Electronic Supplementary Material (ESM) 1

Safety of human papillomavirus vaccines: An updated review

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ESM 1A and 1B: Summary of select data on adverse events reported in HPV vaccine clinical trials in generally healthy subjects (i.e. those without known immunocompromising or auto-immune medical conditions) published from 10 May 2012 – 11 August 2016

1A: Studies comparing HPV vaccine with a placebo or control (non-HPV vaccine) group

<table>
<thead>
<tr>
<th>Reference (Sponsor)</th>
<th>Region</th>
<th>No. of participants by vaccine &amp; control (type)</th>
<th>Selected Adverse Events (AEs)</th>
<th>Frequency of AEs in vaccine recipients, % or number [95% confidence interval shown where available]</th>
<th>Frequency of AEs in control recipients, % or number [95% confidence interval shown where available]</th>
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<tbody>
<tr>
<td><strong>Studies with 2vHPV vaccine</strong></td>
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<tr>
<td>Angelo et al 2014[1] (GSK)</td>
<td>40 countries, 42 trials (pooled)</td>
<td>33 339 2vHPV 24 241 control (various)</td>
<td>Unsolicited AE MSC SAEs: full study, 30-day FU PIMD</td>
<td>30.8% [30.2-31.3] 9.6% [9.3-10.0] 7.9%, 0.5% 0.2%</td>
<td>29.7% [29.1-30.3] 10.4% [10.0-10.8] 9.3%, 0.6% 0.2%</td>
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<tr>
<td>Skinner et al 2014 [2] (GSK)</td>
<td>Multi: 12 countries</td>
<td>2881 2vHPV 2871 placebo (AlOH)</td>
<td>ISR Solicited general symptoms Unsolicited symptoms MSC SAE (vaccine-related) NOCD, NOAD</td>
<td>85% 65% 40% 41% 5% (&lt;1%, n=5)</td>
<td>67% 58% 41% 40% 6% (&lt;1%, n=8)</td>
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<tr>
<td>Hildesheim et al 2014 [3] (GSK)</td>
<td>Costa Rica</td>
<td>3727 2vHPV 3739 control (Hepatitis A vaccine)</td>
<td>Solicited local AE Solicited general AE Unsolicited AE SAE (vaccine-related) Death NOCD, NOAD Neurological condition</td>
<td>53.7% 90.5% 43.9% 24.5% (1.4%, n=53) 0.2% 10.3%, 0.6% 16.8%</td>
<td>19.9% 89.1% 41.1% 23.8% (1.0%, n=39) 0.2% 11.2%, 0.6% 15.8%</td>
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<tr>
<td>Sow et al 2013 [4] (GSK)</td>
<td>Senegal &amp; Tanzania</td>
<td>450 2vHPV 226 placebo (AlOH)</td>
<td>Local AE General AE Unsolicited AE MSC SAE (vaccine-related) NOCD, NOAD Death Neurological condition</td>
<td>59.7% [57.0–62.4] 35.1% 25.3% [23.0-27.8] 69.3 [64.8–73.6] 3.8 [2.2–6.0] (0) 2.4 [1.2–4.3], 0.4% [0.1–1.6] 0% [0.0-0.8]</td>
<td>43.1% [39.2–47.0] 35.1% 30.2% [26.6–33.9] 75.2 [69.1–80.7] 6.2 [3.4–10.2] (0) 4.9 [2.5–8.5], 0.9% [0.1–3.2] 0% [0.0-1.6]</td>
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<tr>
<td>Zhu et al 2014a [5] (GSK)</td>
<td>China</td>
<td>750 G 9-17 yrs; 1212 W 26-45 yrs 980 2vHPV 982 placebo (G: AlOH; W:</td>
<td>Grade 3 local symptoms Unsolicited symptoms MSC SAE (vaccine-related) NOAD</td>
<td>G: 5.2%; W: 3.0% G: 37.2% [32.3–42.3]; W: 5.3% [3.6–7.4] G: 3.7% [2.1–6.2]; W: 0.8% [0.3–1.9] G:1.3%[0.4–3.1];(0); W: 0.5%[0.1–1.4] G: 0% [0.0–1.0]; W: not reported</td>
<td>G: 2.0%; W: 0.3% G:33.2%[28.5–38.3];W: 5.9%[4.2–8.1] G: 2.9% [1.5–5.2]; W: 1.2% [0.5–2.4] G: 0.5%[0.1–1.9];(0); W:0.5%[0.1–1.4] G: 0.5% [0.1–1.9]; W: not reported</td>
