IJPSR (2015), Vol. 6, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 22 August, 2014; received in revised form, 12 February, 2015; accepted, 22 March, 2015; published 01 April, 2015

SAFETY AND ADVERSE EVENTS OF PROPHYLACTIC HPV VACCINES AMONG HEALTHY WOMEN: A SYSTEMATIC REVIEW & META ANALYSIS

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Keywords:

HPV vaccine, HPV2, HPV4, Safety of HPV vaccine, Meta-analysis

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ABSTRACT: Cervical cancer (CaCx) is the third most common female cancer worldwide with an estimated 5, 27, 624 new cases and 2, 65, 653 deaths in 2014. We conducted a systematic review and meta- analysis to assess safety of prophylactic HPV vaccines compared against placebo. Four unique trials were included out of 607 publications. The total patient data evaluated was 1427(852 in vaccinated arm; 575 in the placebo arm). The pain was the major local side effects with 61% followed by swelling 22% and redness 17% in the vaccinated arm and similarly in the placebo arm pain 72% followed by swelling 18% and redness 10%. Headache was the most frequently experienced systemic side effects 42% in vaccine and placebo group. Unsolicited adverse event in vaccinated and placebo group were 39% and 37% respectively. New onset chronic disease in vaccinated and placebo arm were 3% and 2% respectively. Serious adverse event were 3% in vaccinated and 2% in placebo group. Undesirable pregnancy outcomes were same for both vaccinated and placebo arm 3%. As we had limited studies funnelled through our stringent inclusion exclusion criteria we were not able to separate exclusive adverse event in age group 25-34 and 35-45 years of age. In future, it would be interesting if we have 3 arms for comparison vaccine, Al(OH)3 and saline placebo.

INTRODUCTION: Cervical cancer (CaCx) 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] 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 122,844 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]

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(4).1779-91

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(4).1779-91

The necessary cause of cervical cancer is the HPV infection.[6] Worldwide 70% of invasive cervical cancer cases are caused by Human Papillomavirus (HPV) 16 or 18 and 90% of genital warts are caused by HPV 6 and 11.[7] Cervical cancer and other Human papillomavirus associated malignancies might be prevented by two human papillomavirus vaccines namely, Cervarix™-(HPV2) bivalent and Gardasil®-(HPV4) quadrivalent.[8, 9] 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.[10]

In 2011, Lu et al., performed systematic review and meta-analysis to assess efficacy and safety of prophylactic HPV vaccines against cervical cancer precursor events in women when compared with placebo and Hepatitis vaccines. According to their results, prophylactic HPV vaccines are safe, well

tolerated, and highly efficacious in preventing persistent infections and cervical diseases associated with vaccine-HPV types among young females.[11] However, in this study we have performed a systematic review with all unique randomized controlled trials in which HPV vaccines were compared against placebo only regarding local and general injection site symptoms.

MATERIALS AND METHODS:

Identification of Studies:

A comprehensive search on MEDLINE, Cochrane Library and the Cochrane Central Register of Controlled Trials databases was made from June 1996 to November 2014 to identify reports of RCTs of prophylactic HPV vaccines, using a combination of index terms:" ("safety"[MeSH Terms] OR "safety"[All Fields]) AND ("papillomavirus vaccines"[MeSH Terms] OR ("papillomavirus"[All Fields] AND "vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields] OR ("human"[All Fields] and "papillomavirus"[All Fields] AND "vaccines"[All Fields]) OR "human papillomavirus vaccines"[All Fields]).

Selection Criteria (Inclusion and Exclusion Criteria):

This review focused on randomized, placebo-controlled, double-blind trials in which the vaccines against HPV were evaluated in healthy women. We chose 2 commercial available HPV vaccines that used L1 virus-like particle (L1- VLP): Human papillomavirus bivalent (Types 16 and 18) vaccine, recombinant, AS04 adjuvanted (Cervarix™/ HPV2, GlaxoSmithKline Biologicals) and Human papillomavirus quadrivalent (Types 6, 11, 16, 18) vaccine, recombinant (Gardasil®/ HPV4, Merck & Co., Inc.,).

RCTs published in English of L1 VLP-based HPV vaccines were included. Articles reporting review article, male vaccination or therapeutic vaccination and trials including interventional HPV vaccines disease conditions were excluded. Additionally, we excluded ad hoc subgroup analyses of existing RCTs or combined analyses of multiple RCTs and policy, advocacy studies. We even excluded those studies whose follow up is more than 1 months after giving last dose of HPV vaccination, having alternative vaccination schedule and alternate route of vaccine administration.

Outcome:

The primary objective was to evaluate HPV vaccine safety. The secondary outcome was to evaluate detailed classification of adverse events as local, systemic and severe effects.

Data Extraction:

Data were extracted by three independent reviewers (VCS, BBG and GM) using a standardized data extraction form. Any discrepancies were resolved by consensus or in consultation with another reviewer. We extracted detailed information on trial design, inclusion/exclusion criteria, participant characteristics, vaccine and placebo administered, trial endpoints, efficacy populations, and methodological quality from all included trials.

Data Synthesis and Statistical Analysis:

Effect sizes were summarized as Risk Ratios (RRs) and associated 95 percent confidence intervals. Heterogeneity between studies was assessed using the Tau ^{2} statistics. All analyses were performed in Open Meta[analyst] 12/3/2013 statistical software following the PRISMA guidelines.

RESULTS:

Selection of Studies:

Study identification and selection was demonstrated in the flow diagram in (Figure 1). Of 607 publications identified through an initial search of databases, 597 were excluded for reasons elaborated below. Then from total 10 potential studies only four unique RCTs met the eligibility criteria and were included in the current study.

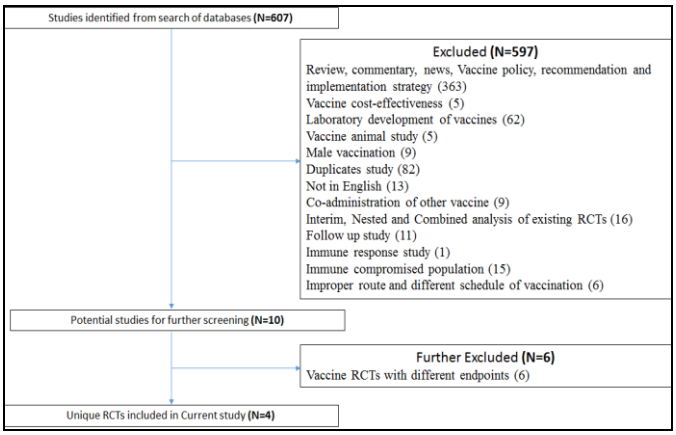


FIG.1: INCLUSION AND EXCLUSION OF TRIALS IN STUDY SELECTION

TABLE 1: CHARACTERISTICS OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN THE REVIEW.

