

Post-licensure Safety Study of Quadrivalent Human Papillomavirus Vaccine among 189,629 Females

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Presentation Outline

1. Study overview
2. Summary of study populations
3. Pregnancy safety
4. Autoimmune safety
5. General safety
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Study Overview

- Background
 - Large, retrospective cohort study with follow-up through electronic medical records (EMRs), supplemented with extensive medical record review
 - Conducted at 2 large Managed Care Organizations (MCOs) in California, USA
- Objective
 - To evaluate safety of GARDASIL administered to females as part of routine medical care

Study Committees

- Safety Review Committee (SRC)
 - 5 members
 - Experts in the field of vaccine safety, pediatric and adolescent medicine, teratology, pediatric rheumatology, & pharmacoepidemiology
 - Independent & external to both study team & Merck
 - Followed pre-specified guideline to review study findings
 - Requested additional analyses or chart reviews, made conclusions regarding safety
- 4 Clinical Case Review Committees (CRCs)
 - 3 members each
 - Clinician experts in their relevant fields
 - 1 pregnancy CRC & 3 autoimmune CRCs
 - Confirmed or refuted potential diagnoses identified from electronic medical records, blinded to vaccination status

Age Range of Vaccinated Study Population, 8/06 – 3/08

Age	All who received Dose 1 N (%)	All who received Dose 2 N (%)	All who received Dose 3 N (%)
All Ages	189,629 (100%)	105,412 (100%)	51,931 (100%)
9-26 yr old	187,905 (99.1%)	104,747 (99.4%)	51,603 (99.4%)
9-15 yr old	96,839 (51.1%)	56,007 (53.1%)	28,443 (54.8%)
11-12 yr old	33,334 (17.6%)	18,736 (17.8%)	9,341 (18.0%)
<9	45 (0.02%)	6 (0.01%)	5 (0.01%)
>26	1,679 (0.9%)	659 (0.6%)	323 (0.6%)

Vaccinated Populations August 2006-March 2008

1. Overall (Secondary) Safety Population (N=189,629; 346,972 doses)
 - All females administered at least 1 dose of GARDASIL™
2. Primary Safety Population (N=44,001)
 - Overall safety population with 3 doses per protocol
3. Autoimmune Population (N=149,306)
 - Overall safety population with 12+ months MCO membership before 1st dose
4. Pregnancy Population (N=2,678)
 - Overall safety population limited to those potentially vaccinated with GARDASIL™ at any time during pregnancy or up to 30 days prior to conception

Pregnancy Safety: Methods and Results

Pregnancy Analyses

- Pregnancy Population (N=2,678)
 - Pregnancy outcomes available in EMRs for 1,740 females: 665 live births, 633 potential miscarriages, 442 potential elective abortions
- Congenital Anomaly (CA) Review
 - Medical records of all 170 potential CA cases identified in EMRs were reviewed
 - Of these, 44 CAs diagnosed up to 6 months after birth were confirmed
 - Spanned wide range of diagnoses
- Miscarriage Review
 - Medical records of random sample of 100 potential miscarriages identified in EMRs were reviewed
 - 9 miscarriages were confirmed
 - Most unconfirmed cases were elective abortions

SRC Review of Pregnancy Results

- Safety Review Committee (SRC) reviewed all findings:
 - Diagnosis, gestational age at vaccination & at miscarriage, maternal age, number of doses, concomitant vaccinations, level of diagnostic certainty of CA or miscarriage determined by CRC
 - Rates of major congenital anomaly up to 6 months after birth (3.6%) consistent with published background rates at birth for California & U.S. (3.0%)
- SRC noted no apparent pattern or distribution of anomalies or miscarriages other than what would be expected in general population
- SRC determined no association with vaccination

Autoimmune Safety: Methods and Results

Autoimmune (AI) Methods

- 16 pre-specified conditions were evaluated for new onset within 6 months after each vaccine dose
- Autoimmune Population (N=149,306)
- Medical records of all potential cases reviewed by expert Case Review Committees to confirm diagnosis and estimate onset date
 - Exception: For 5 conditions (Hashimoto's & Graves' diseases, SLE, RA, JRA), only random sample of cases reviewed

Number of Confirmed Diagnoses within 6 months after vaccination among 149,306 females

Neurologic/Ophthalmologic

- Multiple sclerosis (4)
- Acute disseminated encephalomyelitis (3)
- Other demyelinating conditions of central nervous system (3)
- Optic neuritis (6), Uveitis (15)
- Vaccine-associated demyelination (0), Neuromyelitis optica (0), Guillain-Barré syndrome (0)

Endocrine

- Type 1 diabetes (15)
- Hashimoto's disease (93 reviewed: 39 confirmed; 300 not sampled)
- Graves' disease (32 reviewed: 13 confirmed; 36 not sampled)

Rheumatologic/Autoimmune

- Immune thrombocytopenia (9 confirmed)
- Autoimmune hemolytic anemia (0)
- Systemic lupus erythematosus (24 reviewed: 8 confirmed; 19 not sampled)
- Rheumatoid arthritis (16 reviewed: 3 confirmed; 10 not sampled)
- Juvenile rheumatoid arthritis (11 reviewed: 3 confirmed; 7 not sampled)