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<tr>
<td>Reference (Sponsor)</td>
<td>Region</td>
<td>No. of participants by vaccine &amp; control (type)</td>
<td>Selected Adverse Events (AEs)</td>
<td>Frequency of AEs in vaccine recipients, % or number [95% confidence interval shown where available]</td>
<td>Frequency of AEs in control recipients, % or number [95% confidence interval shown where available]</td>
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<td>PIMD</td>
<td>G: Not reported; W: 0</td>
<td>G: Not reported; W: 0</td>
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<tr>
<td>Zhu et al 2014b [6]</td>
<td>China</td>
<td>3026 2vHPV 3025 placebo (AIOH)</td>
<td>IS pain, redness, swelling</td>
<td>62.6%, 14.5%, 14.4% 26.2% 1% (n=1) 5.2% 0.3%, 0.1%</td>
<td>42.5%, 7.6%, 5.8% 25.6% 1.8% (n=1) 5.2% 0.4%, 0.1%</td>
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<td>Unsolicited symptoms</td>
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<td>SAE (vaccine-related)</td>
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<td>MSC</td>
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<td>NOCD, NOAD</td>
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<td>Lim et al 2014 [7]</td>
<td>Malaysia</td>
<td>135 2vHPV 136 placebo (AIOH)</td>
<td>IS pain, redness, swelling</td>
<td>76.4%, 22.1%, 17.3% 22.2% 7.4% 5.2% 0.4%, 0.1%</td>
<td>49.4%, 14.1%, 6.9% 26.5% 8.1% 5.2% 0.4%, 0.1%</td>
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<td>Unsolicited AE</td>
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<td>SAE (vaccine-related)</td>
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<td>Szarewski et al 2012</td>
<td>14</td>
<td>9319 2vHPV 9325 control (hepatitis A vaccine)</td>
<td>HPV-DNA negative (SN/SP) ISR</td>
<td>SN (Seronegative) / SP (seropositive) 82.0% [81.0–82.9] / 78.0% [75.9–80.0] 80.8%, 29.2%, 26.2%/76.8%, 25.4%, 23.5% 66.7% [65.5–67.9] / 62.2% [59.8–64.5] 4.9% [4.3–5.4] / 6.4% [5.3–7.7]</td>
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<td>(GSK)</td>
<td>countries</td>
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<td>overall ISR</td>
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<td>IS pain, redness, swelling</td>
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<td>Systemic AE</td>
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<td>Fever</td>
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<td>HPV-DNA positive (SN/SP) ISR</td>
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<td>ISR</td>
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<td>IS pain, redness, swelling</td>
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<td>Systemic AE</td>
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<td>Fever</td>
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<td>Naud et al 2014 [11]</td>
<td>Brazil</td>
<td>219 2vHPV 213 placebo (AIOH)</td>
<td>SAE</td>
<td>8.9% [5.5–13.5] 26.5% [21.1–33.1] 2.7% [1.0–5.7], 1.8% [0.5–4.5]</td>
<td>5.2% [2.6–9.1] 17.8% [12.9–23.7] 1.4% [0.3–4.1], 0.5% [0.0–2.6]</td>
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<td>(GSK)</td>
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<td>NOCD, NOAD</td>