	Kim et al., 2011	**Bhatla et al., 2011**	**Sow et al., 2012**	**Lim et al., 2014**
Study Title	A Phase IIIb, Double-blind, Randomized, Controlled Study to Evaluate the Immunogenicity and Safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 Vaccine, Administered Intramuscularly in Healthy Female Subjects Aged 15 - 25 Years.	Phase IIIb, Double-blind, Randomized, Controlled Study to Evaluate the Immunogenicity and Safety of GSK Biologicals' HPV-16/18 VLP/AS04 Vaccine Administered Intramuscularly at 0, 1, 6 Months in Healthy Indian Female Subjects Aged 18-35 Yrs.	Study to Assess the Immunogenicity and Safety of GlaxoSmithKline Biologicals' HPV Vaccine GSK580299 in Healthy Female Subjects Aged 10-25 Years.	Phase IIIb, Double-blind, Randomized, Controlled Study to Evaluate the Immunogenicity & Safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 Vaccine Administered Intramuscularly (0, 1, 6 Month Schedule) in Healthy Women From Malaysia.
Trial registration number	NCT 00485732	NCT00344032	NCT00481767	NCT00345878
Phase	IIIb	IIIb	IIIb	IIIb
Study design	double-blind, placebo-control	double-blind, placebo-control	double-blind, placebo-control	double-blind, placebo-control
Randomization scheme	02:01	01:01	01:01	01:01
No. of study centres	6	4	2	2
Countries included	1	1	2	1
Name of Countries included	Korea	India	S. Africa and Tanzania	Malaysia
Year of study enrolment	June 2007 - March 2008	July 2006 - March 2007	October 2007 - July 2010	September 2006 - December 2007
Funding source	GlaxoSmithKline Biologicals	GlaxoSmithKline Biologicals	GlaxoSmithKline Biologicals	GlaxoSmithKline Biologicals
Age group (yrs)	15 to 25	18 to 35	10 to 25	18 to 35
Study enrolled population	225	354	676	271
Study completed population	208	330	623	266
Inclusion Criteria	1) Subjects who the investigator believes that they or their parents/guardians can and will comply with the requirements of the protocol should be enrolled in the study. 2) A female between, and including, 15 and 25 years of age at the time of the first vaccination. 3) Written informed assent obtained from the subject and informed consent obtained from the parent or guardian of the subject. 4) Healthy subjects as established by medical history and clinical examination before entering into the study. 5) Subjects must have a negative urine pregnancy test. 6) Subjects of childbearing potential at the time of study entry must be abstinent, or must be using adequate contraceptive precautions for 30 days prior to vaccination and must agree to	1) Subjects who the investigator believes that they can and will comply with the requirements of the protocol should be enrolled in the study. 2) A female between, and including, 18 and 35 years of age at the time of the first vaccination. 3) Written informed consent obtained from the subject. 4) Healthy subjects as established by medical history and clinical examination before entering into the study. 5) Subjects must have a negative urine pregnancy test. 6) Subjects of childbearing potential at the time of study entry must be abstinent or must be using adequate contraceptive precautions for 30 days prior to vaccination and must agree to continue such precautions for two months after completion of the vaccination series.	1) Subjects who the investigator believes that they and/or their parents/legally acceptable representative can and will comply with the requirements of the protocol should be enrolled in the study. 2) A female between, and including, 10 and 25 years of age at the time of the first vaccination. 3) Written or oral, signed or thumb printed or witnessed informed consent obtained from the subject prior to enrolment. For subjects below legal age of consent, written or oral, signed or thumb printed or witnessed informed consent obtained from the subject's parent or legally acceptable representative. In addition, a written or oral, signed or thumb printed and witnessed informed assent must be obtained from the subject. 4) Free of obvious health problems as established by	1) Subjects who the investigator believes that they can and will comply with the requirements of the protocol should be enrolled in the study. 2) A female from Malaysia between, and including, 18 and 35 years of age at the time of the first vaccination. 3) Written informed consent obtained from the subject. 4) Healthy subjects as established by medical history and clinical examination before entering into the study. 5) Subjects must have a negative urine pregnancy test. 6) Subjects of childbearing potential at the time of study entry must be abstinent or must be using an effective method of birth control for 30 days prior to vaccination and must agree to continue such precautions for two months after completion of the vaccination series.

	continue such precautions for two months after completion of the vaccination series.		medical history, clinical examination and laboratory testing before entering into the study. 5) Subjects must have a negative urine pregnancy test at the screening visit and at Visit 1 (Day 0). 6) Subjects must be seronegative for human immunodeficiency virus (HIV) at the screening visit. 7) Subjects must be of non-childbearing potential, or, if of childbearing potential, she must be abstinent or have used adequate contraceptive precautions for 30 days prior to vaccination, have a negative pregnancy test and must agree to continue such precautions for two months after completion of the vaccination series. Subjects who reach menarche during the study and therefore are of childbearing potential must agree to follow the same precautions. 8) Subjects must have had no more than 6 sexual partners prior to enrolment. 9) Subjects must be willing to undergo HIV voluntary counselling and testing and must be willing to be informed of their HIV status. Subjects below legal age of consent must also be willing to have their parent or legally acceptable representative informed of their HIV status.	
Exclusion criteria	1) Use of any investigational or non-registered product (drug or vaccine) other than the study/ control vaccine within 30 days preceding the first dose of study/ control vaccine, or planned use during the study period. 2) Pregnant or breastfeeding. 3) Planning to become pregnant or likely to become pregnant. 4) Chronic administration (defined as more than 14 days) of immunosuppressant or other immune-modifying drugs within six months prior to the first vaccine dose. 5) Planned administration/ administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after the first dose of vaccine. However, the administration of routine vaccines up to 8 days before the first dose of study vaccine is allowed. Enrolment will be	1) Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine/ control within 30 days preceding the first dose of study vaccine/ control, or planned use during the study period. 2) Pregnant or breastfeeding. 3)Planning to become pregnant or likely to become pregnant. 4) Chronic administration of immunosuppressant or other immune-modifying drugs within six months prior to the first vaccine dose. 5) Planned administration/ administration of a vaccine not foreseen by the study protocol within 30 days (Days 1 to 30) before and 30 days (Day 0-Day 29) after the first dose of vaccine. Administration of routine meningococcal, hepatitis B, inactivated influenza, diphtheria/tetanus	1) Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period (up to Month 12). 2) Chronic administration of immunosuppressant or other immune-modifying drugs within six months prior to the first vaccine dose or planned administration during the study period. 3) Administration of a vaccine not foreseen by the study protocol within 30 days before the first dose of vaccine. Enrolment will be deferred until the subject is outside of specified window. 4) Planned administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after any	1) 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. 2) Chronic administration (defined as more than 14 days) of immunosuppressant or other immune-modifying drugs within six months prior to the first vaccine dose. 3) Planned administration/ administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after the first dose of vaccine. Administration of routine vaccines up to 8 days before the first dose of study vaccine is allowed. Enrolment will be deferred until the subject is outside of specified window. 4) Previous administration of

