Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 4, 2015

Original Article

POST-MARKETING PASSIVE SURVEILLANCE OFBIVALENT AND QUADRIVALENT HUMAN PAPILLOMAVIRUS RECOMBINANT VACCINES

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Received: 31 Jan 2015 Revised and Accepted: 22 Feb 2015

ABSTRACT

Objective: Cervical cancer and other Human papillomavirus associated malignancies might be prevented by Human papillomavirus vaccines namely Gardasil® (HPV4) - quadrivalent (Merck) and Cervarix™ (HPV2) - bivalent (GlaxoSmithKline) which are marketed internationally. The aim of this study is to analyze vaccines adverse events reporting system (VAERS) which is used for post-marketing passive surveillance (PMS) of licensed vaccines.

Methods: We searched and analyzed reports of adverse events associated with HPV 2 and HPV4 vaccines from Vaccine Adverse Event Reporting System (VAERS). In United States, between the year2006-2013, total 24, 719 adverse events were reported after taking HPV2 and HPV4 vaccines. For HPV2 vaccine, we searched for reports from October 2009 to December 2013 and for HPV4 vaccine, we searched for reports from October 2006 to December 2013.

Results: For HPV4 vaccine during 2006-2013, total 24, 460 adverse events and 84 deaths were reported while for HPV2 vaccine during 2009-2013, total 259 adverse events and 3 deaths were reported. Even after proper route of HPV vaccinesadministration i. e. intramuscular 13, 287 adverse events have been reported for HPV4 while 259 adverse events have been reported for HPV2 vaccine. The most frequently recorded adverse events due to HPV4 vaccine were found to be within the year 2006-2013 which included rash (2306 cases) followed by injection site erythrema (2245 cases) and pyrexia (2142 cases). However, adverse events recorded for HPV2 vaccine were within the period 2009-2013 which included dizziness (37 cases) followed by headache (34 cases) and malaise (19 cases).

Conclusion: In future ongoing HPV vaccines safety surveillance and further studies may shed light on some of the hypothesized associations.

Keywords: Prophylactic Human papillomavirus vaccines, Virus-like particles, Post-marketing surveillance, Vaccine Adverse Event Reporting System, HPV2, HPV4.

INTRODUCTION

Human papillomaviruses are the primary etiological agents of cervical cancer. Thus, cervical cancer and other Human papillomavirus associated malignancies might be prevented by Human papillomavirus vaccines. Currently, two Human papillomavirus L1 Virus -Like Particle vaccines namely Gardasil® (HPV4) - quadrivalent (Merck) and Cervarix™ (HPV2) - bivalent (GlaxoSmithKline) are widely marketed internationally. Gardasil® is a quadrivalent HPV 16/18/6/11 L1 VLP vaccine (HPV4) developed by Merck and Co. Inc. , West Point, Pennsylvania, USA in collaboration with the Australian company CSL. Food and Drug Administration (US FDA) licensed this quadrivalent HPV vaccine in 2006 while INDIA licensed this vaccine in October 2008 for the use in females. Gardasil®issold in 109 countries. [1, 2] Before FDA approved the use of Gardasil®, approximately 21, 000 girls and women were vaccinated with this HPV vaccine to evaluate the safety and its effectiveness. These studies showed that in women who have never been infected by HPV types 6, 11, 16 or 18, the vaccine was found to be highly effective in preventing precancerous lesions that often develop into cancer of the cervix, vagina and vulva and in preventing genital warts. [3] From June 2006 through March 2013, approximately 56 million doses of HPV4 were distributed in United Nation [4].

