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HPV vaccine: One, two, or three doses for cervical cancer prevention?

INTRODUCTION

Cervical cancer, a preventable disease to a large extent, accounts for an estimated 527,624 new cases and 265,672 deaths annually. It is the fourth most common cancer among women globally though in many less developed regions it still remains the most common cancer.[1] Well-organized screening programs have been responsible for reducing the cervical cancer burden in the majority of the more developed regions since several decades. However, women in less developed regions may not undergo a single screen even in their life time, thereby contributing to high disease burden.

Vaccines to prevent cervical cancers are now available. The quadrivalent vaccine protecting against human papilloma virus (HPV) types 16/18/6/11 was licensed in 2006, and the bivalent vaccine protecting against infection with HPV-16/18 was licensed in 2007. Both vaccines protect against the oncogenic varieties of HPV-16/18 that cause 70% of all cervical cancers and precancers, as well as many cancers of the vulva, vagina, anus, and throat.[2] The nonavalent HPV vaccine protecting against HPV types 16/18/6/11/31/33/45/52/58 was approved by the USA Food and Drug Administration in December 2014. All these three vaccines are prepared from purified L1 structural proteins using recombinant technology that self-assemble to form HPV type-specific empty shells or virus-like particles (VLPs). Several other approaches are also being explored including vaccine based on the HPV L2 viral capsid protein.[3] National and regional immunization programs aimed at young adolescent girls and in some countries also for boys have been widely implemented in 58 (30%) countries, by August 2014.[2]

HPV vaccination is a primary prevention tool and does not eliminate the need for screening later in life, since the vaccines do not protect against all high-risk HPV types. The quadrivalent and the bivalent vaccines were both originally licensed and marketed using a three-dose immunization schedule. The cost and logistical difficulties of the standard three-dose vaccine regimen may compromise its implementation in resource-poor settings. Hence, it is necessary to investigate and review the HPV vaccine protection afforded by two doses and by one dose. Kreimer *et al.* based on the clinical efficacy data, argue that there is suggestive evidence that HPV vaccine program using two-dose regimen instead of the standard three-dose regimen could potentially vaccinate 50% more women and could reduce cervical cancer incidence more than a program that uses the same number of total doses but in fewer women.[4] The decision of the GAVI Alliance to support HPV vaccination in 2011, in combination with the acceptance of less than three dose schedule could increase the implementation of HPV vaccination programs in low-income countries.

Evidence from three randomized control trials (RCTs), two nonrandomized/noncontrolled trials, and one yet to be published RCT from India indicate that less than three doses of HPV vaccine are effective. Emerging data from other trials also supports the WHO recommendation for routine vaccination of young girls with two doses, at least 6 months apart.[2]

THREE DOSES

With three-dose schedule, both vaccines have excellent immunogenicity profiles, inducing high peak titers of antibodies in virtually all vaccinees that persist for years. Highest immune responses are observed in girls aged 9-15 years after a three-dose vaccine schedule.[5] High antibody titers are maintained for at least 8.4 years for the bivalent vaccine with 100% seropositivity, and for at least 8 years for the quadrivalent vaccine.[2] The mechanism of protection conferred by HPV vaccines through immune response after vaccination is assumed, based on data from animal models, to be mediated by polyclonal neutralizing antibodies against the major viral coat protein, L1.[6,7] In clinical trials, both vaccines induced peak antibody titers 4 weeks after the third dose that declined within the 1st year and then stabilized at a plateau titer. As compared to the natural infection, the serological response is 1-4 logs higher

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after vaccination. This may be related to better targeting or activation of lymph node cells by parenteral vaccines than by mucosal infections or because of the adjuvants in the existing vaccines. Long-term HPV-specific antibody persistence may be attributed to the long-lived plasma cells, primarily residing in the bone marrow, that continuously produce IgG antibodies.[8]

The quadrivalent vaccine was evaluated in two phase III studies, FUTURE I[9] aimed at investigating the prevention of anogenital diseases associated with HPV types 6, 11, 16, and 18, and FUTURE II[10] with objectives of assessing the prevention of high-grade cervical lesions associated with HPV types 16 and 18. The bivalent vaccine was evaluated in other two phase III studies PATRICIA[11] looking at the efficacy against infection with HPV types included in the vaccine, and the Costa Rica HPV Vaccine Trial[12] aimed at evaluating the population impact of the vaccine in the prevention of cervical cancer precursors. All these trials were relatively large (5, 500-18, 500 vaccinees), blinded, randomized, and controlled trials of young women (mean age 20, range 15-26). After a mean follow-up of 34·9 months post-third dose, using the bivalent vaccine in the PATRICIA trial, high vaccine efficacy was seen against cervical intraepithelial neoplasia grade 2+ (CIN2+) lesions associated with HPV-16 and HPV-18 as well as lesions that were associated with nonvaccine types HPV-31, HPV-33, and HPV-45. The bivalent vaccine also demonstrated high efficacy of 93.2% against CIN3+ in the total vaccinated cohort (TVC)-naïve, irrespective of HPV type, as compared to the efficacy of 45.6% in the TVC analysis.[13] The prelicensure trials of quadrivalent vaccine reported high efficacy (100%) against HPV-16 and HPV-18 CIN3 lesions among vaccine recipients not already infected with HPV. The vaccine also demonstrated clinical efficacy against infection and cervical, vaginal, and vulvar lesions associated with HPV-16 and HPV-18. Lower vaccine efficacy was observed in the intention-to-treat (ITT) analysis as compared to the ITT-naïve (vaccine recipients with no prior exposure to HPV infection) analysis.[5]