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<td>Roteli-Martins 2012</td>
<td>Brazil</td>
<td>223 2vHPV 213 placebo (AIOH)</td>
<td>SAE (vaccine-related)</td>
<td>4.5% [2.2–8.1] (0) 17.9% [13.1–23.6] 2.2% [0.7–5.2], n=2</td>
<td>3.3% [1.3–6.7] (0) 11.3% [7.4–16.3] 0.9% [0.1–3.4], n=2</td>
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<tr>
<td>2012 [12]</td>
<td>(GSK)</td>
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<td>MSC</td>
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<td>NOCD, NOAD</td>
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<td>Konno et al 2014 [13]</td>
<td>Japan</td>
<td>358 2vHPV 348 control (hepatitis A vaccine)</td>
<td>SAE (vaccine-related)</td>
<td>5.0% [3.3–7.3] (n=1) 18.9% [15.6–22.5] 1.2% [0.4–2.5], 0.6% [0.1–1.7] 0.2% [0.0–1.1]</td>
<td>6.5% [4.6–9.0] (n=0) 22.1% [18.6–25.9] 1.5% [0.7–3.0], 0.2% [0.0–1.1%] 0.0% [0.0–0.7]</td>
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<tr>
<td>(GSK)</td>
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<td>NOCD, NOAD</td>
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<td>Death</td>
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<td>Reference (Sponsor)</td>
<td>Region</td>
<td>No. of participants by vaccine &amp; control (type)</td>
<td>Selected Adverse Events (AEs)</td>
<td>Frequency of AEs in vaccine recipients, % or number [95% confidence interval shown where available]</td>
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<td><strong>Studies with 4vHPV</strong></td>
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<td>Mugo et al 2015 [14] (Merck)</td>
<td>Ghana, Kenya &amp; Senegal</td>
<td>227 4vHPV 19 placebo (Aluminium adjuvant); 9-12yrs</td>
<td>ISR: 9-12y, 13-16y, 16-26y Systemic AE:9-12y, 13-16y, 16-26y (vaccine related) SAE: 15-day follow-up</td>
<td>68.4%, 72.4%, 73.9% 48.1% (36.7%), 58.6% (51.7%), 61.3% (35.3%)</td>
<td>47.4% 57.9% (47.4%) 0%</td>
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<tr>
<td>Li et al 2012 [15] (Merck)</td>
<td>China</td>
<td>302 4vHPV 298 placebo (Aluminium adjuvant)</td>
<td>Any AE ISR, ISR pain, IS swelling Systemic AE(vaccine-related) SAE Allergic reaction</td>
<td>50.7% 21.9%, 20.2%<em>, 3.0%</em> 42.7% (28.8%) 0% 2.6%*</td>
<td>44.0% 13.4%, 13.1%<em>, 0.7%</em> 39.9% (27.5%) 0.3% 0.7%*</td>
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<tr>
<td>Clark et al 2013 [16] (Merck)</td>
<td>Europe, Americas</td>
<td>307 4vHPV 393 placebo (Aluminium adjuvant)</td>
<td>ISR Systemic AE (vaccine-related) SAE (vaccine-related)</td>
<td>49.0% 35.8% (23.8%) 1.7%</td>
<td>41.0% 29.1% (18.2%) 1.6%</td>
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<td><strong>Studies with 9vHPV</strong></td>
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<tr>
<td>Garland et al 2015 [17] (Merck)</td>
<td>8 countries</td>
<td>618 9vHPV 306 Placebo (saline) All received prior 4vHPV</td>
<td>ISR Systemic AE (vaccine-related) SAE (vaccine-related)</td>
<td>91.1% / 43.9% 59.7% (30.6%) 0.5% (n=1)</td>
<td>43.9% 55.7% (25.9%) 0.3% (n=1)</td>
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</table>
### 1B: Studies where all participants received HPV vaccine

<table>
<thead>
<tr>
