Monitoring all Drugs for a Specific Outcome in the Sentinel System

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ICPE Disclosure Slide

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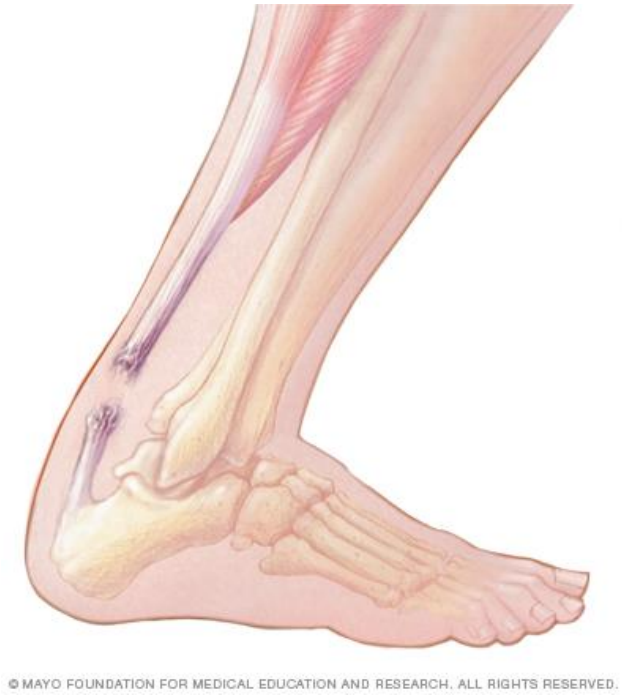
- No relationships to disclose

