

Self-Control Tree Scan Data Mining for Vaccine Adverse Events

Kulldorff M, Balsbaugh C, Dashevsky I, Gil-Prieto R,
Lee G, Dep. of Population Medicine, Harvard Medical
School and Harvard Pilgrim Health Care

Nguyen M, Martin D, Russek-Cohen E, Ball R, Center
for Biologics Evaluation and Research

Robert Davis, Kaiser Permanente Georgia

No Conflicts of Interest

Self-Control Risk Interval Design

Risk Interval, e.g. 1-28 days after vaccination

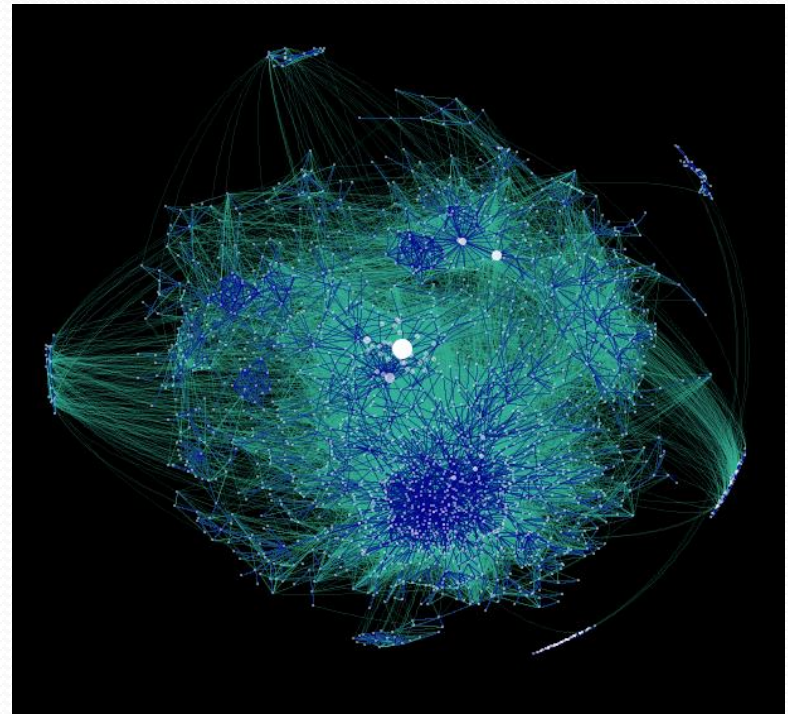
Control Interval, e.g. 29-56 days after vaccination

Only patients with the adverse event are used

Ho: The adverse event is equally likely to be in the risk and control intervals.

Adjusts for all non-time-varying confounders

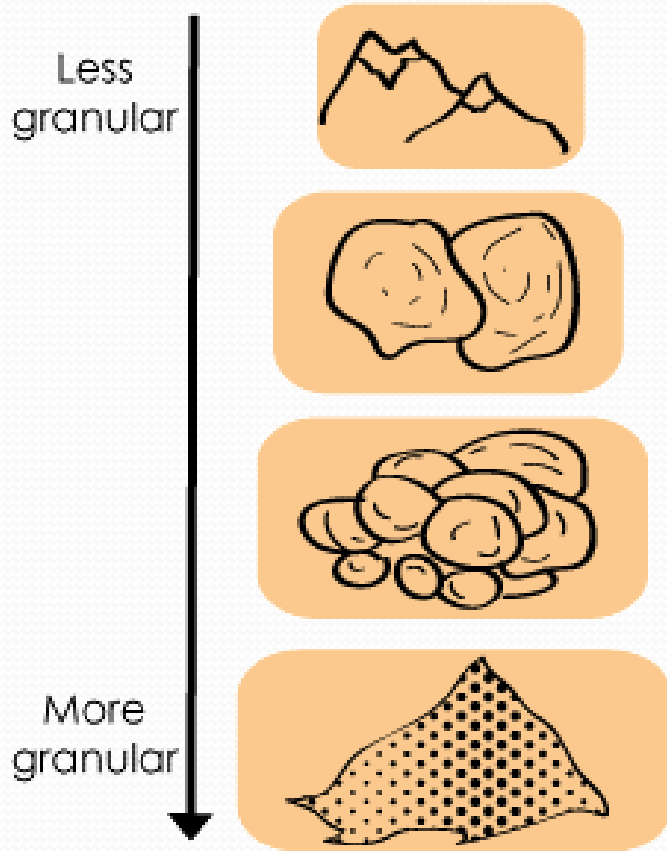
Data Mining



Goal: Complete ascertainment of early onset adverse events after a vaccine

- Find all known adverse events
- Find any additional adverse events, if they exist
- Few false positives, or else, easily explained false positives
- Large enough sample size to detect very rare adverse events

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)?

