Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicenter, prospective, cohort study

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BASED ON ARTICLE

Basu P, Malvi SG, Joshi S et al. Lancet Oncol 2021; 22: 1518–29

ABSTRACT

Background: Bivalent (bHPV) and quadrivalent (qHPV) vaccines are available for prevention of HPV related cervical cancer, and others like vulval, vaginal, anal, penile and oropharyngeal cancers. qHPV also prevents benign genital lesions like warts caused by HPV 6 and 11 types. Nonavalent (HPV9) vaccine has been recently made available in India and covers 5 more oncogenic HPV types besides those covered by qHPV. While, in the West 3 doses of either vaccine are recommended by manufacturers in subjects more than 14 years old and 2 doses 9-14 years old boys and girls, in India HPV9 label says 3 doses for females 9-26 years old and males 9-16 years old as per the label. This study provides evidence that even 1 dose is as effective as 2 or 3 doses of HPV vaccines in long term.

Method: A randomized trial in India using 2 vs 3 doses of qHPV from MSD in 10-18 years old married girls began enrolling subjects from September 1, 2009 with original pan to recruit 10,000 girls in each arm. On April 8, 2010 due to problems in other trial on HPV in India, the government of India suspended recruitment of any further subjects in all HPV trials in India including the current trial (by then 17,729 girls had received at least one dose of qHPV) resulting in several subjects not completing their scheduled number of HPV vaccine doses. This study was hence converted to a longitudinal prospective cohort study by default which resulted in 4 cohorts of subjects available for study; 2 dose cohort (days 0-180), 3 dose recipient cohort (days 0-60-180), 2 dose cohort by default (days 0-60 or later) and 1 dose cohort by default. These subjects were followed up yearly and the same will continue for 5 more years till 2026.

18 months after marriage or 6 months after child birth (whichever was earlier) cervical specimens were collected yearly for 4 consecutive years to study incidence and persistence of HPV infection (with an additional sample in 5th year if a new HPV type was detected in 4th year sample) and analyzed by multiplex PCR for 21 HPV types [19 high-risk or probable high-risk types (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68a, 68b, 70, 73, and 82), and two low-risk types (HPV 6 and 11)] using Luminex assay (Luminex, Austin, TX, USA). Those who were married also underwent screening for cervical cancer at 25 years of age with cervical samples tested for HPV using Hybrid Capture II

(HC-II]; Qiagen, Gaithersburg, MD, USA). Those who were found to be positive were further tested for HPV 16, 18 and 45 and also underwent colposcopy and biopsy as required. A group of unvaccinated women was recruited to serve as controls in 2013-15 and another in 2017-19. Median follow up since vaccination was 9 years.

Primary endpoint was the vaccine efficacy of one dose of qHPV vaccine against persistent HPV 16 and 18 infections (persistent in 2 samples taken at least 10 months apart) compared to 2 and 3 doses. Secondary endpoints were qHPV vaccine efficacy against incident HPV 16 and 18 infections and HPV16/18 related CIN2+ lesions with 1 dose vs 2 or 3 doses.

Results: 4949 women received 1 dose (1 dose default cohort), 4980 women received 2 doses (0-6 mo) and 4384 received 3 doses (0-2-6 mo). 2135 women out of 4949 were evaluated for 1 dose default cohort, 1452 women out 4980 were evaluated for 2 dose cohort (0-6 mo) and 1460 women out of 4384 were evaluated for 3 dose (0-2-6 mo) cohort. Adjusted vaccine efficacy against persistent infection due to HPV types 16 and 18 with 1 dose (default cohort) was 95·4% (95% CI 85·0–99·9); with 2 doses (0-6 mo) was 93·1% (95% CI 77·3–99·8) and with 3 doses (0-2-6 mo) was 93·3% (95% CI 77·5–99·7). Adjusted vaccine efficacy against persistent infection due to any HPV type was 35·4% (95% CI 3·7 to 56·0) with 1 dose, 36·7% (95% CI 1·6 to 57·9) with 2 doses and 39·3% (95% CI 6·8 to 60·2) with 3 doses.

Adjusted vaccine efficacy against incident infection due to HPV 16 and 18 was 63·5% (95% CI 51·2 to 73·1) with 1 dose, 67·7% (95% CI 55·2 to 77·2) with 2 doses (0-6 mo.) and 66·4% (95% CI 53·6 to 76·3) with 3 doses (0-2-6 mo). It shows that the vaccine efficacy with 1 dose was as high and as good as that with 2 doses or 3 doses when vaccinated at 10-18 years of age even at median 9 years follow up since vaccination. 1 case of CIN3 was detected in vaccinated group but was not related to HPV 16 or 18. There were no cases of CIN2 or Ca Cx in vaccinated subjects compared to 5 cases of CIN2+ in unvaccinated subjects of which 3 were due to HPV 16 or 18. There was 1 case of Ca Cx in unvaccinated subjects but was not due to HPV 16 or 18.

Conclusions: In this longitudinal cohort study efficacy of 1 dose of qHPV against HPV 16 and 18 persistent and incident infection was similar to 2 doses or 3 doses in 10-18 years old girls on 9 year follow up since vaccination.

