Editorial

The Debate Over Two-Dose or Three-Dose Human Papillomavirus Vaccine

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Cervical cancer is the fourth most common cancer in women around the world, and HPV types 16 and 18 are responsible for about 70% of cases (1). The HPV vaccine was initially developed in 2006 to be given in three doses over six months, but many countries are now moving to a two-dose schedule for adolescents (2).

Persistent infection with a high-risk human papillomavirus type is necessary for cervical cancer. Two human papillomavirus vaccines are available, a bivalent vaccine with antigens for human papillomavirus 16 and 18 associated with 70-80% of cervical cancers globally (Cervarix), and a quadrivalent vaccine that additionally contains antigens for human papillomavirus 6 and 11 associated with most cases of anogenital warts (Gardasil) (3-5). Female participants receiving three doses of either vaccine in trials were protected against persistent infection and precancerous lesions associated with human papillomavirus 16 and 18. Universal human papillomavirus vaccination of girls before their sexual debut has been found to be cost effective in both developed and developing countries. However, the high cost of purchase and delivery of vaccine has been a barrier to more widespread implementation (4, 5).

Data from the Costa Rica vaccine trial that involved 7499 patients, the patricia trial that involved 18 644 patients, and the Future I and II clinical trials that involved 17 622 patients showed that two doses protect against HPV in much the same way as a three-dose schedule (6).

A two-dose human papillomavirus vaccination program is expected to substantially decrease the incidence of human papillomavirus-related cancers and anogenital warts. If the duration of protection of a two-dose schedule is at least 20 years, then the additional benefit of the third dose is minimal, regardless of whether the vaccine provides cross protection. A two-dose schedule giving 20 years' protection may be sufficient to eliminate human papillomavirus 6/11-associated anogenital warts, so a third dose may have little or no long-term benefit in terms of protection against warts. If the duration of protection with a two-dose schedule is only 10 years, then the benefit of a third dose in terms of reduction in all the examined human papillomavirus-related endpoints is greater, although it is still much smaller than the benefit of the first two doses (6).

Overall conclusions are also similar if a bivalent vaccine is used instead of a quadrivalent vaccine. Giving a third dose is still cost effective only if it extends the duration of protection by the vaccine from ten years to a lifetime. The assumed superior cross protection and lower vaccine cost of the bivalent vaccine partially compensate for the loss of protection against warts and recurrent respiratory papillomatosis. If a discount rate of 1.5% per annum instead of 3.5% per annum is used, then the third dose becomes slightly more cost effective, because outcomes that occur further in the future and are prevented by having a longer duration of protection, are valued more (6).

Also, conclusions are the same for the bivalent vaccine, although the cost effectiveness of two versus three dose schedules differ slightly owing to differing cross protection and protection against warts. Also, evidence about the efficacy and immunogenicity of two doses of each of the two vaccines is not equivalent. For example, no clinical efficacy data using two doses of the quadrivalent vaccine is available (3, 6).

According to the available data from the UK and Canada, dynamic data take into account indirect (herd) vaccine protection due to reduced transmission of human papillomavirus. Herd protection is likely to be a substantial contributor to the impact of two-dose programs with less than lifetime duration of protection. Data also incorporate the full range of human papillomavirus-related outcomes, including cervical cancer (and its precursors), other cancers and anogenital warts. The consistency of results between the two data, despite differences in underlying human papillomavirus epidemiology represented

in each of them, suggests that the main conclusions are generalizable to other high-income countries with similar human papillomavirus epidemiology. However, caution is needed in interpreting the results for poor resource settings owing to differences in sexual behavior, human papillomavirus epidemiology, cervical screening coverage and healthcare costs. Similar analyses for these settings are a priority, particularly following the strategic advisory group of experts on immunization's global recommendation of two-dose schedules (6).

In fact, in April 2014, the world health organization (WHO) strategic advisory group of experts recommended a two-dose HPV schedule for girls if the vaccination series is initiated before the age of 15 (7).

It seems that, in Iran, the inclusion of HPV vaccine in the expanded program on immunization (EPI) is the most important task. Priority vaccination in young women and research studies in relation to vaccine efficacy and effectiveness especially in girls under 10 years of age should be performed.

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