

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-27.

## **SUPPLEMENTARY MATERIAL**

### **METHODS**

#### **Vaccine and Randomization**

Subjects were allocated to treatment assignment using a computer-generated randomized allocation schedule generated by the study statistician with permuted blocks of size six. An interactive voice response system was used to randomize subjects within each study center (1:1 ratio) to receive three 0.5-ml intradeltoid injections of either quadrivalent vaccine or placebo at day 1 (the first study visit after randomization) and months 2 and 6. Embedded within this study was a Consistency Lot substudy. The interactive voice response system assigned a separate block of 18 allocation numbers to each study site upon allocation of the first subject at that site. The block of 18 numbers was used to allocate subjects to one of three lots of quadrivalent vaccine, or placebo, in a 1:1:1:3 ratio using a permuted block size of 6. A total of 3,027 subjects were enrolled in this consistency lot substudy. These subjects contributed to the efficacy analyses, and analyses for persistence of immune response.

#### **Clinical follow-up**

Specimens collected at day 1 and month 7 were tested for HPV-6/11/16/18 DNA using PCR-based assays.<sup>1-3</sup> Blood samples obtained from all subjects on day 1. For a subset of subjects, (n=3,027) the interactive voice response system assigned a separate block of 18 allocation numbers to a study site upon allocation of the first subject at that site. The block of 18 numbers were used to allocate subjects to one of three lots of quadrivalent vaccine, or placebo, in

a 1:1:1:3 ratio. Blood samples from these subjects were obtained at month 7 and 24 were tested for HPV-6/11/16/18 specific neutralizing serum antibodies using a competitive Luminex immunoassay.<sup>4-6</sup> The threshold for determining seropositivity is described in reference 4. A blinded audit conducted by Merck Research Laboratories concluded that there was deviation from Standard Operating Procedure (SOP) for tests of a subset of serum samples. 2262/48581 (4.7 percent) day 1 serology results and 23/22,296 (0.1 percent) post-vaccination serology results were tested outside of Standard Operating Procedure. Day 1 serum samples that tested out of compliance were reanalyzed. The 23 non-conformant post-vaccination test results were removed from the database.

#### Reference List

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3. Bryan J, Taddeo F, Skulsky D et al. Detection of specific human papillomavirus types in paraffin-embedded sections of cervical carcinomas. *J Med Virol* 2006; 78(1):117-124.
4. Opalka D, Lachman CE, MacMullen SA et al. Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11, 16 and 18 by a multiplexed luminex assay. *Clin Diagn Lab Immunol* 2003; 10(1):108-115.
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6. Dias D, Van Doren J, Schlottmann S et al. Optimization and validation of a multiplexed luminex assay to quantify antibodies to neutralizing epitopes on human papillomavirus 6, 11, 16 and 18. *Clin Diagn Lab Immunol* 2005; 12(8):959-969.

**Table 1.** Vaccine effectiveness against HPV-16/18-related cervical intraepithelial neoplasia 2/3 and adenocarcinoma *in situ* by day 1 serostatus and HPV DNA status.

	Vaccine (N = 6,087)			Placebo (N= 6,080)				
<b>HPV-16/18-related cervical intraepithelial neoplasia grade 2/3 or adenocarcinoma <i>in situ</i></b>	n	Cases	Rate*	n	Cases	Rate*	% reduction	95% CI
Subjects who were seronegative and PCR positive to HPV-16 or HPV-18 <sup>†</sup>	423	33	2.9	402	35	3.2	10.6	(<0-46)
Subjects who were seropositive and PCR negative to HPV-16 or HPV-18 <sup>‡</sup>	498	0	0.0	524	4	0.3	100	(<0-100)
Subjects who were seropositive and PCR positive to HPV-16 or HPV-18 <sup>§</sup>	298	47	6.1	332	52	6.2	1.2	(<0-35)

\* Cases per 100 person-years at risk

<sup>†</sup> Includes all subjects who received ≥1 vaccination and who were seronegative and PCR positive for the relevant vaccine HPV type(s) at Day 1.

Cases were counted starting 30 days after Day 1.

‡ Includes all subjects who received  $\geq 1$  vaccination and who were seropositive and PCR negative for the relevant vaccine HPV type(s) at Day 1.