Cervarix™ is the second human papillomavirus (HPV2) vaccine licensed for use in females in the United States which is manufactured by GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium in alliance with MedImmune. In September 2007, Cervarix™ was first approved by the European Union for use in girls and women in the age group of 10-35 years. [5]On October 16, 2009, the FDA licensed bivalent human papillomavirus vaccine for use in females aged 10 through 25 years. Indian regulatory licensed this bivalent HPV vaccine in 2008 for use in females. Cervarix™issold in 100 countries. [1]Before FDA approved use of Cervarix™, its efficacy was assessed in the total of 19, 778 females used 15 through 25 years of age to prevent histopathologically-confirmed CIN2/3 or AIS. [6]Both the HPV vaccines have been designed for prophylactic use only. These HPV vaccines need to administer intramuscularly. [1, 5]From October 2009 through May 2013, a total of 611, 000 doses of HPV2 were distributed. [4]The spontaneous safety reporting of any vaccines adverse events following immunization (AEFI) is the primary mechanism used for post-marketing passive surveillance (PMS) of licensed vaccines. Passive AEFI surveillance is common in many countries like INDIA. [7]Post-licensure safety surveillance is important for a number of reasons. First, adverse events are reported after vaccinations but these are generally rare. Some adverse events are unlikely to be detected in prelicensure clinical trials because of their low frequency, the limited numbers of enrolled subjects, and other study limitations. Therefore, to overcome this post marketing monitoring of adverse events after vaccinations is essential. [8]Second, for established vaccines PMSaims to monitor known adverse reactions and if the observed rate exceeds of adverse reactions the expected rate, further investigationis required. [9]Vaccine Adverse Events Reporting System (VAERS) is a voluntary reporting system co administered by the Centers for Disease Control (CDC) and the Food and Drug Administration(FDA). It was established in 1990. VAERS accepts reports of adverse events after vaccination from vaccine manufacturers, healthcare providers, vaccine recipients, and others from United States of America (USA). VAERS generally cannot assess whether a vaccination caused an adverse event, but can identify possible vaccine safety problems for further investigation [10, 11].

MATERIALS AND METHODS

We searched and analyzed reports of adverse events of HPV2 and HPV4 vaccines which are submitted to theVaccine Adverse Event Reporting System (VAERS) by vaccine manufacturers, healthcare providers, vaccine recipients and others. For HPV2 vaccine, we searched for reports from October 2009 to December 2013. For HPV4 vaccine, we searched for reports from October 2006 to December 2013. Non-US reports were excluded. VAERS is a legally mandated, government-sponsored surveillance system. As a result,

there is no need of institutional review board approval and informed consent for this study. The numbers of adverse event reports in each of the states were calculated by year. For this study, we selected only HPV2 and HPV4 from VAERS database. The numbers of adverse event reports calculated in following age groups:1-10 yrs, 11-20 yrs, 21-30 yrs, 31-40 yrs, 41-50 yrs, 51-60 yrs, 61-70 yrs, 71-80 yrs, 81-90 yrs and 91-100 yrs. Incomplete reports were excluded from this analysis. Information we used from VAERS included demographics on the recipient (age, sex, etc,), type of vaccine, vaccination date, manufacturer, vaccine lot number, doses previously received, date of onset of symptoms and description of the event and deaths.

RESULTS

In U. S. states, within 2006-2013 period, total 24, 719 adverse events reported after taking both (HPV2 and HPV4) vaccines. Out of all U. S. states, 1245 adverse events were reported in CA. Maximum adverse events were recorded in the year 2008. The 12, 500 reported adverse events do not know have the source of information from which states events reported for both vaccines. During 2006-2013, for HPV4 vaccine total 24, 460 adverse events and 84 deaths reported. In CA state, within 2006-2013 periods for HPV4 vaccine1244 adverse events recorded. The 6100 adverse events recorded in the year 2008. There are 12, 427 adverse events that do not have a record of the State from which they have been reported. For HPV2 vaccine during 2009-2013 periods, total 259 adverse events and 3 deaths have been reported. In FR state, within 2009-2013 periods 146 adverse events recorded for HPV2 vaccine. Maximum number of adverse events was recorded in the year 2009 of these total 73 adverse events did not have the source of information from which states such events have been reported.

Table 1: It shows Vaccine Adverse Event Reporting System (VAERS) reported rates for HPV (HP2 and HPV4) vaccines in states United States, 2006-2013

