Humoral, Mucosal, and Cell-Mediated Immunity Against Vaccine and Nonvaccine Genotypes After Administration of Quadrivalent Human Papillomavirus Vaccine to HIV-Infected Children

Adriana Weinberg, Lin-Ye Song, Alfred Saah, Martha Brown, Anna B. Moscicki, William A. Meyer III, Janine Bryan, and Myron J. Levin, for the IMPAACT/PACTG P1047 Team

1University of Colorado–Denver School of Medicine, Aurora; 2Statistical and Data Analysis Center, Harvard School of Public Health, Boston, Massachusetts; 3Merck Research Laboratories, West Point, Pennsylvania; 4School of Medicine, University of California–San Francisco; and 5Quest Diagnostics, Baltimore, Maryland

Objectives. To characterize the immunogenicity of a quadrivalent human papillomavirus vaccine (QHPV) in human immunodeficiency virus (HIV)–infected children, we studied their immune responses to 3 or 4 doses.

Methods. HIV-infected children aged 7–12 years with a CD4 cell percentage of ≥15% of lymphocytes, received 3 doses of QHPV with or without a fourth dose after 72 weeks. Type-specific and cross-reactive antibodies and cell-mediated immunity were measured.

Results. Type-specific antibodies to HPV6, 11, and 16 were detected in 100% and ≥94% of children at 4 and 72 weeks, respectively, after the third QHPV dose. Corresponding numbers for HPV18 were 97% and 76%, respectively. A fourth QHPV dose increased seropositivity to ≥96% for all vaccine genotypes. Four weeks after the third QHPV dose, 67% of vaccinees seroconverted to HPV31, an HPV16-related genotype not in the vaccine; 69% and 39% of vaccinees developed mucosal HPV16 and 18 immunoglobulin G antibodies, respectively; and 60% and 52% of vaccinees developed cytotoxic T lymphocytes (CTLs) for HPV16 and 31, respectively.

Conclusions. Three QHPV doses generated robust and persistent antibodies to HPV6, 11, and 16 but comparatively weaker responses to HPV18. A fourth dose increased antibodies against all vaccine genotypes in an anamnestic fashion. CTLs and mucosal antibodies against vaccine genotypes, as well as cross-reactive antibodies and CTL against nonvaccine genotypes, were detected.

Human papillomavirus (HPV) causes almost all cervical and anal cancers and is responsible for 30%–50% of vulvar, vaginal, penile, and oropharyngeal cancers [1]. The oncogenicity of HPV infections is type specific and associated with viral persistence [2, 3]. Human immunodeficiency virus (HIV)–infected women and men have a higher incidence of HPV-related neoplasias and invasive cancers, compared with the general population [4, 5], which is likely related to failure to clear oncogenic HPV infections [3, 6, 7]. HIV-infected adults also have high rates of genital warts, which are often recalcitrant to conventional therapies [8, 9]. Compared with HIV-infected adult women, HIV-infected adolescents are 3-fold as likely to develop high-grade squamous epithelial lesions as a result of HPV infections [7], suggesting that they have a heightened vulnerability to the oncogenic effects of HPV infections and that special emphasis should be placed in devising strategies to protect them.

HPV16 and 18 account for approximately 70% of cervical cancers and approximately 90% of the other HPV-associated anogenital and oropharyngeal cancers [10–12]. HPV6 and 11 account for 90% of genital warts. Two HPV vaccines are commercially available: a quadrivalent vaccine (QHPV) against HPV6, 11, 16,
and 18 (Gardasil, Merck) and a bivalent vaccine against HPV16 and 18 (Cervarix, GlaxoSmithKline). Both vaccines are 98%-100% effective in protecting immunocompetent women against cervical infections with the vaccine genotypes [13-15]. QHPV confers protection in immunocompetent individuals against vulvar, vaginal, penile, and anal precancerous lesions and genital warts [16-18].