Cases were counted starting 30 days after Day 1.

§ Includes all subjects who received  $\geq 1$  vaccination and who were seropositive and PCR positive for the relevant vaccine HPV type(s) at Day 1.

Cases were counted starting 30 days after Day 1.

**Table 2.** Pregnancy outcome summary for women enrolled in phase 3 trials of quadrivalent HPV vaccine: Merck V501-013 (FUTURE I), 015 (FUTURE II), 016 and 018.

	Quadrivalent vaccine (N = 10,418)	Placebo (N = 9,120)
Number of subjects with reported pregnancy who received at least one dose of vaccine or placebo	1,396/10,418 (13.4)	1,436/9,120 (15.7)
Number of pregnancies <sup>†</sup>	1,598	1,627
Number of fetuses/infants with known outcome	1,315	1,337
Live Births <sup>‡</sup>	868/1,315 (66.0%)	848/1,337 (63.4%)
Method of Delivery		
C-Section <sup>§</sup>	223/868 (25.7%)	212/848 (25.0%)
Repeat or Elective C-Section	39/868 (4.5%)	45/848 (5.3%)
Fetal Distress	38/868 (4.4%)	41/848 (4.8%)
Failure to Progress or Dystocia	55/868 (6.3%)	34/848 (4.0%)
Cephalopelvic Disproportion	22/868 (2.5%)	24/848 (2.8%)
Breech, Malpresentation, or Transverse Lie	31/868 (3.6%)	34/848 (4.0%)

Cord prolapse, placenta previa	2/868 (0.2%)	3/848 (0.4%)
Premature Delivery; Multiple Gestation <sup>  </sup>	28/868 (3.2%)	12/848 (1.4%)
Other	33/868 (3.8%)	53/848 (6.3%)
Vaginal	644/868 (74.2%)	635/848 (74.9%)
Infant Outcome		
Normal	802/868 (92.4%)	795/848 (93.8%)
Abnormal	64/868 (7.4%)	50/848 (5.9%)
Congenital Anomaly reported at birth <sup>¶</sup>	20/868 (2.3%)	15/848 (1.8%)
Other Medical Conditions	48/868 (5.5%)	35/848 (4.1%)
Unknown	2/868 (0.2%)	3/848 (0.4%)
Fetal loss	447/1,315 (34.0%)	489/1,337 (36.6%)
Spontaneous Abortion	288/1,315 (21.9%)	311/1,337 (23.3%)
Late Fetal Death	13/1,315 (1.0%)	11/1,337 (0.8%)
Elective Abortion	146/1,315 (11.1%)	167/1,337 (12.5%)
Fetal outcome (% based on fetal loss)		
Normal	23/447 (5.1%)	17/489 (3.5%)
Abnormal	8/447 (1.8%)	15/489 (3.1%)
Congenital Anomaly <sup>¶</sup>	0/447 (0.0%)	3/489 (0.6%)
Other Medical Conditions	8/447 (1.8%)	9/489 (1.8%)
Unknown	416/447 (93.1%)	457/489 (93.5%)

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<sup>†</sup>Some subjects had >1 pregnancy during the study. Each pregnancy is counted once. A pregnancy with multiple fetuses is counted as a single pregnancy, but outcome for each fetus/infant is counted individually.

<sup>‡</sup>One woman in the quadrivalent vaccine group and one woman in the placebo group reported a live birth whose method of delivery is unknown. Both subjects discontinued from the study and were lost to follow-up.

<sup>§</sup>Some women had >1 reason for C-section for a single pregnancy.

<sup>||</sup>Among women who underwent a C-section due to multiple gestation, there were 11 sets of twins in the quadrivalent vaccine group and one set of twins in the placebo group. Each infant is counted individually.

<sup>¶</sup>A listing of all the congenital anomalies reported at birth, during the neonatal period, or diagnosed in utero, by vaccination group, is provided in Table S3.

**Table 3.** Distribution and listing of congenital anomalies for infants/fetuses born to women enrolled in phase 3 trials of quadrivalent HPV vaccine: Merck V501-013 (FUTURE I), 015 (FUTURE II), 016 and 018.

