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Original Article

COMPARISON OF POST-LICENSURE SAFETY SURVEILLANCE OF BIVALENT AND QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINES IN HEALTHY MUMBAI WOMEN

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ABSTRACT

Objective: This study is the first comprehensive effort after HPV vaccine controversy in INDIA to compare two HPV vaccines without vaccine manufacturers funding in single, randomized, well-defined population of healthy married women aged 18-25 years using identical methodology for assessment.

Methods: The study protocol was approved by an institutional ethical review committee and registered in Clinical trial registry of INDIA prior to subject recruitment. Total 77 women were screened but 69 were randomized to receive either HPV2 or HPV4 vaccines.

Results: According to the present study, both HPV vaccines were well tolerated without any serious vaccine-related adverse event. Adverse drug reactions reported for both HPV vaccinations were 22 (35.48%) after the first dose, 7 (12.05%) after the second dose and 11 (25%) after the third dose. After bivalent and quadrivalent HPV vaccination, 29 and 11 adverse drug events were recorded within seven days after any HPV vaccine dose respectively. Most frequently reported solicited local symptom from both groups was34 injection site pain which was mild in intensity.

Conclusion: Both HPV vaccines appear to be safe, HPV4 being more cost-effective. However, large scale post-marketing studies are needed in view of amount of disease burden.

Keywords: HPV2, HPV4, Safety, Adverse drug reactions (ADRs), Injection-site pain, India.

INTRODUCTION

Cervical cancer (Ca Cx) is the third most common female cancer worldwide with an estimated 5,27,624 new cases and 2,65,653 deaths in 2014 [1]. About 86% of the cases occur in developing countries and may constitute up to 25% of all female cancers [2,3]. According to WHO: Human Papilloma virus and Related Cancers Summary Report (2010), in India, cervical cancer is reported to be responsible for almost 20% of all female deaths and takes the lives of 8 women every hour [4]. India recorded 83,195 new cases out of these cases 67,477 cases lost their lives. The age-standardized incidence and mortality rate of cervical cancer in India are 22.0 and 12.4 respectively [5].

According to Gissmann and zur Hausen, 1980, human papilloma viruses are the primary etiologic agents of cervical cancer [6]. Cervical cancer and other Human papillomavirus associated malignancies might be prevented by two human papillomavirus vaccines namely, Cervarix™- (HPV2) bivalent and Gardasil®- (HPV4) quadrivalent [7, 8]. Both HPV vaccines markedly differ in their composition and their adjuvants. These vaccines were approved by Indian regulatory authority in 2008 for use in females [9].

Around mid-2009, two HPV vaccine trials were initiated in INDIA. However, following media allegations of vaccine induced deaths of four girls in Khammam during HPV vaccine clinical trial, clinical trials on HPV vaccines were suspended by the union government in 2010. The deaths are found to be vaccine unrelated [10, 11]. However, these studies have not been resumed till the time of writing this article. Therefore, it is crucial to conduct post marketing surveillance study in order to establish whether the adverse events reported after vaccination with prophylactic bivalent and quadrivalent HPV vaccines are the same as those expected and listed in the package insert. This research study is comprehensive effort to compare two vaccine candidates without HPV vaccine manufacturers funding in single, randomized, well-defined population of healthy married women aged 18-25 years using identical methodology for assessment of safety because there is no comparable safety study data available on post-marketing surveillance of HPV2 and HPV4 vaccines in any developing country like INDIA. In this study, age range of 18-25 years was chosen because HPV vaccines were well tolerated and highly immunogenic when administered to young adolescent females and the common age group as mentioned in their package inserts [12].

MATERIALS AND METHODS

Ethical approval and CTRI registration

The study protocol was approved by Haffkine Institute for Training, Research and Testing (HITRT), Parel ethical review committee (HITRT/IEC/12/2013). This study was registered in Clinical trial registry of INDIA (CTRI/2013/11/004140) prior to subject recruitment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design

Type and duration of study

This Phase IV observational cohort study was conducted in the metropolitan city like Mumbai. The study was conducted from December 2013 to July 2014.

