

## **Den största effektstudien av ett vaccin mot livmoderhalscancer visade att *Cervarix*<sup>®</sup> skyddar mot fem av de vanligaste cancerframkallande virustyperna**

**Publicerat i *The Lancet*: Ytterligare effekt kan tolkas som cirka 11–16 procents extra skydd mot livmoderhalscancer**

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Den slutliga analysen av den största effektstudien av ett vaccin mot livmoderhalscancer publicerades idag i *The Lancet*. Studien, som omfattade 18 644 kvinnor, bekräftade att GlaxoSmithKlines *Cervarix*<sup>®</sup> är mycket effektivt när det gäller skydd mot de två vanligaste typerna av humant papillomvirus (HPV), 16 och 18, som ger upphov till livmoderhalscancer.<sup>1</sup> Studien visade också att vaccinet ger korskydd mot HPV typ 31, 33 och 45, de tre vanligaste cancerframkallande virustyperna förutom 16 och 18.<sup>1</sup>

Hillar Kangro, medicinsk rådgivare vid GlaxoSmithKline i Sverige sade i en kommentar: "Dessa utmärkta studieresultat bekräftar den effekt som *Cervarix*<sup>®</sup> ger mot HPV 16 och 18. För första gången visar resultaten att detta vaccin är effektivt mot de förstadium till cancer i livmoderhalsen som associeras med de fem vanligaste cancerframkallande virustyperna. Detta är verkligen goda nyheter för primär prevention av livmoderhalscancer, eftersom det visar att vaccinet kan ge kvinnor ytterligare skydd mot livmoderhalscancer utöver vad som först hade förväntats."

Studien visade att hos kvinnor som följde studieprotokollet (87 procent av det totala urvalet) gav vaccinet 92,9 procents skydd mot de förstadium till cancer i livmodern (cervikal intraepitelial neoplasia 2+ eller CIN 2+) som associeras med HPV 16 eller 18.<sup>1</sup> En ytterligare analys av samma kohort, vilken uteslöt lesioner som troligtvis inte orsakats av HPV 16 och 18, visade att vaccinet hade 98,1 procents effekt mot de förstadium till cancer i livmoderhalsen (CIN 2+) som orsakas av dessa två typer.<sup>1</sup>

Studien visade att *Cervarix*<sup>®</sup> ger ett betydande korskydd mot precancerösa lesioner som inte innehåller HPV typ 16 och/eller 18.<sup>1</sup> Denna ytterligare effekt motsvarar cirka 11–16 procents extra skydd mot livmoderhalscancer utöver det skydd som ges genom effekt mot HPV 16 och 18 enbart.<sup>1</sup> Denna effekt berodde huvudsakligen på skyddet mot HPV typ 31, 33 och 45.

Professor Jorma Paavonen från Helsingfors universitet i Finland – prövningsledare i studien och huvudförfattare till publikationen – kommenterade: "Resultaten visar att *Cervarix*<sup>®</sup> är mycket effektivt mot de virustyper som oftast ger upphov till cancer i livmoderhalsen och har potential att kraftigt

minska förekomsten av förstadier till cancer i livmoderhalsen, livmoderhalscancer och dithörande diagnostiska och kirurgiska åtgärder. Resultaten bekräftar än en gång att vaccinering som primär preventiv åtgärd mot livmoderhalscancer är tillförlitlig när den används tillsammans med screening.”

I studien var frekvensen av allvarliga biverkningar och medicinskt signifikanta förhållanden i den grupp som vaccinerats med *Cervarix*<sup>®</sup> jämförbar med den i kontrollgruppen.<sup>1</sup>

### ***För mer information***

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### ***About HPV 008 PATRICIA (PApilloma TRIal Cervical cancer In young Adults)***

- The Phase III multi-centre, double-blind, randomised study involved a total of 18,644 women, aged between 15 and 25 years, from 14 countries across Europe, Asia-Pacific and Latin and North America<sup>1</sup>
- Study participants were randomised to receive either *Cervarix*<sup>®</sup> or a control hepatitis A vaccine and analyses were performed in the following cohorts:<sup>1</sup>
  - According-to-protocol cohort for efficacy (ATP-E; vaccine=8093; control=8069)
  - Total vaccinated cohort (TVC; vaccine=9319, control=9325)
  - Total vaccinated cohort-naïve (TVC-naïve; vaccine=5822; control=5819)
- ATP-E included all women who met eligibility criteria, complied with the trial protocol and received all three doses of study vaccine<sup>1</sup>
- TVC included all women who received at least one vaccine dose. This group comprised a diverse population of women including those with evidence of current or previous HPV infection and with high grade smear test results. This was intended to represent general population of sexually active young women<sup>1</sup>
- TVC-naïve included all women who received at least one vaccine dose and who had no evidence of previous or current HPV infection, and was intended to represent young girls prior to the onset of sexual activity<sup>1</sup>
- Vaccine efficacy against CIN 2+ associated with HPV 31, 33 and 45 — HPV types not in the vaccine — was 92 percent (66.0,99.2; p<0.0001), 51.9 percent (-2.9, 78.9; p=0.0332) and 100 percent (-67.8, 100, p=0.0619) respectively in the ATP-E cohort.<sup>1</sup> Vaccine efficacy against CIN 2+ associated with HPV 31, 33 and 45 was 68.4 percent (34.2, 86.1; p=0.0005), 49.8 percent (4.8, 74.6; p=0.0239) and 100 percent (7.0, 100; p=0.0312) respectively in the TVC cohort<sup>1</sup>
- Vaccine efficacy against CIN 2+ lesions associated with 12 non-vaccine cancer-causing HPV types not in the vaccine was 54 percent (34.0, 68.4; p<0.0001) in the ATP-E cohort.<sup>1</sup> When