The mechanisms of protection of the HPV vaccines have not been completely elucidated, and immune correlates of protection have not been established. The vaccines, which contain the L1 HPV major capsid protein in a virus-like particle conformation, stimulate type-specific neutralizing antibodies, which are thought to play an important role in preventing HPV infection [13, 19, 20]. However, these vaccines also stimulate cell-mediated immunity (CMI) in immunocompetent hosts [21], which may also contribute to protection. Reports that adult women remain protected against HPV infection after loss of detectable antibody [22] and the observations that 1 or 2 doses of HPV vaccine may be as protective against HPV-associated cervical neoplasias as 3 doses of vaccine in the first few years after vaccination, despite inducing lower antibody titers [23], further emphasize the need to elucidate the mechanism(s) of protection by HPV vaccines and to identify an immune correlate of protection.

We and others showed that QHPV is generally safe and immunogenic in HIV-infected children and men who have sex with men [24, 25]. Here we report on the decay of HPV type-specific antibodies in HIV-infected children at 72 weeks after completing a standard 3-dose regimen and on the subsequent response to a fourth QHPV dose. We also describe mucosal and CMI responses to vaccine genotypes and cross-reactive responses to HPV31, which is not in the vaccine but is genetically related to HPV16.

PARTICIPANTS AND METHODS

Study Design

HIV-infected children 7–12 years old with a CD4 cell percentage of ≥15% of lymphocytes and without other immunosuppressive conditions were enrolled after informed consent was obtained from the caregiver and assent was obtained from the subject in accordance with local ethical review committee guidelines. Subjects were randomly assigned at a 3:1 ratio to receive QHPV (the Rx-Immediate group) or placebo (the Rx-Deferred group) at weeks 0, 8, and 24 as previously described [24]. At week 96, Rx-Immediate subjects received a fourth QHPV dose, and Rx-Deferred subjects started the 3-dose standard regimen. Figure 1 summarizes the interventions and the
time points when blood and oral secretions were collected for serum and mucosal antibody assays and for CMI.

**Serum Antibodies**
Serum type-specific, neutralizing HPV6, 11, 16, and 18 antibodies were measured by competitive Luminex immunoassay (cLIA) as previously described [26]. Results were expressed in milli-Merck units (mMU) per milliliter, using assay-defined positive thresholds. The serostatus cutoff was the antibody titer level within the assay’s quantifiable range that reliably distinguished “negative” from “positive” samples. The serostatus cutoffs were originally determined by testing approximately 500 samples and determining the percentage of positive samples at 11 different cutoffs (from 8 mMU/mL to 48 mMU/mL in increments of 4 mMU/mL). Prior to testing, sera were classified into panels according to their potential for being a true positive or negative on the basis of clinical history (number of sex partners, history of sexually transmitted diseases, or history of an abnormal Papanicolaou smear) and HPV polymerase chain reaction (PCR) results. The serostatus cutoff was selected as the lowest concentration such that all or nearly all of the known PCR-negative samples and likely negative samples yielded negative results. The resulting serostatus cutoffs for HPV types 6, 11, 16, and 18 were 20, 16, 20, and 24 mMU/mL, respectively.

Total immunoglobulin G (IgG) anti-HPV6, 11, 16, 18, and 31 antibodies were measured by LIA as previously described [27]. Results were expressed in mMU per milliliter, using assay-defined positive thresholds.

**Mucosal Antibodies**
Oral secretions were collected using OraSure kits (OraSure Technologies). Only IgG and immunoglobulin A (IgA) antibodies against HPV16 and 18 were measured using the enzyme-linked immunosorbent assay (ELISA) described in the Supplementary Materials. Results were expressed in titers (GMTs) and 95% confidence intervals (CIs). Serum type-specific, neutralizing HPV6, 11, and 16 in the Rx-Immediate and Rx-Deferred groups, or history of an abnormal Papanicolaou smear) and HPV polymerase chain reaction (PCR) results. The serostatus cutoff was selected as the lowest concentration such that all or nearly all of the known PCR-negative samples and likely negative samples yielded negative results. The resulting serostatus cutoffs for HPV types 6, 11, 16, and 18 were 20, 16, 20, and 24 mMU/mL, respectively.

The baseline characteristics are shown in Table 1. All but 2 participants were receiving highly active antiretroviral therapy.

**RESULTS**

**Demographic and HIV Disease Characteristics**
The baseline characteristics are shown in Table 1. All but 2 participants were receiving highly active antiretroviral therapy.

