Safety and immunogenicity of two doses of the HPV-16/18 AS04 adjuvanted vaccine Cervarix

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A recent study in the journal *Human Vaccines & Immunotherapeutics*, showed that two doses of the HPV-16/18 AS04-adjuvanted vaccine Cervarix (GlaxoSmithKline) are non-inferior to three-doses in the current schedule.

Since high coverage and compliance rates can be difficult to achieve with the current three-dose HPV vaccineregimen, several studies have looked at the possibility of reducing the number of doses. Proof-of-principle that a two-dose schedule can provide sufficient protection against cervical cancer came initially from a study performed in Costa Rica in 2011. Since then, several countries have considered switching to a two-dose schedule or have already done so. The European Commission recently granted marketing authorization for Cervarix as a two-dose schedule for girls aged 9-14 years, and outside of the EU, the Cervarix two-dose schedule is approved in more than ten countries, including Panama, Guatemala, Honduras, El Salvador, Haiti, Suriname, Chile, Guyana, Nigeria, Ghana, Pakistan, and Bangladesh.

The randomized, partially-blinded Phase I/II clinical trial evaluated the immunogenicity and safety of two doses of the licensed formulation of Cervarix (20 µg each of HPV-16 and HPV-18 L1 VLPs, ‚20/20') or an alternative formulation (40 µg of each HPV-16 and HPV-18 VLPs; ‚40/40') in different age groups, compared with the standard three-dose schedule of the licensed formulation. Healthy females (age stratified:

9-14, 15-19, 20-25 years) were randomized to receive two doses of vaccine at months 0 and 6, or three doses of the vaccine at months 0, 1, and 6.

The trial was initiated in 2007 and conducted at 21 centers in Canada and Germany. Results from 24 months of analysis were previously published in *HV&I*, and the current study presents results from 48 months of analysis. Since the two-dose 40/40 formulation gave no added benefit, the current study focused on data for the two-dose 20/20 formulation in girls aged 9-14 years and the standard three-dose 20/20 schedule in women aged 15-19 years.

The researchers reported that all initially seronegative subjects seroconverted for HPV-16 and HPV-18 antibodies and remained seropositive up to 48 months. The kinetics of HPV-16, -18, -31, and -45 antibody responses were similar for both groups, and the HPV-16 and -18 geometric mean antibody titers were substantially higher than titers following natural infection. The vaccine had a clinically acceptable safety profile in both groups. In summary, antibody responses to a two-dose schedule of the licensed vaccine formulation in girls aged 9-14 years appeared comparable to the standard three-dose schedule in women aged 15-19 years for up to four years after first vaccination.

These results show that a two-dose schedule should confer a similar level of protection against HPV infections and subsequent development of cervical lesions and cancer as the current three-dose schedule. A two-dose schedule obviously would be more convenient for physicians and patients, and could help reduce associated costs. The authors think that these benefits could facilitate the implementation of HPV immunization programs in low-income countries, as well as improve the relatively low vaccine coverage and series completion rates observed in some developed countries.

"Compliance has been a major challenge for HPV vaccination. These data reinforce the value of the two-dose schedule and should lead to increased utilization of this vaccine, with consequent decreases in morbidity and mortality from cervical cancer," said Dr. Ronald Ellis, Editor-in-Chief of *Human Vaccines & Immunotherapeutics*.

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