excluding all CIN 2+ lesions associated with non-vaccine types in which HPV 16 and 18 was also detected, vaccine efficacy was 37.4 percent (7.4, 58.2; p=0.0092) in the ATP-E cohort.<sup>1</sup> These two analyses suggest that the true vaccine efficacy against CIN 2+ associated with 12 non-vaccine cancer-causing HPV types lies between 37 percent and 54 percent<sup>1</sup>

- The vaccine also substantially reduced the number of colposcopy referral and cervical excision procedures in both the TVC and TVC-naïve cohorts<sup>1</sup>
- The efficacy and safety results from the interim analysis of the HPV 008 study were previously published in *The Lancet*.<sup>2</sup> The data reported today are from the final event driven analysis, also published in *The Lancet*. Further to the final analysis, additional follow-up results will be forthcoming from the end of study

### **About Cervarix<sup>®</sup>**

*Cervarix<sup>®</sup>* was specifically designed with a novel adjuvant, AS04, to deliver high and sustained levels of antibodies aimed at providing long-term protection against HPV 16 and 18, the most common cervical cancer-causing HPV types.<sup>3</sup> It has been shown to be generally well tolerated. The most common symptoms after vaccination included pain, redness and swelling at the injection site, fatigue, fever, aching, headache, itching, rash or gastrointestinal disturbances.<sup>4</sup>

To date, *Cervarix<sup>®</sup>* has been approved in 96 countries around the world, including the 27 member states of the European Union (EU), Australia, Brazil, South Korea, Mexico and Taiwan. Licensing applications have been submitted in more than 20 additional countries including Japan and the United States. *Cervarix<sup>®</sup>* was granted prequalification by the World Health Organization (WHO) in July 2009.

### **About HPV and cervical cancer**

Women are at risk of HPV infection throughout their sexually active lives.<sup>5</sup> Approximately 100 types of HPV have been identified to date<sup>6</sup> and, of these, approximately 15 virus types are known to cause cervical cancer.<sup>7</sup> HPV types 16 and 18 are responsible for approximately 70 percent of cervical cancers globally, with types 45, 31 and 33 among the next most common cervical cancer-causing HPV strains.<sup>8,9</sup> Persistent infection with cancer-causing HPV types can lead to abnormal Pap smears, cervical pre-cancer and cervical cancer. Cervical intraepithelial neoplasia (CIN), graded as CIN 1, 2 and 3 refers to pre-cancerous cells found on the surface of the cervix. The higher the grading number, the higher the probability the abnormal cells will become cancer cells.<sup>10</sup> CIN 1, 2 and 3 refers to mild, moderate or severe cell changes respectively. CIN 2+ is the surrogate marker for cervical cancer. Worldwide, more than 500,000 women will be newly diagnosed with cervical cancer and 280,000 women will die from it each year.<sup>11</sup>

HPV types 16, 18 and 45 are particularly important because these types are associated with nearly 90 percent of adenocarcinoma cases,<sup>8</sup> a very aggressive type of cervical cancer more common in younger women and more difficult to detect through screening.<sup>12,13</sup>

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*Cervarix*<sup>®</sup> is a registered trademark of the GlaxoSmithKline group of companies.

## References

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HPV 008 Corporate Press Release Reference Pack

PAGE	CLAIM	SUPPORTING REFERENCE	LOCATION OF CLAIM IN REFERENCE
1	The study, involving 18,644 women, confirmed GlaxoSmithKline's Cervarix® is highly effective at protecting against the two most common cervical cancer-causing human papillomavirus (HPV) types, 16 and 18.	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>The HPV-16/18 AS04-adjuvanted vaccine shows substantial efficacy against all HPV-16/18 endpoints evaluated, including CIN2+ and CIN3+.</i></p>	Page 17; paragraph 4; lines 3-4 (manuscript)
1	The study also showed that the vaccine provides significant protection against HPV types 31, 33 and 45, the three most common cancer-causing virus types beyond 16 and 18.	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>Statistically significant vaccine efficacy against HPV-31 was observed for 6-month persistent infection, 12-month persistent infection and CIN2+ in all three cohorts (ATP-E, TVC-E and TVC). For HPV-45, cross-protection was seen for 6-month and 12-month persistent infection in all three cohorts. No CIN2+ cases with HPV-45 DNA in the lesion were seen in the vaccine group; however, because only four cases were observed in the control group, vaccine efficacy did not reach statistical significance in the ATP-E cohort. In the broader TVC, additional cases of CIN2+ associated with HPV-45 were observed in the control group; vaccine efficacy was 100% (7.0, 100; p=0.0312). Vaccine efficacy was also seen against HPV-33 for 6-month persistent infection (all three cohorts), 12-month persistent infection (TVC-E and TVC) and CIN2+ (TVC-E and TVC).</i></p> <p><i>In addition, cross protection was demonstrated against 12 non-vaccine oncogenic HPV types combined as well as against several individual non-vaccine types, including types 31, 33 and 45. Together with HPV-16 and 18, HPV-31, -33 and -45 are the five most frequent types, responsible for approximately 82% of all cervical cancers</i></p>	<p>Page 10-11; paragraph 6; lines 1-11 (manuscript)</p> <p>Page 17; paragraph 4; lines 5-8 (manuscript)</p>
1	The study showed that in women who complied with the trial protocol procedures (43% of the total sample), the vaccine provided 92.9 percent protection against cervical pre-cancers (cervical intraepithelial neoplasia 2+ or CIN 2+) associated with HPV 16 or 18.	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>Vaccine efficacy (VE) against cervical intraepithelial neoplasia (CIN)2+ associated with HPV 16/18 was 92.9% (96.1% CI: 79.9; 98.3) in the primary analysis</i></p>	Abstract; page 3; paragraph 3 'findings'; lines 2-3