	deferred until the subject is outside of specified window. 6) Previous administration of components of the investigational vaccine. 7) Previous vaccination against HPV or planned administration of any HPV vaccine other than that foreseen by the study protocol during the study period. 8) Any medically diagnosed or suspected immunodeficient condition such as HIV infection based on medical history and physical examination. 9) History of thrombocytopenia or hemostatic disorder in which case the study vaccine should under no circumstances be administered intramuscularly. 10) History of allergic disease, suspected allergy or reactions likely to be exacerbated by any component of the study/control vaccines. 11) Hypersensitivity to latex. 12) Known acute or chronic, clinically significant neurologic, pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by previous physical examination or laboratory tests. 12) History of chronic condition(s) requiring treatment. 13) Administration of immunoglobulins and/or any blood product within three months preceding the first dose of study/control vaccine or planned administration during the study period. Enrolment will be deferred until the subject is outside of specified window. 14) Acute disease at the time of enrolment.	and/or diphtheria/tetanus-containing vaccine up to 8 days before the first dose of study vaccine is allowed. 6) Previous administration of components of the investigational vaccine. 7) Previous vaccination against HPV. 8) Any medically diagnosed or suspected immunodeficient condition based on medical history and physical examination. 9) History of allergic disease, suspected allergy or reactions likely to be exacerbated by any component of the study vaccines. 10) Hypersensitivity to latex. 11) Known acute or chronic, clinically significant neurologic, hepatic or renal functional pulmonary, cardiovascular abnormality, as determined by previous physical examination or laboratory tests. History of chronic condition(s) requiring treatment. 12) Administration of immunoglobulins and/or any blood product within three months preceding the first dose of study vaccine/ control or planned administration during the study period. Enrolment will be deferred until condition is resolved. 13) Acute disease at the time of enrolment. Acute disease is defined as the presence of a moderate or severe illness with or without fever.	dose of study vaccine. 5) Previous vaccination against HPV, or planned administration of any HPV vaccine other than that foreseen by the study protocol during the study period. 6) Previous administration of components of the investigational vaccine. 7) Cancer or autoimmune disease under treatment. 8) Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection based on laboratory testing performed during the screening visit. 9) Hypersensitivity to latex. 10) History of allergic disease or reactions likely to be exacerbated by any component of the vaccine/control. 11) Acute disease at the time of enrolment. Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory testing performed at the screening visit. 12) History of any neurologic disorders or seizures. 13) Administration of immunoglobulins and/or any blood products within the three months preceding the first dose of study vaccine or planned administration during the study period. 14) Pregnant or breastfeeding female. 15) A women planning to become pregnant, likely to become pregnant or planning to discontinue contraceptive precautions during the study period, up to two months after the last vaccine dose. 16) Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).	components of the investigational vaccine 5) Previous vaccination against HPV or planned administration of any HPV vaccine other than that foreseen by the study protocol during the study period. 6) Any confirmed or suspected Immunosuppressive or immunodeficient condition, based on medical history and physical examination. 7) History of allergic disease or reactions likely to be exacerbated by any component of the vaccine(s). 8) Hypersensitivity to latex. 9) Acute disease at the time of enrolment. 10) Known acute or chronic, clinically significant neurologic, pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by previous physical examination or laboratory tests. 11) History of chronic condition(s) requiring treatment. 12) Administration of immunoglobulins and/or any blood product within three months preceding the first dose of study vaccine(s) or planned administration during the study period. Enrolment will be deferred until the subject is outside of specified window. 13) Pregnant or lactating female. 14) Female planning to become pregnant or planning to discontinue contraceptive precautions.

Intervention & Comparator				
Vaccine used	HPV-16/18 VLP/AS04 vaccine	HPV-16/18 VLP/AS04 vaccine	HPV-16/18 VLP/AS04 vaccine	HPV-16/18 VLP/AS04 vaccine
VLP amount (µg)	20 µg of HPV16 and 18	20 µg of HPV16 and 18	20 µg of HPV16 and 18	20 µg of HPV16 and 18
Adjuvant	500 µg	500 µg	500 µg	500 µg

