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Reply to Letter to the Editor

A mixed vaccination schedule of HPV vaccine induces a 100% seropositivity to all 9 HPV types included in 9vHPV vaccine

Dear Editor,

In their letter about our article [1], Dr. Rosberger et al. incorrectly states that we concluded "9vHPV and 2vHPV was as immunogenic as two doses of 9vHPV vaccine" and mentions that we "do not present data to suggest adequate protection". Our study shows that while the mixed schedule (whatever the order of vaccines) induces lower titers than two doses of 9vHPV against the 7 genotypes not included in the 2vHPV, it induces a 100% seropositivity to all 9 HPV types included in 9vHPV and titers higher to carcinogenic HPV types than following a single dose of 9vHPV. Although our study did not assess efficacy outcomes, numerous studies assessing protection found that any detectable antibody titer induced by vaccination is protective and even when titers decline under detectable threshold individuals remain protected [2,3]. The immune correlates of protection for HPV vaccines is still undefined as no "breakthrough cases" had been reported yet in individuals vaccinated before being exposed to HPV even in the context of declining vaccine induced antibody titers over time. Rosberger et al. appear to apply a double standard when they assert that "the 9-valent vaccine provides long-term protection against anogenital warts" and when they conclude without any scientific evidence that "a mixed two-dose schedule is unlikely to be protective". There are no long-term efficacy data available of the recently marketed 9vHPV vaccine [4]. The manufacturer obtained from regulatory authorities their approval of the indication of the 4 and 9vHPV for pre-adolescents and adolescents based on immunogenicity data without any direct efficacy result. The double standard applied by Rosberger et al. against less than two doses of 9VHPV is also apparent when they mention that 8–10 years are needed to evaluate the effectiveness of a single dose of 9vHPV" as the 4vHPV and 9vHPV were in fact licensed based on 3–4 year-long studies in women/men, and exclusively on immunogenicity studies in girls/boys [4]. They also try to undermine our results by mentioning that our study is a "small study: n = 47 boys and 47 girls". These numbers reflects participants who received 9vHPV followed by 2vHPV but ignore the same number of participants whose mixed schedule had the reverse order (2vHPV + 9vHPV) with similar immunogenicity results and the size of the comparative group receiving 2 dose of 9vHPV vaccine (total n = 371). They also ignore that no difference in immune response was observed between boys and girls [1], and that at least four other studies have shown mixed schedules are highly immunogenic and safe [5–8].

We agree with them when they state that "We have much to learn from our current, effective programs". One of the most important finding from these programs is that any detectable post-vaccination antibody titer seems sufficient to protect against HPV related diseases. While antibody titers after a single dose of vaccine are lower than after 2 or 3 doses, several rigorously conducted studies [9–11] show similarly high levels of protection for at least up to 7-11 years post-vaccination whatever the number of doses.

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