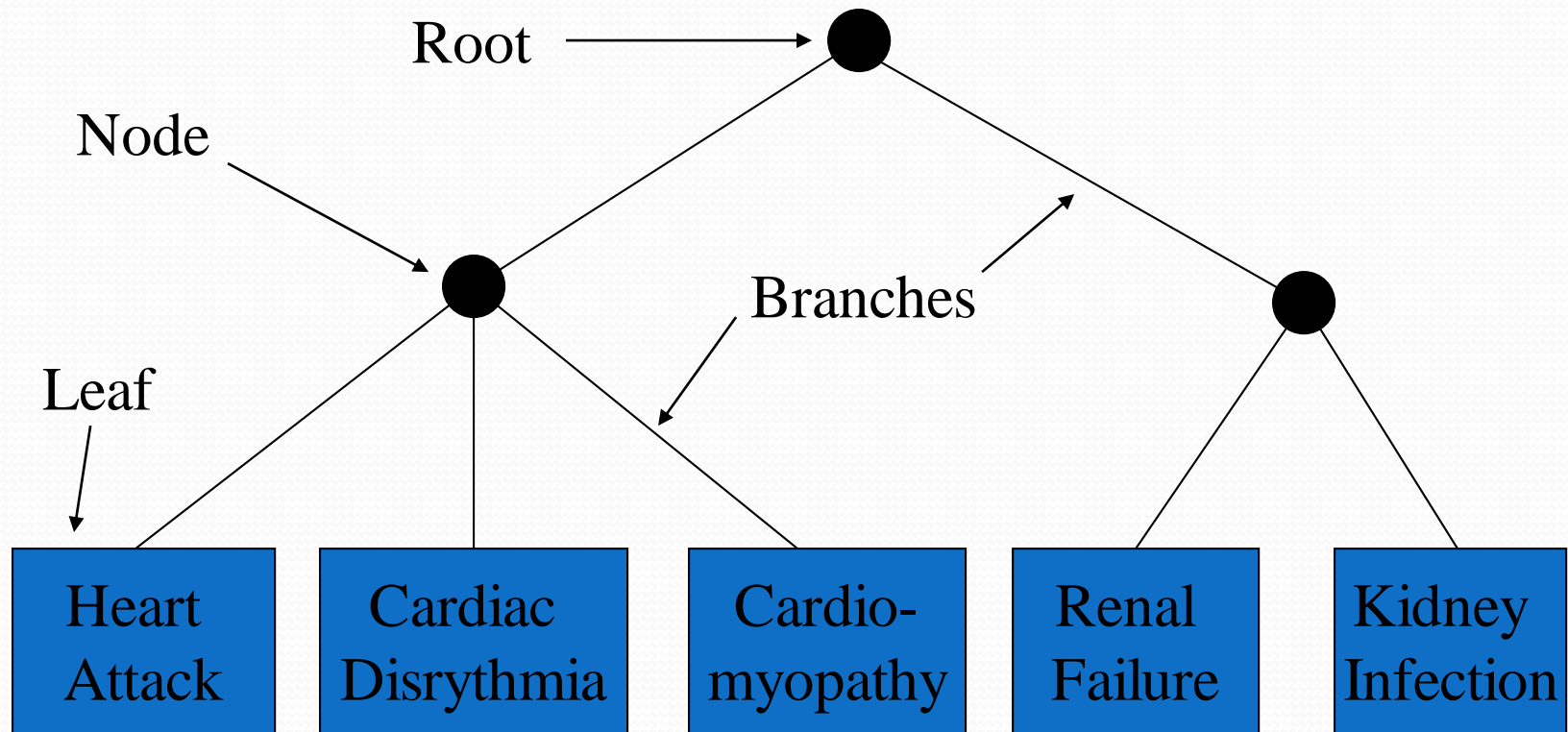
Tree-Based Scan Statistic



Tree-Based Scan Statistic



A Small Two-Level Tree Variable



Lowest Level: 6,162 ICD-9 codes



Some Diagnoses Removed

- Well-care visits
- Accidents
- Common infectious diseases
- Cancer and other chronic diseases
- Pregnancy
- Fever



Sample of the Multi-Level Clinical Classification Tree

| | |
|-------------|--|
| 07 | ' <u>DISEASES OF THE CIRCULATORY SYSTEM</u> ' |
| 07.01 | 'HYPERTENSION' |
| 07.01.01 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.01.00 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.02 | 'HYPERTENSION WITH COMPLICATIONS AND SECONDARY HYPERTENSION [99.]' |
| 07.01.02.01 | 'HYPERTENSIVE HEART AND/OR RENAL DISEASE' |
| 07.01.02.02 | 'OTHER HYPERTENSIVE COMPLICATIONS' |
| 07.02 | 'DISEASES OF THE HEART' |
| 07.02.01 | 'HEART VALVE DISORDERS [96.]' |
| 07.02.01.01 | 'CHRONIC RHEUMATIC DISEASE OF THE HEART VALVES' |
| 07.02.01.02 | 'NONRHEUMATIC MITRAL VALVE DISORDERS' |
| 07.02.01.03 | 'NONRHEUMATIC AORTIC VALVE DISORDERS' |
| 07.02.01.04 | 'OTHER HEART VALVE DISORDERS' |
| 07.02.02 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.00 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.01 | 'CARDIOMYOPATHY' |
| 07.02.02.02 | 'OTHER PERI-; ENDO-; AND MYOCARDITIS' |
| 07.02.03 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.03.00 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.04 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.00 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.01 | 'ANGINA PECTORIS' |
| 07.02.04.02 | 'UNSTABLE ANGINA (INTERMEDIATE CORONARY SYNDROME)' |
| 07.02.04.03 | 'OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE' |
| 07.02.04.04 | 'CORONARY ATHEROSCLEROSIS' |
| 07.02.04.05 | 'OTHER FORMS OF CHRONIC HEART DISEASE' |



Sample of the Multi-Level Clinical Classification Tree

| | |
|-------------|--|
| 07 | 'DISEASES OF THE CIRCULATORY SYSTEM' |
| 07.01 | 'HYPERTENSION' |
| 07.01.01 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.01.00 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.02 | 'HYPERTENSION WITH COMPLICATIONS AND SECONDARY HYPERTENSION [99.]' |
| 07.01.02.01 | 'HYPERTENSIVE HEART AND/OR RENAL DISEASE' |
| 07.01.02.02 | 'OTHER HYPERTENSIVE COMPLICATIONS' |
| 07.02 | ' <u>DISEASES OF THE HEART</u> ' |
| 07.02.01 | 'HEART VALVE DISORDERS [96.]' |
| 07.02.01.01 | 'CHRONIC RHEUMATIC DISEASE OF THE HEART VALVES' |
| 07.02.01.02 | 'NONRHEUMATIC MITRAL VALVE DISORDERS' |
| 07.02.01.03 | 'NONRHEUMATIC AORTIC VALVE DISORDERS' |
| 07.02.01.04 | 'OTHER HEART VALVE DISORDERS' |
| 07.02.02 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.00 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.01 | 'CARDIOMYOPATHY' |
| 07.02.02.02 | 'OTHER PERI-; ENDO-; AND MYOCARDITIS' |
| 07.02.03 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.03.00 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.04 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.00 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.01 | 'ANGINA PECTORIS' |
| 07.02.04.02 | 'UNSTABLE ANGINA (INTERMEDIATE CORONARY SYNDROME)' |
| 07.02.04.03 | 'OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE' |
| 07.02.04.04 | 'CORONARY ATHEROSCLEROSIS' |
| 07.02.04.05 | 'OTHER FORMS OF CHRONIC HEART DISEASE' |



Sample of the Multi-Level Clinical Classification Tree

| | |
|-------------|--|
| 07 | 'DISEASES OF THE CIRCULATORY SYSTEM' |
| 07.01 | 'HYPERTENSION' |
| 07.01.01 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.01.00 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.02 | 'HYPERTENSION WITH COMPLICATIONS AND SECONDARY HYPERTENSION [99.]' |
| 07.01.02.01 | 'HYPERTENSIVE HEART AND/OR RENAL DISEASE' |
| 07.01.02.02 | 'OTHER HYPERTENSIVE COMPLICATIONS' |
| 07.02 | 'DISEASES OF THE HEART' |
| 07.02.01 | ' <u>HEART VALVE DISORDERS [96.]'</u> |
| 07.02.01.01 | 'CHRONIC RHEUMATIC DISEASE OF THE HEART VALVES' |
| 07.02.01.02 | 'NONRHEUMATIC MITRAL VALVE DISORDERS' |
| 07.02.01.03 | 'NONRHEUMATIC AORTIC VALVE DISORDERS' |
| 07.02.01.04 | 'OTHER HEART VALVE DISORDERS' |
| 07.02.02 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.00 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.01 | 'CARDIOMYOPATHY' |
| 07.02.02.02 | 'OTHER PERI-; ENDO-; AND MYOCARDITIS' |
| 07.02.03 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.03.00 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.04 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.00 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.01 | 'ANGINA PECTORIS' |
| 07.02.04.02 | 'UNSTABLE ANGINA (INTERMEDIATE CORONARY SYNDROME)' |
| 07.02.04.03 | 'OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE' |
| 07.02.04.04 | 'CORONARY ATHEROSCLEROSIS' |
| 07.02.04.05 | 'OTHER FORMS OF CHRONIC HEART DISEASE' |