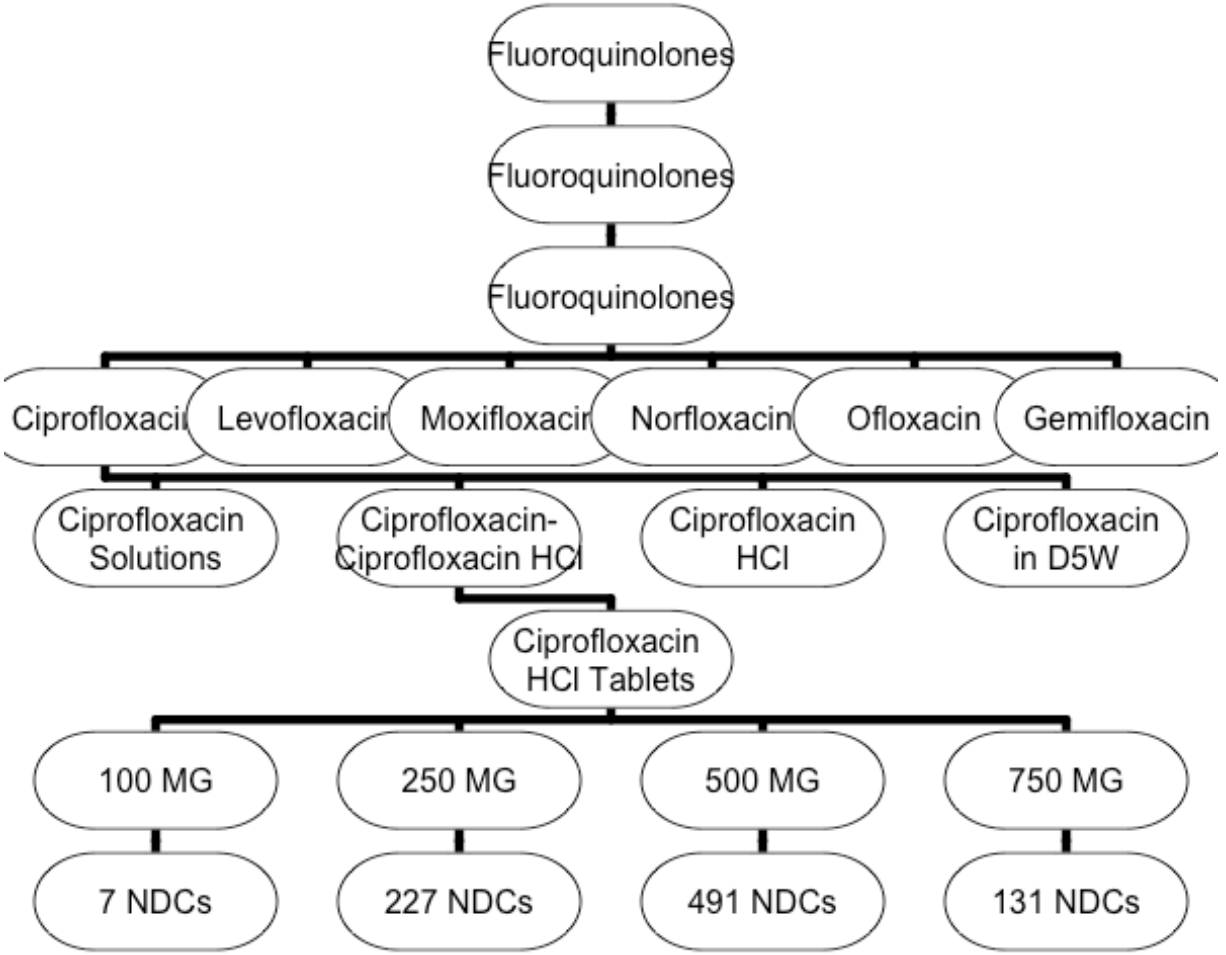
What is

- A signal detection / data-mining method
- Scans electronic health data that are grouped into hierarchical tree structures
- Automatically adjusts for multiple hypothesis testing

http://www.treescan.org

What is an Outcome-Oriented Scan / DrugScan (1 Outcome: M Exposures)?





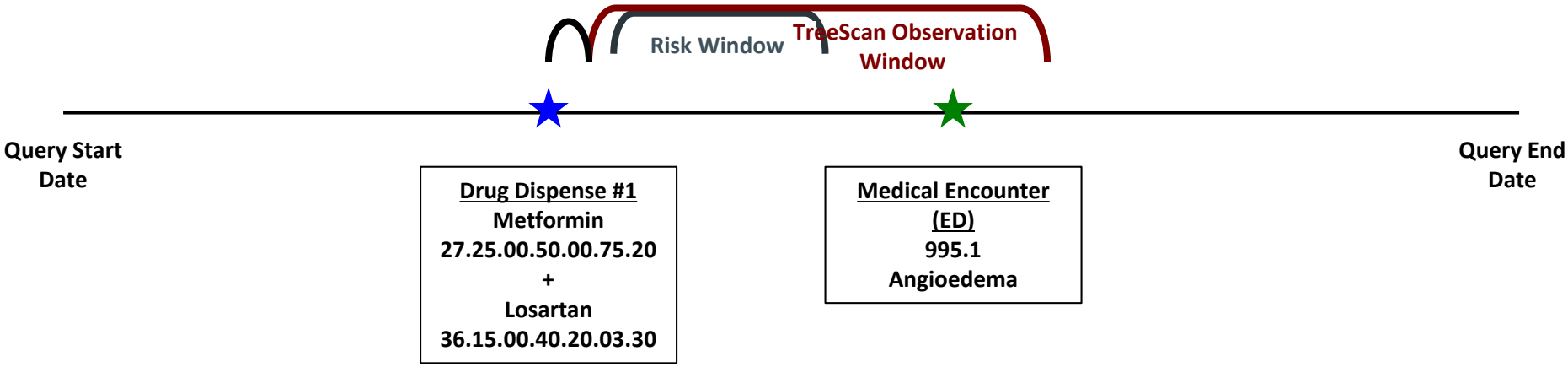
Total Nodes: 35,583 aggregate + 326,497 NDC codes

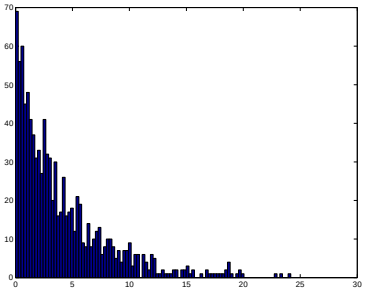
Surveillance Population

- Claims Data from 3 Data Partner Sites (2000-2014)
  - Not all sites had data back to 2000
- Males and Females >=18 years with medical and drug coverage and incident outcome of interest
- Outcome of Interest
  - Angioedema

DrugScan Analytic Design and Statistics

- Case-Crossover Design (Self-Controlled)
- Incident Exposures or New “Starts” of Therapeutic
- Duration of Treatment Ignored
  - not “As Treated”
- Fixed and Variable Risk Window Scan Statistics





Conditional Tree-Based Scan Statistic Hypotheses for Outcome-Oriented Scan

H_0: The probability of an outcome after the dispensing of a drug is modified (conditioned) by the total number of events in the dataset across the observation window on that given day.

