



US Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Collaboration



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Team

Northeastern University

- David Madigan
- Michael Pollastri
- Karina Alexander

University of California, Los Angeles

- Marc Suchard
- Jianxiao Yang
- Kelly Li

Johns Hopkins University

- Akihiko Nishimura



US Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST)

The Center for Biologics Evaluation and Research (CBER) is one Center within the Food and Drug Administration (FDA)

CBER's mission is to protect and enhance the public health through the regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies.

Biologics Effectiveness and Safety (BEST) System

Launched in 10/2017 as part of (CBER) to expand and enhance CBER's access to new and better data sources, methods, tools, expertise and infrastructure to conduct surveillance and epidemiologic studies.



US Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST)

- Vision
 - For it to be the pre-eminent resource for evaluating biologic product safety and effectiveness that leverages high-quality data, analytics and innovation to enhance surveillance, real-world evidence generation, and clinical practice that benefits patients
- Objectives are to:
 - Build data, analytics, infrastructure for an active, large-scale, efficient surveillance system for biologic products, develop innovative methods to utilize electronic health records (EHR) establish automated adverse events reporting utilizing natural language processing and artificial intelligence



FDA BEST OHDSI Collaboration

FDA BEST CONVENER

GOAL

Provide support to the FDA's BEST initiative to address safety and effectiveness of biological products (vaccines, blood and blood products, tissues and advanced therapeutics).

Task 1	Management & Governance
Task 2	Meetings and Workshops (seminar series)
Task 3	Methods Research Development
Task 4	Training, Outreach and Engagement
Task 5	Management Plan
Task 6	Risk Management Registry
Task 7	Publish and Post Documents



FDA BEST OHDSI Collaboration

FDA BEST CONVENER

- **Meetings and workshops (seminar series)** designed to host meetings and execute workshops for the FDA and external stakeholders. Led primarily by Michael Pollastri and David Madigan (NU)
- **Methods research development** designed to develop methods for using observational data (EHR and claims data). Lead primarily by Marc Suchard (UCLA)
- **Training, outreach and engagement** designed to educate FDA staff, stakeholders and the research community BEST infrastructure, capabilities, and applications that serve FDA and stakeholder needs. Led by Rita Kukafka (Columbia)



Meetings and Workshops (OHDSI Center @ Roux)



Meetings and Workshops

Working in collaboration with the FDA we will convene meetings and workshops to aid in CBER's public health mission

CBER-regulated product areas: A public assembly with participation from specific regulated biologic product stakeholders and communities including manufacturers, academia, researchers, patients, and others.

Methods development topics: Focused presentations and discussions on methods development topic areas including but not limited to epidemiological, informatics, statistical and others to support BEST and related CBER programs.

Technology topics: Potential discussions of artificial intelligence, machine learning, natural language processing, supercomputing, computational sciences, next generation sequencing, modeling, systems biology and others.

Issue-based topics: Topics may range from real-world data, real-world evidence, RWD and RWE-generation, digital technologies, patient input science, clinical trial design, benefit-risk assessment, observational study design, and others.

FDA BEST Annual Meeting, an additional day coordinated with OHDSI annual Symposium.



OHDSI Center @ Roux

- Build a research portfolio related to core OHDSI activities
- Develop a suite of related educational programs – badges, certificates, degrees
- Provide support services to the OHDSI community
- Create a legal entity for OHDSI
- Coming soon: ohdsi.northeastern.edu





FDA BEST @ NU

- Hosting a seminar series:

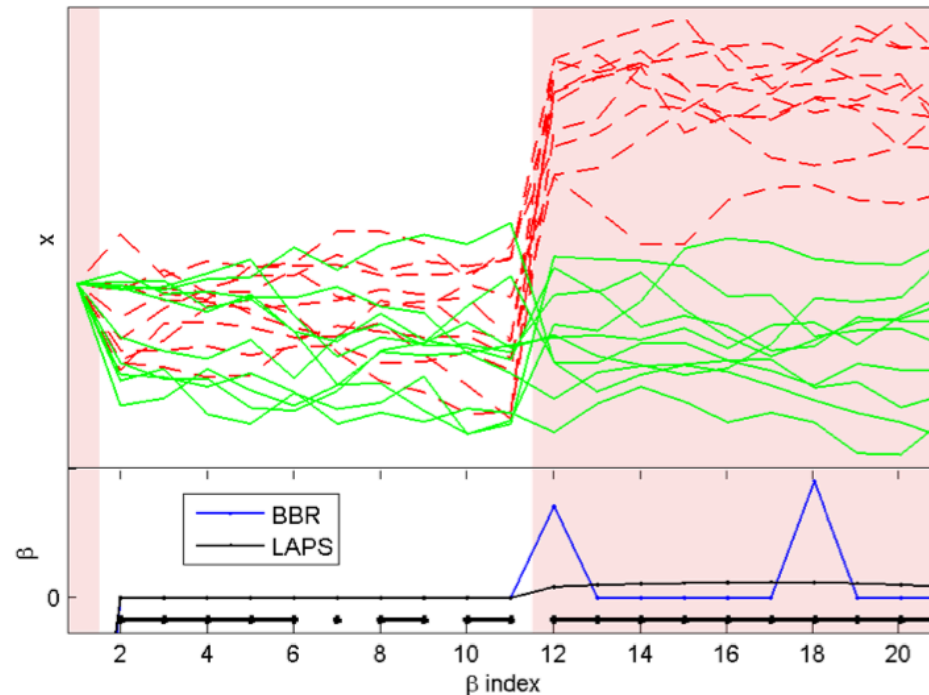
Seminar Speakers

Date	Speaker	Affiliation	Title
3/24/21	Dr. Daniel Salmon	Johns Hopkins University	Vaccine safety surveillance systems for routine and pandemic immunization programs
5/5/21	Dr. Ben Goldstein	Duke	Understanding Informed Presence Bias in EHR Data
6/16/21	Bruce Fireman	Kaiser Permanente	
7/28/21	Dr. Jessica <u>Gronsbell</u>	University of Toronto	



FDA BEST @ NU

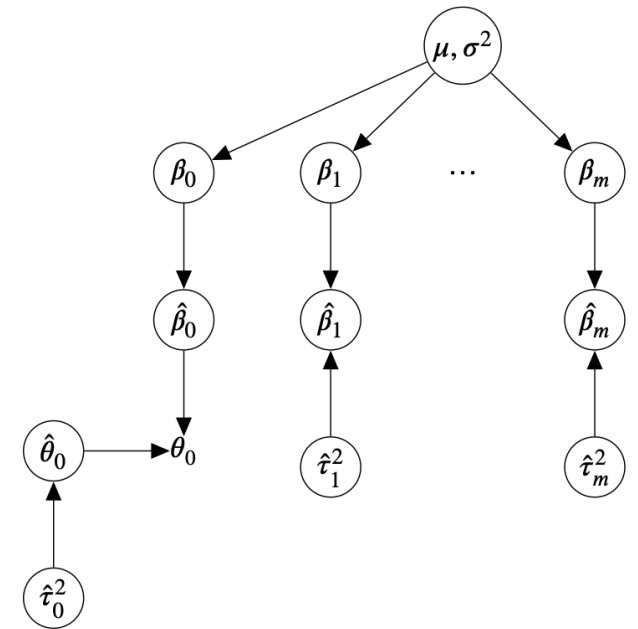
- Methods work just beginning
- Focus on predictive modeling and causal inference from longitudinal data





FDA BEST @ NU

- Bayesian calibration
- Melding of diverse causal estimates
- Prediction with functional inputs like EKG traces and MRI images