Sample of the Multi-Level Clinical Classification Tree

| | |
|-------------|--|
| 07 | 'DISEASES OF THE CIRCULATORY SYSTEM' |
| 07.01 | 'HYPERTENSION' |
| 07.01.01 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.01.00 | 'ESSENTIAL HYPERTENSION [98.]' |
| 07.01.02 | 'HYPERTENSION WITH COMPLICATIONS AND SECONDARY HYPERTENSION [99.]' |
| 07.01.02.01 | 'HYPERTENSIVE HEART AND/OR RENAL DISEASE' |
| 07.01.02.02 | 'OTHER HYPERTENSIVE COMPLICATIONS' |
| 07.02 | 'DISEASES OF THE HEART' |
| 07.02.01 | 'HEART VALVE DISORDERS [96.]' |
| 07.02.01.01 | 'CHRONIC RHEUMATIC DISEASE OF THE HEART VALVES' |
| 07.02.01.02 | 'NONRHEUMATIC MITRAL VALVE DISORDERS' |
| 07.02.01.03 | 'NONRHEUMATIC AORTIC VALVE DISORDERS' |
| 07.02.01.04 | 'OTHER HEART VALVE DISORDERS' |
| 07.02.02 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.00 | 'PERI-; ENDO-; AND MYOCARDITIS; CARDIOMYOPATHY (EXCEPT THAT CAUSED BY TB O |
| 07.02.02.01 | 'CARDIOMYOPATHY' |
| 07.02.02.02 | 'OTHER PERI-; ENDO-; AND MYOCARDITIS' |
| 07.02.03 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.03.00 | 'ACUTE MYOCARDIAL INFARCTION [100.]' |
| 07.02.04 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.00 | 'CORONARY ATHEROSCLEROSIS AND OTHER HEART DISEASE [101.]' |
| 07.02.04.01 | 'ANGINA PECTORIS' |
| 07.02.04.02 | 'UNSTABLE ANGINA (INTERMEDIATE CORONARY SYNDROME)' |
| 07.02.04.03 | 'OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE' |
| 07.02.04.04 | 'CORONARY ATHEROSCLEROSIS' |
| 07.02.04.05 | 'OTHER FORMS OF CHRONIC HEART DISEASE' |



Tree-Based Scan Statistic

- Use the Hierarchical Tree
- Evaluate Cuts on that Tree
- Adjust for the multiple testing



Cohort Tree-Based Scan Statistic

Based Observed and Expected Counts

Poisson Distribution

Occupational Disease Surveillance (Kulldorff, Fang, Walsh. A tree-based scan statistic for database disease surveillance. *Biometrics*, 2003.)

Drug Safety Surveillance (Kulldorff, Dashevsky, Avery, Chan, Davis, Graham, Platt, Andrade, Boudreau, Gunter, Herrinton, Pawloski, Raebel, Roblin, Brown. Drug safety data mining with a tree-based scan statistic. *Pharmacoepidemiology and Drug Safety*, 2013.)

Self-Control Tree-Based Scan Statistic

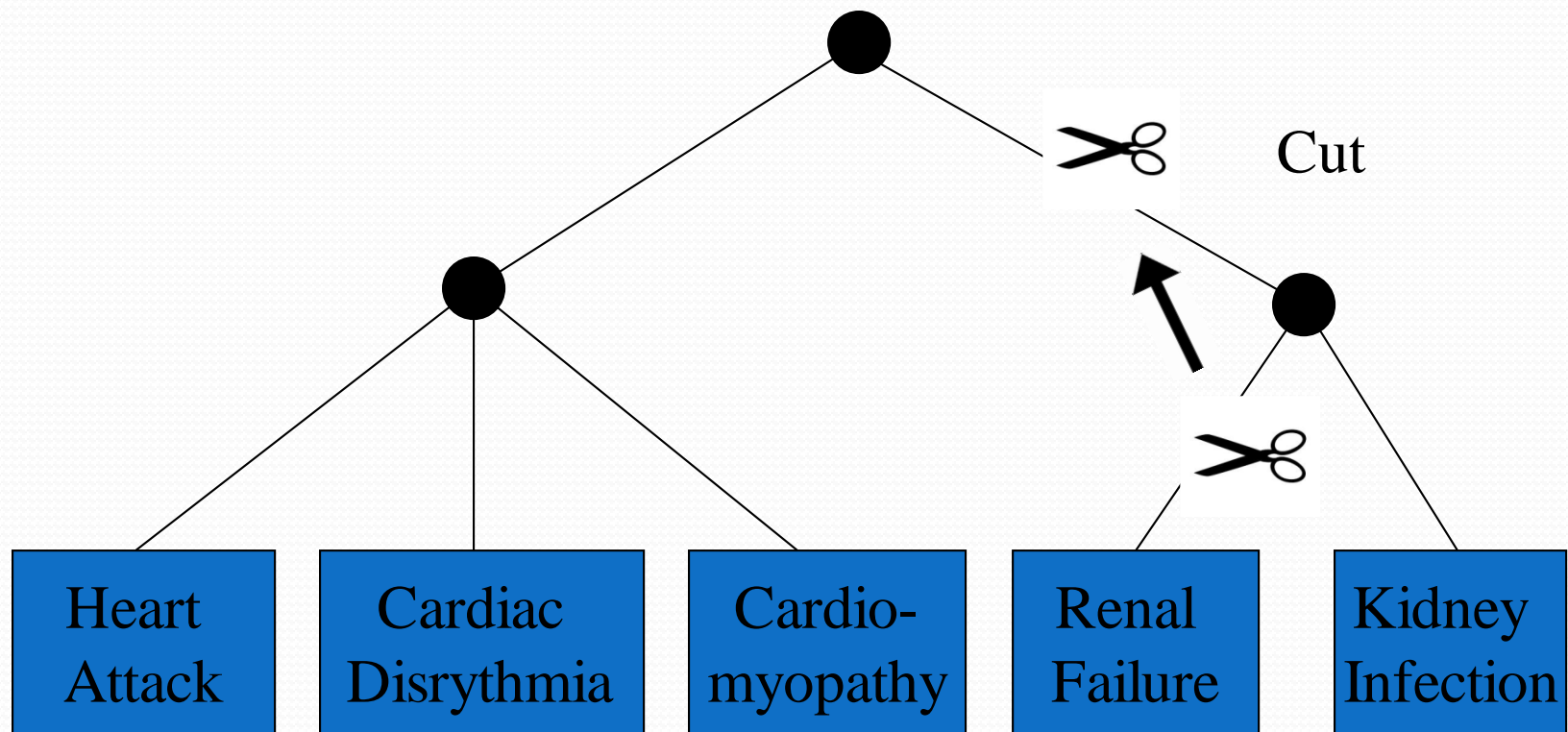
For each leaf, note the observed adverse events in the risk and control intervals.



For each higher level branch, add the observed number of events of its leaves.



A Small Three-Level Tree Variable



Tree-Based Scan Statistic

1. Scan the tree by considering all possible cuts on any branch.
2. For each cut, calculate the likelihood.
3. Denote the cut with the maximum likelihood as the most likely cut (cluster).
4. Generate 9999 Monte Carlo replications under H_0 .
5. Compare the most likely cut from the real data set with the most likely cuts from the random data sets.
6. If the rank of the most likely cut from the real data set is R , then the p-value for that cut is $R/(9999+1)$.