	Vaccine	Placebo
<b>A. Distribution of Congenital Anomaly Cases</b>		
Infant/Fetus Congenital Anomalies	<b>25</b>	<b>22</b>
EDCn within 30 days of a study vaccination	5	0
Live birth reported in the neonatal period	5	0
Live birth reported beyond the neonatal period	0	0
Fetal Loss	0	0
Intra-uterine diagnosis	0	0
EDCn beyond 30 days of a study vaccination	20	22
Among live births (Reported at birth or during the neonatal period)	16	15
Among live births (reported beyond the neonatal period)	3	2
Fetal Loss	0	3
Intra-uterine diagnosis	1	2
<b>B. Listing of Congenital Anomalies</b>		

Abdominal wall defect	0	5
Exomphalos	0	3*
Hernia, congenital	0	2
Cardiac	12	10
Anomalous pulmonary venous return	1	0
Atrial Septal Defect	1¶	3*,†,††
Atrioventricular septal defect	1	0
Cardiac septal defect	1	0
Cardiac murmur NOS	1	0
Congenital heart defect NOS	1	0
Congenital pulmonary valve atresia	1	0
Heart disease congenital	1	0
Persistent fetal circulation (PDA)	2	1 <sup>§§</sup>
Tetralogy of Fallot	0	1
Tricuspid valve incompetence	1	1 <sup>††</sup>
Ventricular septal defect	1¶	4 <sup>†,††,§§</sup>
Congenital malformation NOS	0	1
Congenital anomaly NOS	0	1
Chromosomal abnormality	2	0
Trisomy 21	1	0

Partial trisomy 16 and partial monosomy 9 <sup>††</sup>	1 <sup>¶</sup>	0
Craniofacial/ENT	7	4
Accessory Auricle	1	0
Ankyloglossia	1 <sup>§</sup>	0
Anotia	0	1
Branchial cyst	1	0
Choanal atresia	1	0
Cleft lip and palate	0	2
Ear malformation	1	0
Low set ears	1 <sup>‡</sup>	0
Mandibulofacial dysostosis	0	1
Palpebral ptosis	1	0
Gastrointestinal	3	0
Duodenal atresia	1 <sup>  </sup>	0
Congenital megacolon	1	0
Pyloric stenosis	1 <sup>§</sup>	0
Hematological	1	1
G6PD deficiency	0	1
Thalassaemia, alpha	1	0
Orthopedic/musculoskeletal	4	6

Amniotic band	0	1
Adactyly	0	1
Chondrodystrophy	0	1
Hip deformity	0	1*
Hip dysplasia	1	1
Limb malformation NOS	1‡	0
Polydactyly	1	1
Talipes equinovarus	1	0
Renal	4	1
Congenital hydronephrosis	1	1
Kidney malformation	1¶	0
Kidney duplex	1¶	0
Renal aplasia	1	0

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NOS=Not otherwise specified

PDA=Patent ductus arteriosus.

EDCn = Estimated Date of Conception

\*Exomphalos, atrial septal defect, and hip deformity occurred in the same infant.

†Atrial septal defect and ventricular septal defect occurred in the same infant.

‡Low set ears and limb malformation NOS occurred in the same infant.

§Ankyloglossia and pyloric stenosis occurred in the same infant.

<sup>||</sup>Duodenal atresia, congenital heart disease NOS and Trisomy 21 occurred in the same infant.

<sup>¶</sup>Partial trisomy 16 and partial monosomy 9, atrial septal defect, ventricular septal defect, kidney malformation and kidney duplex occurred in the same infant.

<sup>††</sup>Atrial septal defect, ventricular septal defect and tricuspid valve incompetence occurred in the same infant.

<sup>‡‡</sup>Originally reported as translocation of chromosome 9 and 15.

<sup>§§</sup>Ventricular septal defect and patent ductus arteriosus occurred in the same infant.

**Table 4.** Pregnancies with estimated date of conception within 30 days of any vaccination and greater than 30 days of any vaccination for women enrolled in phase 3 trials of quadrivalent HPV vaccine: Merck V501-013 (FUTURE I), 015 (FUTURE II), 016 and 018.