Autoimmune Rate Comparison

Condition	Vaccinated	Non-Vaccinated	Incidence Rate Ratio (RR)	95% CI (for RR)
	Incidence (per 100,000 py)			
Graves' Disease	18.23	25.84	0.72	0.50 – 1.01
Hashimoto's Disease	104.82	81.10	1.29	1.08 – 1.56
Type 1 Diabetes	10.25	18.00	0.57	0.47 – 0.73
ITP	6.84	5.88	1.16	0.85 – 1.83
JRA	3.42	7.66	0.48	0.26 – 0.91
MS	3.42	2.50	1.37	0.74 – 3.20
Optic Neuritis	5.70	3.92	1.45	1.00 – 2.91
Other Demyelinating Diseases of CNS	1.14	1.60	0.71	0.38 – 2.13
RA	4.56	6.95	0.71	0.39 – 1.45
SLE	11.39	10.34	1.07	0.69 – 1.60
Uveitis	7.98	11.94	0.67	0.49 – 1.02

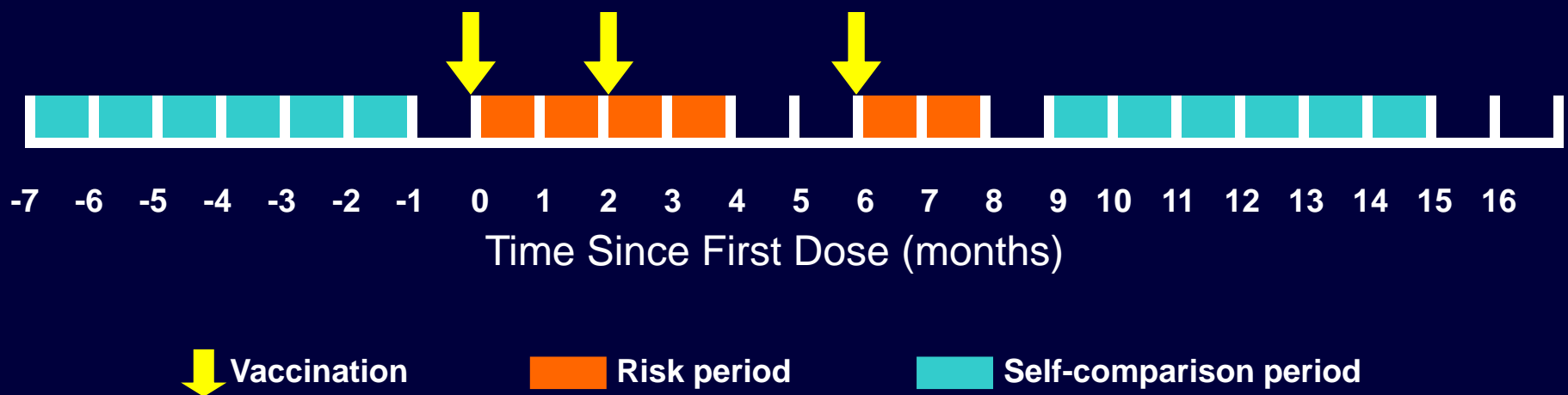
SRC Review of Autoimmune Results

- No apparent patterns or timing of diagnosis with respect to vaccination
- Temporal distribution graphs & extensive medical record reviews revealed that some cases with confirmed diagnoses after vaccination had symptom onset prior to vaccination
- Rates not elevated above background rates
- Safety Review Committee (SRC) reviewed all results
 - Found no association with vaccination
 - Noted vaccine visit often included work-up for existing symptoms leading to new diagnosis of prevalent disease

General Safety: Methods and Results

General Safety Methods

- Evaluated all medical events resulting in emergency room (ER) visit or hospitalization
 - 14 days following each dose; 60 days following each dose
 - On day of vaccination (for allergic events, syncope, epilepsy/convulsion)
 - Comparison (i.e., “control”) windows: 180-day self-comparison period pre- & post-vaccination



General Safety Results

- Syncope diagnosis codes more likely to occur on day of vaccination than in post-vaccination self-comparison period
 - Relative risk (95% CI): 6.00 (3.91-9.21)
 - SRC reviewed all findings
 - Requested several case summaries
 - Noted temporal association
 - Noted clinical plausibility: known syncope association with vaccination in this age group
 - SRC determined that syncope associated with vaccination
- Local skin infection (cellulitis/abscess) diagnosis codes more likely within 14 days after vaccination than in post-vaccination comparison period
 - Relative risk (95% CI): 1.64 (1.17-2.3)
 - SRC requested several case summaries
 - SRC determined cellulitis/abscess possibly associated with vaccination; however, also noted possibility that cases were injection site reactions

Other General Safety Results

- All medical events resulting in ER or hospitalization in the immediate post-vaccination period were analyzed
- SRC requested medical record reviews for many events
 - SRC noted no association of any other diagnosis (including venous thromboembolism, deaths) with GARDASIL
 - SRC noted no apparent patterns of elevation by population, dose, or age
 - SRC noted tendency of increased non-specific health care utilization after vaccination visit

Summary

- Favorable safety profile; no association between vaccination with GARDASIL and:
 - Congenital anomalies, miscarriages
 - 16 pre-specified autoimmune conditions
 - Venous thromboembolism
 - Death
 - Any other general safety events (except syncope & possibly local skin infection)
- Syncope associated with GARDASIL: injection-related
- Local skin infection (cellulitis/abscess) possibly associated with GARDASIL: could be injection site reaction
- All safety conclusions were made by independent, external Safety Review Committee of 5 experts

Quadrivalent HPV Vaccine Female Safety Study Team

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