Comparator	$Al(OH)_3$	$Al(OH)_3$	$Al(OH)_3$	$Al(OH)_3$
Administration schedule	0, 1 and 6 months	0, 1 and 6 months	0, 1 and 6 months	0, 1 and 6 months
Compliance to the 3-dose vaccination course				
HPV	95.30%	*	*	96.30%
Placebo	89.50%	*	*	97.80%
Compliance rate for returning the diary cards				
HPV	98.45%	97.50%	*	*
Placebo	97.20%	98.10%	*	*
Outcome Measures				
Primary	Number of Subjects Seroconverted for Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-human Papilloma Virus 18 (Anti-HPV-18) Antibodies.	Number of Subjects Who Seroconverted for Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-human Papilloma Virus 18 (Anti-HPV-18) Antibodies.	Number of Seroconverted Subjects for Anti-human Papillomavirus (HPV)-16 and 18 Antibodies; Geometric Mean Titers (GMTs) of Anti-HPV-16 and Anti-HPV-18 Antibodies.	Number of Subjects Who Seroconverted for Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-human Papilloma Virus 18 (Anti-HPV-18) Antibodies.
Secondary	1) Anti-HPV-16 and Anti-HPV-18 Antibody Titres. 2) Number of Subjects Reporting Solicited Local Symptoms. 3) Number of Subjects Reporting Solicited General Symptoms. 4) Number of Subjects Reporting Unsolicited Adverse Events (AE). 5) Number of Subjects Reporting New Onset of Chronic Diseases (NOCDs) and Medically Significant Conditions. 6) Number of Subjects Reporting Serious Adverse Events (SAE). 7) Number of Subjects With Pregnancies and Their Outcome.	1) Titers of Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-human Papilloma Virus 18 (Anti-HPV-18) Antibodies. 2) Number of Subjects Reporting Solicited Symptoms. 3) Number of Subjects Reporting Unsolicited Adverse Events. 4) Number of Subjects Reporting Unsolicited Adverse Events as New Onset Chronic Diseases (NOCDs) and Other Medically Significant Adverse Events (AEs). 5) Number of Subjects Reporting Serious Adverse Events	1) Number of Seroconverted Subjects for Anti-HPV-16 and Anti-HPV-18 Antibodies. 2) GMTs for Anti-HPV-16 and Anti-HPV-18 Antibodies. 3) Number of Subjects With Solicited Local and General Symptoms. 4) Number of Subjects With Any, Grade 3 and Related Unsolicited Adverse Events (AEs). 5) Number of Subjects With New Onset of Chronic Diseases (NOCDs) and Medically Significant Conditions (MSCs). 6) Number of Subjects With Serious Adverse Events (SAEs). 7) Number of Subjects With Pregnancies and Their Outcomes. 8) Number of Senegalese Subjects With Clinically Relevant Abnormalities in Biochemical and Haematological Parameters Assessed. 9) Number of Tanzanian Subjects With Clinically Relevant Abnormalities in Biochemical and Haematological Parameters Assessed. 10) Number of Senegalese Subjects With Clinically Relevant Abnormalities in Biochemical and Haematological Parameters Assessed. 11) Number of Tanzanian Subjects With Clinically Relevant Abnormalities in Biochemical and Haematological Parameters Assessed.	1) Titers of Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-human Papilloma Virus 18 (Anti-HPV-18) Antibodies. 2) Number of Subjects Reporting Solicited Symptoms. 3) Number of Subjects Reporting Unsolicited Adverse Events (AEs). 4) Number of Subjects Reporting Unsolicited Adverse Events as New Onset Chronic Diseases (NOCDs) and Other Medically Significant Adverse Events (AEs). 5) Number of Subjects Reporting Serious Adverse Events.

TABLE 2: BASELINE CHARACTERISTICS OF RANDOMIZED CONTROLLED TRIALS PARTICIPANTS.

	Kim et al., 2011		Bhatla et al., 2011		Sow et al., 2012		Lim et al., 2014	
	Vaccine (n)	Control (n)	Vaccine (n)	Control (n)	Vaccine (n)	Control (n)	Vaccine (n)	Control (n)
Age, mean (SD)	22.0 ± 2.37		28.5 ± 4.83		16.9 ± 4.29		24.9 ± 4.02	
	22.0 ± 2.24	21.9 ± 2.63	28.5 ± 4.70	28.5 ± 4.97	16.9 ± 4.36	16.8 ± 4.16	24.8 ± 3.91	25.0 ± 4.14
Study enrolled population	225		354		676		271	
	149	76	176	178	450	226	135	136
Study completed population	208		330		623		266	
	141	67	162	168	418	205	131	135
Not completed	8	9	14	10	32	21	4	1
Adverse event	0	0	0	1	0	0	1	0
Protocol Violation	1	3	0	0	0	0	0	0
Withdrawal by Subject	5	4	6	2	16	11	0	0
Lost to Follow-up	2	2	4	6	16	10	2	1
Physician decision	0	0	4	1	0	0	0	0
Unkown	0	0	4	1	0	0	1	0
Mean duration of local symptoms (days)	3.4-3.7	2.3-2.4	*	*	*	*	2.8–2.9	2.1–2.5
Mean duration of solicited general symptoms (days)	2.1-3	1-2.6	*	*	*	*	1.6–3.8	1.5–2.7
Solicited Local Symptoms	145	72	171	174	450	226	132	135
Pain	140	64	137	105	375	166	121	101
Redness	109	35	56	24	0	0	48	0
Swelling	89	19	69	35	74	27	42	25
Solicited General Symptoms	145	72	171	174	450	226	132	135
Arthralgia	35	8	19	16	77	32	39	26
Fatigue	103	39	84	83	111	42	52	48
Fever	7	2	51	48	147	70	19	17
Gastrointestinal symptoms	52	16	25	28	118	56	18	18
Headache	73	30	72	71	189	109	46	47
Myalgia	97	33	10	11	90	36	48	32
Rash	29	8	5	8	71	30	4	7
Urticaria	12	2	4	6	68	27	4	2
Unsolicited Adverse Events	66	19	20	26	243	147	30	36
New Onset of Chronic Diseases (NOCDs)	5	6	0	2	10	8	1	0
Medically Significant Conditions	34	10	13	24	289	161	10	11
Serious Adverse Events	2	1	2	4	12	10	3	3
Pregnancy outcomes	0	1	0	1	14	10	1	0
Elective abortion	0	1	0	1	3	3	1	0
Ectopic pregnancy	0	0	0	0	1	0	0	0
Live infant	0	0	0	0	5	5	0	0
Premature live infant	0	0	0	0	3	1	0	0
Lost to follow-up	0	0	0	0	1	0	0	0
Spontaneous abortion	0	0	0	0	1	1	0	0

Characteristics of Included Trials and baseline characteristics of Trial Participants:

Characteristics of RCTs included in the current review are summarized in **(Table 1)**. Unique trials were identified by first authors of associated publications. Three trials were multicentre trials with 1:1 randomization scheme except Kim et al., (2011) Korea trial where they used 2:1 randomization scheme. In all trials, HPV2vaccines (20µg of HPV16 and 18) and controls (placebo) were administered in a three-dose regimen within a 6-month time frame.

Proprietary adjuvant was used with each type of vaccine to enhance immunogenicity. All trials used placebo (500 µg of aluminium as $Al(OH)_3$) as the comparator are summarized in (**Table 2**).