<th>Reference (Sponsor)</th>
<th>Region</th>
<th>No. of participants by vaccine type (group)</th>
<th>Selected Adverse Events (AEs)*</th>
<th>Frequency of AEs in Group A recipients, % or number [95% confidence interval shown where available]</th>
<th>Frequency of AEs in Group B recipients % or number [95% confidence interval shown where available]</th>
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<tbody>
<tr>
<td><strong>Studies with 9vHPV vaccine used in all subjects (no placebo arms)</strong></td>
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<tr>
<td>Castellsague et al 2015 [18] (Merck)</td>
<td>17 countries</td>
<td>2520 9vHPV 1101 women (A) 1419 men (B)</td>
<td>ISR, Severe pain Systemic AE (vaccine-related) SAE (vaccine-related)</td>
<td>84.1% 1.9% 48.8% (23.4%) 2.4% (0)</td>
<td>67.2% 0.6% 37.1% (16.0%) 1.6% (0)</td>
</tr>
<tr>
<td>Van Damme et al 2015 [19] (Merck)</td>
<td>17 countries</td>
<td>2800 9vHPV 1800 girls 9-15y (A1) 600 boys 9-15y (A2) 400 women 16-26y (B)</td>
<td>ISR, Severe IS pain Systemic AE (vaccine-related) Fatigue Headache Fever SAE (vaccine-related) Death</td>
<td>A1: 81.9%, 4.1% A2: 72.8%, 0.5% A1:45.0%(20.8%)A2:41.8%(21.8%) A1: 1.0% A2: 0.5% A1: 9.5% A2: 9.1% A1: 6.7% A2: 8.6% A1: 0.9% (n=0) A2: 1.7% (n=1) A1: 0.1% A2: 0%</td>
<td>85.4%, 2.6% 57.1% (26.0%) 2.6% 9.9% 6.9% 3.2% (n=1) 0.2%</td>
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<tr>
<td>Kosalaraksa et al 2015 [20] (Merck)</td>
<td>6 countries</td>
<td>1054 9vHPV 525 concomitant(A) &amp; 528 non-concomitant Tdap-IPV (B)</td>
<td>ISR PD-1, 2, 3 PD-1 IS pain, erythema, swelling PD-any IS pain erythema, swelling Systemic AE PD-1, 2, 3 SAE (vaccine-related)</td>
<td>93.9%, 60.7%, 68.3% 59.2%, 8.2%, 13.0% 84.8%, 30.5%, 40.6% 48.6%, 19.2%, 21.5% 1.7% (0)</td>
<td>90.1%, 60.2%, 66.1% 60.5%, 5.7%, 8.2% 83.7%, 24.1%, 31.1% 48.6%, 18.0%, 19.8% 1.3% (0)</td>
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<tr>
<td>Schilling et al 2015 [21] (Merck)</td>
<td>5 countries</td>
<td>1241 9vHPV 621 concomitant(A) &amp; 620 non-concomitant MCV4 &amp; Tdap (B)</td>
<td>ISR PD-1, 2, 3 ISR PD-1 pain, erythema, swelling Systemic AE PD-1, 2, 3 SAE (vaccine-related)</td>
<td>80.9%, 46.7%, 52.1% 58.3%, 10.0%, 14.4% 43.1%, 16.1%, 14.8% 0.8% (0)</td>
<td>80.4%, 46.5%, 48.4% 55.0%, 8.9%, 9.4% 42.4%, 15.0%, 16.2% 0.8% (0)</td>
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<tr>
<td>Moreira et al 2016 [22] (Merck)</td>
<td>31 countries, Post-hoc pooled analysis (7 trials)</td>
<td>15,776 all 9vHPV (A) 12,583 female 9vHPV (B1) 3,193 male 9vHPV (B2)</td>
<td>ISR IS pain, swelling, erythema Systemic AE (vaccine-related)</td>
<td>84.8% 83.2%, 36.1%, 30.8% 51.9% (26.7%)</td>
<td>B1: 88.1%; B2: 71.6% B1: 86.9%, 39.1%, 32.9% B2: 68.3%, 24.4%, 22.4% B1:53.8%(27.8%); B2:44.2%(22.5%) B1:5.8%(n=734); B2:6.9%(n=221) B1: 0.3% (n=34); B2: &lt;0.1% (n=2) B1: 2.5% (n=6); B2: 1.4% (n=1) NR B1: 0.1 (n=7); B2: 0</td>
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<tr>
<td>Reference (Sponsor)</td>
<td>Region</td>
<td>No. of participants by vaccine type (group)</td>
<td>Selected Adverse Events (AEs)*</td>
<td>Frequency of AEs in Group A recipients, % or number [95% confidence interval shown where available]</td>
