of RZV recipients, respectively, after two doses of RZV. The magnitude of the immune responses was comparable to those seen in older immune competent adults; the third vaccine dose did not substantially improve either the humoral or cellular responses. Most had a positive immunologic response to vaccination regardless of baseline CD4+ count, but too few subjects with CD4+ counts less than 200/μl were enrolled to rigorously assess vaccine responses in that cohort. Neither plasma HIV RNA concentration nor CD4+ T cell counts were significantly impacted by HZV.

### Renal transplantation

Transplant recipients ($n = 240$) were vaccinated when on stable maintenance regimens at least four months after transplantation [34,35]. An antibody response was observed in 80% with a mean 15-fold increase in antibody titer. Antibody persisted in 67% of vaccinees with a mean 6.5-fold increase at one year after vaccination. gE-specific $CD4^{2+}$ CMI responses were increased in 71%; the magnitude of these responses at one month and at one year after vaccination were comparable to those in older immune competent adults. The rate of kidney rejection was low and not greater than that in the placebo-recipients.

### Patients with solid tumors undergoing chemotherapy

Patients with a variety of solid tumors ($n = 185$) received RZV or placebo 8–30 days before treatment or at the start of chemotherapy [36]. In general, immune responses were lower if RZV was given at the start of chemotherapy. With pre-therapy administration, 94% had a rise in

gE-specific antibody with a mean fold-rise of 10. Fifty percent of RZV recipients developed gE-specific CMI responses with a mean-fold rise of 3.6; at one year, only 18% retained CMI responses over baseline.

## Conclusions

RZV demonstrates very high efficacy against HZ in older adults and has been approved for use in many countries. The very high efficacy of RZV, the lack of any limitation of age on the protection it provides, and the preservation of its efficacy over time makes it unique among vaccines recommended for older individuals. This is likely explained by the synergistic action of the components of the adjuvant system, especially in the lymph node draining the site of administration. Recent and ongoing studies indicate that RZV will be also prevent HZ in many patients with a variety of immune compromising illnesses. Moreover, the success of the RZV and the $AS01_B$ adjuvant system in circumventing immunosenescence suggests that subunit antigens combined with this or other novel adjuvants may represent a general strategy for vaccines in ageing or immune compromised individuals.

Extended follow-up of RZV recipients is needed to address two major unanswered questions: 1) its duration of protection, especially in individuals of advanced age or with immune compromise; and 2) its long-term safety profile. In addition, further studies are required to define RZV efficacy in a broader range of immune compromised populations, including in persons being treated for immune mediated diseases. Additional questions to be answered that may maximize the value of this important vaccine are: defining its immunogenicity in VZV-naïve individuals to support its use in pediatric populations and perhaps allogeneic transplant recipients; and the potential to separate adjuvant-related reactogenicity and immunogenicity to produce an equally efficacious but less reactogenic next-generation vaccine.

## Conflict of interest statement

**Thomas C. Heineman** is a former employee of the GSK. He is an inventor on a patent owned by GSK and relevant to RZV and holds shares of GSK stock from GSK as part of former employee remuneration. He served as a paid consultant to GSK outside the submitted work. **Anthony Cunningham** received honoraria paid to his institution from GSK, Merck Sharp & Dohme (Merck), and BioCSL/Sequirus outside the submitted work. **Myron Levin** received fees for serving on advisory boards from Merck and GSK, grant support from Merck and GSK, and royalties from a patent related to a zoster vaccine held with Merck.

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