Both vaccines have high and similar efficacy for a range of cervical endpoints from persistent infection to CIN3 in women naïve at the time of vaccination to the corresponding type and against incident anogenital infection and subsequent neoplastic disease by the types specifically targeted by the vaccines. Both vaccines have no therapeutic effect on prevalent infection or disease either to induce regression or prevent progression of established infections. The quadrivalent vaccine has demonstrated strong protection against genital warts and vulvar/vaginal neoplasia associated with the vaccine types in women and protected men for incident infection, genital warts, and anal intraepithelial neoplasia by the vaccine types. The bivalent vaccine protects against vaccine-targeted anal infections in women. Though these vaccine studies were conducted in women aged 15-26 years for practical reasons, immunogenicity bridging studies have demonstrated excellent safety and strong immune responses in adolescent girls and boys.[5]

Einstein *et al.* compared the immunogenicity of the bivalent and quadrivalent vaccines after three-dose schedule, at month 7 and after 48 months of follow-up and found that in women aged 18-26 years at month 7 the neutralizing antibodies were 3.7- and 7.3-fold higher against HPV-16 and HPV-18, respectively, for the bivalent compared to the quadrivalent vaccine. Similar differences were observed in older age groups. The geometric mean titers (GMTs) remained 2.0-5.2-fold higher for HPV-16 and 8.6-12.8-fold higher for HPV-18 even after 48 months of follow-up in those receiving the bivalent vaccine across all age strata.[14,15] However, as both vaccines have demonstrated high efficacy and very high antibody titers as compared to natural infection, the clinical relevance of these findings remains unclear.[2]

Both vaccines are generally safe. The principal adverse events reported are mainly minor injection-site symptoms. Both vaccines given in three doses induce partial cross-protection from incident infection or disease from nonvaccine types.[5] Different intervals in a three-dose schedule were compared in a systematic review that included five RCTs with varied intervals (0, 1, 12 vs. 0, 1, 6 months; 0, 2, 12 vs. 0, 2, 6 months; 0, 3, 9 vs. 0, 2, 6 months; 0, 6, 12 vs. 0, 2, 6 months; 0, 12, 24 vs. 0, 2, 6 months; 0, 3, 6 vs. 0, 2, 6 months) which showed that longer interval to the booster (third) dose and longer interval between priming doses (first two-doses) resulted in superior geometric mean concentrations (GMCs) compared with the standard three-dose schedule.[16]

LESS THAN THREE DOSES

Three-dose regimens for HPV vaccines are expensive and difficult to complete. The Centers for Disease Control and Prevention, reports that in the United States in 2012, only 53.8% of girls aged 13-17 years had initiated HPV vaccination and that only 33.4% of them had received all three-doses.[17] The nonrandomized analysis of the nested phase III Costa Rica trial, 4 years after vaccination of women who appeared to be uninfected with bivalent vaccine, provides the first clinical evidence of high efficacy of bivalent HPV vaccine when given in less than three-doses (two doses as well as single dose) in preventing incident HPV-16 and HPV-18 infections that persist for at least 1 year. There is the absence of biases in terms of similar antibody concentrations after the first dose, similar HPV infection rates and similar reasons for missing doses which were unrelated to the vaccination group assigned.[4] These findings are confirmed in the PATRICIA trial and in the

combined analysis of data from the Costa Rica vaccine and PATRICIA trials that show similar vaccine efficacy against incident HPV-16/18 infections, 4 years after vaccination, among women 15-25 years, whether the women received one dose, two doses, or three doses. High HPV-16/18 vaccine efficacy irrespective of the dose was replicated in a cohort of women naive to HPV-16/18 infection at the time of vaccination. This suggests that the findings of efficacy of fewer than three doses are probably relevant to girls in the preferred age range for HPV vaccination (i.e., 11-12 years).[18] A systematic review of alternative vaccination schedules that assessed the seroconversion and seropositivity comparing girls receiving 2-doses with women receiving 3-doses at different time points up to 24 months after vaccination found them to be noninferior or inconclusive at all time-points. The benefit of vaccine efficacy against heterologous HPV types is retained with two doses given 6 months apart, but perhaps not with the administration of one dose or two closely spaced, priming doses. Two RCTs compared two dose schedules administered at different intervals (0, 2 vs. 0, 6 months; 0, 6 vs. 0, 12 months) and showed that 6 months interval resulted in superior GMCs compared with the 2 months interval, 1 month after the last vaccine dose in all age groups enrolled (9-14, 15-19, and 20-25 years).[16]