	Quadrivalent vaccine (N = 10,418)		Placebo (N = 9,120)	
	Pregnancies with estimated date of conception ≤30 days of any vaccination	Pregnancies with estimated date of conception > 30 days of any vaccination	Pregnancies with estimated date of conception ≤30 days of any vaccination	Pregnancies with estimated date of conception > 30 days of any vaccination
Number of subjects with reported pregnancy who received at least one dose of vaccine or placebo	112	1307	114	1347
Number of pregnancies <sup>†</sup>	114	1478	114	1509
Number of fetuses/infants with known outcome	112	1198	115	1218

Live Births <sup>†</sup>	70/112 (62.5%)	796/1198 (66.4%)	66/115 (57.4%)	781/1218 (64.1%)
Method of Delivery				
C-Section <sup>§</sup>	22/70 (31.4%)	200/796 (25.1%)	18/66 (27.3%)	194/781 (24.8%)
Repeat or Elective C-Section	2/70 (2.9%)	37/796 (4.6%)	3/66 (4.5%)	42/781 (5.4%)
Fetal Distress	2/70 (2.9%)	35/796 (4.4%)	3/66 (4.5%)	38/781 (4.9%)
Failure to Progress or Dystocia	7/70 (10.0%)	48/796 (6.0%)	3/66 (4.5%)	31/781 (4.0%)
Cephalopelvic Disproportion	3/70 (4.3%)	19/796 (2.4%)	2/66 (3.0%)	22/781 (2.8%)
Breech, Malpresentation, or Transverse Lie	6/70 (8.6%)	25/796 (3.1%)	4/66 (6.1%)	30/781 (3.8%)
Cord prolapse, placenta previa	0/70 (0.0%)	2/796 (0.3%)	0/66 (0.0%)	3/781 (0.4%)
Premature Delivery; Multiple Gestation	3/70 (4.3%)	25/796 (3.1%)	3/66 (4.5%)	9/781 (1.2%)
Other	4/70 (5.7%)	29/796 (3.6%)	6/66 (9.1%)	47/781 (6.0%)
Vaginal	48/70 (68.6%)	595/796 (74.7%)	47/66 (71.2%)	587/781 (75.2%)
Infant Outcome				
Normal	56/70 (80.0%)	744/796 (93.5%)	59/66 (89.4%)	735/781 (94.1%)
Abnormal	14/70 (20.0%)	50/796 (6.3%)	6/66 (9.1%)	44/781 (5.6%)
Congenital Anomaly reported at birth <sup>  </sup>	5/70 (7.1%)	15/796 (1.9%)	0/66 (0.0%)	15/781 (1.9%)
Other Medical Conditions	9/70 (12.9%)	39/796 (4.9%)	6/66 (9.1%)	29/781 (3.7%)

Unknown	0/70 (0.0%)	2/796 (0.3%)	1/66 (1.5%)	2/781 (0.3%)
Fetal loss	42/112 (37.5%)	402/1198 (33.6%)	49/115 (42.6%)	437/1218 (35.9%)
Spontaneous Abortion	19/112 (17.0%)	266/1198 (22.2%)	26/115 (22.6%)	283/1218 (23.2%)
Late Fetal Death	2/112 (1.8%)	11/1198 (0.9%)	0/115 (0.0%)	11/1218 (0.9%)
Elective Abortion	21/112 (18.8%)	125/1198 (10.4%)	23/115 (20.0%)	143/1218 (11.7%)
Fetal outcome (% based on fetal loss)				
Normal	2/42 (4.8%)	21/402 (5.2%)	0/49 (0.0%)	17/437 (3.9%)
Abnormal	0/42 (0.0%)	8/402 (2.0%)	1/49 (2.0%)	14/437 (3.2%)
Congenital Anomaly	0/42 (0.0%)	0/402 (0.0%)	0/49 (0.0%)	3/437 (0.7%)
Other Medical Conditions	0/42 (0.0%)	8/402 (2.0%)	1/49 (2.0%)	8/437 (1.8%)
Unknown	40/42 (95.2%)	373/402 (92.8%)	48/49 (98.0%)	406/437 (92.9%)

<sup>†</sup>Some subjects had >1 pregnancy during the study. Each pregnancy is counted once. A pregnancy with multiple fetuses is counted as a single pregnancy, but outcome for each fetus/infant is counted individually. For this sub-analysis, there were 9 subjects (5 quadrivalent vaccine; 4 placebo) whose estimated conception dates could not be determined and who are not included in this table.