Inclusion and exclusion criteria for the study

Healthy women of age 18–25 years were eligible to participate. Participants were required to have an intact cervix. The negative urine pregnancy test was required at study entry and prior to each vaccine dose. If study participant women of child bearing potential, such women were advised to use adequate contraception for 30 days prior to vaccination and to agree to continue such precautions for two months after the final vaccine dose. Lifetime number of sexual partners was not a limiting factor for inclusion in the study. Women who had some types of chronic illnesses, hypersensitivity to latex and hospitalization within 21 days prior to study entry were excluded from the study. In addition to this, use of any investigational or non-registered product (drug or vaccine) other

than the study vaccine(s) within 30 days preceding the first dose of study vaccine or planned use during the study period was excluded. A formal written consent was obtained from each participant. Prior to that, project was explained to participants in the language they understand. They were also briefed that their participation is voluntary and they have full right to withdraw from the study at any point of time during the study period. The subject was given the opportunity to inquire about details of the study and to consider participation. If they decided to enter into study, written informed consent was taken from each participant. After they signed written informed consent, they were provided with a copy of the signed informed consent and the original file maintained in the investigator's study file. Then special study identification number was provided to participants. Each participant was asked to fill up the question naire related to cervical cancer and HPV vaccines and answers were noted. Reproductive tract infections related history taken from participants. Strict privacy and confidentiality maintained during the interview and in the entire phase of the study. The subject was informed in a timely manner that if new information becomes available they can take the decision to participate in the study. The communication of this information was documented.

Blood, cervical sampling and urine collection

The 4-6 ml of blood was withdrawn from each participant in a sterile vacutainers by employing expert phlebotomist and screened for routine biochemical, haematological parameters and sexually, transmitted disease like HIV. The remaining blood was stored at -80^{0}C. Cervicovaginal samples (CVS) were collected using sterile an endocervical brush and spatula from each participant. In cases of menstruation or bleeding, the collection of samples was delayed until one day after cessation of menstrual flow. These cervical samples were used to assess both baseline HPV DNA status and HPV genotypes by polymerase chain reaction (PCR). Each women were advised to collect mid-stream urine in provided urine container to performed urine pregnancy test and urine analysis.

All testing was carried out by laboratory technicians who were blinded to treatment group assignment.

Vaccine and immunization schedule

Women were randomized to receive 0.5 ml doses of either HPV2 or HPV4 vaccine which is manufactured by GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium and Merck and Co. Inc., West Point, Pennsylvania, USA. This vaccine was administered into the deltoid muscle of the non-dominant arm according to their recommended three-dose schedules [7,8].

During completion of HPV2 vaccination schedule for dose 1 and 2 batch number- AHPVA198AK (Expiry date-2015-04) and for dose 3 batch number- AHPVA225BP (Expiry date- 2016-01) were used. On other hand, during completion of HPV4 vaccination schedule for dose 1 batch number J000876 (Expiry date- 2015-07), for dose 2 J0007039 (Expiry date- 2015-10) and for dose 3 K000432 (Expiry date- 2016-05) were used. table 1 shows study vaccine composition and administration schedules. Prior to immunization any injection site clinical findings like rash and bruising that could impact on the assessment of local injection site reactions were documented.