In India, a cluster randomized trial designed to evaluate the effectiveness of two versus three doses of quadrivalent HPV vaccination was suspended resulting in a cohort study of four groups; one that received three doses, second two doses, third two dose by default, and fourth one dose by default. The results indicate that the immune response is similar in two-dose and three-dose group; but inferior in the two-dose default and one-dose default groups. The geometric mean avidity indices and the frequency of incident HPV-16/18/6/11 infections were similar in girls receiving less than three-doses and those receiving three doses. There was the absence of any persistent HPV-16/18 infections in any of the study groups.[19]

Early assessment, 5 years after the commencement of the large-scale HPV vaccination catch-up program in Australia show that less than three doses of vaccine provide protection against cervical disease.[20] The HPV vaccine coverage in England for 2012/13 for at least one dose was 90.9%, at least two doses 89.6%, and three doses 86.1%. It is anticipated that with the two-dose schedule, coverage will be maintained at these high levels. In March 2014, the Joint Committee on Vaccination and Immunisation revised its existing recommendation on the HPV vaccination program for adolescent girls aged <15 years to change from a three-dose to a two-dose schedule.[21] Cost-effectiveness analysis of two versus three-dose HPV vaccine schedule was performed based on modeling by Jit *et al.*, which showed that if two-dose vaccine schedule gives only 10 years' protection and adding a third dose extends this to lifetime protection, then the third dose also seems likely to be cost-effective whereas, if two doses provide more than 20 years' protection, then they are likely to be the most cost-effective option.[22]

A partially-blind RCT, to evaluate a two dose bivalent HPV vaccine schedule administered at 0 and 6 months to girls 9-14 years had acceptable safety profile and elicited HPV-16 and 18 immune responses that were noninferior to those elicited by the same vaccine given as a three-dose schedule in young women aged 15-25 years 1 month and 24 months after the last vaccine dose. When 0, 2 months schedule was used in girls aged 9-14 years, even with a higher dose of HPV antigen, the vaccine did not achieve immunological noninferiority compared with the licensed three-dose schedule in women aged 15-25 years at month 24. This indicates that with a two-dose formulation the interval between the two doses is an important factor for the induction of immune response.[23]

Evidence from 3 RCTs as well as nonrandomized/noncontrolled trials indicates that a two-dose HPV schedule in girls induces noninferior levels of GMT to HPV-16 and 18 than a three-dose schedule in girls or women. Bridging studies allow assumption of the efficacy of a 2-dose vaccination schedule in girls (9-14 years).[2]

Safaeian *et al.* found that the HPV-16/18 GMTs were at least 24 and 14 times higher in the two-dose group and 9 and 5 times higher among one-dose vaccines, respectively, as compared to natural infection. Stable antibody levels remained from month 6 through month 48 following one-dose which were higher than that following natural infection. The titers following one dose were lower than after two or three doses, and the number of one and two dose recipients was limited. The high efficacy following single dose implies that 5-fold higher titers as seen after three doses of the vaccine may not be required to induce long-term protection. This gives the likelihood that even a single dose of HPV VLPs may induce long-term protection.[24] The duration of protection for fewer than three doses needs to be studied.

Greater cross-protection against heterologous HPV types may be conferred by full three-dose regimen.[13] Protection against phylogenetically related HPV types, which is probably attributable to cross-neutralizing antibodies, is likely to be lower with alternate vaccine schedule as compared with the standard three-dose schedule.[24] The combined FUTURE I/II analysis demonstrated 32.5% efficacy of quadrivalent vaccine when given in three doses in reducing the risk of CIN2-3/AIS associated with 10 nonvaccine types. However, significant protection of 70% against CIN2+ was observed for infection with

HPV3.[25] Although, two doses separated by 6 months may provide some cross-protection against HPV-31/33/45 similar to those receiving three dose regimen. Kreimer *et al.* also demonstrated some cross-protection against HPV-31/33/45 in women receiving two doses at least 6 months apart. However, one-dose or two priming doses separated by a short interval like 1 month might not be adequate to induce measurable cross-protection.[18]