Assessment of Adverse Events: Adverse events (AEs) were monitored by the use of daily vaccination report cards within 15 or 30 days of injection, as well as solicitation throughout the study. Occurrence of AEs was reported in all RCTs. Adverse events were categorized into local side effects, systemic side effects, unsolicited adverse events, new onset of chronic disease, medically significant condition, serious side effect and impact on pregnancy outcome. Patients who had received 1 more dose of vaccines or placebo were included in the assessment of adverse events.

Local side effects:

Local side effects were evaluated were pain, redness and swelling. These effects were monitored for 1 month after each dose of vaccination. According to meta-analysis, major local side effects were measured in HPV vaccinated group were pain 773(85%) followed by swelling 274(30%) and redness 213(23%) while in control group major local side effects were pain 436(71%) followed by swelling 106 (17%) and redness 59(10%). Duration of local side effects were longer in vaccinated group as compared into placebo **Fig. 2**

Pain:

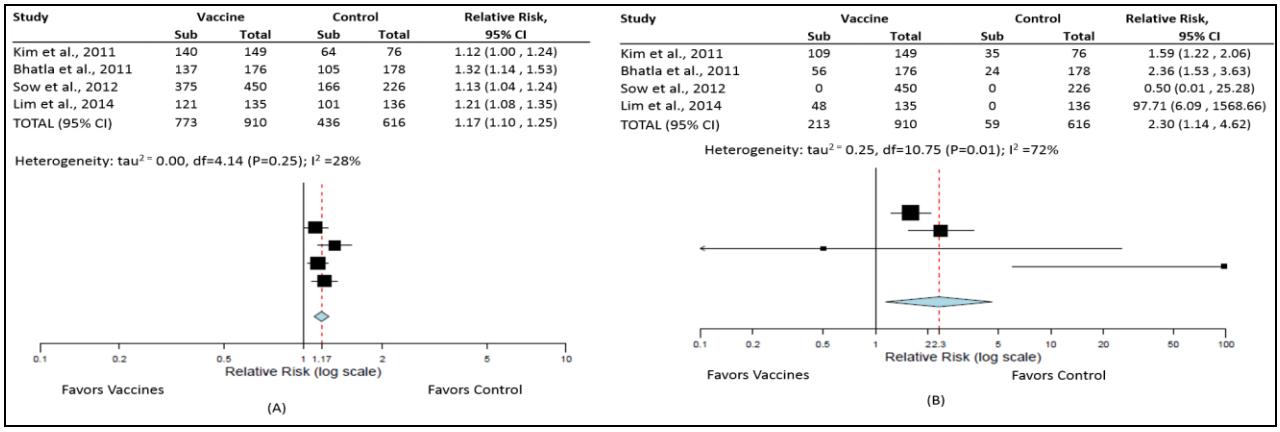
In vaccinated arm, percentage of people reporting pain was 85%(78-94%) while in control the frequency of pain was 71%(59-84%). Participants from Kim et al. (2011) study, experienced pain as major adverse events in both HPV vaccinated (94%) and placebo group (84%).

Redness:

In vaccinated arm, percentage of people reporting redness was 23%(0-73%) while in control the frequency of redness was 10%(0-46%). For this study parameters also participants from Kim et al. (2011) study, experienced pain as major adverse events in both HPV vaccinated (73%) and placebo group (46%).

Swelling:

In vaccinated arm, percentage of people reporting swelling was 30%(16-60%) while in control the frequency of redness was 17%(12-25%). For swelling study parameters participants from Kim et al. (2011) study, experienced swelling as major adverse events in both HPV vaccinated (60%) and placebo group (25%).



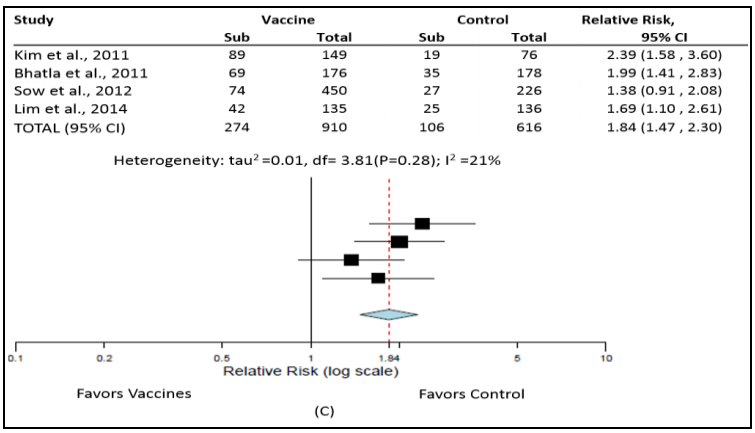


FIG. 2: ASSESSMENT OF LOCAL ADVERSE EVENTS (A) PAIN, (B) REDNESS AND (C) SWELLING.

Systemic side effects:
Systemic side effects evaluated were arthralgia, fatigue, fever, GI, headache, myalgia, rash and urticaria. Two most common adverse events were seen in both groups were headache and fatigue **Fig.3**