Table 1: Study vaccine composition and administration schedules

S. No.	Parameter	HPV2	HPV4
1	Vaccine composition	20 µg HPV 16,20 µg HPV 18	20 µg HPV 6,40 µg HPV 11, 40 µg HPV 16,20 µg HPV 18
2	Expression system	Trichoplusia ni insect cell line infected with L1 encoding recombinant Baculovirus	Saccharomyces cerevisiae expressing L1
3	Adjuvant	AS04 50 µg of aluminium hydroxide	AAHS 225 µg of aluminium hydroxyphosphate sulphate
4	Administration		
	Schedule	HPV2	HPV4
	Month 0	HPV2	NA
	Month 1	NA	HPV4
	Month 2	HPV2	HPV4
	Month 6		

Reactogenicity and safety

After HPV immunization, immunized women were kept under observation for 30 minutes time period in accordance with local standard of practice where they were re-examined for any local or systemic reactions. After that, they were educated not only with a tutorial on how to complete all subject report forms,symptoms checklist, correct method for taking an oral temperature daily using a digital thermometer but also they were instructed to record the temperature measurement on the diary card at any time when they feel feverish. Safety profile assessments of local injection site symptoms like pain, redness and swelling and general symptoms like fever, headache, fatigue, nausea, vomiting, diarrhea, abdominal pain, arthralgia, myalgia, rash and urticaria were recorded for 7 consecutive days after each dose. The intensity of each symptom was graded on a non-quantifiable scale from mild, moderate and severe based on the extent of discomfort subjects experienced. Unwanted events were followed for 14 days after each vaccination. Number of adverse events with 3 doses by two vaccines were calculated by OpenEpi, Version 2.3, 2009 (The original portions of OpenEpi itself are: Copyright (c) 2003, 2008 Andrew G. Dean and Kevin M. Sullivan, Atlanta, GA, USA).

Data entry, storage and confidentiality

All data were entered using the paper case report form and de-identifying patient information was minimized by using a unique subject identification number to each patient. Any AE/SAE was documented to respective vaccine ADRreporting system. Subject demographic and reactogenicity data were collected on case report forms and double entered and verified using an MS Access database. Laboratory results were also imported into the password protected study database and matched using a unique subject number. The whole study data was stored on a password-protected computer and made accessible only to the study personnel. All patient data including consent forms were kept in a locked filing cabinet accessible only to the project personnel.

RESULTS

Total 77healthy married women of aged 18-25 years old were consented to participate and then they were evaluated for eligibility. Of these 77 subjects, 69 subjects were eligible for vaccine randomization study. During screening 8 women, were excluded because 7 women were not comfortable to undergo pap smear testing and 1 woman had the vaginal infection with *Candida albicans*. As a result, baseline characteristics of the only 69 subjects were considered.

Table 2 showsdemographic characteristics of study participants**.** The mean age of study women were22.1 years with SD 1.85 (range: 20.25- 23.95 years). The 64 participants (92.75%) were from Hindu religion followed by Buddhism- 3 (4.34%) and Christian- 2 (2.89%). The 38 (55.07%) participants had done college education while others completed graduation 23 (33.33%). Twenty-one (30.43%) participants reported 1st age of intercourse as 20. Forty-

four(63.76%) are not employed and twenty-five (36.23%) participants were employed during an interview process. All study participants (100%) never consumed tobacco products. Out of 69 study participants, 35 (51%) participants preferred to use contraceptives as a preventive measures their sexual activity. Mostly participants relied on condoms - 22 (62.85%) followed by Intra-uterine device- 9 (25.71%), oral contraceptive pills- 3 (8.57%) and jelly 1 (2.85%) as a contraceptive. Out of 69 participants, 9 (13.04%) reported family history of cancer. table 3 shows baseline study reports of urine pregnancy test, HPV PCR and HPV genotypic testing found negative for all study participants.

Figure1 shows total 69 subjects were eligible for vaccine randomization study. Out of that, 35 subjects were allocated to receive HPV2 while 34 allocated to receive HPV4 vaccine. Around 43 (62.31%) subjects attended all visits to receive all three HPV vaccination dose as planned.