<p>1</p>	<p>A further analysis of the same cohort which excluded lesions not likely to be caused by HPV 16 and 18 revealed that the vaccine was 98.1 percent effective against cervical pre-cancers (CIN 2+) caused by these two types.</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>In the analysis evaluating the HPV types most likely to be the cause of the lesion (HPV type assignment algorithm), vaccine efficacy was 98.1% (88.4, 100; p&lt;0.0001) against HPV-16/18</i></p>	<p><b>Page 10; paragraph 1; lines 1-3 (manuscript)</b></p>
<p>2</p>	<p>The study showed — for the first time for any cervical cancer vaccine — that <i>Cervarix</i><sup>®</sup> provided significant cross-protection against pre-cancerous lesions not containing HPV types 16 and/or 18.</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>To address the complexity of co-infection with multiple HPV types, we conducted a conservative post hoc analysis which excluded all CIN2+ lesions associated with non-vaccine types in which HPV-16/18 was also detected. Vaccine efficacy was 37.4% (7.4, 58.2) against non-vaccine types, with 48 versus 77 CIN2+ lesions in the vaccine versus control groups, respectively.</i></p>	<p><b>Page 15; paragraph 3; Lines 5-9</b></p>
<p>2</p>	<p>This additional efficacy could translate into approximately 11-16 percent extra protection against cervical cancer over and above the protection afforded by efficacy against HPV 16 and 18 alone.</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>'Thus, our analyses suggest that cross-protective efficacy of the vaccine could translate into approximately 11-16% additional protection against cervical cancer over and above protection afforded by efficacy against HPV-16/18.'</i></p>	<p><b>Page 16; paragraph 1; lines 1-2 (manuscript)</b></p>
<p>2</p>	<p>In the study, rates of serious adverse events and medically significant conditions in the group vaccinated with <i>Cervarix</i><sup>®</sup> were similar to the control group.</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>The proportion of women with SAEs was similar in the HPV 16/18 vaccine and control groups . . . The proportion of women with medically significant conditions, new onset chronic diseases and new onset autoimmune diseases was similar in the HPV 16/18 vaccine and control groups</i></p>	<p><b>Page 12; paragraph 2; lines 1, 7-9 (manuscript)</b></p>
<p>2</p>	<p>The Phase III multi-centre, double-blind, randomised study involved a total of 18,644 women, aged between 15 and 25 years, from 14 countries across Europe, Asia-Pacific and Latin and North America</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>The PApilloma TRIal against Cancer In young Adults (PATRICIA) is a large, phase III, randomised, double-blind, controlled trial</i></p> <p><i>A total of 18,644 women were included in the TVC.</i></p> <p><i>Healthy women aged 15 to 25 years at the time of first vaccination were enrolled in the trial between May 2004 and June 2005, at 135 centres in 14 countries in Asia Pacific, Europe, Latin America, and North America.</i></p>	<p><b>Page 5; Methods; line 1-2</b></p> <p><b>Page 9; Results; paragraph 1; line 1 (manuscript)</b></p> <p><b>Page 5; Participants; line 1-3</b></p>