<td>Frequency of AEs in Group B recipients % or number [95% confidence interval shown where available]</td>
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<tr>
<td><strong>Studies comparing 9vHPV and 4vHPV</strong></td>
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</table>
| Joura et al 2015 [23] (Merck) | 18 countries | 7071 9vHPV (A) 7078 4vHPV (B) | ISR  
Severe IS Pain  
Systemic AE (vaccine-related)  
SAE (vaccine-related)  
Death | 90.7%  
4.3%  
55.8% (29.5%)  
3.3% (n=2, <1%)  
0.1% | 84.9%  
2.6%  
54.9% (27.3%)  
2.6% (n=2, <1%)  
0.1% |
| Vesikari et al 2015 [24] (Sanofi Pasteur/Merck) | 6 countries | 299 9vHPV (A) 300 4vHPV (B) | ISR  
IS swelling  
Systemic AE (vaccine-related), Fever  
SAE (vaccine-related) | 91.6%  
47.8%  
47.5% (20.7%), 5.0%  
0.3% (0) | 88.3%  
36.0%*  
52.0% (24.3%), 2.7%  
0.7% (0) |
| **Studies comparing 2vHPV and 4vHPV** |
| Einstein et al 2014a [25] (GSK) | USA | 205 2vHPV(A) 216 4vHPV (B) | SAE (vaccine-related)  
NOCD, NOAD  
MSC  
Spontaneous abortion | 6.7% [4.8–9.1] (n=1)  
6.0% [4.1–8.3], 1.3% [0.5–2.6]  
45.4% [41.2–49.6]  
13% | 6.1% [4.3–8.5] (n=1)  
6.0% [4.1–8.3], 2.2% [1.1–3.8]  
39.1% [35.0–43.3]  
15% |
| Einstein et al 2014b [26] (GSK) | USA | 159 2vHPV (A) 156 4vHPV (B) | SAE (vaccine-related)  
NOCD, NOAD  
MSC  
Spontaneous abortion (no anomaly) | 8.0% [5.8–10.5] (n=1)  
7.1% [5.1–9.5], 1.3% [0.5–2.6]  
46.8% [42.6–51.1]  
15.6% | 6.7% [4.8–9.1] (n=1)  
7.8% [5.7–10.3], 2.4% [1.3–4.0]  
40.9% [36.7–45.1]  
14.5% |
| Gilca et al 2015 [27] (Investigator) | Quebec, Canada | 366 randomised 1:1 2vHPV (A) or 4vHPV (B). All 2 prior doses 4vHPV | IS Pain (grade 3), swelling, redness  
Systemic AE  
SAE | 89.1%* (9%), 26.2%*, 28.4%  
58%  
0 | 72.1%* (2%)*, 17.5%*, 21.9%  
59%  
0 |
| Leung et al 2015 [28] (GSK) | 4 countries | 359 2vHPV 2 dose (A) 358 4vHPV 2 dose (B1) 358 4vHPV 3 dose (B2) | ISR  
IS pain, redness, swelling  
IS pain grade 3  
Solicited Systemic AE, Fever  
Unsolicited AE (grade 3)  
SAE (vaccine-related)  
MSC  
PIMD | 93%  
91.6%, 53.2%, 45.4%  
11.7% [8.6–15.5]  
74%, 14.8%  
25% (5%)  
3.6% (0)  
14%  
0.8% (n=3) | B1: 81%; B2: 86%  
B1: 77.3%, 37.5%, 27.5%;  
B2: 82.9%, 44.1%, 33.1%  
B1:4.8%[2.8–7.5];B2: 5%[3.0–7.9]  
B1: 75%, 16.5%; B2:74%, 13.2%  
B1: 27% (2%); B2: 28% (6%)  
B1: 0.6% (0); B2: 0.3% (0)  
B1: 16%; B2: 13%  
B1: 0.8% (n=3); B2: 0 |
<table>
<thead>
<tr>
<th>Reference (Sponsor)</th>
<th>Region</th>
<th>No. of participants by vaccine type (group)</th>
<th>Selected Adverse Events (AEs)*</th>
<th>Frequency of AEs in Group A recipients, % or number [95% confidence interval shown where available]</th>
<th>Frequency of AEs in Group B recipients % or number [95% confidence interval shown where available]</th>
</tr>
</thead>
</table>
| Nelson et al 2013 [29] (Investigator) | Hong Kong | Pilot: 10 males, 5 2vHPV (A), 5 4vHPV (B)  
Main study: 40 females, 19 2vHPV (A), 21 4vHPV (B) | Pilot (intradermal administration); ISR  
Main study (various doses/methods):  
IS Pain, Redness, Swelling, Tenderness  
Headache  
Tiredness  
Muscle ache  
Dizziness | n=5  
n=18*, 12, 11, 17*  
n=4  
n=4  
n=3  
n=2 | n=5  
n=11*, 11, 8, 10*  
n=2  
n=10  
n=5  
n=3 |