However, on the day of 1st dose of HPV vaccination, out of 69 subjects 7 subjects refused to take HPV vaccines because they developed abrupt fear of HPV vaccines side-effects. As a result, only 31 subjects were vaccinated from each group to receive 1st dose of HPV2 and HPV4 vaccine. On the day of 2nd dose of HPV vaccination, we vaccinated 28 subjects from each group to receive HPV2 and HPV4 vaccines. Total 6 women from both groups were excluded. In HPV2 group, 1 woman UPT test result was found positive before vaccination while 2 women withdraw consent due to family pressure and not because of vaccine adverse drug reactions. Similar result found in HPV4 group, 1 women was found pregnant before vaccination while 2 women excluded from study because they migrated from study area due to husband transfer to the different city. During last dose of HPV vaccination, we vaccinated 21 subjects from HPV2 vaccine group and 23 subjects from HPV4 vaccine group. In HPV2 group, 3 women withdraw consent due to family pressure regarding social taboo of cervical cancer vaccine and not because of vaccine adverse drug reactions, 2 women refused to complete vaccination course due to lack of fund to travel and 2 because of loss of follow-up. In HPV4 group, 3 women withdraw consent because those participants partner pressuring them to start family, 1 woman refused to complete vaccination course due to gynaecology advice and 1 women participant was out of town for next 3 months at the time of HPV vaccination schedule.

Table 2: Demographic characteristics of study participants

Age (years)		
Mean- 22.11	SD 1.85	
Religion	**N**	**%**
Hindu	64	92.75%
Buddhism	3	4.34%
Christian	2	2.89%
Education	**N**	**%**
>Higher school	8	11.59%
College	38	55.07%
Graduated	23	33.33%
Age at 1st intercourse (Years)	**N**	**%**
16	2	2.89%
17	0	0.00%
18	10	14.49%
19	19	27.53%
20	21	30.43%
21	7	10.14%
22	6	8.69%
23	2	2.89%
24	2	2.89%
Employment	**N**	**%**
Yes	25	36.23%
No	44	63.76%
Tobacco use	**N**	**%**
Yes	0	0
No	69	100%
Contraceptive use	**N**	**%**
Yes	35	51%
Intra- Uterine Device (IUD)	9	25.71%
Condom	22	62.85%
Jelly	1	2.85%
Oral contraceptive (OC) pills	3	8.57%
No	34	49%
Pregnancy History	**N**	**%**
0	11	15.94%
1	40	57.97%
2	18	26.08%
Family History of cancer	**N**	**%**
Yes	9	13.04%
No	60	86.95%