Commentary: Oncogenic HPV infection is a necessary cause of cervical cancer and other genital cancers like vulval, vaginal, anal and penile cancers in humans, besides genital warts. Worldwide 2869 million women > 15 years of age are at the risk of developing cervical cancer of which 483.5 million women are in India. Worldwide annual incidence of Ca Cx in 15-44 years old women is 10.6 per 100,000 and that of Ca Cx mortality is 3.39 per 100,000 which translates in to 604,127 cases and 341,831 deaths due to Ca Cx annually; of which 123,907 cases and 77,348 deaths are in India. HPV types 16 & 18 contribute to 70% of cases of cervical cancers worldwide and 83.2% in India1. With HPV9 being introduced in Indian and International market, the oncogenic HPV type coverage by HPV9 goes up to 82% worldwide and 98% in India. However, HPV vaccines are expensive and HPV9 is even more expensive, especially for developing countries like India which are planning to introduce

HPV vaccine in their National Immunization Program. Hence, if one can use qHPV or HPV9 in less than 3 doses per woman, it will save a lot of money for the nation and individuals paying out of their pocket. The above mentioned study shows that efficacy of 1 dose of qHPV is similar to 2 or 3 doses on 9 years long term follow up of girls vaccinated at 10-18 years of age.

Another study that is recently published was done in Kenya where 15-20 years old women received either 1 dose of bHPV (N=760) or 1 dose of HPV9 (N=758) or control placebo Meningococcal vaccine (N=757)2. Subjects were then followed up at 3 mo, 6 mo and then every 6 months till 18 months. Cervical samples were taken every 6 months and 1 self-collected vaginal swab was taken at 3 mo visit. Samples were subjected to multiplex PCR for HPV types. The primary trial end point was vaccine efficacy of 1 dose against persistent cervical HPV infection in subjects HPV DNA negative (cervical sample at enrollment and vaginal swab at 3 mo negative) and seronegative at enrollment. Persistent infection was defined as positive HPV PCR on two samples taken at least 4 months apart. Vaccine efficacy at short follow up of 18 months against HPV 16 and 18 persistent infection was 97.5% (95% CI, 81.6 to 99.7) with 1 dose of bHPV and 97.5% (95% CI, 81.7 to 99.7) with 1 dose of HPV9. ($P<0.0001$). Vaccine efficacy of 1 dose of HPV9 against persistent infection caused by HPV 16, 18, 31, 35, 45, 52, 58 was 88.9% (95%CI, 68.5 to 96.1) ($P<0.0001$). At 18 months the subjects will receive cross over vaccine and will be followed up for another 18 months for long term efficacy, the data for which will be available in future.

Long term follow up of CVT trial in Cost Rica using varying doses of bHPV showed that at 6.9 years follow up the cumulative incident cervical infection with HPV 16 and 18 was 4.3% (95% CI 3.5-5.3) with 3 doses, 3.8% (95% CI 1.0-10.1) with 2 doses (0-1 month schedule), 3.6% (95% CI 1.6-7.1) with 2 doses (0-6 mo schedule), and 1.5% (95% CI 0.3-4.9) with 1 dose. One dose was similar to 2 or 3 doses of HPV[3].

World Health Organization has observed that HPV 16 & 18 seropositivity did not decrease between 4 to 11 years since vaccination regardless of number of doses given although titers after one dose were statistically significantly lower than after 2 or 3 dose4. However long-term efficacy of HPV vaccines with 1 dose was similar to 2 or 3 doses on long term follow up as seen in above studies.

Based on these recent publications World Health Organization its 2022 position paper on HPV have stated that the current evidence supports the recommendation of a 2-dose schedule be used in the primary target group from 9 years of age and for all older age groups for which HPV vaccines are licensed. As an off-label option, a single-dose schedule can be used in girls and boys aged 9–20 years. Immunocompromised or HIV infected should receive at least two dose of HPV vaccine and if possible 3 doses 4. The minimum interval between first and second dose is 6 months. A 12-month schedule results in higher GMTs and is suggested for programmatic and efficiency reasons4. Recently the ACVIP has recommended only 2 dose of HPV9 for girls and boys from 9-14 years of age even when the label says 3 doses at this age. Serum Institute of India has obtained license for their indigenous qHPV. This vaccine is likely to be supplied at much lesser cost for public health use in India as per media report. Further reduction in number of doses based on discussion above will help it even more cost-effective public health program in India.

REFERENCES

1.https://hpvcentre.net/datastatistics.php Accessed on 12th January 2023

2.Barnabas RV, Brown ER, Onono MA et al. NEJM Evid 2022;1(5) doi: 10.1056/EVIDoa2100056,

3.Safaeian M, Sampson JN, Pan Y et al. JNCI J Natl Cancer Inst (2018) 110(2): djx158. doi:10.1093/jnci/djx158.

4.Human papillomavirus vaccines: WHO position paper (2022 update). Weekly epidemiological record. 16th December 2022; No 50, 2022, 97, 645–672.