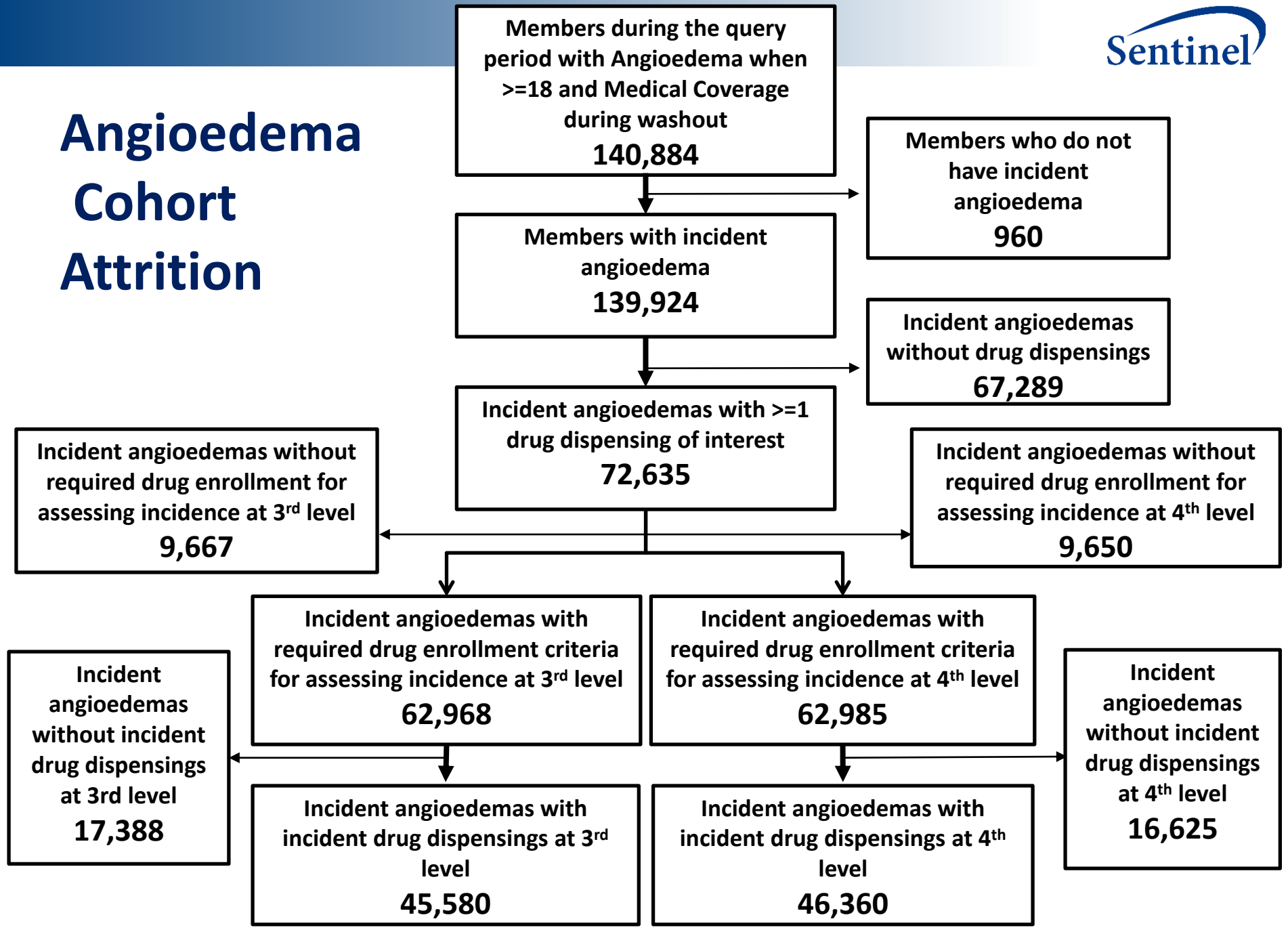
H_A: There are at least some time periods in the observation window when the probability of an outcome is higher . . . after various adjustments