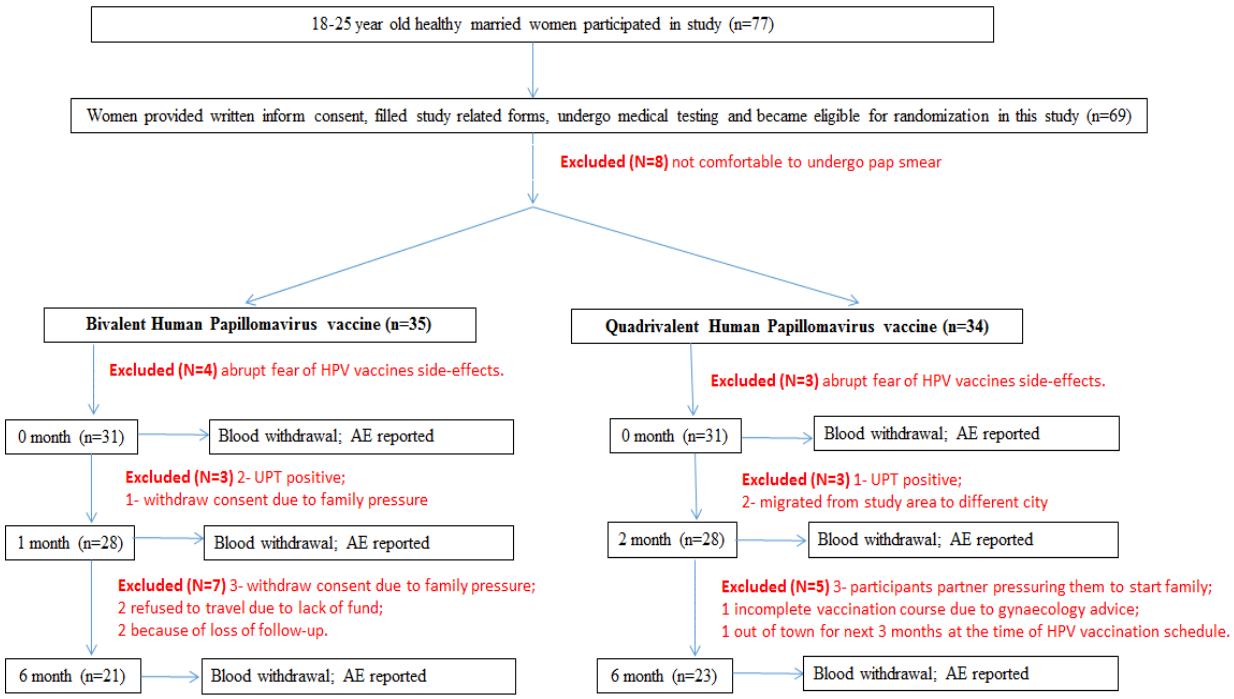

Fig. 1: Study flow diagram

Table 3: Baseline characteristics of study participants

Urine pregnancy	**N**	**%**
Yes	0	0
No	77	100
Pap smear	**N**	**%**
Positive	0	0
Negative	69	100
HIV rapid test	**N**	**%**
Positive	0	0
Negative	77	100
HPV DNA PCR	**N**	**%**
Positive	0	0
Negative	77	100

Safety profiles

Information on vaccine reactogenicity was provided by all participants with 100% response rate. The bivalent and quadrivalent HPV vaccine was well tolerated with no reports of serious vaccine-related ADRs experiences between enrolment and month 7. After bivalent and quadrivalent HPV vaccination, 29 and 11 adverse drug reactions events recorded respectively within seven days after any HPV vaccine dose. The percentage of women reporting at least one solicited local or general symptom within seven days after any vaccine dose was higher in theHPV2 group than in the HPV4 group. Five participants (16.12%) from HPV2 vaccine group experienced adverse drug reactions events after administration of every dose while one participant (3.22%) from HPV2 vaccine group reported ADRs events after administration of every dose.

Fig. 2 shows percentage of one or more adverse drug reactions by doses. Fig. 3 and fig. 4 shows percentage of adverse drug reactions dose-wise in HPV2 and HPV4 vaccination subjects. Among HPV vaccinated group, about 22 (35.48%) after the first dose, 7 (12.05%) after the second dose and 11 (25%) after the third dose of vaccination had reported adverse drug reactions. table 4 shows participants from HPV2 vaccination groupreported adverse events after first dose 16 (51.61%), 5 (28.57%) after the second dose and 8 (25.80%) after the third dose. On other hand, for HPV4 vaccination, about 6 (19.35%) after the first dose, 2 (7.14%) after the second dose and 3 (13.04%) after the third dose of vaccination had reported adverse drug reactions. Number of adverse events with 3 doses by two vaccines was calculated by OpenEpi, Version 2.3, 2009.