<sup>‡</sup>One woman in the quadrivalent vaccine group and one woman in the placebo group reported a live birth whose method of delivery is unknown.

Both subjects discontinued from the study and were lost to follow-up.

<sup>§</sup>Some women had >1 reason for C-section for a single pregnancy.

<sup>||</sup>Study investigators reported 5 infants with a total of 6 congenital anomalies in the vaccine group for pregnancies with an estimated date of conception within 30 days of any vaccination under live births: hip dysplasia; congenital ankyglossia/congenital pyloric stenosis; congenital hydronephrosis; congenital megacolon; and talipes.

**Table 5.** Specific systemic adverse experiences by organ system: detailed safety cohort.\*

	Vaccine	Placebo	Risk difference <sup>†</sup>	95% CI <sup>†</sup>
Number (%) of subjects with one or more systemic adverse experiences	275/448 (61.4)	268/447 (60.0)	1.4	(-5.0–7.8)
Blood And Lymphatic System Disorders	4 (0.9)	5 (1.1)	-0.2	(-1.8–1.3)
Cardiac Disorders	2 (0.4)	0 (0.0)	0.4	(-0.4–1.6)
Ear And Labyrinth Disorders	5 (1.1)	3 (0.7)	0.4	(-1.0–2.0)
Eye Disorders	3 (0.7)	4 (0.9)	-0.2	(-1.7–1.2)
Gastrointestinal Disorders	93 (20.8)	95 (21.3)	-0.5	(-5.9–4.9)
General Disorders And Administration Site Conditions	47 (10.5)	49 (11.0)	-0.5	(-4.6–3.6)
Hepatobiliary Disorders	0 (0.0)	1 (0.2)	-0.2	(-1.3–0.6)
Immune System Disorders	10 (2.2)	2 (0.4)	1.8	(0.3–3.7)
Seasonal allergy	10 (2.2)	2 (0.4)	1.8	(0.3–3.7)
Infections And Infestations	83 (18.5)	74 (16.6)	2.0	(-3.0–7.0)
Injury, Poisoning And Procedural Complications	17 (3.8)	8 (1.8)	2.0	(-0.2–4.4)
Investigations	1 (0.2)	1 (0.2)	0.0	(-1.1–1.0)

Metabolism And Nutrition Disorders	2 (0.4)	6 (1.3)	-0.9	(-2.5–0.4)
Musculoskeletal And Connective Tissue Disorders	30 (6.7)	58 (13.0)	-6.3	(-10.3– -2.4)
Arthralgia	4 (0.9)	3 (0.7)	0.2	(-1.2–1.7)
Back pain	13 (2.9)	24 (5.4)	-2.5	(-5.3–0.1)
Bone pain	0 (0.0)	1 (0.2)	-0.2	(-1.3–0.6)
Flank pain	0 (0.0)	1 (0.2)	-0.2	(-1.3–0.6)
Joint stiffness	2 (0.4)	1 (0.2)	0.2	(-0.9–1.4)
Joint swelling	0 (0.0)	1 (0.2)	-0.2	(-1.3–0.6)
Muscle spasms	2 (0.4)	4 (0.9)	-0.4	(-1.9–0.8)
Muscle tightness	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Muscular weakness	0 (0.0)	2 (0.4)	-0.4	(-1.6–0.4)
Musculoskeletal discomfort	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Musculoskeletal stiffness	2 (0.4)	3 (0.7)	-0.2	(-1.6–1.0)
Myalgia	4 (0.9)	9 (2.0)	-1.1	(-3.0–0.5)
Neck pain	2 (0.4)	10 (2.2)	-1.8	(-3.7 – -0.3)
Pain in extremity	4 (0.9)	8 (1.8)	-0.9	(-2.7–0.7)
Pain in jaw	1 (0.2)	2 (0.4)	-0.2	(-1.4–0.9)
Sensation of heaviness	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Shoulder pain	2 (0.4)	5 (1.1)	-0.7	(-2.2–0.6)

Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Nervous System Disorders	133 (29.7)	131 (29.3)	0.4	(-5.6–6.4)
Pregnancy, Puerperium And Perinatal Conditions	3 (0.7)	3 (0.7)	0.0	(-1.4–1.4)
Psychiatric Disorders	12 (2.7)	12 (2.7)	0.0	(-2.3–2.3)
Renal and Urinary Disorders	1 (0.2)	1 (0.2)	0.0	(-1.1–1.0)
Reproductive System And Breast Disorders	32 (7.1)	29 (6.5)	0.7	(-2.7–4.1)
Respiratory, Thoracic And Mediastinal Disorders	47 (10.5)	49 (11.0)	-0.5	(-4.6–3.6)
Skin And Subcutaneous Tissue Disorders	18 (4.0)	7 (1.6)	2.5	(0.3–4.9)
Acne	1 (0.2)	2 (0.4)	-0.2	(-1.4–0.9)
Alopecia	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Dermatitis allergic	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Dermatitis contact	2 (0.4)	0 (0.0)	0.4	(-0.4–1.6)
Dry skin	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Erythema	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Hangnail	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Hyperhidrosis	2 (0.4)	0 (0.0)	0.4	(-0.4–1.6)
Night sweats	1 (0.2)	1 (0.2)	0.0	(-1.1–1.0)
Rash	6 (1.3)	2 (0.4)	0.9	(-0.4–2.5)

Skin irritation	1 (0.2)	0 (0.0)	0.2	(-0.6–1.3)
Urticaria	2 (0.4)	2 (0.4)	0.0	(-1.2–1.2)
Vascular Disorders	0 (0.0)	1 (0.2)	-0.2	(-1.3–0.6)

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\*The subset of subjects who completed the vaccination report card from days 1-15 following each vaccination.

†Vaccine minus Placebo. A 95% confidence interval which does not include zero indicates a statistically significant difference at the  $\alpha = 0.05$  (two-sided) level. No multiplicity adjustments were made for these comparisons.

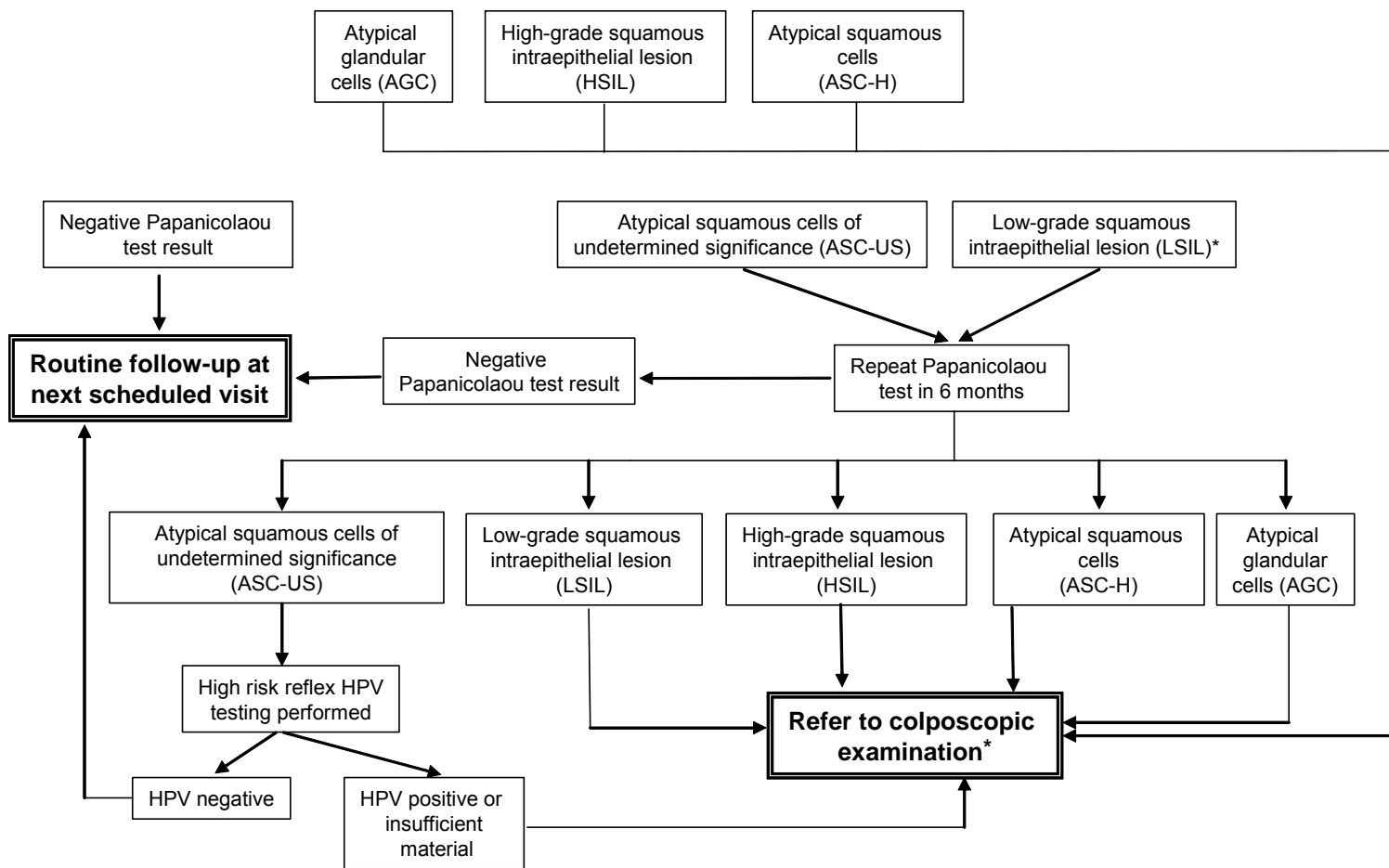
**Table 6.** Specific serious adverse experiences by organ system among all vaccinated subjects.