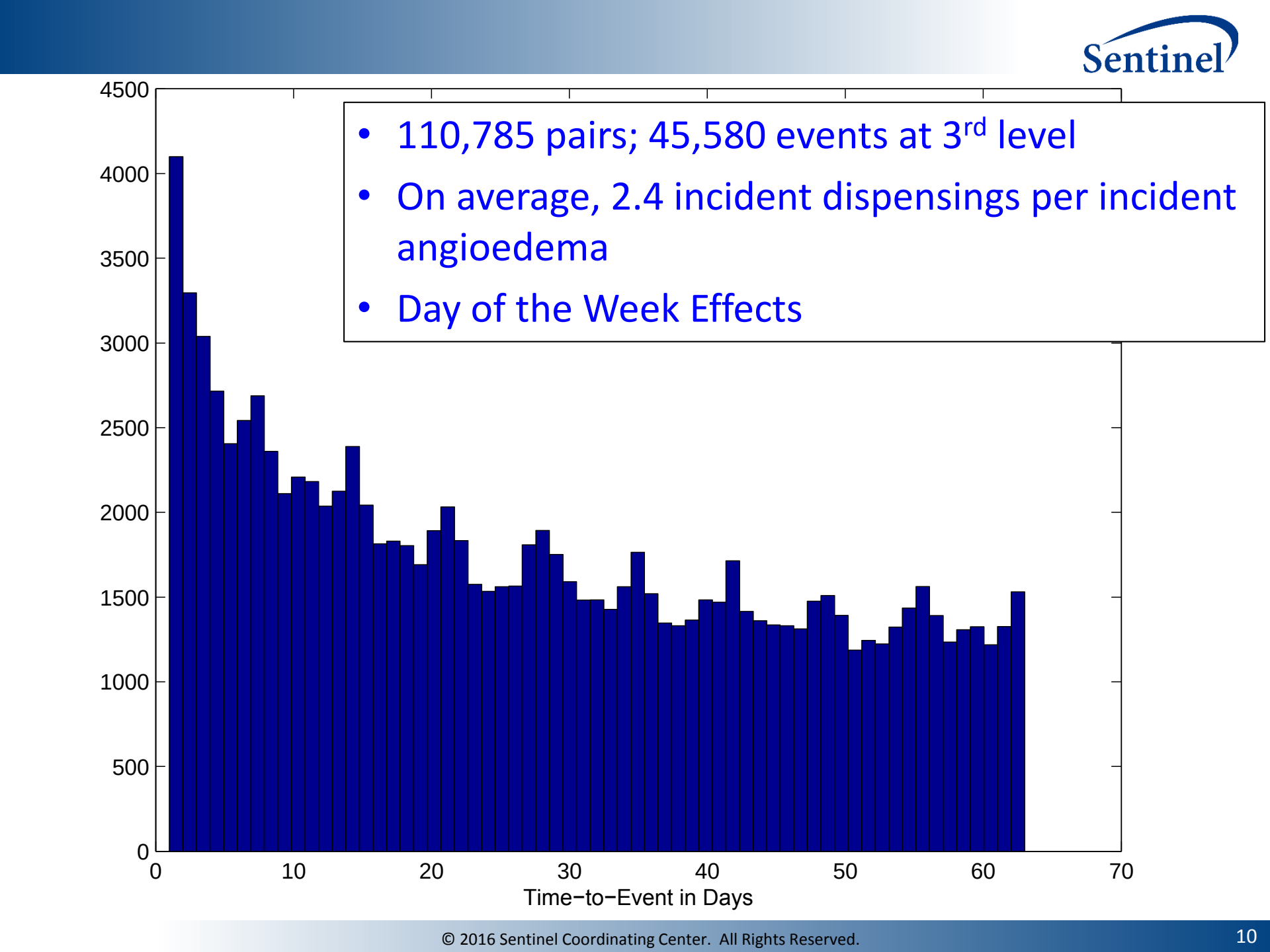
Angioedema Takeaways

1) Manageable Total Number of Alerts
2) More Potential Misclassification of Disease Onset than Anticipated