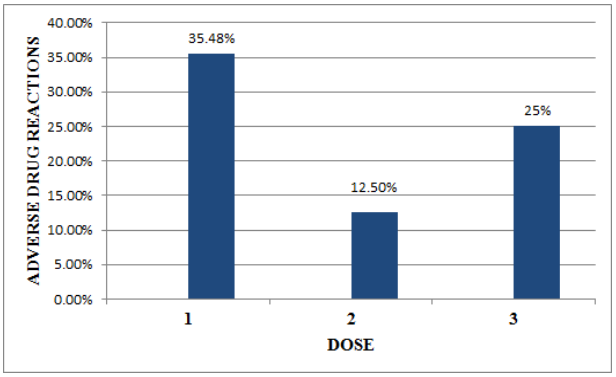

Fig. 2: Percentage of one or more adverse drug reactions by doses

Table 4: Number of adverse drug reactions by doses in study participants

	HPV2	**HPV4**	**P Value**
Dose 1	16/31	6/31	0.01594*
Dose 2	5/28	2/28	0.4216
Dose 3	8/21	3/23	0.1156
Total	29/80	11/82	0.001273**

* denoted for comparison between HPV2 and HPV4 Chi-square test *p<0.05, Chi-square test **p<0.01.

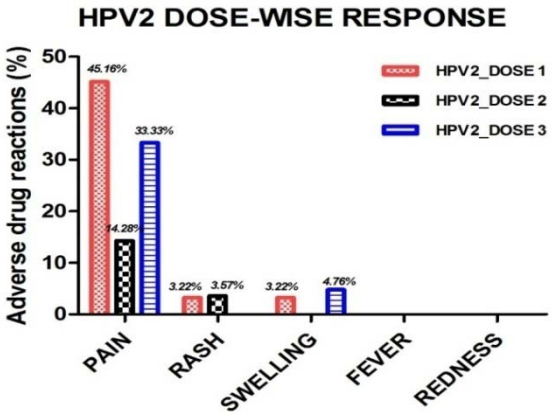

Fig. 3: Percentage of adverse drug reactions dose-wise in HPV2 vaccination subjects

Table 5 shows casualty assessment of the ADRs after HPV2 and HPV4 vaccination dose by Naranjos Algorithm. Injection site pain was the most frequent solicited local symptom in both group participants. Total 34 injection-site pain were recorded in HPV vaccines recipients which were mild in intensity. Twenty-five (80.64%) injection-site pain reported as ADR event by participants during completion of HPV2 vaccine schedule while nine (29.03%) injection-site pain reported as ADR event by participants during completion HPV4 vaccine schedule. Other reported ADR events among participants after HPV2 administration were rash 2 (6.45%) and swelling 2 (6.45%). Other reported ADR events after HPV4 vaccine recipients were fever 1 (3.22%) and redness 1 (3.22%). No serious adverse events (SAEs) experienced by vaccinated participants after each dose of respective vaccination. No rash recorded within 30 minutes of vaccination. As a result, the HPV vaccines schedule was well tolerated.

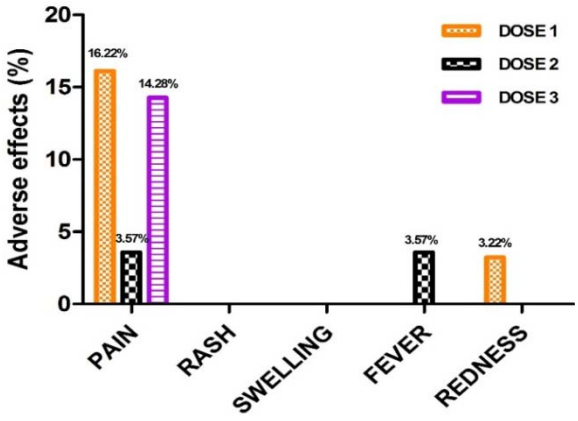

Fig. 4: Percentage of adverse drug reactions dose-wise in HPV4 vaccination subjects

Table 5: Casualty assessment of the ADRs after HPV2and HPV4 vaccination dose by Naranjos Algorithm (Doubtful, Possible, Probable, Definite)

Adverse drug reaction	Dose 1		Dose 2		Dose 3		Total	
	HPV2	HPV4	HPV2	HPV4	HPV2	HPV4	HPV2	HPV4
Pain								
Probable	14	5	4	1	7	3	25	9
Rash								
Probable	1	0	1	0	0	0	2	0
Swelling								
Probable	1	0	0	0	1	0	2	0
Fever								
Probable	0	0	0	1	0	0	0	1
Redness								
Probable	0	1	0	0	0	0	0	1