**Magnitude and Persistence of Specific Antibody Responses to QHPV**
Four weeks after completion of a standard 3-dose regimen, the proportions of seropositives measured by cLIA were 100% for HPV6, 11, and 16 in the Rx-Immediate and Rx-Deferred groups. Results were expressed in titers (GMTs) and 95% confidence intervals (CIs). Serum type-specific, neutralizing HPV6, 11, and 16 in the Rx-Immediate and Rx-Deferred groups, or history of an abnormal Papanicolaou smear) and HPV polymerase chain reaction (PCR) results. The serostatus cutoff was selected as the lowest concentration such that all or nearly all of the known PCR-negative samples and likely negative samples yielded negative results. The resulting serostatus cutoffs for HPV types 6, 11, 16, and 18 were 20, 16, 20, and 24 mMU/mL, respectively.

**Statistical Analysis**
cLIA and LIA results were described using geometric mean titers (GMTs) and 95% confidence intervals (CIs). Results below the lower limit of quantitation (LOQ) were arbitrarily assigned a value of ≤50% of the LOQ. cLIA and LIA comparisons were performed using parametric tests. ELISPOT and ELISA results were described by medians and 95% CIs and were analyzed using nonparametric tests. Univariate linear regression was used to identify predictors of week 96 cLIA titers. For categorical variables with >2 categories, Tukey-Kramer simulation-based adjusted P values were used when F tests were statistically significant (P < .05).

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<th>Table 1. Baseline Demographic and Human Immunodeficiency Virus Disease Characteristics of Participants</th>
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<td><strong>Characteristic</strong></td>
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Data are mean values ± SD or no. (%) of subjects.

a Calculated by the t-test.

b Calculated by the F test, followed by Tukey-Kramer tests when appropriate.
groups, 97% for HPV18 in the Rx-Immediate group, and 100% for HPV18 in the Rx-Deferred group. Titers are shown in Figure 2A–D. The cLIA titers in the Rx-Immediate group rapidly decreased over the first year after the third QHPV dose (from 2.2-fold to 6.3-fold for all genotypes). This was followed by a much slower 1.0–1.1-fold decrease in the subsequent 6 months. At 18 months after the third QHPV dose, HPV6, 11, 16, and 18 cLIA seropositivity in the Rx-Immediate group was 94%, 97%, 99%, and 76%, respectively.

A fourth dose of QHPV administered to Rx-Immediate participants increased cLIA titers against all vaccine-contained genotypes to 100% seropositivity for HPV6, 11, and 16 and to 96% for HPV18. cLIA titers at 4 weeks after the fourth QHPV dose were significantly higher than those at 4 weeks after the third QHPV dose for all genotypes (Figure 2A–D; P < .0001). Both the magnitude and the kinetics of the antibody response to the fourth QHPV dose indicated an anamnestic response. This was further demonstrated by the comparison of the antibody response in Rx-Immediate subjects (corresponding to 1 week after the fourth dose) and Rx-Deferred subjects (corresponding to 1 week after the first dose) at week 97. Using week 96 antibody concentrations as a reference, the Rx-Immediate group had geometric mean fold-rises (GMFRs) of 11, 8, 6, and 10, respectively for HPV6, 11, 16, and 18, whereas the Rx-Deferred group had GMFRs of 2, 1, 1, and 1, respectively. Furthermore, the 17 Rx-Immediate subjects who seroreverted for HPV18 between weeks 28 and 96 had an HPV18 GMFR of 10 (95% CI, 3–32), which was similar to that of the 79 Rx-Immediate subjects who maintained seropositivity between weeks 28 and 96 and was significantly higher (P = .003) than that of 24 Rx-Deferred subjects (P = .003).

**cLIA-Measured Responses After a Single Dose of QHPV**

Antibody responses after a single dose of QHPV were studied only in Rx-Deferred subjects (Figure 2A–D). Four weeks after the first QHPV dose, 22 of 24 subjects (92%) seroconverted to HPV6 and 11, 21 (86%) seroconverted to HPV16, and 8 (33%) seroconverted to HPV18.

**Cross-reactive Antibody Responses to QHPV**

Total serum IgG antibody responses to QHPV were measured by LIA at entry and week 28. LIA is less HPV-type specific...
Mucosal HPV16- or 18-specific increases in the Rx-Deferred subjects before vaccination. None were detected in Rx-Immediate or Rx-Deferred subjects.