Results

Angioedema Cohort Attrition





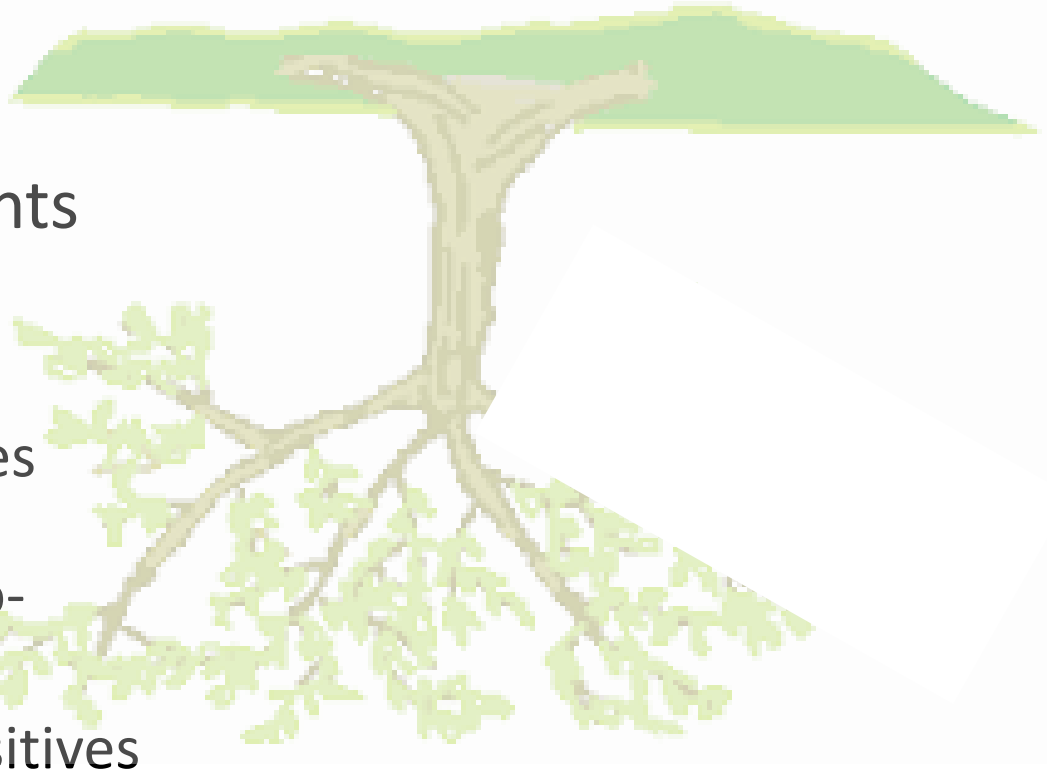
- 110,785 pairs; 45,580 events at 3rd level
- On average, 2.4 incident dispensings per incident angioedema
- Day of the Week Effects

Angioedema Results

- 28 unique alerts at 0.05 level, 20 meaningfully different
  - 9 were angioedema treatments
    - e.g., Glucocorticosteroids, Hydroxyzine, Diphenhydramine
  - Rest were known positives or likely positives
    - ACE inhibitors, Buproprion, Simvastatin, Antibiotics

Angioedema Sensitivity Analyses

1. Pruned out all anti-histamines and other angioedema treatments (e.g., hydroxyzine, glucocorticosteroids)
   - Strong known positives remain with slight adjustment of time-to-event
   - Lose some known positives (adjusted conditional analysis)
   - Some new alerts



Tree-Temporal Alerts after Pruning

- 13 unique at 3rd level, 9 meaningfully different
- Some new antibiotics, ACEI Combos are statistically significant.
- Some alerts become not statistically significant at 0.05 level (e.g., simvastatin)

Angioedema Summary

1. Misclassification of Disease Onset is present
   - DESIGN: Prune out anti-histamines from the tree *a priori*

     OR
   - DESIGN: Refine outcome definitions with MORE exclusions

     OR
   - ANALYSIS: Prune based at analysis phase
2. Detects known positives without too many false positives