DISCUSSION

Several safety trials conducted in western countries with either bivalent or quadrivalent HPV vaccines through HPV vaccines manufactures funding and they demonstrated high safety results. During literature review search on comparative safety study of bivalent or quadrivalent HPV vaccines, only two study trials published in western countries like America and England. However, from developing countries like INDIA, there is no comparative safety or PMS study of bivalent or quadrivalent HPV vaccines performed where the HPV vaccines manufacturers earn millions of money through Indian consumers [13,14]. As a result, study was planned to conduct PMS safety trial among Indian married women of 18-25 year old for both HPV vaccines in the same study to start the foundation for HPV vaccines head to head safety data study.

The present study showed that HPV2 and HPV4 cervical cancer vaccine among Indian married women of 18-25 year old had a clinically acceptable high safety profile. In this study, enrolled healthy participants were free from HPV, HIV and STD infections and as a result, they may have affected vaccine safety responses. In this study, HPV2 vaccine recipients has reported more ADRs events than HPV4 recipients. The incidence of solicited symptoms was generally higher with HPV2 mainly with respect to local injection site reactions which may be related to the use of $AS0_4$. These solicited local symptoms were transient and they typically lasted not more than two days. All the incidence of solicited symptoms was as per manufacturers kit insert.

Furthermore, compliance with the three-dose vaccination schedule was high in HPV4 group. These study participant's results regarding the safety profiles of both HPV vaccines were consistent with results of previous comparative safety clinical trials of Cervarix™ and Gardasil®. In USA, Einstein et al. (2009) observer-blind study compared the prophylactic human papillomavirus (HPV) vaccines, Cervarix™ (GlaxosmithKline) and Gardasil® (Merck) by assessing immunogenicity and safety through one month after completion of the three-dose vaccination course. Women (n = 1106) were stratified by age (18-26, 27-35, 36-45 years) and then randomized (1:1) to receive Cervarix™ (Months 0, 1, 6) or Gardasil® (Months 0, 2, 6). The percentage of women reporting at least one solicited local or general symptom within seven days after any vaccine dose was higher in the Cervarix™ group than in the Gardasil® group [95.1% (95% CI: 92.8, 96.7) versus 85.1% (95% CI: 81.8, 88.1), respectively]. Injection site pain was the most frequent solicited local symptom in both groups reported by 92.9% [95% CI: 90.4, 95.0] of women who received Cervarix™ and 71.6% [95% CI: 67.5, 75.4] of women who received Gardasil®. Redness and swelling were also reported more frequently in the Cervarix™ group than the Gardasil® group [13]. In England, Draper et al., (2013) conducted a randomized, observer-blinded immunogenicity trial of Cervarix™ and Gardasil® vaccines in 12-15 year old girls. Injection site pain was the most frequently reported symptom in 93.8% of Cervarix™ vaccinees compared to 86.3% of Gardasil® vaccinees (p.0.05); 24% of Cervarix™ vaccinees reported an incident of moderate or severe pain which was higher than the 6.9% reported for the Gardasil® vaccinees (p=0.001). Local swelling and redness were commonly reported, but these reactions were mild (<50 mm) and similar between the vaccines (p.0.05) [14]**.** In, the present study local rash and local swelling were recorded more in the Cervarix™ group than the Gardasil® group.