Vaccines



| <u>Vaccine</u> | <u>vaccinees / dose</u> |
|------------------------------|-------------------------|
| Measles-Mumps-Rubella: MMR | ~1,000,000 |
| MMR-V (ProQuad) | ~100,000 |
| Pneumococcal: PCV7 (Prevnar) | ~850,000 |

Participating Health Plans



GroupHealth

HealthCore

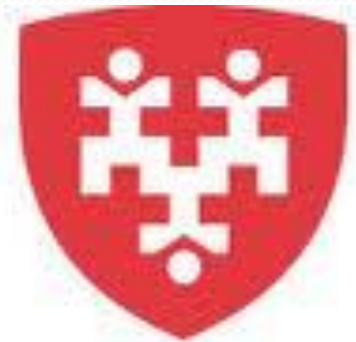


KAISER PERMANENTE®

Georgia, Colorado



HUMANA



Harvard Pilgrim
HealthCare

Risk Interval

Primary Risk Interval:

- 1-28 days after vaccination

Secondary Risk Intervals:

- 1-2 days after vaccination
- 7-10 days after vaccination

Control Interval:

- 29-56 days after vaccination

MMRV, 1-2 years, 1-28 days

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|--------------------------|--|------------|--------------|------------|-----------|-------------|---------------|
| 06 | Diseases of Nervous System and Sense Organs | 180 | 111.2 | 1.6 | 69 | 17.9 | 0.0001 |
| 06.04 | Epilepsy; Convulsions | 84 | 47.4 | 1.8 | 37 | 11.5 | 0.0008 |
| 06.04.02 | Convulsions | 81 | 45.0 | 1.8 | 36 | 11.6 | 0.0008 |
| 06.04.02 (780.3) | Convulsions | 3 | 0.4 | 7.0 | 3 | 3.3 | 0.94 |
| 06.04.02 (780.31) | Febrile Convulsions NOS | 66 | 39.1 | 1.7 | 27 | 7.6 | 0.04 |
| 06.04.02 (780.32) | Complex Febrile Convulsion | 2 | 0.3 | 8.0 | 2 | 2.4 | 0.99 |
| 06.06 | Coma; Stupor; Brain Damage | 12 | 3.5 | 3.5 | 9 | 6.4 | 0.13 |
| 06.06 (780.09) | Alter Consciousness NEC | 10 | 3.3 | 3.0 | 7 | 4.4 | 0.64 |
| 12 | Diseases of Skin and Subcutaneous Tissue | 110 | 63.0 | 1.7 | 47 | 14.3 | 0.0001 |
| 12.04 | Other Skin Disorders | 66 | 37.2 | 1.8 | 29 | 9.0 | 0.01 |
| 12.04 (782.1) | Nonspecific Skin Eruption NEC | 63 | 34.0 | 1.9 | 29 | 9.8 | 0.004 |



MMRV, 1-2 years, 1-2 days

Nothing with $p < 0.05$

MMRV, 1-2 years, 7-10 days

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|----------------------------|--|-----------|------------|-------------|-----------|-------------|---------------|
| 06 | Diseases of Nervous System and Sense Organs | 72 | 16.0 | 4.5 | 56 | 52.2 | 0.0001 |
| 06.04 | Epilepsy; Convulsions | 43 | 6.7 | 6.4 | 36 | 43.7 | 0.0001 |
| 06.04.01 | Epilepsy | 2 | 0.3 | 6.1 | 2 | 1.9 | 0.96 |
| 06.04.02 | Convulsions | 41 | 6.4 | 6.5 | 35 | 41.8 | 0.0001 |
| 06.04.02 (780.31) | Febrile Convulsions NOS | 36 | 5.5 | 6.6 | 31 | 37.1 | 0.0001 |
| 06.04.02 (780.39) | Other Convulsions | 4 | 0.7 | 5.4 | 3 | 3.5 | 0.59 |
| 06.06 | Coma; Stupor; and Brain Damage | 6 | 0.5 | 11.7 | 5 | 9.3 | 0.006 |
| 06.06 (780.09) | Alteration of Consciousness NEC | 6 | 0.5 | 12.4 | 6 | 9.6 | 0.003 |
| 12 | Diseases of The Skin and Subcutaneous Tissue | 34 | 9.3 | 3.6 | 25 | 19.3 | 0.0001 |
| 12.01 | Skin and Subcutaneous Tissue Infections | 9 | 2.8 | 3.2 | 6 | 4.4 | 0.37 |
| 12.01.01 | Cellulitis and Abscess | 9 | 2.4 | 3.8 | 7 | 5.3 | 0.18 |
| 12.01.01.05 (682.6) | Leg Cellulitis | 5 | 0.4 | 11.4 | 5 | 7.6 | 0.03 |
| 12.01.01.07 | Other Cellulitis and Abscess | 3 | 0.9 | 3.3 | 2 | 1.5 | 0.99 |
| 12.01.01.07 (682.5) | Buttock Cellulitis | 2 | 0.3 | 6.8 | 2 | 2.1 | 0.93 |
| 12.02 | Other Inflammatory Condition of Skin | 4 | 1.0 | 3.9 | 3 | 2.5 | 0.87 |
| 12.02.00 | Other Inflammatory Condition of Skin | 4 | 1.0 | 4.0 | 3 | 2.5 | 0.86 |
| 12.02.00 (695.1) | Erythema Multiforme | 2 | 0.3 | 6.1 | 2 | 1.9 | 0.96 |
| 12.04 | Other Skin Disorders | 21 | 5.5 | 3.8 | 15 | 12.5 | 0.0001 |
| 12.04 (782.1) | Nonspecific Skin Eruption NEC | 21 | 5.1 | 4.1 | 16 | 13.9 | 0.0001 |