	Risk			
	Vaccine	Placebo	Difference*	95% CI*
Number (%) of subjects with one or more serious adverse experiences	44/6,019 (0.7)	54/6,031 (0.9)	-0.2	(-0.5–0.2)
Blood and Lymphatic System Disorders	1 (0.0)	0 (0.0)	0.0	(-0.1–0.1)
Cardiac Disorders	2 (0.0)	1 (0.0)	0.0	(-0.1–0.1)
Gastrointestinal Disorders	2 (0.0)	2 (0.0)	0.0	(-0.1–0.1)
General Disorders And Administration Site Conditions	0 (0.0)	2 (0.0)	0.0	(-0.1–0.0)
Hepatobiliary Disorders	1 (0.0)	0 (0.0)	0.0	(-0.1–0.1)
Immune System Disorders	0 (0.0)	2 (0.0)	0.0	(-0.1–0.0)
Infections And Infestations	9 (0.1)	10 (0.2)	0.0	(-0.2–0.1)
Injury, Poisoning And Procedural Complications	6 (0.1)	4 (0.1)	0.0	(-0.1–0.2)
Musculoskeletal And Connective Tissue Disorders	0 (0.0)	1 (0.0)	0.0	(-0.1–0.1)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	0 (0.0)	1 (0.0)	0.0	(-0.1–0.1)
Nervous System Disorders	4 (0.1)	1 (0.0)	0.0	(-0.0–0.2)

Pregnancy, Puerperium And Perinatal Conditions	19 (0.3)	26 (0.4)	-0.1	(-0.4–0.1)
Psychiatric Disorders	1 (0.0)	2 (0.0)	0.0	(-0.1–0.1)
Renal And Urinary Disorders	0 (0.0)	1 (0.0)	0.0	(-0.1–0.1)
Reproductive System And Breast Disorders	2 (0.0)	3 (0.0)	0.0	(-0.1–0.1)
Respiratory, Thoracic And Mediastinal Disorders	2 (0.0)	3 (0.0)	0.0	(-0.1–0.1)
Skin And Subcutaneous Tissue Disorders	1 (0.0)	1 (0.0)	0.0	(-0.1–0.1)
Vascular Disorders	3 (0.0)	1 (0.0)	0.0	(-0.1–0.1)

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\*Vaccine minus Placebo. A 95 percent confidence interval which does not include zero indicates a statistically significant difference at the  $\alpha$  =0.05 (two-sided) level. No multiplicity adjustments were made for these comparisons.



\*A subject with a Day 1 Papanicolaou result of LSIL was referred for colposcopic examination.

Figure 1. Mandatory regimen for triage of abnormal Papanicolaou tests to colposcopic examination.