Reply to Harper

TO THE EDITOR—We are thankful for the interest in our article [1] by Harper and take this opportunity to clarify points that may have caused confusion.

Our follow-up study is a continuation of our original randomized controlled trial of alternative dosing schedules for quadrivalent human papillomavirus (HPV) vaccine among adolescent girls in Vietnam [2] and includes the same population. The original trial end point was immunogenicity 1 month after dose 3 [2] and resulted in type-specific results for noninferiority between the standard 0-, 2-, and 6-month dosing schedule and 3 alternative dosing schedules of 0, 3, and 9 months; 0, 6, and 12 months; and 0, 12, and 24 months [2]. Because other studies have demonstrated a waning immune response (measured in terms of geometric mean titers [GMTs]) over time among recipients of HPV vaccine [3–5], we studied whether the same would be true for adolescents vaccinated using alternative dosing schedules. Therefore, we re-enrolled most of the original participants for collection of a follow-up blood specimen 29–32 months after their last dose of HPV vaccine. Because of the staggered start of the original trial, 66 girls vaccinated according to the standard 0-, 2-, and 6-month schedule were not eligible to be recruited for the follow-up study, because the time between their third dose and the start of our follow-up study was 36 months, which exceeded our planned immune response measurement 32 months after dose 3 [1].

All participants in the original trial and, thus, all girls included in our follow-up study received all 3 doses of quadrivalent HPV vaccine according to their designated schedules. There were no additional doses of HPV vaccine given during our follow-up study; only a blood sample was taken to measure antibody response 29–32 months after dose 3. Because the timing of the alternative dosing schedules varied (as per the original trial design) [2], the length of follow-up between receipt of the first dose and measurement of the immune response 1 month after dose 3 varied by schedule, as noted by Harper. As such, the time of measurement of the immune response before dose 3 also varied. We provided Figure 1 to illustrate the vaccination schedule, timing for measuring antibody responses, and length of time between each measurement for all dosing schedules [1].

For all vaccine schedules, immune responses were significantly higher 1 month after the administration of the third dose, compared with those measured before dose 3 (ie, after 2 doses of HPV vaccine had been administered) [1, 2]. The magnitude of the boosting measured 1 month after dose 3 varied by schedule, with a larger boost observed for the standard 0-, 2-, and 6-month schedule (Figure 3 [1]). However, over time, and most likely because of the kinetics of waning antibody levels that has been demonstrated in other immunogenicity studies of quadrivalent HPV vaccine [3, 4], the antibody concentrations 29–32 months after the third dose of HPV vaccine were similar, regardless of the original dosing schedule, and were noninferior to those associated with the standard 0-, 2-, and 6-month schedule (Table 1 [1]). Although our results 1 month after dose 3 differed from those in the study by Zimmerman et al [6], the long-term finding is that our alternative (extended) schedules are noninferior to those of the standard schedule. We assert that antibody concentrations measured 1 month after the third dose may be less clinically relevant than the long-term robustness of the response.

Even though our original trial and follow-up study were not designed to compare 2 versus 3 doses, we had an
opportunity to investigate immune responses for all schedules after 2 doses because we obtained a blood specimen just before administering the third dose (Figure 1 [1]). This analysis was exploratory, as subjects were not randomly assigned to a 2-dose schedule. For all schedules, by 3 months after dose 3, antibody titers waned to the level observed before dose 3 (ie, after the second dose) [1]. Intriguingly, for the 3 doses delivered on the alternative annual schedule of 0, 12, and 24 months, the immune response 12 months after dose 2 (at month 24) was similar to the immune response 32 months after dose 3 [1]. Additionally, the GMTs before dose 3 for this group (1572; 95% confidence interval [CI], 1366–1810) [1] were similar to those reported by Dobson et al for the 0- and 6-month 2-dose schedule, also measured 12 months after dose 2 (at month 18; 1579 [95% CI, 1322–1885]) [4]. This suggests that the antibody kinetics for 2 doses delivered at 0 and 6 months may not differ from those delivered at 0 and 12 months, but a properly conducted randomized controlled trial comparing these 2 schedules and the standard 0-, 2-, and 6-month 3-dose schedule, with long-term follow-up, will be necessary to provide a conclusive answer.

Although Harper has been an advocate for bivalent HPV vaccine [7], the dramatic decline in genital warts in Australia and Denmark [8, 9] and the mounting evidence that flexible schedules for quadrivalent HPV vaccine are noninferior suggest that there is still a role for quadrivalent HPV vaccine in public health programs.

In conclusion, we found that delivery of 3 doses of quadrivalent HPV vaccine on alternative dosing schedules, including an annual schedule of 0, 12, and 24 months, did not result in inferior immune responses after >2.5 years of follow-up after the third dose. This new evidence for dosing flexibility could be helpful for settings where delivering 3 doses of HPV vaccine on a precise 0-, 2-, and 6-month schedule is challenging.

**Note**

**Potential conflict of interest.** Author certifies no potential conflicts of interest.

The author has 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.

**D. Scott LaMontagne**

Vaccine Access and Delivery, PATH, Seattle, Washington

**References**


Received 18 January 2014; accepted 21 January 2014; electronically published 5 February 2014.

Correspondence: D. Scott LaMontagne, PhD, Vaccine Access and Delivery, PATH, 2201 Westlake Ave, Ste 200, Seattle, WA 98121 (slamontagne@path.org)