Mucosal Antibodies

Oral secretions collected at baseline and week 28 were tested for HPV16- and 18-specific IgG and IgA by ELISA. Sixty-one (69%) and 35 (39%) of 89 subjects with paired samples in the Rx-Immediate group developed HPV16 and 18 mucosal IgG antibodies, respectively, after vaccination; median antibody titers, corresponding to the highest positive serum dilution, were 6248 ± 1780 mMU/mL (95% CI, 2499–11 170) vs 1687 mMU/mL (95% CI, 1107–2572) for HPV16 [P < .0001]; GMT, 3893 mMU/mL [95% CI, 2530–5989] vs 420 mMU/mL [95% CI, 263–671] for HPV28 [P < .0001]). There were no mucosal HPV-specific IgG increases in the Rx-Deferred subjects before vaccination. Mucosal HPV16- or 18-specific IgA antibodies were not detected in Rx-Immediate or Rx-Deferred subjects.

Magnitude, Persistence, Cross-reactivity, and T-cell Subsets of CMI Responses to QHPV

At baseline, there were no HPV16 IFN-γ ELISPOT responses in 60 Rx-Immediate or 21 Rx-Deferred subjects (Figure 4A). At week 28, ELISPOT responses were present in 60% of Rx-Immediate subjects (36 of 60) and in 5% of Rx-Deferred subjects (1 of 21) (P < .001). There were no significant ELISPOT changes between weeks 28 and 96 when the fourth QHPV dose was administered in the Rx-Immediate group and when the first QHPV dose was administered in the Rx-Deferred group. At week 100, Rx-Immediate and Rx-Deferred subjects showed increases in ELISPOT values, although they were not statistically significant (P = .09 and 0.26, respectively). At week 100, 72% of Rx-Immediate subjects (31 of 43) versus 37% of Rx-Deferred subjects (7 of 9) had HPV16 ELISPOT responses (P = .01), reflecting the higher number of QHPV doses.

We performed parallel ELISPOT assays using whole and CD8-depleted PBMCs. The difference between whole and CD8-depleted results was interpreted as a measure of cytotoxic T lymphocytes (CTLs). Among 30 subjects in the Rx-Immediate group who developed HPV16 ELISPOT responses after the third QHPV dose, CD8 depletion almost completely abrogated the response (Figure 4B), indicating that the ELISPOT assay primarily detected CTLs.

Correlation analyses of week 28 HPV16 ELISPOT results with nadir CD4 cell counts and percentages, entry CD4 and CD8 cell counts and percentages, and HIV load showed only a weak association with entry CD4 cell counts (ρ = 0.24; P = .06). There was a weak correlation at week 28 between HPV16 ELISPOT and cLIA results (ρ = 0.25; P = .06).

Cross-reactive CMI was measured using HPV31-specific IFN-γ ELISPOT (Figure 4C and 4D). Fifty-two percent of subjects in the Rx-Immediate group (31 of 60) and 5% in the Rx-Deferred group (1 of 21) developed HPV31 responses at week 28 (P < .0001). These responses were also completely abrogated by CD8 depletion (data not shown). Week 28 HPV31 and 16 ELISPOT values in the Rx-Immediate group were highly correlated (P < .0001).

Correlates of HPV Antibody Persistence

To determine the factors that influenced the cLIA antibody persistence after QHPV vaccination in HIV-infected children, several independent variables, including age, sex, race, ethnicity, CD4 cell count, CD8 count, CD19 cell counts and/or percentages HIV viral load, IFN-γ ELISPOT results (where available), and HPV antibody concentrations at week 28 were used in a univariate analysis in which the outcome measure was the week 96 HPV antibody concentrations in Rx-Immediate subjects. Higher HPV antibody concentrations at week 28 were the strongest predictors of higher antibody concentrations at week 96 for all HPV genotypes (P < .0001). Other variables significantly associated with this outcome were CD4 cell counts and percentages, entry CD4 and CD8 cell counts and percentages, nadir CD4 cell counts and percentages, entry CD4 and CD8 cell counts and/or percentages HIV viral load, and HPV antibody concentrations at week 28.
counts and/or percentages for all genotypes and week 28 ELISPOT results for HPV16 ($P \leq .04$). Entry CD8 cell counts and/or percentages and HIV load were negatively correlated with HPV antibody concentrations at week 96. In a multivariate analysis with week 96 HPV16 antibody concentration as the outcome measure and CD4 cell percentage, HIV load, ELISPOT, and week 28 HPV antibody concentrations as predictors, only the week 28 antibody concentrations remained significantly associated with persistence.