MMR, 1-2 years, 1-28 days, part 1

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|--------------------------|---|------------|--------------|------------|------------|-------------|---------------|
| 04 | Diseases of Blood & Blood-Forming Organs | 167 | 134.7 | 1.2 | 32 | 3.6 | 0.97 |
| 04.02 | Coagulation and Hemorrhagic Disorders | 48 | 26.5 | 1.8 | 22 | 7.1 | 0.10 |
| 04.02.02 | Thrombocytopenia | 21 | 8.1 | 2.6 | 13 | 7.2 | 0.10 |
| 04.02.02 (287.31) | Immune Thrombocytopenic Purpura | 11 | 1.7 | 6.5 | 9 | 11.2 | 0.001 |
| 04.02.03 | Other Coagulation and Hemorrhagic Disorders | 25 | 13.4 | 1.9 | 12 | 4.0 | 0.90 |
| 04.02.03 (782.7) | Spontaneous Ecchymoses | 19 | 9.5 | 2.0 | 10 | 3.7 | 0.94 |
| 06 | Diseases of Nervous System & Sense Organs | 1195 | 929.8 | 1.3 | 265 | 34.7 | 0.0001 |
| 06.04 | Epilepsy; Convulsions | 603 | 398.6 | 1.5 | 204 | 45.2 | 0.0001 |
| 06.04.02 | Convulsions | 576 | 379.3 | 1.5 | 197 | 44.0 | 0.0001 |
| 06.04.02 (780.31) | Febrile Convulsions NOS | 516 | 326.7 | 1.6 | 189 | 46.6 | 0.0001 |
| 07 | Diseases of the Circulatory System | 210 | 161.9 | 1.3 | 48 | 6.5 | 0.17 |
| 07.02 | Diseases of the Heart | 171 | 124.7 | 1.4 | 46 | 7.7 | 0.048 |
| 07.02.01 | Heart Valve Disorders | 22 | 11.9 | 1.8 | 10 | 3.4 | 0.99 |
| 07.02.02.02 | Other Peri-; Endo-; and Myocarditis | 5 | 1.4 | 3.7 | 4 | 2.8 | 0.99 |
| 07.02.02.02 (423.9) | Pericardial Disease NOS | 4 | 0.7 | 6.0 | 3 | 3.8 | 0.93 |
| 07.02.09 | Cardiac Dysrhythmias | 67 | 39.7 | 1.7 | 27 | 7.8 | 0.046 |
| 07.02.09.07 | Other Cardiac Dysrhythmias | 61 | 35.8 | 1.7 | 25 | 7.3 | 0.07 |
| 07.02.09.07 (785.0) | Tachycardia NOS | 50 | 27.9 | 1.8 | 22 | 7.1 | 0.10 |
| 07.02.11.02 (428.9) | Heart Failure NOS | 7 | 2.1 | 3.3 | 5 | 3.5 | 0.98 |

MMR, 1-2 years, 1-28 days, part 2

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|----------------------|---|------------|--------------|------------|------------|-------------|---------------|
| 12 | Diseases of Skin and Subcutaneous Tissue | 793 | 477.5 | 1.7 | 316 | 86.8 | 0.0001 |
| 12.01 | Skin and Subcutaneous Tissue Infections | 206 | 156.6 | 1.3 | 49 | 7.1 | 0.10 |
| 12.01.01 | Cellulitis and Abscess | 187 | 133.7 | 1.4 | 53 | 9.4 | 0.008 |
| 12.01.01.04 (682.4) | Hand Cellulitis | 11 | 4.8 | 2.3 | 6 | 2.9 | 0.99 |
| 12.01.01.05 (682.6) | Leg Cellulitis | 46 | 25.0 | 1.8 | 21 | 7.0 | 0.10 |
| 12.01.01.07 | Other Cellulitis and Abscess | 71 | 48.3 | 1.5 | 23 | 4.6 | 0.70 |
| 12.02 | Other Inflammatory Condition of Skin | 84 | 55.9 | 1.5 | 28 | 6.1 | 0.25 |
| 12.02 (695.10) | Erythema Multiforme NOS | 18 | 7.7 | 2.3 | 10 | 5.0 | 0.59 |
| 12.02 (695.11) | Erythema Multiforme Min | 4 | 0.7 | 5.9 | 3 | 3.8 | 0.94 |
| 12.02 (698.9) | Pruritic Disorder NOS | 16 | 7.0 | 2.3 | 9 | 4.2 | 0.84 |
| 12.02.00 | Other Inflammatory Condition of Skin | 84 | 55.1 | 1.5 | 29 | 6.5 | 0.17 |
| 12.04 | Other Skin Disorders | 503 | 265.1 | 1.9 | 238 | 84.3 | 0.0001 |
| 12.04 (782.1) | Nonspecific Skin Eruption NEC | 467 | 241.1 | 1.9 | 226 | 82.9 | 0.0001 |
| 17 | Symptoms; Signs; and Ill-Defined Conditions | 986 | 872.0 | 1.1 | 114 | 7.1 | 0.10 |
| 17.01.09 | Allergic Reactions | 349 | 278.6 | 1.3 | 70 | 8.2 | 0.03 |



MMR, 1-2 years, 1-2 days

Nothing with $p < 0.05$

MMR, 1-2 years, 7-10 days

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|----------------------------|---|------------|-------------|------------|------------|--------------|---------------|
| 03 | Endocrine; Nutritional; and Metabolic Diseases and Immunity Disorders | 104 | 62.7 | 1.7 | 41 | 11.3 | 0.001 |
| 03.08 | Fluid and Electrolyte Disorders | 94 | 52.9 | 1.8 | 41 | 12.9 | 0.0002 |
| 03.08.01 (276.1) | Hyposmolality | 8 | 1.9 | 4.1 | 6 | 5.3 | 0.34 |
| 03.08.02 | Hypovolemia | 77 | 45.9 | 1.7 | 31 | 8.8 | 0.01 |
| 03.08.02 (276.5) | Volume Depletion | 18 | 10.3 | 1.8 | 8 | 2.3 | 0.99 |
| 03.08.02 (276.50) | Volume Depletion NOS | 6 | 1.4 | 4.4 | 5 | 4.3 | 0.70 |
| 03.08.02 (276.51) | Dehydration | 53 | 34.1 | 1.6 | 19 | 4.5 | 0.63 |
| 06 | Diseases of Nervous System & Sense Organs | 380 | 133.1 | 2.9 | 247 | 151.8 | 0.0001 |
| 06.04 | Epilepsy; Convulsions | 258 | 56.3 | 4.6 | 202 | 191.0 | 0.0001 |
| 06.04.02 | Convulsions | 252 | 53.5 | 4.7 | 199 | 192.2 | 0.0001 |
| 06.04.02 (780.31) | Febrile Convulsions NOS | 224 | 46.5 | 4.8 | 177 | 174.5 | 0.0001 |
| 06.04.02 (780.39) | Other Convulsions | 26 | 6.0 | 4.3 | 20 | 18.0 | 0.0001 |
| 06.06 | Coma; Stupor; and Brain Damage | 12 | 4.2 | 2.9 | 8 | 4.8 | 0.51 |
| 06.06 (780.09) | Alter Consciousness NEC | 12 | 4.0 | 3.0 | 8 | 5.3 | 0.34 |
| 07 | Diseases of The Circulatory System | 55 | 24.1 | 2.3 | 31 | 14.5 | 0.0001 |
| 07.02 | Diseases of The Heart | 48 | 18.7 | 2.6 | 29 | 16.0 | 0.0001 |
| 07.02.01 | Heart Valve Disorders | 6 | 2.2 | 2.8 | 4 | 2.3 | 0.99 |
| 07.02.05 | Nonspecific Chest Pain | 13 | 6.5 | 2.0 | 6 | 2.5 | 0.99 |
| 07.02.07 (429.9) | Heart Disease NOS | 3 | 0.2 | 16.7 | 3 | 5.6 | 0.25 |
| 07.02.09 | Cardiac Dysrhythmias | 22 | 5.8 | 3.8 | 16 | 13.1 | 0.0001 |
| 07.02.09.07 | Other Cardiac Dysrhythmias | 20 | 5.2 | 3.8 | 15 | 12.0 | 0.0006 |
| 07.02.09.07 (785.0) | Tachycardia NOS | 19 | 4.2 | 4.5 | 15 | 13.8 | 0.0001 |
| 08.09 (478.19) | Nasal & Sinus Disease NEC | 31 | 14.0 | 2.2 | 17 | 7.7 | 0.04 |
| 09 | Diseases of the Digestive System | 192 | 133.0 | 1.4 | 59 | 11.5 | 0.001 |