States	Numbers								Total
	2006	2007	2008	2009	2010	2011	2012	2013	
AK	0	4	15	10	4	4	0	3	40
AL	0	23	25	19	15	13	0	7	102
AR	0	10	26	18	13	17	0	2	86
AZ	0	64	65	57	32	50	0	20	288
CA	1	272	334	239	157	168	0	74	1245
CO	0	60	70	59	24	28	0	8	249
CT	0	34	48	28	16	30	0	5	161
DC	0	9	9	16	5	8	0	4	51
DE	0	10	9	7	7	6	0	0	39
FL	0	105	154	108	49	89	0	58	563
FR	0	0	0	146	0	0	0	0	146
GA	0	88	96	77	36	46	0	11	354
GU	0	3	1	1	0	1	0	1	7
HI	0	11	9	13	8	11	0	3	55
IA	0	41	40	35	11	20	0	3	150
ID	0	15	22	18	5	20	0	7	87
IL	0	70	100	91	46	61	0	36	404
IN	0	52	59	63	30	25	0	12	241
KS	0	14	20	94	17	12	0	2	159
KY	0	36	37	41	16	33	0	7	170
LA	0	24	26	24	11	22	0	5	112
MA	0	79	97	74	34	51	0	23	358
MD	0	47	59	45	36	31	0	12	230
ME	0	23	26	14	8	19	0	5	95
MI	0	102	128	99	48	50	0	25	452
MN	0	71	70	63	28	40	0	11	283
MO	1	64	68	65	30	39	0	5	272
MS	0	14	15	13	9	12	0	4	67
MT	0	12	21	26	5	8	0	2	74
NC	0	78	125	108	45	59	0	21	436
States	**Numbers**								**Total**
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	
ND	0	16	13	6	2	8	0	4	49
NE	0	23	31	20	7	8	0	2	91
NH	0	14	20	18	13	10	0	11	86
NJ	0	56	83	60	36	37	0	22	294
NM	0	34	26	20	8	17	0	6	111
NV	0	22	15	23	10	11	0	5	86
NY	0	160	139	126	78	75	0	34	612
OH	0	110	146	78	51	66	0	22	473
OK	0	32	28	27	14	20	0	9	130
OR	0	31	59	46	14	24	0	15	189
PA	0	155	172	116	72	78	0	27	620
PR	0	6	7	8	7	2	0	3	33
RI	0	14	10	15	8	4	0	1	52
SC	0	27	33	27	14	15	0	13	129
SD	0	7	14	7	4	5	0	6	43
TN	0	44	60	55	24	25	0	12	220
TX	0	180	197	147	64	107	0	38	733
UT	0	16	25	26	5	22	0	7	101
VA	0	85	83	86	35	42	0	25	356
VI	0	4	3	2	1	1	0	0	11

VT	0	5	15	6	6	8	0	1	41
WA	0	89	81	80	34	57	0	23	364
WI	0	61	71	72	28	48	0	14	294
WV	0	22	23	24	5	15	0	6	95
WY	0	12	8	1	3	6	0	0	30
Unknown	426	3060	2964	637	1462	634	2530	787	12500
Total	428	5720	6100	3404	2750	2318	2530	1469	24719

In U. S. states, within 2006-2013 period, on the basis of gender total 24, 742 adverse events reported after taking HPV vaccines. Total 4352 adverse events were reported in male and 8682 adverse events were reported in female. For HPV4 vaccine during 2006-2013 period, total 24, 483 adverse events were reported. While 4334 adverse events were reported in male and 8509 adverse events reported in female. In the year 2008, 6100 adverse events have been recorded. Total 11, 640 adverse events reported for which information regarding gender was unknown. During 2009-2013 periods 259 adverse events were reported. Of these 18 adverse events reported in male and 173 adverse events were reported in female. In the year 2009, 146 adverse events recorded. Of which 68 adverse events had been reported whose information regarding gender was unknown.

Table 2: It shows vaccine Adverse Event reporting System (VAERS) reported rates on the basis of sex for HPV (HP2 and HPV4) vaccines in United States, 2006-2013

Sex	Numbers								Total
	2006	2007	2008	2009	2010	2011	2012	2013	
M	0	923	1105	915	524	612	0	273	4352
F	2	1935	2242	1966	883	1164	0	490	8682
Unknown	426	2862	2753	523	1366	542	2530	706	11708
Total	428	5720	6100	3404	2773	2318	2530	1469	24742

In U. S. Nation, for HPV4 vaccine during 2006-2013 periods, on the basis of month total 26, 439 adverse events were reported. In the month October, 2141 adverse events were recorded. Total 9739 adverse events were reported for which information regarding month was unknown. For HPV2 vaccine during 2009-2013 periods, on the basis of month total 249 adverse events were reported. In the month November, 76 adverse events recorded. Total 37 adverse events reported whose source of information regarding month was unknown.