<p>2</p>	<p>Study participants were randomised to receive either <i>Cervarix</i><sup>®</sup> or a control hepatitis A vaccine and analyses were performed in the following cohorts:<sup>1</sup></p> <ul style="list-style-type: none"> <li>• According-to-protocol cohort for efficacy (ATP-E; vaccine=8093; control=8069)</li> <li>• Total vaccinated cohort (TVC; vaccine=9319, control=9325)</li> <li>• Total vaccinated cohort-naïve (TVC-naïve; vaccine=5822; control=5819)</li> </ul>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>Participants were randomised (1:1) to receive either the HPV-16/18 AS04-adjuvanted vaccine (Cervarix<sup>™</sup>, GlaxoSmithKline Biologicals, Rixensart, Belgium) or a control hepatitis A vaccine (GlaxoSmithKline Biologicals, Rixensart, Belgium) in a 0, 1, 6 month schedule</i></p> <p><i>Analyses were performed in the according-to-protocol cohort for efficacy (ATP-E; vaccine=8093; control=8069), total vaccinated cohort (TVC; vaccine=9319, control=9325) and TVC-naïve (vaccine=5822; control=5819).</i></p>	<p><b>Page 5; Procedures; line 1-4</b></p> <p><b>Page; abstract; methods</b></p>
<p>2</p>	<p>ATP-E included all women who met eligibility criteria, complied with the trial protocol and received all three doses of study vaccine</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>(ATP-E) included all evaluable women (i.e. those meeting all eligibility criteria, complying with the protocol procedures, with no protocol violations) who received three vaccine doses, had normal or low-grade cytology at baseline, and were evaluable for efficacy.</i></p>	<p><b>Page 6; statistical analysis; line 9 - 12</b></p>
<p>2</p>	<p>TVC included all women who received at least one vaccine dose. This group comprised a diverse population of women including those with evidence of current or previous HPV infection and with high grade smear test results. This was intended to represent general population of sexually active young women</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>The total vaccinated cohort (TVC) included all women who received at least one vaccine dose and were evaluable for efficacy (i.e. had a baseline PCR or cytology sample and one further sample available) regardless of other criteria, and was intended to represent a general population of sexually active young women.</i></p>	<p><b>Page 6; statistical analysis; line 1- 6</b></p>
<p>2</p>	<p>TVC-naïve included all women who received at least one vaccine dose and who had no evidence of previous or current HPV infection, and was intended to represent young girls prior to the onset of sexual activity</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>The total vaccinated naïve cohort (TVC-naïve) included women who received at least one vaccine dose, were evaluable for efficacy, and at baseline had normal cytology, were DNA negative for all 14 oncogenic HPV types evaluated, and were seronegative for HPV-16 and -18</i></p>	<p><b>Page 6; statistical analysis; line 13-17</b></p>