MMR, 1-2 years, 7-10 days (cont)

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|----------------------|---|-----|------|------|-----|------|--------|
| 10 | Diseases of the Genitourinary System | 71 | 30.9 | 2.3 | 40 | 18.9 | 0.0001 |
| 10.01 | Diseases of the Urinary System | 53 | 23.3 | 2.3 | 30 | 13.9 | 0.0001 |
| 10.01.04 | Urinary Tract Infections | 32 | 15.7 | 2.0 | 16 | 6.5 | 0.14 |
| 10.01.04.01 | Infections of Kidney | 12 | 2.9 | 4.2 | 9 | 8.0 | 0.03 |
| 10.01.04.01 (590.10) | Ac Pyelonephritis NOS | 7 | 1.3 | 5.6 | 6 | 6.3 | 0.16 |
| 10.01.04.01 (590.80) | Pyelonephritis NOS | 5 | 1.5 | 3.4 | 4 | 2.6 | 0.99 |
| 10.01.07 | Other Diseases of Bladder and Urethra | 4 | 0.6 | 6.3 | 3 | 4.0 | 0.80 |
| 10.01.08 | Genitourinary Symptoms and Ill-Defined Conditions | 13 | 3.8 | 3.4 | 9 | 6.7 | 0.11 |
| 10.02 | Diseases of Male Genital Organs | 13 | 5.5 | 2.4 | 8 | 3.7 | 0.89 |
| 12 | Diseases of the Skin and Subcutaneous Tissue | 203 | 74.3 | 2.7 | 129 | 75.3 | 0.0001 |
| 12.01 | Skin and Subcutaneous Tissue Infections | 48 | 23.0 | 2.1 | 25 | 10.3 | 0.003 |
| 12.01.01 | Cellulitis and Abscess | 40 | 20.0 | 2.0 | 20 | 7.7 | 0.04 |
| 12.01.01.05 (682.6) | Leg Cellulitis | 13 | 3.9 | 3.4 | 9 | 6.6 | 0.12 |
| 12.01.02 | Other Skin and Subcutaneous Infections | 8 | 3.0 | 2.7 | 5 | 2.8 | 0.99 |
| 12.02 | Other Inflammatory Condition of Skin | 21 | 8.6 | 2.5 | 12 | 6.4 | 0.15 |
| 12.02.00 | Other Inflammatory Condition of Skin | 21 | 8.5 | 2.5 | 13 | 6.5 | 0.13 |
| 12.02.00 (695.1) | Erythema Multiforme | 7 | 2.7 | 2.6 | 4 | 2.3 | 0.99 |
| 12.02.00 (695.10) | Erythema Multiforme NOS | 6 | 1.4 | 4.4 | 5 | 4.3 | 0.70 |
| 12.02.00 (695.11) | Erythema Multiforme Min | 3 | 0.1 | 31.4 | 3 | 7.4 | 0.052 |
| 12.04 | Other Skin Disorders | 134 | 42.8 | 3.1 | 91 | 61.8 | 0.0001 |
| 12.04 (782.1) | Nonspecific Skin Eruption NEC | 125 | 39.2 | 3.2 | 86 | 59.2 | 0.0001 |

MMR, 1-2 years, 7-10 days (cont)

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|-------------------|--|------------|--------------|------------|-----------|-------------|---------------|
| 17 | Symptoms; Signs; and Ill-Defined Conditions and Factors Influencing Health Status | 211 | 127.2 | 1.7 | 84 | 23.0 | 0.0001 |
| 17.01.06 | Nausea and Vomiting | 112 | 74.9 | 1.5 | 37 | 8.0 | 0.03 |
| 17.01.06 (787.01) | Nausea with Vomiting | 20 | 11.9 | 1.7 | 8 | 2.3 | 0.99 |
| 17.01.06 (787.03) | Vomiting Alone | 92 | 62.6 | 1.5 | 29 | 6.0 | 0.19 |
| 17.01.09 | Allergic Reactions | 75 | 41.7 | 1.8 | 33 | 10.8 | 0.002 |
| 17.01.09 (693.0) | Drug Dermatitis NOS | 11 | 2.9 | 3.8 | 8 | 6.5 | 0.13 |
| 17.01.09 (708.0) | Allergic Urticaria | 13 | 5.4 | 2.4 | 8 | 3.8 | 0.86 |
| 17.01.09 (708.9) | Urticaria NOS | 15 | 7.3 | 2.1 | 8 | 3.1 | 0.97 |

MMR, 1-2 years, 8-21 days

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|--------------------------|---|------------|--------------|------------|------------|--------------|---------------|
| 06 | Diseases of Nervous System & Sense Organs | 690 | 464.4 | 1.5 | 226 | 47.6 | 0.0001 |
| 06.04 | Epilepsy; Convulsions | 365 | 200.2 | 1.8 | 165 | 54.4 | 0.0001 |
| 06.04.02 | Convulsions | 349 | 190.5 | 1.8 | 159 | 52.8 | 0.0001 |
| 06.04.02 (780.31) | Febrile Convulsions NOS | 312 | 165.2 | 1.9 | 147 | 51.6 | 0.0001 |
| 12 | Diseases of Skin and Subcutaneous Tissue | 521 | 239.1 | 2.2 | 282 | 123.8 | 0.0001 |
| 12.01 | Skin and Subcutaneous Tissue Infections | 123 | 76.9 | 1.6 | 46 | 11.7 | 0.0007 |
| 12.01.01 | Cellulitis and Abscess | 109 | 66.1 | 1.7 | 43 | 11.6 | 0.0008 |
| 12.01.01.04 (682.4) | Hand Cellulitis | 7 | 2.6 | 2.7 | 4 | 2.6 | 0.99 |
| 12.01.01.05 (682.6) | Leg Cellulitis | 27 | 12.5 | 2.2 | 15 | 6.4 | 0.17 |
| 12.01.01.07 | Other Cellulitis and Abscess | 45 | 24.0 | 1.9 | 21 | 7.2 | 0.08 |
| 12.01.01.07 (682.5) | Buttock Cellulitis | 17 | 9.4 | 1.8 | 8 | 2.5 | 0.99 |
| 12.02 | Other Inflammatory Condition of Skin | 57 | 27.2 | 2.1 | 30 | 12.4 | 0.0005 |
| 12.02.00 | Other Inflammatory Condition of Skin | 57 | 26.8 | 2.1 | 30 | 12.8 | 0.0003 |
| 12.02.00 (695.1) | Erythema Multiforme | 17 | 8.7 | 2.0 | 8 | 3.1 | 0.99 |
| 12.02.00 (695.10) | Erythema Multiforme NOS | 15 | 3.7 | 4.0 | 11 | 9.6 | 0.007 |
| 12.02.00 (695.11) | Erythema Multiforme Min | 4 | 0.3 | 12.4 | 4 | 6.4 | 0.17 |
| 12.02.00 (698.9) | Pruritic Disorder NOS | 10 | 3.5 | 2.8 | 6 | 3.9 | 0.89 |
| 12.04 | Other Skin Disorders | 341 | 135.1 | 2.5 | 206 | 109.9 | 0.0001 |
| 12.04 (782.1) | Nonsp Skin Eruption NEC | 324 | 122.9 | 2.6 | 201 | 112.9 | 0.0001 |
| 17 | Symptoms; Signs; and Ill-Defined Conditions | 526 | 440.6 | 1.2 | 85 | 7.8 | 0.051 |
| 17.01.09 | Allergic Reactions | 204 | 141.3 | 1.4 | 63 | 12.2 | 0.0005 |
| 17.01.09 (691.0) | Diaper or Napkin Rash | 53 | 31.6 | 1.7 | 21 | 6.0 | 0.23 |
| 17.01.09 (693.0) | Drug Dermatitis NOS | 22 | 9.2 | 2.4 | 13 | 6.4 | 0.16 |
| 17.01.09 (708.0) | Allergic Urticaria | 32 | 18.4 | 1.7 | 14 | 4.1 | 0.85 |
| 17.01.09 (708.9) | Urticaria NOS | 37 | 25.1 | 1.5 | 12 | 2.4 | 0.99 |