DISCUSSION

We showed that, at 72 weeks after the last vaccination, >90% of HIV-infected children remained cLIA seropositive for HPV6, 11, and 16 but that only 76% remained positive for HPV18. Studies of similar length in immunocompetent children showed >90% cLIA antibody persistence for all vaccine genotypes [30]. The antibodies produced by HIV-infected children in response to QHPV rapidly decayed within the first 48 weeks after the last vaccination and much slower thereafter, up to 72 weeks. Assuming that the antibody decay between 48 and 72 weeks after the last vaccination represents steady state, we estimated by linear regression that 50% of the HIV-infected children might become cLIA seronegative to the vaccine genotypes 4–5 years after the standard vaccination regimen. A follow-up study of this cohort is in progress to determine antibody persistence over 5 years.

HPV antibody persistence in this study was influenced by several factors, the most important of which was the antibody titer achieved at the completion of the vaccination regimen. In
addition, traditional markers of HIV-associated loss of immune competence, including CD4 and CD8 absolute and relative cell numbers and HIV load, also correlated with persistence. It is interesting to note that we previously found in HIV-infected subjects that antibodies measured 4 weeks after the completion of the 3-dose standard HPV vaccination regimen were not affected by CD4 cell counts or percentages [24]. It is possible that significantly reduced CD4 cell percentage may impact the conversion of plasmablasts into memory B cells with a downstream effect of reduced measurable persistent antibodies.

A fourth dose of QHPV significantly increased the antibody concentrations through an anamnestic response against all HPV genotypes in the vaccine, including in participants who had lost antibodies at 72 weeks. Furthermore, unlike the 3-dose QHPV regimen [24], the fourth dose of vaccine brought the anti-HPV18 antibody concentrations of the HIV-infected children to levels comparable to those achieved after a 3-dose regimen in uninfected same-age historical controls [30, 31]. The antibody titer generated after primary vaccination determines the antibody persistence. However, the importance of persistent neutralizing antibodies against HPV with respect to protection against HPV-associated neoplasias has been disputed. Immunocompetent women vaccinated with QHPV maintained protection against HPV-associated cervical neoplasias even after their cLIA antibody titers fell below the assay-defined positive threshold [22]. This disconnect has been ascribed to a lack of sensitivity of the cLIA test [27] and/or to the ability of the vaccine to generate anamnestic responses in seroreverters. However, more studies are needed to clarify the latter, because if protection exclusively resulted from neutralizing antibodies generated by the vaccine, these antibodies might have to be present at the time of exposure. Typically, neutralizing antibodies do not block cell-to-cell transmission. Hence, if the virus established infection because of a lack of neutralizing antibodies at the time of exposure, antibodies raised by an anamnestic response might not be able to clear the infection.

In HIV-infected children, the HPV16 antibody and CTL responses to QHPV were positively correlated. Hence, in this population, antibody responses to QHPV may reflect not only B-cell immunity but the overall immunogenicity of the vaccine. Our data suggest that HIV-infected children may require additional doses of QHPV to achieve the same level of immune protection as same-age uninfected historical controls do for HPV18. Since HPV18 is the second most common cause of genital cancers overall and, in some areas, may even cause more cancers than HPV16 [32–34], it is very important to further investigate the short- and long-term consequences of a weaker antibody response to HPV18 in HIV-infected children and adolescents.