<p>2</p>	<p>Vaccine efficacy against CIN 2+ for HPV types not in the vaccine (HPV 31, 33 and 45) was 92%, 51.9% and 100% respectively in the ATP-E cohort</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <p><i>Table 3:</i></p> <table border="1"> <thead> <tr> <th colspan="6">CIN2+</th> </tr> </thead> <tbody> <tr> <td rowspan="2">HPV-31</td> <td>Vaccine</td> <td>7583</td> <td>2</td> <td rowspan="2">92.0 (86.0, 99.2)</td> <td rowspan="2">&lt;0.0001</td> </tr> <tr> <td>Control</td> <td>7599</td> <td>25</td> </tr> <tr> <td rowspan="2">HPV-33</td> <td>Vaccine</td> <td>7720</td> <td>12</td> <td rowspan="2">51.9 (-2.9, 78.9)</td> <td rowspan="2">0.0332</td> </tr> <tr> <td>Control</td> <td>7708</td> <td>25</td> </tr> <tr> <td rowspan="2">HPV-45<sup>†</sup></td> <td>Vaccine</td> <td>7782</td> <td>0</td> <td rowspan="2">100 (-67.8, 100)</td> <td rowspan="2">0.0619</td> </tr> <tr> <td>Control</td> <td>7745</td> <td>4</td> </tr> <tr> <td rowspan="2">HPV-52</td> <td>Vaccine</td> <td>7461</td> <td>12</td> <td rowspan="2">14.3 (-108.1, 65.4)</td> <td rowspan="2">0.7000</td> </tr> <tr> <td>Control</td> <td>7414</td> <td>14</td> </tr> <tr> <td rowspan="2">HPV-58</td> <td>Vaccine</td> <td>7709</td> <td>8</td> <td rowspan="2">64.5 (1.5, 89.2)</td> <td rowspan="2">0.0225</td> </tr> <tr> <td>Control</td> <td>7702</td> <td>17</td> </tr> <tr> <td rowspan="2">HPV-31/33/45/52/58</td> <td>Vaccine</td> <td>7862</td> <td>30</td> <td rowspan="2">53.0 (24.7, 71.3)</td> <td rowspan="2">0.0004</td> </tr> <tr> <td>Control</td> <td>7853</td> <td>64</td> </tr> <tr> <td rowspan="2">Any oncogenic type except HPV-16/18 (with or without HPV-16/18 co-infection)<sup>†</sup></td> <td>Vaccine</td> <td>7863</td> <td>50</td> <td rowspan="2">54.0 (34.0, 68.4)</td> <td rowspan="2">&lt;0.0001</td> </tr> <tr> <td>Control</td> <td>7853</td> <td>109</td> </tr> <tr> <td rowspan="2">Any oncogenic type</td> <td>Vaccine</td> <td>7863</td> <td>54</td> <td rowspan="2">61.9 (46.7, 73.2)</td> <td rowspan="2">&lt;0.0001</td> </tr> <tr> <td>Control</td> <td>7853</td> <td>142</td> </tr> </tbody> </table>	CIN2+						HPV-31	Vaccine	7583	2	92.0 (86.0, 99.2)	<0.0001	Control	7599	25	HPV-33	Vaccine	7720	12	51.9 (-2.9, 78.9)	0.0332	Control	7708	25	HPV-45 <sup>†</sup>	Vaccine	7782	0	100 (-67.8, 100)	0.0619	Control	7745	4	HPV-52	Vaccine	7461	12	14.3 (-108.1, 65.4)	0.7000	Control	7414	14	HPV-58	Vaccine	7709	8	64.5 (1.5, 89.2)	0.0225	Control	7702	17	HPV-31/33/45/52/58	Vaccine	7862	30	53.0 (24.7, 71.3)	0.0004	Control	7853	64	Any oncogenic type except HPV-16/18 (with or without HPV-16/18 co-infection) <sup>†</sup>	Vaccine	7863	50	54.0 (34.0, 68.4)	<0.0001	Control	7853	109	Any oncogenic type	Vaccine	7863	54	61.9 (46.7, 73.2)	<0.0001	Control	7853	142	<p>Page 31; table 3</p>
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<p><b>3</b></p>	<p>These two analyses suggest that the true vaccine efficacy against CIN2+ associated with non-vaccine HPV types lies between 37 percent and 54 percent</p>	<p>Paavonen J et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). 2009. Published online, <i>The Lancet</i> July 7 2009.</p> <table border="1" data-bbox="483 342 1286 698"> <thead> <tr> <th colspan="6">CIN2+</th> </tr> </thead> <tbody> <tr> <td rowspan="2">HPV-31</td> <td>Vaccine</td> <td>7583</td> <td>2</td> <td rowspan="2">92.0 (86.0, 99.2)</td> <td rowspan="2">&lt;0.0001</td> </tr> <tr> <td>Control</td> <td>7599</td> <td>25</td> </tr> <tr> <td rowspan="2">HPV-33</td> <td>Vaccine</td> <td>7720</td> <td>12</td> <td rowspan="2">51.9 (-2.9, 78.9)</td> <td rowspan="2">0.0332</td> </tr> <tr> <td>Control</td> <td>7708</td> <td>25</td> </tr> <tr> <td rowspan="2">HPV-45<sup>2</sup></td> <td>Vaccine</td> <td>7782</td> <td>0</td> <td rowspan="2">100 (-67.8, 100)</td> <td rowspan="2">0.0619</td> </tr> <tr> <td>Control</td> <td>7745</td> <td>4</td> </tr> <tr> <td rowspan="2">HPV-62</td> <td>Vaccine</td> <td>7461</td> <td>12</td> <td rowspan="2">14.3 (-108.1, 65.4)</td> <td rowspan="2">0.7000</td> </tr> <tr> <td>Control</td> <td>7414</td> <td>14</td> </tr> <tr> <td rowspan="2">HPV-58</td> <td>Vaccine</td> <td>7709</td> <td>8</td> <td rowspan="2">64.5 (1.5, 89.2)</td> <td rowspan="2">0.0225</td> </tr> <tr> <td>Control</td> <td>7702</td> <td>17</td> </tr> <tr> <td rowspan="2">HPV-31/33/45/62/58</td> <td>Vaccine</td> <td>7862</td> <td>30</td> <td rowspan="2">53.0 (24.7, 71.3)</td> <td rowspan="2">0.0004</td> </tr> <tr> <td>Control</td> <td>7853</td> <td>64</td> </tr> <tr> <td rowspan="2">Any oncogenic type except HPV-18/18 (with or without HPV-18/18 co-infection)<sup>1</sup></td> <td>Vaccine</td> <td>7863</td> <td>50</td> <td rowspan="2">54.0 (34.0, 68.4)</td> <td rowspan="2">&lt;0.0001</td> </tr> <tr> <td>Control</td> <td>7853</td> <td>109</td> </tr> <tr> <td rowspan="2">Any oncogenic type</td> <td>Vaccine</td> <td>7863</td> <td>54</td> <td rowspan="2">61.9 (46.7, 73.2)</td> <td rowspan="2">&lt;0.0001</td> </tr> <tr> <td>Control</td> <td>7853</td> <td>142</td> </tr> </tbody> </table> <p><i>To address the complexity of co-infection with multiple HPV types, we conducted a conservative post hoc analysis which excluded all CIN2+ lesions associated with non-vaccine types in which HPV-16/18 was also detected. Vaccine efficacy was 37.4% (7.4, 58.2) against non-vaccine types, with 48 versus 77 CIN2+ lesions in the vaccine versus control groups, respectively.