Self Control, PCV7, 1-2 yrs, TreeScan, 1-28 d

| MLCCS (ICD9) | Disease Name | O | E | O/E | O-E | LLR | p= |
|---------------------|---|------|-------|-----|-----|------|--------|
| 12 | Diseases of Skin & SubcutaneousTissue | 1029 | 914 | 1.1 | 115 | 14.5 | 0.0001 |
| 12.01.01.05 (682.6) | Leg Cellulitis | 69 | 51 | 1.4 | 18 | 6.5 | 0.05 |
| 12.04 | Other Skin Disorders | 623 | 539.5 | 1.2 | 83 | 13.0 | 0.0003 |
| 12.04 (782.1) | Nonspecific Skin Eruption NEC | 566 | 481.5 | 1.2 | 84 | 14.9 | 0.0001 |
| | Symptoms; Signs; And Ill-Defined Conditions And Factors Influencing Health Status | | | | | | |
| 17 | | 2720 | 2565 | 1.1 | 155 | 9.4 | 0.003 |
| 17.01.09 | Allergic Reactions | 691 | 621.5 | 1.1 | 70 | 7.8 | 0.01 |

Self Control, PCV7, 1-2 yrs, TreeScan 1-2 days

| MLCCS (ICD9) | Disease Name | O | E | O/E | LLR | p= |
|----------------------------|-----------------------|-----------|------------|------------|-------------|---------------|
| 12.01.01.05 (682.6) | Leg Cellulitis | 15 | 3.2 | 4.7 | 13.1 | 0.0004 |
| 13.08 (729.81) | Limb Swelling | 11 | 2.9 | 3.8 | 7.5 | 0.02 |

Limitation: Time Varying Confounders

- Concomitant vaccines (innocent bystander)
- Seasonal vaccines and outcomes
- Very young age
- Vaccine visit initiates diagnostic tests with subsequent diagnosis
- Vaccination as preparation for subsequent planned medical intervention

Self Control, PCV7, 1-3 mths, TreeScan, 1-28 d, part 1

| MLCCS (ICD9) | Disease Name | O | E | O/E | LLR | p= |
|----------------------|--|------------|------------|------------|-------------|---------------|
| 03 | Endocrine; Nutritional; And Metabolic Diseases And Immunity Disorders | 1343 | 1196.5 | 1.1 | 18.0 | 0.0001 |
| 03.11 | Other Nutritional; Endocrine; And Metabolic Disorders [58.] | 350 | 274.5 | 1.3 | 21.0 | 0.0001 |
| 03.11.03 | Other And Unspecified Metabolic; Nutritional; And Endocrine Disorders | 339 | 264 | 1.3 | 21.6 | 0.0001 |
| 03.11.03 (783.3) | Feeding Problem | 232 | 179 | 1.3 | 15.9 | 0.0001 |
| 04 | Diseases Of The Blood And Blood-Forming Organs | 523 | 436 | 1.2 | 17.5 | 0.0001 |
| 04.01 | Anemia | 218 | 164 | 1.3 | 18.1 | 0.0001 |
| 04.01.03 | Deficiency And Other Anemia [59.] | 206 | 149.5 | 1.4 | 21.9 | 0.0001 |
| 04.01.03.07 | Anemia; Unspecified | 160 | 115 | 1.4 | 18.1 | 0.0001 |
| 04.01.03.07 (285.9) | Anemia NOS | 160 | 115 | 1.4 | 18.1 | 0.0001 |
| 07 | Diseases Of The Circulatory System | 1198 | 1067 | 1.1 | 16.1 | 0.0001 |
| 07.02 | Diseases Of The Heart | 906 | 793.5 | 1.1 | 16.0 | 0.0001 |
| 07.02.01 | Heart Valve Disorders [96.] | 162 | 129.5 | 1.3 | 8.2 | 0.0101 |
| 07.02.01.04 | Other Heart Valve Disorders | 139 | 108.5 | 1.3 | 8.7 | 0.0059 |
| 07.02.01.04 (785.2) | Cardiac Murmurs NEC | 122 | 93 | 1.3 | 9.2 | 0.0038 |
| 07.02.09.07 (427.89) | Oth Cardiac Dysrhythmias | 104 | 72 | 1.4 | 14.7 | 0.0001 |

Self Control, PCV7, 1-3 mths, TreeScan, 1-28 d, part 1

| MLCCS (ICD9) | Disease Name | O | E | O/E | LLR | p= |
|----------------------|--|------------|------------|------------|-------------|---------------|
| 03 | Endocrine; Nutritional; And Metabolic Diseases And Immunity Disorders | 1343 | 1196.5 | 1.1 | 18.0 | 0.0001 |
| 03.11 | Other Nutritional; Endocrine; And Metabolic Disorders [58.] | 350 | 274.5 | 1.3 | 21.0 | 0.0001 |
| 03.11.03 | Other And Unspecified Metabolic; Nutritional; And Endocrine Disorders | 339 | 264 | 1.3 | 21.6 | 0.0001 |
| 03.11.03 (783.3) | Feeding Problem | 232 | 179 | 1.3 | 15.9 | 0.0001 |
| 04 | Diseases Of The Blood And Blood-Forming Organs | 523 | 436 | 1.2 | 17.5 | 0.0001 |
| 04.01 | Anemia | 218 | 164 | 1.3 | 18.1 | 0.0001 |
| 04.01.03 | Deficiency And Other Anemia [59.] | 206 | 149.5 | 1.4 | 21.9 | 0.0001 |
| 04.01.03.07 | Anemia; Unspecified | 160 | 115 | 1.4 | 18.1 | 0.0001 |
| 04.01.03.07 (285.9) | Anemia NOS | 160 | 115 | 1.4 | 18.1 | 0.0001 |
| 07 | Diseases Of The Circulatory System | 1198 | 1067 | 1.1 | 16.1 | 0.0001 |
| 07.02 | Diseases Of The Heart | 906 | 793.5 | 1.1 | 16.0 | 0.0001 |
| 07.02.01 | Heart Valve Disorders [96.] | 162 | 129.5 | 1.3 | 8.2 | 0.0101 |
| 07.02.01.04 | Other Heart Valve Disorders | 139 | 108.5 | 1.3 | 8.7 | 0.0059 |
| 07.02.01.04 (785.2) | Cardiac Murmurs NEC | 122 | 93 | 1.3 | 9.2 | 0.0038 |
| 07.02.09.07 (427.89) | Oth Cardiac Dysrhythmias | 104 | 72 | 1.4 | 14.7 | 0.0001 |