Globally, HPV 16 and HPV 18 are the predominant oncogenic types which are responsible for over 70% of all invasive cervical cancer cases and HPV 6 and HPV 11 are responsible for 90% genital warts [15]. In 2012, Blomberg et al., conducted a large national cohort study to examine the standardized incidence risk (SIR) for cancer among women with genital warts and as per their study a diagnosis of GW was strongly related to anal (SIR-7.8), vulvar (SIR-14.8), vaginal (SIR-5.9), cervical (SIR-1.5). The risk remained elevated for >10 years following GW diagnosis [16]. To get protection from cervical cancer and genital warts, implementation of Gardasil® is initiated. Gardasil®is indicated in females aged 9 through 45 years "for prevention of cervical, vulvar, and vaginal cancer, precancerous or dysplastic lesions, genital warts, and infections caused by Human Papillomavirus (HPV) Types 6, 11, 16 and 18 (which are included in the vaccine). In 2009, Fairley et al., conducted study in Australian population using Gardasil®HPV vaccination to check the impact of vaccination in genital warts reduction. The study data showed a rapid and marked reduction in the incidence of genital warts among Gardasil®vaccinated women [17].

According to Diaz et al., (2008) published study on health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in INDIA. Figure6 shows the impact of HPV vaccination of preadolescent girls in INDIA was calculated by assuming 70% coverage of target population. Vaccination alone was able to reduce the lifetime risk of cervical cancer by 44%.

However, combined approach of preadolescent vaccination and screening three times per lifetime after the age of 30 using single visit by VIA at 70% target population was more than 1.25 million cervical cancer deaths. At a cost per vaccinated child of 2005 international $10 preadolescent vaccination followed by screening 3 times per lifetime using VIA is considered cost-effective using country's per capita gross domestic product $3582 (Rs. 2,18,788.56) [18,19]. So, if Gardasil®(MRP Rs. 1781/dose; 1781×3 dose= Rs.5343) is given to an Indian population, to prevent cervical cancer and genital warts (GWs), it becomes more cost-effective than Cervarix™ (MRP Rs. 1999/dose; 1999×3 dose= Rs.5997).

From the safety results of this study, protection against 4 HPV genotypes coverage and cost-effective analysis point of view it will be better to use Gardasil® than Cervarix™ in National Immunization program.

This study has few limitations. Due to limited funding, in this study only 77 women were screened and out of that only 69 women were enrolled to receive HPV vaccinations. Indian women from only one Metropolitan city were included which might not reflect the overall safety issue of HPV vaccines in India. Further, only women of 18-25 years old were enrolled. Inclusion of above 25 year age group women can gives us clear idea about how much different ADRs events can take place after HPV vaccinations. In addition to this, due to time constraint these participants could not be followed for more than 7 months.

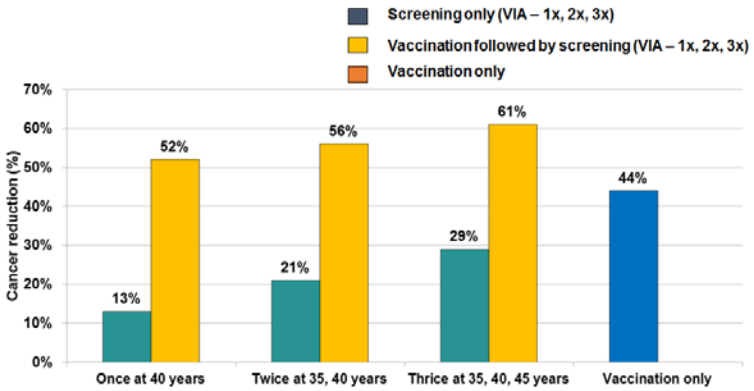

Fig. 6: Health impact of HPV vaccination followed bycervical cancer screening in India

CONCLUSION

Data from this trial support the safety of the HPV2 and HPV4 vaccine in healthy women of Mumbai region. Effective cervical cancer screening coverage in Metropolitan city like Mumbai is generally low. Therefore, HPV2 and HPV4 prophylactic vaccination before and after sexual debut offers the potential to decrease cervical cancers incidence and related mortality.

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CONFLICT OF INTERESTS

Declared None

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