| Sangar et al 2015 [30] (Investigator) | India | 31 2vHPV (A)  
31 4vHPV (B) | Any AE post-dose 1, 2, 3, any IS pain  
Solicited symptom  
SAE | 51.6%*, 17.9%, 38.1%, 36.25%*  
80.6%  
28 of 80*  
0 | 19.4%*, 7.1%, 13.0%, 13.4%*  
29.0%  
11 of 82*  
0 |

### Studies with 2vHPV or 4vHPV and no control group

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Vaccine Type</th>
<th>No. of Participants</th>
<th>Selected Adverse Events (AEs)*</th>
<th>Frequency of AEs in Group A recipients, % or number [95% confidence interval shown where available]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luna et al 2013 [31] (Merck)</td>
<td>Columbia</td>
<td>1360 4vHPV</td>
<td>New onset medical condition</td>
<td>13%</td>
<td>No control group</td>
</tr>
</tbody>
</table>
SAE | N=11  
N=3 | |
| Giuliano et al 2015 [33] (Merck) | US, Mexico | 145 males 4vHPV | Total AEs (vaccine-related)  
Vaccine-related ISR  
Vaccine-related systemic  
Vaccine-related grade 3 AE | N=144 (107 in 63 men (42%))  
N=50  
N= 57  
N=1 | |
| Walter et al 2015 [34] (Investigator) | USA | 72 4vHPV (concomitantly with other vaccines) | IS Pain  
Higher pain score in HPV vaccine site | | |
| Levi et al 2013 [35] (Investigator) | Italy | 271 2vHPV | IS pain, IS swelling  
Medical attention post-dose 1 | 83.4%, 20.8%  
0.9% | |

**Footnotes for ESM 1A and 1B:** Abbreviations: AE – adverse event; AlOH – aluminum hydroxide; d – day; G – girls; GSK – GlaxoSmithKline; IS – injection site; ISR – injection site reaction; IPV – inactivated polio vaccine; MCV4 – quadrivalent meningococcal conjugate vaccine; MSC: medically significant conditions; NOAD – new onset autoimmune disease; NOCD – new onset chronic disease; PD – post-dose; PIMD – potential immune-mediated disease; SAE – serious adverse event; Tdap – tetanus, diphtheria, acellular pertussis vaccine; VLP – virus like particles; yo – year olds; SN – seronegative; SP – seropositive; NR – not reported; yrs – years; FU – follow-up; PD – post dose; W – women. *Significant at p<0.05

*aThe terms used regarding adverse events reflect those presented and defined within each individual study, thus are not necessarily consistent across this summary of data. In general, a solicited AE includes those for which information was specifically sought from the study participants. Unsolicited AEs were those that were spontaneously reported by the subject. Solicited local AEs typically included injection-site pain, erythema, swelling and/or redness. AE given as ‘vaccine-related’ are those determined by the study investigators. MSCs were conditions prompting emergency room or physician visits that were not related to common diseases or routine visits for physical examination or vaccination, or SAEs not related to common disease (which included upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury). SAEs were typically predefined as any AE that resulted in death, were deemed by the investigator to be life-threatening, resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing in-patient hospitalisation or was a congenital anomaly, a cancer or an "other important medical event". SAEs were typically followed for the entire duration of patient follow-up, unless otherwise specified in the table."
References