Methods Research Development



COVID-19 Vaccine Safety Methods Research

- AstraZeneca vaccine
 - March 11-15, 2021 – 13 European countries suspend use for fears of blood clots
 - Denmark, Norway, Iceland, Bulgaria, Ireland, Netherlands, Spain, Germany, Italy, France, ...
 - As of March 16, 2021 – of 20 million persons vaccinated in Europe several deaths
 - 469 thromboembolic events reported after vaccination
 - 7 cases disseminated intravascular coagulation (DIC)
 - 18 cases cerebral venous sinus thrombosis (CVST)
 - March 18, 2021 – EMA determines benefits outweigh the risks
 - Thromboembolic events “lower than that **expected in the general population**”
 - DIC and CVST above baseline but very rare
 - “The number of reported events **exceeds those expected**, and causality although not confirmed, cannot therefore be excluded. However, given the rarity of the events, and the **difficulty of establishing baseline incidence** since COVID-19 itself is resulting in hospitalisations with thromboembolic complications, the strength of any association is uncertain.”
 - March 22, 2021 – US effectiveness: 79% infection (incl. older adults), 100% severe



COVID-19 Vaccine Safety Methods Research

- Adverse events of special interest (AESI)
 - Vaccine-induced outcomes
- One approach: compare COVID-19 vaccine incidence rates to baseline rates
 - European EMA protocol – compare reports to overall rates
 - FDA protocols – use database-specific rates
- OHDSI methods research
 - Phenotyping the AESI
 - Produce rates for use by agencies along with caveats
 - *Sensitivity of background rates to design choices – initial FDA emphasis
 - Compare surveillance methods (Martijn Schuemie PLE/PLP WG)



Broader OHDSI Initiative

- Patrick Ryan
- Anna Ostropolets
- George Hripcsak
- David Madigan
- Marc Suchard
- Daniel Prieto-Alhambra
- Xintong Li
- Talita Duarte-Salles
- Rupa Makadia
- Gowtham Rao
- Martijn Schuemie
- Anthony Sena
- Azza Shoaibi
- Eugenia Martinez-Hernandez
- Antonella Delmestri
- Katia Verhamme
- Peter Rijnbeek

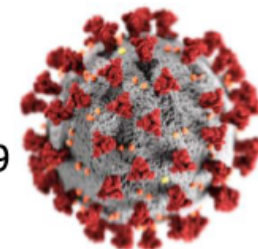


European Medicines Agency

- vACCine covid-19 monitoring readinESS (ACCESS)
 - Estimate baseline rates of AESI in general population 2017-2020
 - Year, sex, age, data source
 - 10 data sources, 7 countries
 - Incidence rates (and 95% exact CIs) per time at risk by year
 - AESI (23): Guillain-Barré Syndrome (GBS), Acute disseminated encephalomyelitis (ADEM), Narcolepsy, Acute aseptic arthritis, Type I Diabetes, Thrombocytopenia, etc.
 - Control events to assess the effect of the pandemic
 - Colonic diverticulitis, Hypertension

ACCESS

vACCine covid-19



monitoring readinESS



US Food and Drug Administration

- Plan to compare incidence rates in COVID-19 vaccinated persons to baseline rates from the same database
 - 4 claims, 4 EHR data sources
- Poisson MaxSPRT model
 - Poisson process, spend alpha on sequential hypotheses, test margin
- Looking at pre-COVID and peri-COVID baseline rates, and influenza
- Leads to signal verification if positive

Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring

Draft Protocol

Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Biologics Effectiveness and Safety (BEST) Initiative



Outcomes

- Acute myocardial infarction (MI)
- Anaphylaxis
- Appendicitis
- Bell's palsy
- Deep vein thrombosis (DVT)
- Disseminated intravascular coagulation (DIC)
- Encephalomyelitis
- Guillain-Barre syndrome (GBS)
- Hemorrhagic stroke
- Non-hemorrhagic stroke
- Immune thrombocytopenia
- Myocarditis/pericarditis
- Narcolepsy
- Pulmonary embolism (PE)
- Transverse myelitis.