Table 3: It shows vaccine adverse event reporting system (VAERS) reported rates on the basis of month for HPV (HP2 and HPV4) vaccines in United States, 2006-2013

Months	Numbers								Total
	2006	2007	2008	2009	2010	2011	2012	2013	
January	0	153	169	235	76	108	80	129	950
February	0	108	232	213	65	86	83	93	880
March	0	269	302	400	89	67	93	118	1338
April	0	140	203	214	134	105	94	108	998
May	0	298	367	561	120	109	77	134	1666
June	0	257	316	287	75	107	91	77	1210
July	0	393	496	391	108	177	102	33	1700
August	0	142	207	143	73	121	153	29	868
September	0	191	261	861	182	173	227	11	1906
October	0	417	349	726	184	173	296	37	2182
November	2	402	383	595	132	372	149	43	2078
December	0	176	168	338	158	171	102	23	1136
Unknown	426	2766	2617	457	1367	564	940	639	9776
Total	428	5712	6070	5421	2763	2333	2487	1474	26688

Table 4: It shows vaccine Adverse Event reporting System (VAERS) reported rates on the basis of age group for HPV (HP2 and HPV4) vaccines in United States, 2006-2013

Year	Numbers											Total
	Age groups											
	0 to 10	11 to 20	21 to 30	31 to 40	41 to 50	51 to 60	61 to 70	71 to 80	81 to 90	91 to 100	Unknown	
2006	1	0	0	0	0	1	0	0	0	0	426	428
2007	961	586	265	157	158	183	201	141	37	5	3026	5720
2008	1084	691	317	201	202	223	289	154	51	4	2884	6100
2009	865	624	301	236	211	203	217	86	30	2	614	3389
2010	429	184	152	111	120	121	149	80	35	5	1375	2761
2011	466	241	174	126	150	189	241	114	40	7	555	2303
2012	0	0	0	0	0	0	0	0	0	0	2493	2493
2013	223	113	49	60	50	86	117	30	10	0	724	1462
Total	4029	2439	1258	891	891	1006	1214	605	203	23	12097	24656

In U. S. states, within 2006-2013 period, maximum 4029 adverse event reported in the age group (0 to 10 years) after taking HPV vaccines. In US states, for HPV4 vaccine during 2006-2013 periods, on the basis of age group total 24, 483 adverse events were reported. The 4015 adverse events was recorded for the age group 0 to 10 yr. Total 12, 097 adverse events reported whose source of information regarding age group was unknown. For HPV2 vaccine during 2009-2013 periods, on the basis of age group total 173 adverse events were reported. The 122 adverse events recorded for the age group 11 to 20 yr. VAERS data must be interpreted cautiously. VAERS is a passive surveillance system with limitations that include both underreporting and biased reporting that can affect the outcome and analysis [8].

In U. S. states, within 2006-2013 period, 5218 adverse events reported after taking 1st dose of HPV vaccines. For HPV4 vaccine during 2006-2013 periods, based onthe vaccine doses total 24, 497 adverse events were reported. For HPV4 vaccine, after administration of 1st dose maximum 5168 of adverse events reported from 2006- 2013. For HPV2 vaccine during 2009-2013 periods, on the basis of vaccine dose total 259 adverse events were reported. Total 110 adverse events reported whose source of information regarding vaccine dose was unknown.

Table 5: It shows vaccine adverse event reporting system (VAERS) reported rates on the basis of dose administration for HPV (HP2 and HPV4) vaccines in United States, 2006-2013

Vaccine dose	Numbers								Total
	2006	2007	2008	2009	2010	2011	2012	2013	
0	205	2855	2799	1484	1275	1188	996	444	11246
1	27	1052	1326	790	572	452	614	385	5218
2	2	322	856	594	437	365	430	216	3222
3	0	6	39	32	27	11	21	10	146
4	0	1	3	1	1	0	0	0	6
5	0	1	5	2	0	1	0	0	9
6	0	0	0	0	1	0	0	0	1
7	0	0	2	0	0	0	0	0	2
8	0	0	0	0	0	1	0	0	1
20	0	0	1	0	0	0	0	0	1
Unknown	192	1483	1069	521	437	339	469	414	4924
Total	426	5720	6100	3424	2750	2357	2530	1469	24776

Within 2006-2013 period, intramuscular route of HPV vaccine administration reported maximum adverse events. For HPV4 vaccine during 2006-2013 periods in US, on the basis of HPV vaccination route total 24, 522 adverse events were reported. For HPV4 vaccine, adverse events reported after administration of HPV4 vaccine via proper route i. e. intramuscular is 13287. However, in reported 10665 adverse events the route of HPV4 vaccination is unknown. For HPV2 vaccine during 2009-2013 periods in US, on the basis of HPV vaccination route total 259 adverse events were reported. For HPV2 vaccine, adverse events reported after administration of HPV2 vaccine via proper route i. e. intramuscular is 157. However, in reported 89 adverse events the route of HPV4 vaccination is unknown.