</i></p>	CIN2+						HPV-31	Vaccine	7583	2	92.0 (86.0, 99.2)	<0.0001	Control	7599	25	HPV-33	Vaccine	7720	12	51.9 (-2.9, 78.9)	0.0332	Control	7708	25	HPV-45 <sup>2</sup>	Vaccine	7782	0	100 (-67.8, 100)	0.0619	Control	7745	4	HPV-62	Vaccine	7461	12	14.3 (-108.1, 65.4)	0.7000	Control	7414	14	HPV-58	Vaccine	7709	8	64.5 (1.5, 89.2)	0.0225	Control	7702	17	HPV-31/33/45/62/58	Vaccine	7862	30	53.0 (24.7, 71.3)	0.0004	Control	7853	64	Any oncogenic type except HPV-18/18 (with or without HPV-18/18 co-infection) <sup>1</sup>	Vaccine	7863	50	54.0 (34.0, 68.4)	<0.0001	Control	7853	109	Any oncogenic type	Vaccine	7863	54	61.9 (46.7, 73.2)	<0.0001	Control	7853	142	<p><b>Page 31; table 3</b></p> <p><b>Page 15; paragraph 3; Lines 5-9</b></p>																																																																																										
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Vaccine efficacy against CIN2+, CIN3+, colposcopy referrals and cervical excision procedures associated with HPV-16/18, five non-vaccine oncogenic types and irrespective of HPV DNA in lesion</p> <table border="1" data-bbox="491 1173 1281 1890"> <thead> <tr> <th>Endpoint</th> <th>Group</th> <th>N</th> <th>n</th> <th>Vaccine efficacy, % (96.1% CI)</th> <th>P</th> </tr> </thead> <tbody> <tr> <td colspan="6"><b>TVC</b></td> </tr> <tr> <td colspan="6"><b>CIN2+</b></td> </tr> <tr> <td rowspan="2">HPV-16/18 DNA in lesion</td> <td>Vaccine</td> <td>8667</td> <td>82</td> <td rowspan="2">52.8 (37.5, 64.7)</td> <td rowspan="2">&lt;0.0001</td> </tr> <tr> <td>Control</td> <td>8682</td> <td>174</td> </tr> <tr> <td rowspan="2">HPV-31/33/45/52/58</td> <td>Vaccine</td> <td>8667</td> <td>95</td> <td rowspan="2">31.5 (9.1, 48.5)</td> <td rowspan="2">0.0046</td> </tr> <tr> <td>Control</td> <td>8682</td> <td>139</td> </tr> <tr> <td rowspan="2">Irrespective of HPV DNA in lesion</td> <td>Vaccine</td> 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<p>3</p>	<p>Cervarix<sup>®</sup> was specifically designed with a novel adjuvant, AS04, to deliver high and sustained levels of antibodies aimed at providing long-term protection against HPV 16 and 18, the most common cervical cancer-causing HPV types</p>	<p>Aguilar JC. Vaccine adjuvants revisited. <i>Vaccine</i> 2007; 25: 3752-3762</p> <p><i>“...This vaccine develops more rapid, intense and long lasting immune response compared with control vaccine in these high-risk groups, showing safety and clinically acceptable local reactions similar to other licensed hepatitis B vaccines. The AS04 adjuvant formulation has been tested as part of a promising HPV vaccine development.”</i></p>	<p>Page 3757; paragraph 4; lines 5-11</p>																																																																																																																																																																																																																							
<p>3</p>	<p>It has been shown to be generally well tolerated. The most common symptoms after vaccination included pain, redness and swelling at the injection site, fatigue, fever, aching, headache, itching, rash or gastrointestinal disturbances.</p>	<p>Descamps D, Hardt K, Spiessens B et al. Safety of human papillomavirus (HPV)-16/18 AS04 adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. <i>Human Vaccine</i>, 2009; 55: 1-9.</p> <p><i>“In conclusion, analysis of this large database shows the HPV-16/18 ASO4-adjuvanted cervical cancer vaccine to have favourable safety profile in women of all ages.”</i></p> <p>Table 2 Incidence (% [95% CI]) of solicited general symptoms (overall/dose) reported during the 7-day period after each vaccine dose (total vaccinated cohort)</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2">10-14 years</th> <th colspan="2">15-25 years</th> <th colspan="2">&gt;25 years</th> </tr> <tr> <th></th> <th>HPV-16/18 vaccine</th> <th>HAV360</th> <th>HPV-16/18 vaccine</th> <th>HAV720</th> <th>All(OH)<sub>3</sub></th> <th>HPV-16/18 vaccine</th> <th>All(OH)<sub>3</sub></th> </tr> </thead> <tbody> <tr> <td>No. of doses</td> <td>3,529</td> <td>3,058</td> <td>15,015</td> <td>8,748</td> <td>1,565</td> <td>4,258</td> <td>2,916</td> </tr> <tr> <td>Fatigue</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>  Any</td> <td>29.2 [27.7, 30.7]</td> <td>24.6 [23.1, 26.2]</td> <td>37.0 [36.2, 37.7]</td> <td>35.3 [34.3, 36.3]</td> <td>31.7 [29.4, 34.1]</td> <td>22.6 [21.4, 23.9]</td> <td>18.0 [16.6, 19.4]</td> </tr> <tr> <td>  Grade 3</td> <td>1.6 [1.2, 2.0]</td> <td>1.1 [0.8, 1.6]</td> <td>1.7 [1.5, 1.9]</td> <td>1.3 [1.1, 1.6]</td> <td>2.0 [1.4, 2.9]</td> <td>0.8 [0.5, 