HPV-specific immune responses at the portal of entry of HPV, mucosa and skin, probably play a pivotal role in the fate of infection. On the basis of recent evidence that a common mucosal immune system ensures a level of uniformity in responses at mucosal surfaces of different systems after systemic administration of vaccines [35–37], we used oral secretions to evaluate mucosal responses to QHPV. The presence of the HPV16- and 18-specific antibodies in the oral secretions most likely resulted from transudation of serum antibodies, since HPV-specific IgG antibodies, but not IgA antibodies, were detected in the oral secretions, and the mucosal and serum IgG antibody concentrations were highly correlated. This was also in agreement with earlier studies involving immunocompetent vaccinees [38]. Mucosal antibodies against HPV16 and 18 were detected only in 69% and 35%, respectively, of the 89 subjects tested in our study. This is in contrast to studies involving immunocompetent vaccinees, where 100% of participants had HPV16 antibodies in the oral fluid (HPV18 was not examined) [38]. There are differences between the assays used to measure HPV antibodies in our study and the previous study that may partially account for the disparity between these studies. Furthermore, innate and/or adaptive local CMI, which were not examined in this study, may also play a role in mucosal protection against HPV. More studies are needed to completely characterize mucosal responses to QHPV in HIV-infected and -uninfected individuals.

QHPV generated HPV16 CTLs in a majority of our vaccinees. HPV-specific CTLs are thought to play a critical role in the natural history of HPV, being responsible for the clearance of established HPV genital infection [39]. QHPV was previously shown to induce CMI in immunocompetent individuals [21, 40, 41], but the participation of CMI in vaccine-induced protection is less well understood. Animal studies that showed that passively transferred antibodies resulted in complete protection against HPV infection [42] did not investigate innate or adaptive CMI. In contrast, de novo infection with HPV genotypes contained in the vaccines has been demonstrated in vaccinated women [43, 44]. These infections are typically transient, suggesting the participation of innate or adaptive CMI in the clearance of the infections incompletely controlled by neutralizing antibodies, and underscore the important role that vaccine-generated CTL may play in the overall protection conferred by QHPV.

There are clinical data to suggest that HPV vaccines generate limited cross-protection against HPV genotypes not included in vaccines. This cross-protection was observed between genotypes that belong to the same family [45]. Cross-reactive antibody responses were demonstrated in healthy recipients of HPV vaccines [46, 47]. This is the first published study to demonstrate that QHPV also generates cross-reactive antibodies in HIV-infected individuals. We also show cross-reactive CTL responses to QHPV. The correlation between HPV cross-reactive immune responses against nonvaccine genotypes and cross-protection has not been studied. Hence, the importance of the cross-reactive immune responses for
protection against infection with vaccine-related HPV genotypes remains to be established.

The information generated in this report was limited by the relatively small study population, by its relatively homogeneous HIV disease characteristics, and by the limited follow-up after the fourth QHPV dose. Our main vaccine immunogenicity outcome measures were HPV neutralizing antibodies, which may underrepresent the overall humoral protection conferred by QHPV, either because neutralizing antibodies represent one of several antibody-mediated protective mechanisms generated by the vaccine or because the assay used to measure neutralizing antibodies has limited sensitivity [27]. We did not assess HPV18 CTLs, which, retrospectively, would have been an important measure of immunogenicity of the vaccine in our study population, considering the lower levels of HPV18 neutralizing and mucosal antibodies.

In conclusion, the standard 3-dose QHPV vaccination regimen generated robust antibody responses against HPV6, 11, and 16 that lasted for at least 72 weeks in HIV-infected children with good control of viral replication and high CD4 cell counts. Antibody responses to HPV18 were lower both in serum and oral secretions, and almost a quarter of the study participants lost HPV18 serum antibodies 72 weeks after completion of the 3-dose standard vaccination regimen. In the absence of certainty regarding the mechanism of protection of the HPV vaccines and of an immune correlate of protection, the clinical implications of the lower HPV18 antibody response in the HIV-infected population are unclear. Efficacy trials of QHPV are needed to determine whether additional doses of vaccine are needed for full protection of HIV-infected individuals against the oncogenic genotypes in QHPV.

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 copyedited. 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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Potential conflicts of interest. Dr Saah and Ms Brown are employees of Merck Research Laboratories; Dr Bryan was an employee of Merck Research Laboratories when this study was conducted; Dr Weinberg received research grants from Merck; Dr Modell is a consultant for Merck and receives travel and meeting support from GlaxoSmithKline; Dr Levin is a consultant for Merck and for GlaxoSmithKline, receives research grants from GlaxoSmithKline and Merck, and receives intellectual property royalties for Zostavax, which is manufactured by Merck. All other authors report no potential conflicts.

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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