Assessing Quadrivalent HPV Vaccine Safety using the Self-Controlled Tree-Temporal Scan Statistic

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Disclaimer

- Funding source: U.S. Food and Drug Administration
  - Postlicensure Rapid Immunization Safety Monitoring (PRISM 2012) Task Order FDA CBER 2014 HHSF22301013T
  - Under contract: FDA HHSF223200910006I
  - To develop resources and methods for using a distributed network of health data sources for active surveillance of the safety of marketed biological products

- No relationships to disclose

- Some PRISM/Sentinel studies ask, *"Is there an association between Vaccine X and Outcome A, B, or C?"*
  - Signal refinement or signal evaluation
- But with the methods described here, we are asking, *"Is Vaccine X safe?"*
  - Signal detection

How can we detect unsuspected adverse reactions?

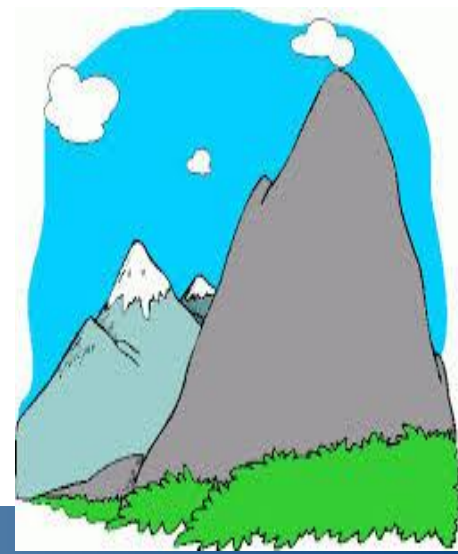How can we try to ensure that there are no unknown adverse reactions?

Tree Scan Statistics

For selected vaccine, uses Sentinel data to:

- Evaluate thousands of potential adverse events and groups of closely related adverse events

- Evaluate multiple potential risk windows

- Adjust for the multiple testing

Level of Granularity

Is there increased risk for a very specific diagnosis (acute liver failure), or for a range of related diagnoses (any liver problems)?

A Small Three-Level Tree

Cut

Heart Attack

Cardiac Disrhythmia

Cardio-myopathy

Kidney Failure

Kidney Infection
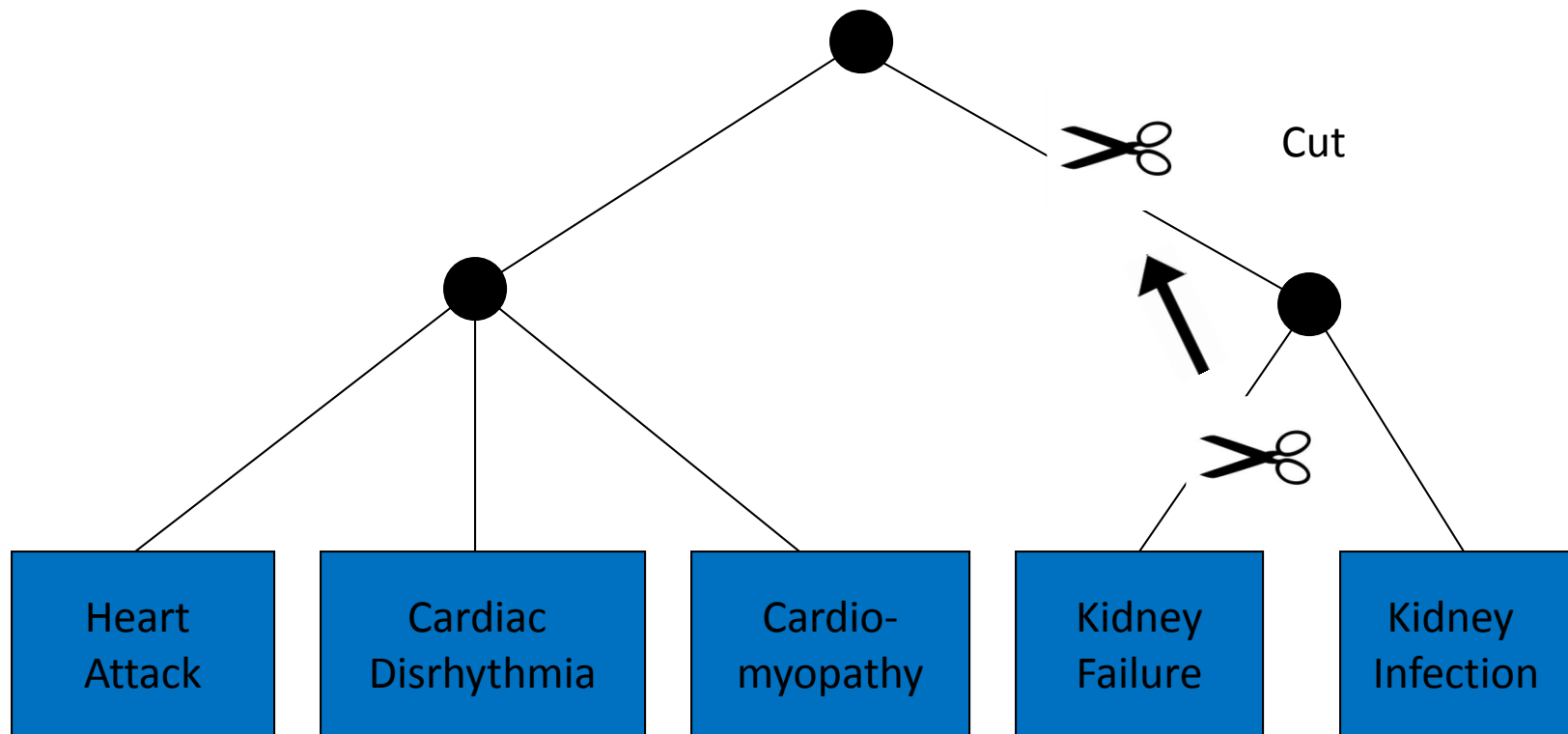
Lowest Level: ~6,000 ICD-9 codes