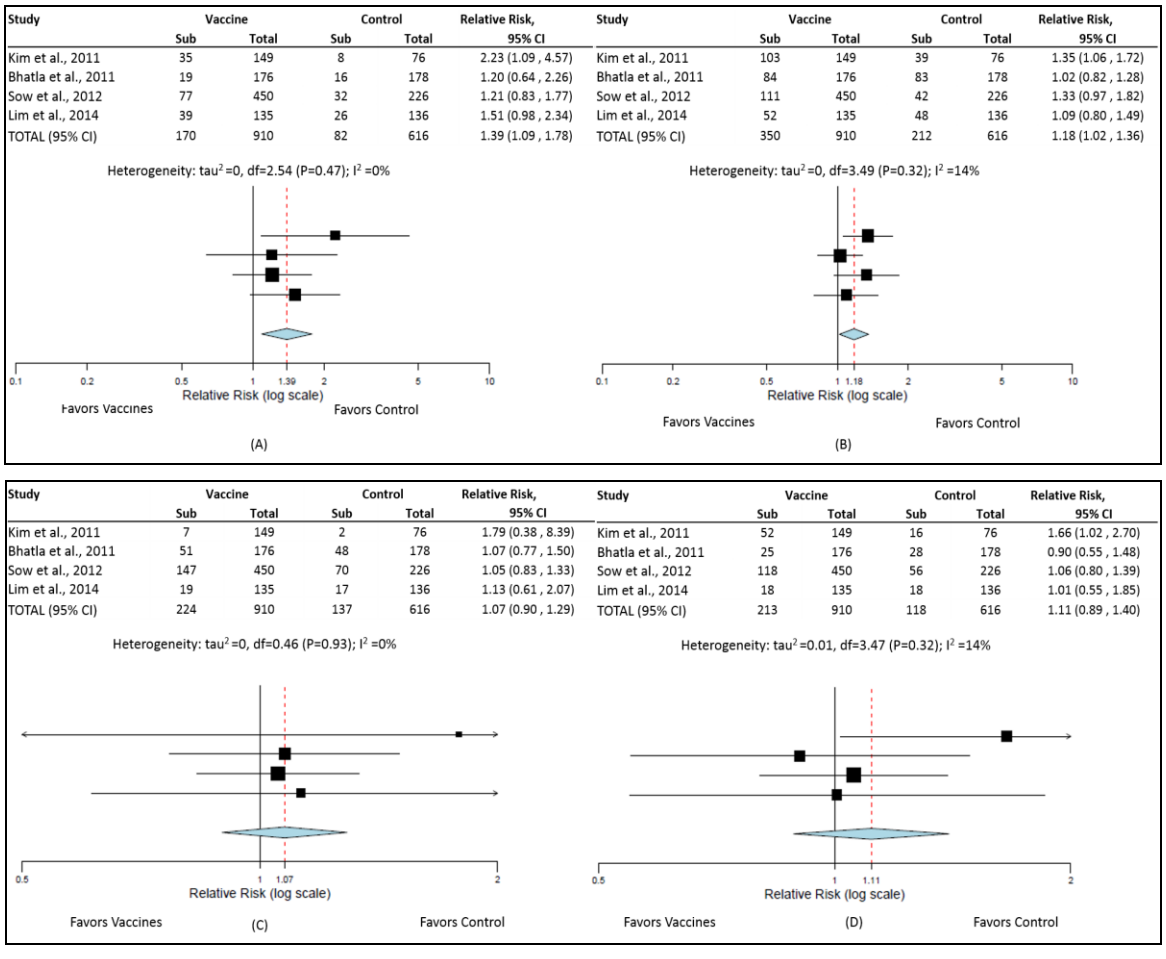
Arthralgia:
For arthralgia as expected from previous studies, participants from vaccinated group 19%(11-29%) experienced higher adverse events than control group 13(9-19%). For this study parameters participants from Lim et al. (2014) study, experienced arthralgia as major adverse events in both HPV vaccinated (29%) and placebo group (19%).

Fatigue:
For fatigue, participants from vaccinated group 38%(25-69%) experienced higher adverse events than control group 34(19-51%). For this study parameters participants from Kim et al. (2011) study, experienced fatigue as major adverse events in both HPV vaccinated (69%) and placebo group (51%).

Fever:
In HPV vaccinated group 25% (5-33%) fever adverse event slightly higher than control group 22% (3-31%). Sow et al., (2012) study participants experienced higher adverse events in HPV vaccinated group (33%) than placebo group (31%).

Gastrointestinal (GI) Systems:
In HPV vaccinated group 23% (13-35%) fever adverse event slightly higher than control group 19% (13-25%). For this parameter in Kim et al., (2011) study in HPV vaccinated group adverse event was 35% while for placebo adverse event was 25% in Sow et al., (2012) study participants.

Headache:
In HPV vaccinated and control group headache adverse event was found similar 42%. Kim et al., (2011) study in HPV vaccinated group adverse event was 49% while for placebo adverse event was 48% in Sow et al., (2012) study participants.