Acknowledgments

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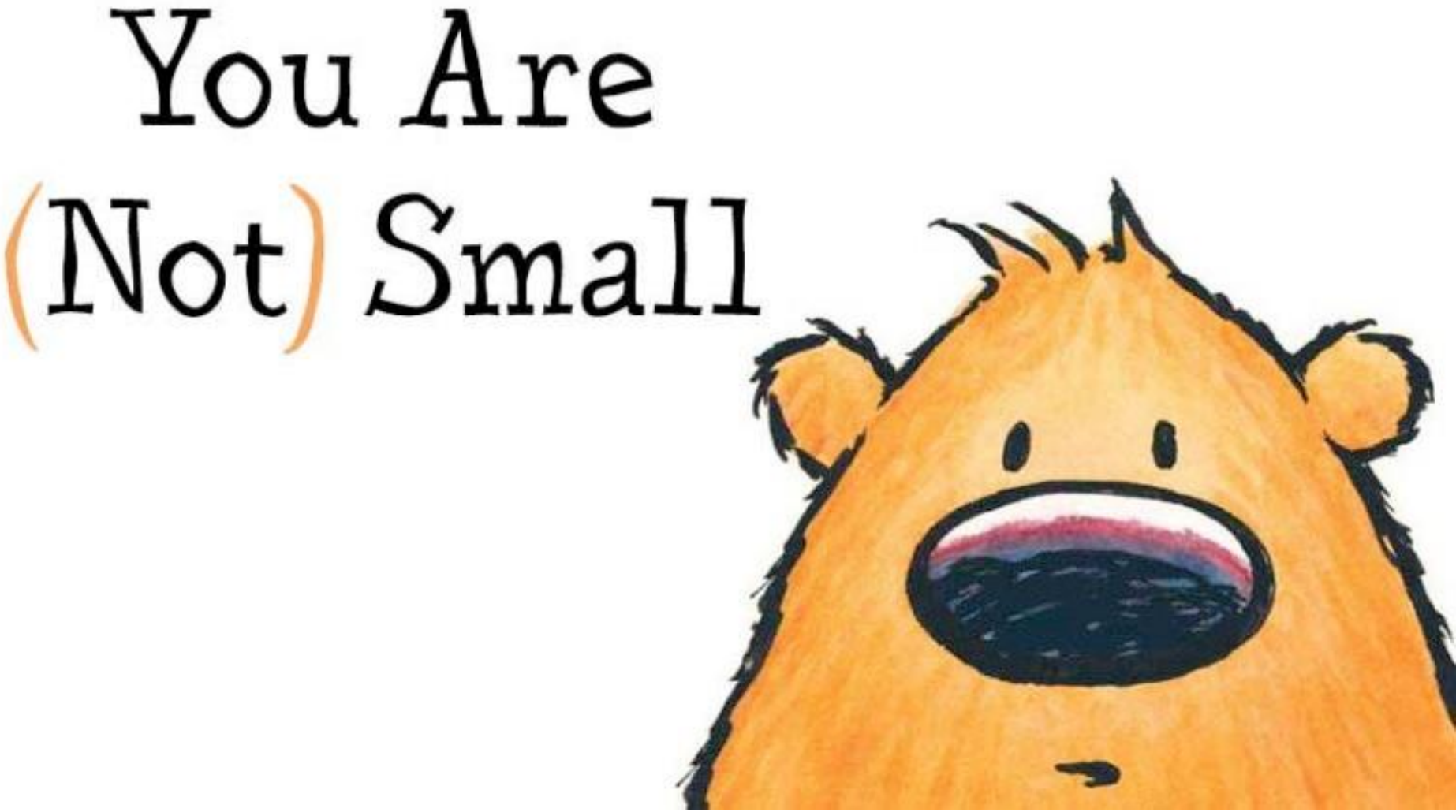
Q&A