Phenotyping

- Patrick Ryan, lead
- Literature review, protocol definitions
- Knowledge engineering
 - Concept prevalence, PHEOBE, cohort diagnostics
- Evaluation
 - Phevaluator, face validity of incidence rates
- Comparison to FDA
 - FDA in general more specific; some codes to check either way



Descriptive epidemiology of AESI for COVID-19 vaccines

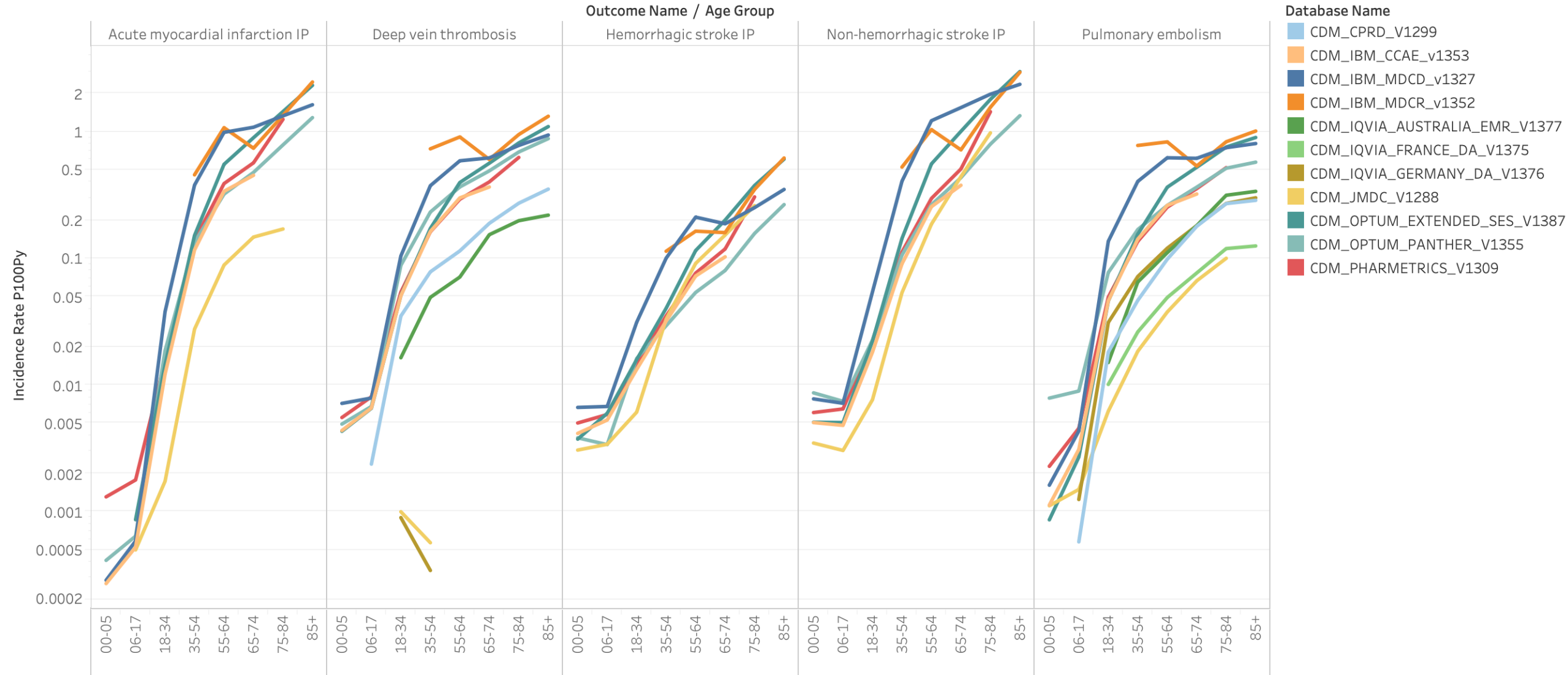
- Xintong Li, lead
- Best estimate of background incidence rates from 2017 to 2019
- 5 claims, 8 EHR databases from 8 countries
- Estimates stratified by age, sex, database
- 227,043,370 total person-years of follow up (largest ever)
- Incidence per 100K person years from 1 (transverse myelitis 1-17yo) to 1523 (non-hemorrhagic stroke >85yoF)