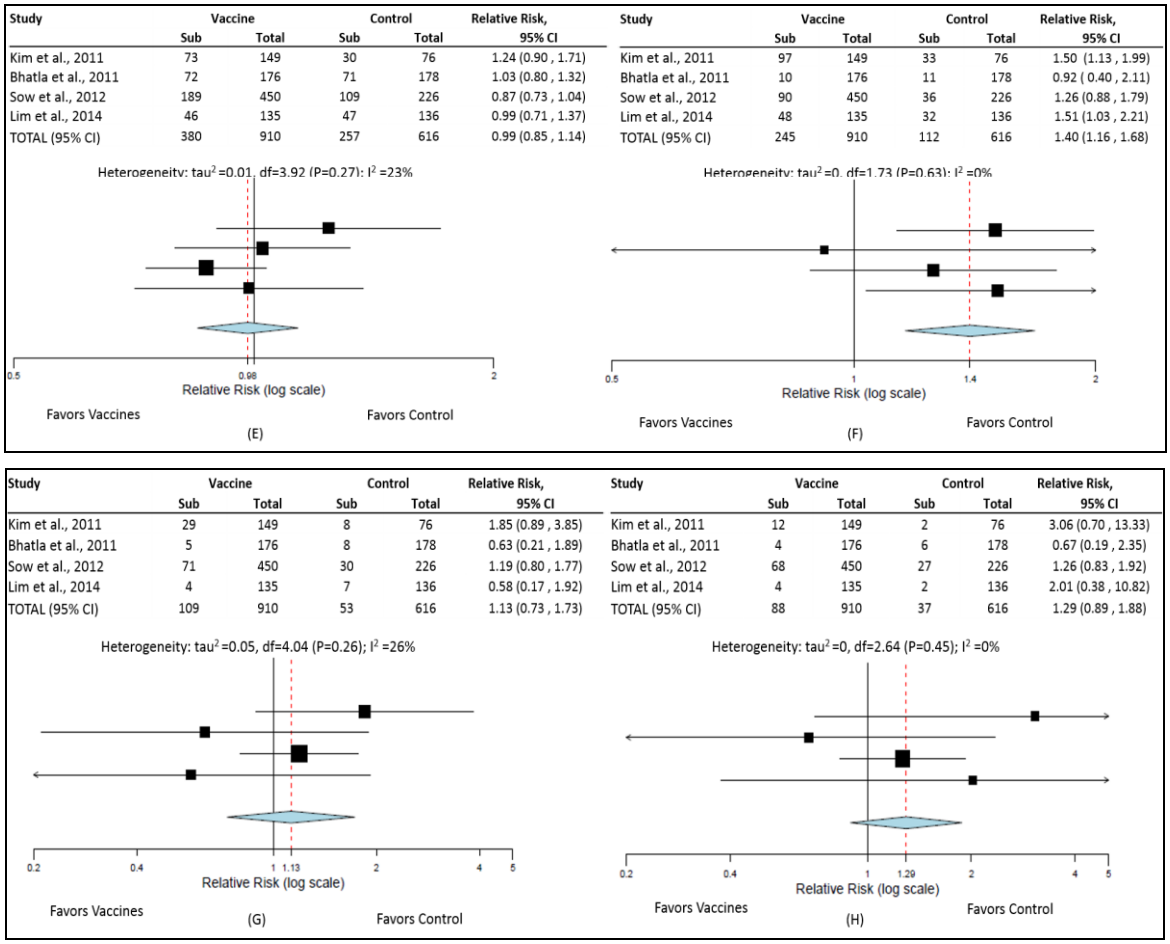


FIG.3: ASSESSMENT OF SYSTEMIC SIDE EFFECTS (A) ARTHRALGIA, (B) FATIGUE, (C) FEVER, (D) GI, (E) HEADACHE, (F) MYALGIA, (G) RASH AND (H) URTICARIAMYALGIA

In HPV vaccinated group 27% (6-65%) fever adverse event slightly higher than control group 18% (6-43%). For this parameter Kim et al., (2011) study participants experienced higher adverse events in HPV vaccinated group (65%) than placebo group (43%).

Rash:

In HPV vaccinated group 12% (3-19%) fever adverse event slightly higher than control group 9% (4-13%). For this parameter in Kim et al., (2011) study in HPV vaccinated group adverse event was 19% while for placebo adverse event was 13% in Sow et al., (2012) study participants.

Urticaria:

For urticarial, in HPV vaccinated group 10% (2-15%) fever adverse event slightly higher than control group 6% (1-12%). For this parameter Sow et al., (2012) study participants experienced higher adverse events in HPV vaccinated group (15%) than placebo group (12%).

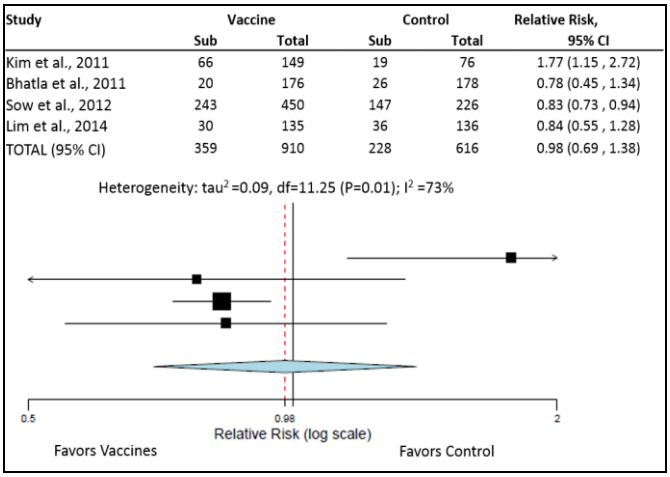


FIG.4: ASSESSMENT OF UNSOLICITED ADVERSE EVENTS.

Unsolicited adverse events:

Unsolicited adverse event was observed higher in HPV vaccinated group 39% (11-54%) than control group 37% (15-65%). For this parameter Sow et al., (2012) study participants experienced lower adverse events in HPV vaccinated group (54%) than placebo group (65%) **Fig.4**

New onset of chronic disease:

In new onset of chronic disease parameter, control vaccinated group 3% (0-8%) adverse event slightly higher than vaccinated group 2% (0-3%). Kim et al., (2011) study participants experienced higher adverse events in placebo group (8%) than HPV vaccinated group (3%) **Fig.5**

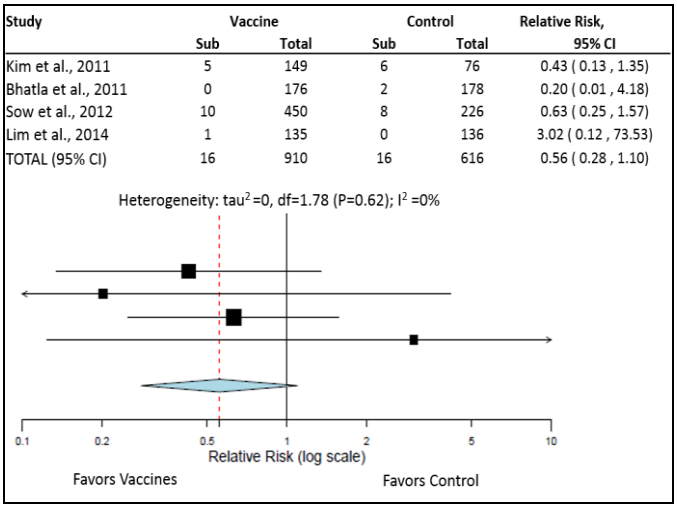


FIG.5: ASSESSMENT OF NEW ONSET OF CHRONIC DISEASE.

Medically significant condition:

Medically significant condition event was observed higher in HPV vaccinated group 38% (7-64%) than control group 33% (8-71%). Sow et al., (2012) study participants experienced higher adverse events in placebo group (71%) than HPV vaccinated group (64%) **Fig.6**

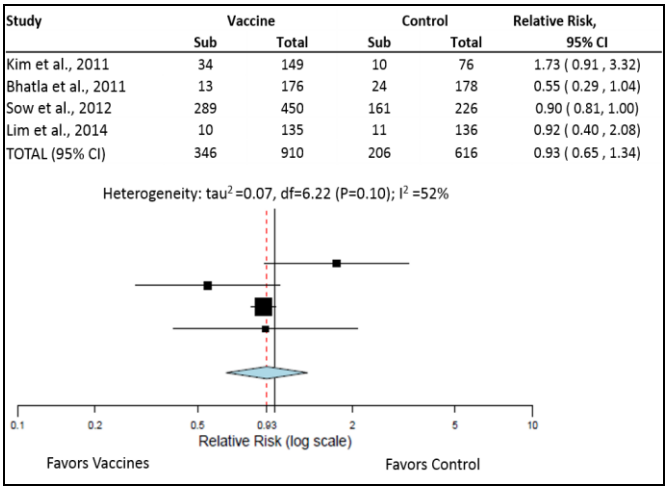


FIG.6: ASSESSMENT OF MEDICALLY SIGNIFICANT CONDITION.