If HPV vaccines could be delivered as one dose, while retaining their efficacy against the most oncogenic HPV types 16 and 18, it opens a great opportunity to extend the reach of protection using HPV vaccines to more people. This could help in substantially decreasing the global burden of cervical cancer. Programmatically, this would be much more feasible to implement as seen with the experience of single vaccine dose pulse campaigns even in the most resource-poor settings (e.g., meningitis A vaccine in Sub-Saharan Africa). This gives an opportunity for HPV vaccine mass campaigns every 5-10 years to vaccinate a particular age group, for example, all 9-14 years old girls.[26]

Safaeian *et al.* attribute at least in part of the durable antibody responses observed after a single dose of HPV vaccine in prevaccination seronegative women to the fact that HPV vaccines are the first noninfectious licensed vaccines whose virus-like surface characteristics truly mimic the ordered, high-density structure of authentic capsids.[24] If repetitive display of the VLPs is mainly responsible for the protection afforded by a single dose, then the effect is likely to be seen in the quadrivalent and nonavalent HPV vaccines as well.[27] Strong vaccine efficacies in less than three doses as seen with HPV-16/18 AS04-adjuvanted vaccine could be its unique feature, if the efficacy is mainly due to the adjuvant used or due to differences in manufacturing of the VLPs.[18]

Based on all this evidence, WHO in its policy paper in 2014[2] has recommended bivalent or quadrivalent vaccine in the 2-dose schedule with a 6-month interval between doses for females <15 years, including females 15 years or older at the time of the second dose. WHO does not recommend any maximum interval between the two doses. However, the suggested interval should not be greater than 12-15 months to complete the schedule promptly, before the females become sexually active. A third dose is recommended at least 6 months after the first dose, if the interval between the two doses is shorter than 5 months. A three-dose schedule (0, 1-2, and 6 months) is recommended for females ≥15 years and for females are known to be immunocompromised and/or HIV-infected (regardless of whether they are receiving antiretroviral therapy). The need for a booster is not yet established.[2]

NEXT GENERATION HUMAN PAPILLOMA VIRUS PROPHYLACTIC VACCINES

L2-based vaccines

Immunization with L2 peptides or proteins elicits cross-reactive, neutralizing antibodies,[28-31] making ann L2-based immunogen a promising candidate for a broad-spectrum, pan-HPV vaccine. Further, because an L2 vaccine would not be based on the relatively complex HPV VLP production, an L2-based vaccine might be easier and cheaper to produce, thus benefiting low resource settings. However, the major challenge in developing an L2-based vaccine has been in eliciting a strong immune response to L2. While L2 and L1 can be recombinantly co-expressed and will assemble into an HPV VLP, L2 is immunologically subdominant to L1.[28] There are several second generation HPV prophylactic vaccines in various phases of commercial development like the nonavalent VLPs, Escherichia coli VLPs, Saccharomyces cerevisiae VLPs, Komagataella (Pichia) pastoris VLPs, Hansenula VLPs, Measles L1, Salmonella enterica serotype Typhi L1 and Concatenated L2.[32]

CURRENT STATUS OF INDIGENOUS VACCINE DEVELOPMENT

Bharati and Ganguly argue that India needs to develop and manufacture its own HPV vaccine in order for it to be affordable and cheap so as to reach of most people and vaccinate the target population. Several private sector organizations like the Indian Immunologicals Ltd., Hyderabad, Shantha Biotechnics Ltd. (wholly owned subsidiary of Sanofi), Hyderabad, Bharat Biotech Interl Ltd., Hyderabad, Serum Institute of India Ltd., Pune, Gennova Biopharmaceuticals Ltd., Pune, Virchow Biotech Pvt. Ltd. Hyderabad and also public sector organizations like Translational Health Science and Technology Institute, Gurgaon, Haryana and Institute of Cytology and Preventive Oncology, Noida, Uttar Pradesh are actively involved in HPV vaccine development efforts in India.[33]

CONCLUSIONS

Currently, national immunization program with two doses of HPV vaccine have been initiated in some countries; however, more data are needed before a single HPV vaccine could be recommended. Single dose vaccine lacks cross-protection. Though, it appears that a single dose of the bivalent HPV vaccine may offer full protection against HPV types 16 and 18, a new randomized study will be needed to confirm these findings. In addition, the duration of protection following a single dose needs to be assessed. Furthermore, the persistence of antibody responses after a single dose has not been evaluated for quadrivalent HPV vaccine as yet. Thus, the data till date gives an optimistic projection of the long-term efficacy of less than the recommend three doses. Although we know

that if one dose is sufficient, it could reduce vaccination and administration costs and improve uptake, it still remains unclear whether two doses or a single priming dose of a VLP vaccine is sufficient to induce an antibody response that stabilizes over time.

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There are no conflicts of interest.

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