1.1]</td> <td>0.8 [0.5, 1.1]</td> </tr> <tr> <td>Fever</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>  Any</td> <td>7.3 [6.4, 8.2]</td> <td>6.8 [5.9, 7.8]</td> <td>4.8 [4.5, 5.2]</td> <td>4.6 [4.1, 5.0]</td> <td>5.5 [4.4, 6.7]</td> <td>4.5 [3.9, 5.2]</td> <td>5.1 [4.3, 6.0]</td> </tr> <tr> <td>  Grade 3</td> <td>0.7 [0.4, 1.0]</td> <td>0.6 [0.3, 0.9]</td> <td>0.1 [0.1, 0.2]</td> <td>0.1 [0.1, 0.2]</td> <td>0.4 [0.2, 0.9]</td> <td>0.2 [0.1, 0.3]</td> <td>0.1 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</table>		10-14 years		15-25 years		>25 years			HPV-16/18 vaccine	HAV360	HPV-16/18 vaccine	HAV720	All(OH) <sub>3</sub>	HPV-16/18 vaccine	All(OH) <sub>3</sub>	No. of doses	3,529	3,058	15,015	8,748	1,565	4,258	2,916	Fatigue								Any	29.2 [27.7, 30.7]	24.6 [23.1, 26.2]	37.0 [36.2, 37.7]	35.3 [34.3, 36.3]	31.7 [29.4, 34.1]	22.6 [21.4, 23.9]	18.0 [16.6, 19.4]	Grade 3	1.6 [1.2, 2.0]	1.1 [0.8, 1.6]	1.7 [1.5, 1.9]	1.3 [1.1, 1.6]	2.0 [1.4, 2.9]	0.8 [0.5, 1.1]	0.8 [0.5, 1.1]	Fever								Any	7.3 [6.4, 8.2]	6.8 [5.9, 7.8]	4.8 [4.5, 5.2]	4.6 [4.1, 5.0]	5.5 [4.4, 6.7]	4.5 [3.9, 5.2]	5.1 [4.3, 6.0]	Grade 3	0.7 [0.4, 1.0]	0.6 [0.3, 0.9]	0.1 [0.1, 0.2]	0.1 [0.1, 0.2]	0.4 [0.2, 0.9]	0.2 [0.1, 0.3]	0.1 [0.0, 0.3]	Gastrointestinal								Any	12.4 [11.3, 13.5]	11.3 [10.2, 12.5]	14.3 [13.8, 14.9]	14.0 [13.2, 14.7]	15.9 [14.1, 17.8]	8.4 [7.6, 9.3]	9.4 [8.3, 10.5]	Grade 3	1.1 [0.8, 1.5]	0.8 [0.5, 1.1]	0.7 [0.6, 0.8]	0.7 [0.5, 0.9]	0.5 [0.2, 1.0]	0.4 [0.2, 0.6]	0.9 [0.6, 1.3]	Headache								Any	28.8 [27.3, 30.3]	25.4 [23.9, 27.0]	31.9 [31.2, 32.7]	30.8 [29.8, 31.8]	36.5 [34.1, 38.9]	21.6 [20.4, 22.8]	20.2 [18.8, 21.7]	Grade 3	2.5 [2.0, 3.0]	1.6 [1.2, 2.1]	1.6 [1.4, 1.9]	1.4 [1.1, 1.6]	2.1 [1.5, 2.9]	0.9 [0.6, 1.2]	0.7 [0.4, 1.1]	Rash								Any	4.6 [3.9, 5.3]	2.6 [2.1, 3.2]	4.1 [3.8, 4.4]	3.6 [3.2, 4.0]	4.2 [3.3, 5.3]	2.3 [1.9, 2.8]	1.9 [1.4, 2.4]	Grade 3	0.3 [0.2, 0.6]	0.1 [0.0, 0.3]	0.1 [0.0, 0.1]	0.1 [0.0, 0.1]	0.0 [0.0, 0.2]	0.0 [0.0, 0.1]	0.1 [0.0, 0.2]	Arthralgia*								Any	11.7 [10.7, 12.8]	9.3 [8.3, 10.3]	10.1 [9.6, 10.6]**	8.6 [8.0, 9.2]	-	9.3 [8.4, 10.2]	7.6 [6.7, 8.6]	Grade 3	0.7 [0.4, 1.0]	0.2 [0.1, 0.4]	0.3 [0.2, 0.4]**	0.3 [0.2, 0.4]	-	0.3 [0.2, 0.6]	0.2 [0.1, 0.4]	Myalgia*								Any	29.2 [27.7, 30.7]	17.1 [15.8, 18.5]	31.5 [30.7, 32.3]**	26.5 [25.6, 27.5]	-	16.7 [15.6, 17.9]	9.9 [8.9, 11.1]	Grade 3	2.0 [1.5, 2.5]	0.5 [0.3, 0.8]	1.5 [1.3, 1.8]**	0.6 [0.4, 0.8]	-	0.6 [0.4, 0.8]	0.2 [0.1, 0.5]	Urticaria*								Any	2.5 [2.0, 3.0]	2.1 [1.6, 2.7]	3.6 [3.3, 3.9]**	3.7 [3.3, 4.1]	-	2.1 [1.7, 2.6]	2.6 [2.1, 3.3]	Grade 3	0.3 [0.1, 0.5]	0.2 [0.1, 0.4]	0.2 [0.2, 0.3]**	0.4 [0.2, 0.5]	-	0.2 [0.1, 0.4]	0.3 [0.1, 0.6]	<p>Page 1; column 1; paragraph 1; lines 19-27</p> <p>Page 3 ; Table 2</p>
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<p>3</p>	<p>Women are at risk of HPV infection throughout their sexually active lives</p>	<p>Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections <i>J Clin Virol</i> 2005; 32 Suppl 1; S16-24</p> <p><i>Acquisition of HPV is very common, particularly among sexually active young adults</i></p> <p><i>The prevalence of HPV infection is highest among young women and appears to drop off with increasing age</i></p>	<p>Page 18; section 3, line 1</p> <p>Page 2; section 2.1, lines 1-2</p>																																																																																																																																																																																																																							
<p>3</p>	<p>Approximately 100 types of human papillomavirus have been identified to date</p>	<p>WHO. Expert Committee on Biological Standardization. Guidelines to assure the quality, safety and efficacy of recombinant Human Papillomavirus virus-like particle vaccines, accessed on 27/3/2009 at <a href="http://screening.iarc.fr/doc/WHO_vaccine_guidelines_2006.pdf">http://screening.iarc.fr/doc/WHO_vaccine_guidelines_2006.pdf</a></p> <p><i>Over 100 different types of HPV have been identified and molecularly characterized.</i></p>	<p>Page 3; paragraph 4; lines 1-2</p>																																																																																																																																																																																																																							
<p>3</p>	<p>... of these, approximately 15 virus types are known to cause cervical cancer</p>	<p>Muñoz N et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. <i>N Engl J Med</i> 2003; 348: 518-527</p> <p><i>‘Our epidemiologic classification, based on HPV-type-specific odds ratios and HPV prevalence among patients and controls, identified 15 HPV types as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82).’</i></p>	<p>Page 524; column 2; paragraph 4; lines 1-5</p>																																																																																																																																																																																																																							