Serious adverse events (SAE):

In Serious adverse events (SAE), control vaccinated group 3% (1-4%) adverse event slightly higher than vaccinated group 2% (1-3%). Sow et al., (2012) study participants reported higher adverse events in placebo group (4%) than HPV vaccinated group (3%) **Fig.7**

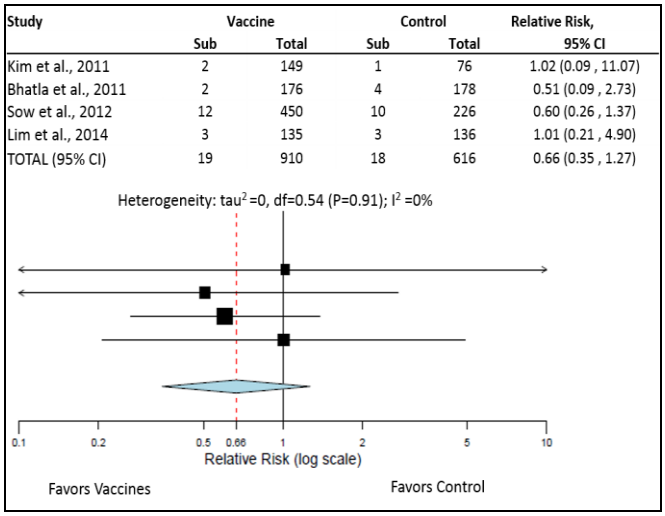


FIG.7: ASSESSMENT OF SERIOUS ADVERSE EVENTS.

Pregnancy outcome:

In HPV vaccinated and control group headache adverse event was found similar 2%. For this parameter Sow et al., (2012) study participants experienced higher adverse events in placebo group (4%) than HPV vaccinated group (3%) **Fig.8**

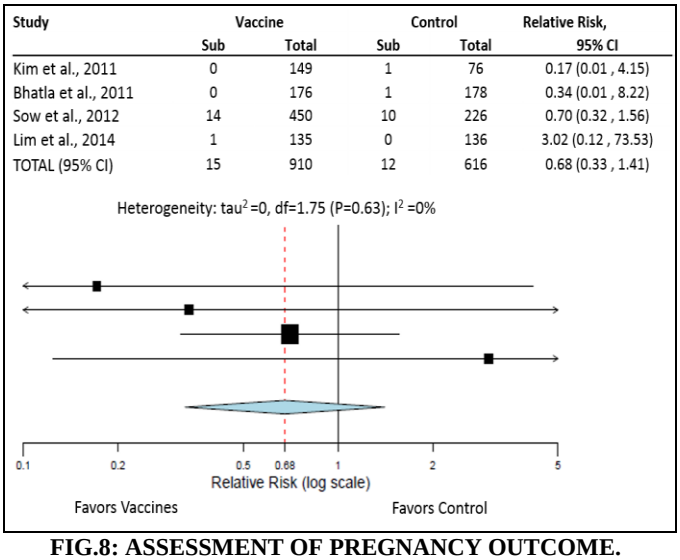


FIG.8: ASSESSMENT OF PREGNANCY OUTCOME.

Adverse Event in women up to 25 years vs women upto 35 years:

As we analysed the data it was evident that side effects were more in younger age group as compared to older but with the limited no of side effects in both the age group no statistical significance was achieved.

DISCUSSION: Only 4 studies passed the strict inclusion criteria, all the studies were done using the HPV2 vaccines and the placebo used was $Al(SO_4)$. We did not have any study with HPV4 as most of the studies with HPV4 have males included in the study and we had excluded males from our study. The reason why we intended to have females is that in most of the country's HPV vaccine is recommended for female population only and hence it would be import to understand the adverse event profile in females. We have 2 studies where patient age was up to 25 and 2 studies in which patient age was up to 35 years. As we had limited studies funnelled through our stringent inclusion exclusion criteria we were not able to separate exclusive adverse event in age group 25-34 and 35-45 years of age. The analysis done on adverse event in group upto 35 was overlapping with the other arm of upto 25 years and hence the analysis has to be rerun among specific age groups i.e. 25-34 and 35-45.

The total patient data evaluated was 1427(852 in vaccinated arm; 575 in the placebo arm). The percentage of patients experiencing serious side effects were small and hence absolute number of severe side evaluated was not large enough and we would have to wait and possible include data from other studies to make it more robust and have good powered analysis. The studies only compared the side-effect profile of vaccine against placebo $Al(OH)_3$ it would be interesting if we have 3 arms for comparison vaccine, $Al(OH)_3$ and saline placebo. It would be interesting to analysis regional/ geographical/racial difference in pain perception to both vaccine and placebo. This analysis might bring up different precautions to be followed while vaccinating people of different geographical area.

CONCLUSION: In the meta-analysis we could find and conclude that pain was the major local side effects with 61% followed by swelling 22% and redness 17% in the vaccinated arm and similarly in the placebo arm pain 72% followed by swelling 18% and redness 10%. Duration of local side effects was longer in vaccinated group as compared into placebo. Headache was the most frequently experienced systemic side effects 42% in vaccine and placebo group. Unsolicited adverse event in vaccinated and placebo group were 39% and 37% respectively. New onset chronic disease in vaccinated and placebo arm were 3% and 2% respectively. Serious adverse event were 3% in vaccinated and 2% in placebo group. Undesirable pregnancy outcomes were same for both vaccinated and placebo arm 3%. We would say that HPV vaccine do have high rate of local side effects but comparable with placebo. Serious adverse events and adverse pregnancy outcomes rates are low and comparable in both the arms.

CONFLICT OF INTEREST: Gaurav Mathur serves as an employee of MSD Pharmaceuticals Pvt. Ltd, India.

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How to cite this article:
Sangar VC, Ghongane BB, Mathur G and Chowdhary AS: Safety and Adverse Events of Prophylactic HPV Vaccines among Healthy Women: A Systematic Review & Meta Analysis. Int J Pharm Sci Res 2015; 6(4): 1779-91.doi: 10.13040/IJPSR.0975-8232.6(4).1779-91.