HPV4 (Gardasil) Pilot

- Medically attended adverse events
- Conditional Tree-Temporal Scan Statistic
- Self-Controlled, adjusting for all fixed (non-time-varying) confounders
- First dose after 9th birthday or enrollment
- 1.9 million doses
- Four health plans

Scanning Risk Window

Follow-Up Period: 1-56 days

Risk Window Start Range: 1-28 days after vaccination

Risk Window End Range: 2-42 days after vaccination

Minimum Length: 2 days   Maximum Length: 28 days

Comparison Window

- Those days 1-56 after vaccination that are not in the risk window

Results, HPV4, Dose 1

MLCCS (ICD9)	Disease Name	Window	Obs	AR/ 100K	P=
12	Diseases of skin and subcutaneous tissue	2-4	214	3.8	0.0019
12.01	Skin and subcutaneous tissue infections	2-4	111	2.3	0.04
12.01.01	Cellulitis and abscess	2-4	93	2.0	0.20
... 682.3	Cellulitis and abscess of upper arm and forearm	2-3	31	1.3	0.00001
12.02	...				
... 695.9	Unspecified erythematous condition	2-3	13	0.5	0.25
16	Injury and Poisoning	1-3	48	2.2	0.00001
16.10.02.07	Other complications of surgical and medical procedures	1-3	36	1.8	0.00001
... 780.63	Post vaccination fever	1-2	4	0.2	0.31
... 999.5	Other serum reaction NEC	1-3	7	0.4	0.011
... 999.52	Other serum reaction due to vaccination	1-2	11	0.6	0.00001
... 999.9	Other and unspecified complications of medical care, NEC	1-6	12	0.6	0.0018

Cases in "Other Complications…" Signal

31 (86%) of the 36 cases received ≥ 1 other vaccine along with HPV4

Conditions	No.
With conditions identified in package insert as possible vaccine-associated adverse events*	29
No specified symptoms and no further medical visits within 60 days	3
With diverse symptoms, different in each case	4
Total	36

* e.g., headache, fever, nausea, and dizziness; local injection site reactions

What was Not Found?

MLCCS (ICD9)	Disease Name	Window	Obs	RR	P=
787.20	Dysphagia	25-26	17	3.8	0.29
568	Other disorders of peritoneum	15-17	6	17.7	0.33
724.5	Backache, unspecified	17-18	40	2.0	0.61
789.67	Abdominal tenderness, generalized	22-23	4	36.0	0.71
791	Nonspecific findings on examination of urine	5-6	5	15.0	0.88
272.0	Pure hypercholesterolemia	4-5	6	9.5	0.95
616.3	Abscess of Bartholin's gland	1-6	7	14.6	0.97
250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled	1-4	6	13.0	0.99

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Conclusions

The self-controlled tree-temporal scan statistics worked well for the HPV4 vaccine

- Known adverse reactions found

- No false alerts

- High power to detect rare adverse reactions

- Adjusts for multiple testing

- Only early onset adverse reactions evaluated

- We only looked at first dose

TreeScan Software

- Free

- www.treescan.org

- Windows, Mac, Linux

- User Guide (47p)

Future

- Apply method for HPV9 safety surveillance

- May be used for drugs as well as vaccines

- Can scan all drugs for risk of specific adverse events (with CDER)

  – J.C. Maro et al.'s poster, "Monitoring All Drugs for a Specific Outcome in the Sentinel System," Poster Session A (Friday)

Tree Scan Team Members

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