<p>3</p>	<p>Cervical intraepithelial neoplasia (CIN), graded as CIN 1, 2 and 3 refers to pre-cancerous cells found on the surface of the cervix. The higher the grading number, the higher the probability the abnormal cells will become cancer cells.</p>	<p>Cancer Research UK accessed on 11 June 2009 at <a href="http://www.cancerhelp.org.uk/help/default.asp?page=1673">http://www.cancerhelp.org.uk/help/default.asp?page=1673</a></p> <p><i>CIN stands for cervical intraepithelial neoplasia, which means pre-cancerous cells found on the surface of the cervix. The cells are found by cervical screening with either a cervical smear test or liquid based cytology. The cell changes can be classed as CIN 1, 2, or 3. The higher the number, the more like cancer cells the abnormal cells are and so treatment is given to remove the cells. CIN 1 often goes back to normal without treatment, but a repeat smear is needed to check that the cells have gone.</i></p>	<p><b>Webpage</b></p>																																													
<p>3</p>	<p>Worldwide, more than 500,000 women will be newly diagnosed with cervical cancer and more than 280,000 women will die from it each year.</p>	<p>World Health Organization. Initiative for Vaccine Research. <a href="http://www.who.int/vaccine_research/diseases/hpv/en/">http://www.who.int/vaccine_research/diseases/hpv/en/</a> Accessed on April 20, 2009.</p> <p><i>Disease burden: Human Papillomavirus (HPV) causes cervical cancer, and is the second biggest cause of female cancer mortality worldwide with 288,000 deaths yearly. About 510,000 cases of cervical cancer are reported each year with nearly 80% in developing countries: 68 000 in Africa, 77 000 in Latin America, and 245 000 in Asia.</i></p>	<p><b>Page 1, Disease burden, Lines 3-4</b></p> <p><b>Page 1, Disease burden, Lines 1-3</b></p>																																													
<p>1</p>	<p>Protection against HPV types 16, 18 and 45 is particularly important because these types are associated with nearly 90% of cases of adenocarcinoma</p>	<p>Bosch X, Burchell A, Schiffmann M et al. Epidemiology and Natural History of Human Papillomavirus Infections and Type-Specific Implications in Cervical Neoplasia. <i>Vaccine</i> 26S (2008) K1–K16</p> <p><b>Figure 4.</b> Type-specific HPV prevalence across the spectrum of HPV related cervical diagnoses. Multiple infections counted several times. ADC: Adenocarcinoma; HSIL: High squamous intraepithelial lesions; SCC: Squamous cervical carcinoma</p> <table border="1" data-bbox="475 1137 911 1442"> <thead> <tr> <th></th> <th>Normal</th> <th>HSIL</th> <th>SCC</th> <th>ADC</th> </tr> </thead> <tbody> <tr> <td>HVP-16</td> <td>2.6</td> <td>45.3</td> <td>55.2</td> <td>48.4</td> </tr> <tr> <td>HPV-18</td> <td>0.9</td> <td>6.9</td> <td>12.8</td> <td>36.3</td> </tr> <tr> <td>HPV-31</td> <td>0.6</td> <td>8.6</td> <td>3.8</td> <td>0.7</td> </tr> <tr> <td>HPV-45</td> <td>0.4</td> <td>2.3</td> <td>4.6</td> <td>5.8</td> </tr> <tr> <td>HPV-33</td> <td>0.5</td> <td>7.3</td> <td>3.7</td> <td>2.0</td> </tr> <tr> <td>HPV-52</td> <td>0.9</td> <td>5.1</td> <td>2.9</td> <td>0</td> </tr> <tr> <td>HPV-58</td> <td>0.9</td> <td>7.0</td> <td>2.8</td> <td>0.7</td> </tr> <tr> <td>Others</td> <td>6.8</td> <td>23.9</td> <td>7.6</td> <td>7.7</td> </tr> </tbody> </table>		Normal	HSIL	SCC	ADC	HVP-16	2.6	45.3	55.2	48.4	HPV-18	0.9	6.9	12.8	36.3	HPV-31	0.6	8.6	3.8	0.7	HPV-45	0.4	2.3	4.6	5.8	HPV-33	0.5	7.3	3.7	2.0	HPV-52	0.9	5.1	2.9	0	HPV-58	0.9	7.0	2.8	0.7	Others	6.8	23.9	7.6	7.7	<p><b>Page 8 ; Figure 4</b></p>
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