Self Control, PCV7, 1-3 months, Treescan, 1-28 days, part 2

| MLCCS (ICD9) | Disease Name | O | E | O/E | LLR | p= |
|----------------------|---|------|--------|-----|------|--------|
| 08 | Diseases of the Respiratory System | 5879 | 5485 | 1.1 | 28.3 | 0.0001 |
| 08.08 | Other Lower Respiratory Disease | 3551 | 3310 | 1.1 | 17.6 | 0.0001 |
| 08.08.03 | Other And Unspecified Lower Respiratory Disease | 3541 | 3300 | 1.1 | 17.6 | 0.0001 |
| 08.08.03 (786.03) | Apnea | 174 | 125 | 1.4 | 19.7 | 0.0001 |
| 08.08.03 (786.09) | Resp Abnormality NEC | 729 | 614.5 | 1.2 | 21.5 | 0.0001 |
| 08.09 | Other Upper Respiratory Disease | 1112 | 1006.5 | 1.1 | 11.1 | 0.0004 |
| 08.09 (784.99) | Sx Involv Head/Neck NEC | 132 | 104 | 1.3 | 7.6 | 0.0199 |
| 09 | Diseases Of The Digestive System | 2985 | 2547.5 | 1.2 | 75.5 | 0.0001 |
| 09.04 | Upper Gastrointestinal Disorders | 1008 | 795.5 | 1.3 | 57.5 | 0.0001 |
| 09.04.01 | Esophageal Disorders | 759 | 600.5 | 1.3 | 42.3 | 0.0001 |
| 09.04.01.02 | Other Esophageal Disorders | 713 | 564.5 | 1.3 | 39.5 | 0.0001 |
| 09.04.01.02 (530.81) | Esophageal Reflux | 705 | 559.5 | 1.3 | 38.3 | 0.0001 |
| 09.04.04 | Other Disorders Of Stomach And Duodenum [141.] | 190 | 145.5 | 1.3 | 13.8 | 0.0001 |
| 09.04.04 (537.0) | Acq Pyloric Stenosis | 49 | 28.5 | 1.7 | 16.4 | 0.0001 |

Self Control, PCV7, 1-3 months, Treescan, 1-28 days, part 3

| MLCCS (ICD9) | Disease Name | O | E | O/E | LLR | p= |
|----------------------|---|------|-------|-----|------|--------|
| 09.05 | Abdominal Hernia | 188 | 128.5 | 1.5 | 28.6 | 0.0001 |
| 09.05.01 | Inguinal Hernia | 100 | 66.5 | 1.5 | 17.7 | 0.0001 |
| 09.05.01.01 | Inguinal Hernia With Obstruction Or Gangrene | 20 | 11.5 | 1.7 | 7.0 | 0.0374 |
| 09.05.01.02 | Inguinal Hernia Without Obstruction Or Gangrene | 80 | 55 | 1.5 | 11.8 | 0.0002 |
| 09.05.01.02 (550.90) | Unilat Inguinal Hernia | 68 | 46 | 1.5 | 11.0 | 0.0005 |
| 09.05.03 | Other Abdominal Hernia | 83 | 55.5 | 1.5 | 14.2 | 0.0001 |
| 09.05.03.04 | Umbilical Hernia Without Obstruction/Gangrene | 61 | 42 | 1.5 | 8.9 | 0.004 |
| 09.05.03.04 (553.1) | Umbilical Hernia | 61 | 42 | 1.5 | 8.9 | 0.004 |
| 09.12 | Other Gastrointestinal Disorders | 728 | 634 | 1.2 | 14.0 | 0.0001 |
| 10 | Diseases Of The Genitourinary System | 1053 | 920 | 1.1 | 19.3 | 0.0001 |
| 10.01 | Diseases Of The Urinary System | 883 | 791 | 1.1 | 10.7 | 0.0005 |
| 10.01.04 | Urinary Tract Infections | 625 | 563 | 1.1 | 6.8 | 0.0444 |
| 10.02 | Diseases Of Male Genital Organs | 143 | 105.5 | 1.4 | 13.6 | 0.0001 |
| 10.02.03 | Other Male Genital Disorders | 124 | 88.5 | 1.4 | 14.6 | 0.0001 |
| 10.02.03 (603.9) | Hydrocele NOS | 61 | 40.5 | 1.5 | 10.9 | 0.0005 |
| 16 | Injury And Poisoning | 129 | 102.5 | 1.3 | 6.9 | 0.0402 |

Self Control, PCV7, 1-3 months, Treescan, 1-28 days, part 4

| MLCCS (ICD9) | Disease Name | O | E | O/E | LLR | p= |
|-------------------|--|------|--------|-----|------|--------|
| 17 | Symptoms; Signs; And Ill-Defined Conditions And Factors Influencing Health Status | 2520 | 2335 | 1.1 | 14.7 | 0.0001 |
| 17.01 | Symptoms; Signs; And Ill-Defined Conditions | 2520 | 2335 | 1.1 | 14.7 | 0.0001 |
| 17.01.06 | Nausea And Vomiting [250.] | 1496 | 1392.5 | 1.1 | 7.7 | 0.0188 |
| 17.01.06 (787.03) | Vomiting Alone | 1323 | 1218.5 | 1.1 | 9.0 | 0.004 |
| 17.01.07 | Abdominal Pain [251.] | 570 | 477 | 1.2 | 18.2 | 0.0001 |
| 17.01.07 (789.00) | Abdominal Pain-Site NOS | 487 | 404.5 | 1.2 | 16.9 | 0.0001 |
| 18 | Residual Codes; Unclassified; All E Codes [259. And 260.] | 748 | 668 | 1.1 | 9.6 | 0.0022 |
| 18.00 (783.0) | Anorexia | 80 | 58.5 | 1.4 | 8.1 | 0.0112 |

Due to age bias, none of this should be considered to be signals.

Total Events

| | | | Observed Cases | | |
|-------------|-----------|-------------|----------------|---------------|-------------|
| Vaccine | Age | Days | Risk Interval | Ctrl Interval | RR |
| PCV7 | 30 | 1-28 | 18681 | 17017 | 1.22 |
| PCV7 | 120 | 1-28 | 12027 | 11897 | 1.02 |
| PCV7 | 180 | 1-28 | 11301 | 11340 | 0.99 |
| PCV7 | 360 | 1-28 | 15074 | 14504 | 1.08 |

Conclusions

- Using three pilot products, the self-control tree based scan statistic worked well for vaccine safety data mining
 - Known adverse reactions were found
 - Very few false alerts; adjusts for multiple testing
- Limitations
 - Problem for very young toddlers due to age bias
 - Only acute events were evaluated
 - Only three products were examined

Thank You!