Angioedema, 3rd level, Tree-temporal, Conditional

-28 unique
-20 different

Grey=Mis-classification of onset

Green=Known Positive

Yellow=Likely Positive

Pink=Likely False Positive

Node Name	Node ID	Node Events	Window Start	Window End	Cases in Window	Expected Cases	Observed/ Expected	Test Statistic	P-value
*Glucocorticosteroids***	221000	11127	1	8	3526	2324.33	1.52	274.41	1.00E-05
Prednisone	2210004500	7009	1	7	2145	1314.87	1.63	222.79	1.00E-05
Methylprednisolone	22100030	3893	1	8	1141	813.21	1.4	59.12	1.00E-05
Methylprednisolone	2210003000	3891	1	8	1140	812.8	1.4	58.95	1.00E-05
Epinephrine	3890004000	3640	1	15	1925	1256.27	1.53	154.87	1.00E-05
*H-2 Antagonists***	492000	1917	1	6	606	313.11	1.94	107.65	1.00E-05
Famotidine	4920003000	781	1	6	296	127.56	2.32	80.85	1.00E-05
Ranitidine HCl	4920002010	939	1	6	251	153.37	1.64	26.05	1.00E-05
Hydroxyzine	57200040	2174	1	4	467	257.99	1.81	68.31	1.00E-05
*Antianxiety Agents Misc.***	572000	2268	1	4	472	269.15	1.75	62.47	1.00E-05
Hydroxyzine HCl	5720004010	1931	1	4	407	229.15	1.78	56.09	1.00E-05
Hydroxyzine Pamoate	5720004020	243	1	10	104	60.23	1.73	13.04	0.00517
Sulfamethoxazole-Trimethoprim	1699000230	1812	3	13	641	431.96	1.48	44.16	1.00E-05
*Antihistamines Ethanolamines***	412000	169	1	6	73	27.6	2.64	25.61	1.00E-05
Diphenhydramine HCl	4120003010	159	1	6	70	25.97	2.7	25.39	1.00E-05
Diphenhydramine	41200030	160	1	6	70	26.13	2.68	25.11	1.00E-05
Lisinopril	3610003000	2169	2	8	502	372.83	1.35	20.24	1.00E-05
*ACE Inhibitors***	361000	2649	2	8	594	455.34	1.3	19.33	2.00E-05
Minocycline HCl	400004010	199	12	19	63	28.26	2.23	15.78	0.0002
Bupropion HCl	5830004010	390	19	30	122	72.96	1.67	13.69	0.00254
*Central Muscle Relaxants***	751000	1243	54	63	222	153.14	1.45	13.60	0.00279
Levofloxacin	500003400	1115	1	3	161	104.99	1.53	12.84	0.00669
Levofloxacin	5000034	1116	1	3	161	105.09	1.53	12.79	0.00718
*Benzodiazepines***	571000	1491	41	63	531	425.52	1.25	12.16	0.01492
Simvastatin	3940007500	802	42	54	188	129	1.46	11.82	0.0217
*HMG CoA Reductase Inhibitors***	394000	2008	42	54	414	322.99	1.28	11.80	0.02207
*Selective Serotonin Reuptake Inhibitors (SSRIs)***	581600	1044	32	59	469	372.2	1.26	11.66	0.02514
Triazolam	6020104000	35	51	52	8	0.77	10.41	11.51	0.02985

Tree-Temporal Alerts after Pruning

Node Name	Node ID	Node Cases	Window Start	Window End	Cases in Window	Expected Cases	Observed/ Expected	Test Statistic	P-Value
Sulfamethoxazole-Trimethoprim	1699000230	1812	3	12	598	373.06	1.6	57.51	1.00E-05
Lisinopril	3610003000	2169	1	8	590	402.72	1.47	38.23	1.00E-05
*ACE Inhibitors***	361000	2649	2	8	594	407.13	1.46	37.71	1.00E-05
Levofloxacin	500003400	1115	1	6	249	158.23	1.57	22.18	1.00E-05
Levofloxacin	5000034	1116	1	6	249	158.39	1.57	22.08	1.00E-05
*Fluoroquinolones***	50000	3159	1	6	588	447.95	1.31	20.02	1.00E-05
Minocycline HCl	400004010	199	15	19	44	15.95	2.76	16.60	3.00E-05
Clindamycin	16220020	770	1	7	189	127.28	1.48	13.02	0.0012
Clindamycin HCl	1622002010	769	1	7	188	127.1	1.48	12.71	0.0018
Bupropion HCl	5830004010	390	18	31	136	85.58	1.59	12.59	0.00199
Lisinopril & Hydrochlorothiazide	3699180255	748	2	9	188	128.84	1.46	11.90	0.00465
ACE Inhibitors & Thiazide/Thiazide-Like	36991802	814	2	9	201	139.95	1.44	11.74	0.00571
Triazolam	6020104000	35	51	52	8	0.94	8.48	10.05	0.0463

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