Table 6: It shows vaccine Adverse Event reporting System (VAERS) reported rates on the basis of route of HPV vaccine administration for HPV (HP2 and HPV4) vaccines in United States, 2006-2013

Vaccine route	Numbers								Total
	2006	2007	2008	2009	2010	2011	2012	2013	
ID	0	9	10	11	2	0	1	1	34
IJ	0	30	16	37	111	91	0	0	285
IM	238	3062	3152	1860	1405	1342	1494	891	13444
IN	0	6	4	0	0	0	0	0	10
PO	1	2	3	1	0	0	0	0	7
SC	1	42	30	16	5	15	12	9	130
SYR	0	0	0	0	0	9	65	43	117
Unknown	188	2569	2885	1479	1250	900	958	525	10754
Total	428	5720	6100	3404	2773	2357	2530	1469	24781

In 2006-2013 period, 24, 775 adverse events were recorded by different sources in VAERS system after HPV vaccines administration. Out of reported total 24, 775 adverse events within 2006-2013 period, maximum adverse events reported after the administration HPV4 vaccine by unknown source are 11469. Others reported source are PVT- 5101, OTH- 4856 and PUB-2355. Out of reported total 259 adverse events within 2009-2013 period, maximum adverse events reported after the administration HPV2 vaccine by other source 184 followed by unknown- 40, PVT- 21 and PUB-11.

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Table 7: It shows vaccine adverse event reporting system (VAERS) reported rates on the basis of route of HPV vaccine administration for HPV (HP2 and HPV4) vaccines in United States, 2006-2013

Vaccine administered by	Numbers								Totals
	2006	2007	2008	2009	2010	2011	2012	2013	
MIL	0	118	172	199	75	72	74	34	744
PUB	1	433	472	499	282	322	240	117	2366
PVT	0	1199	1248	923	447	635	434	236	5122
OTH	0	963	1080	836	509	600	683	363	5034
Unknown	427	3007	3128	941	1460	728	1099	719	11509
Totals	428	5720	6100	3398	2773	2357	2530	1469	24775

In 2006-2013 period, the most frequently recorded adverse event recorded adverse events due to HPV vaccination were rash- 2319 followed by injection site erythema- 2260 and pyrexia-2155. The most frequently recorded adverse event for HPV4 vaccine within 2006-2013 period was rash- 2306 followed by injection site erythema- 2245 and pyrexia- 2142. The most common local adverse reactions reported due to HPV4 were injection site pain-1459, injection site swelling- 1638, injection site erythema- 2260, injection site pruritus- 405 and injection site bruising- 34. However, the most frequently recorded adverse event for HPV2 vaccine within 2009-2013 period is dizziness- 37 followed by headache- 34 and malaise- 19. The most common local adverse reactions reported due to HPV2 were injection site pain- 12 and injection site swelling- 10. The most common general adverse events were fatigue- 15, headache- 34, myalgia- 4 and arthralgia- 9. Most reports cannot prove whether vaccination caused the subsequent symptoms. Not all adverse events that occur after vaccination are reported and many reports describe events that may have been caused by confounding factors, including medications and diseases [11].

CONCLUSION

Vaccination with HPV2 and HPV4 has the great potential to decrease the global morbidity and mortality of HPV associated diseases, including cervical cancer. First time due to this study we are able to compare the HPV2 and HPV4 vaccine risk profile by using VAERS data. VAERS has been used as an important surveillance tool and demonstrated to be very helpful when assessing vaccine safety. Among all reports, frequencies of solicited adverse events after vaccination with HPV2 and HPV4 vaccine were higher than those reported in prior studies and those currently listed in the package insert. Therefore, the safety profile of both HPV vaccines needs to be considered in the context of the benefits of vaccination which includes the disease epidemiology and the vaccine effectiveness. In future ongoing HPV vaccines safety surveillance and further studies may shed light on some of the hypothesized associations.

CONFLICT OF INTERESTS

Declared None

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