Methods study related to estimating incidence rates for AESI

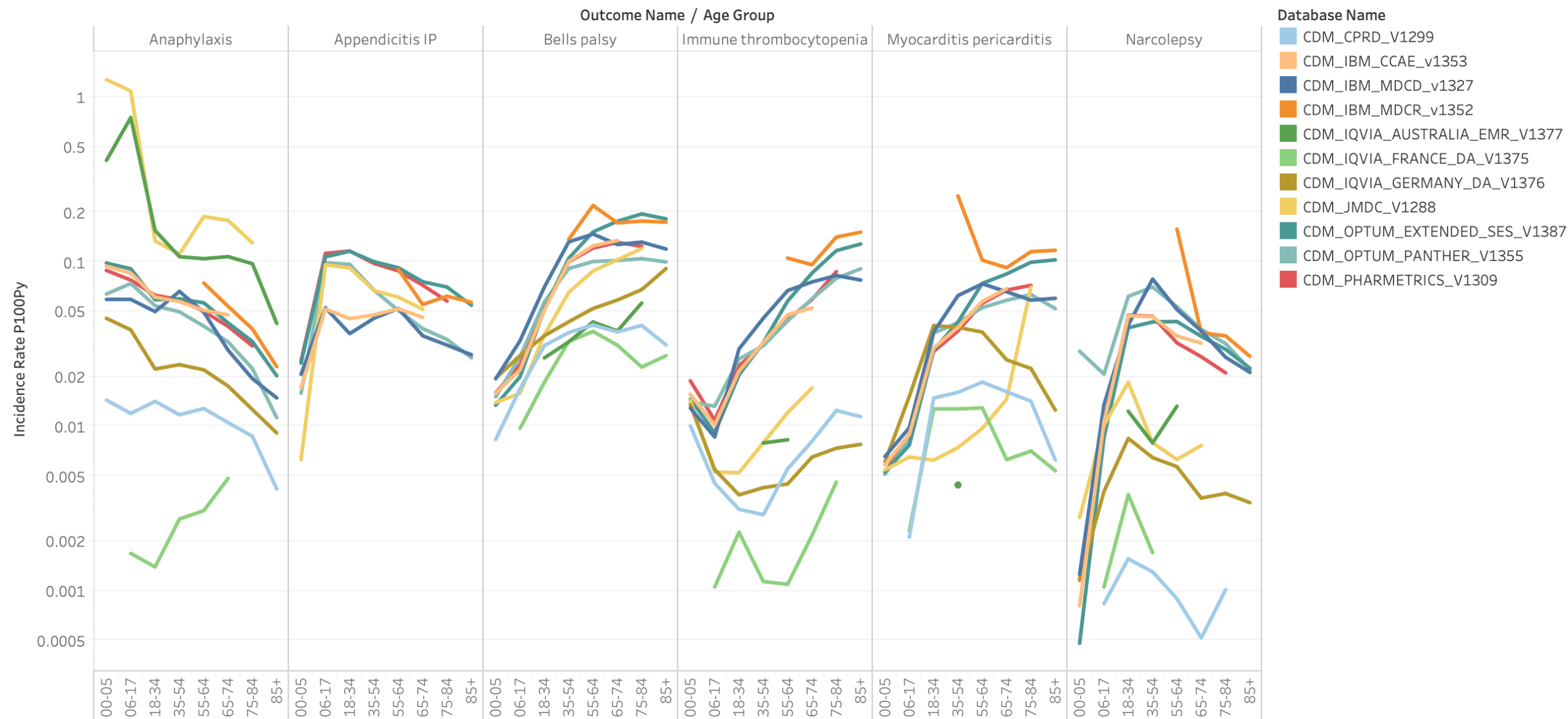
- Anna Ostropolets, lead
- Study factors that affect incidence rates
 - Age, sex, database
 - Target population
 - FDA required visit in year for EHR databases to ensure patient is active
 - Time at risk
 - Vaccine cohorts will have limited time at risk (2, 28, 42, 90, 365 days) but baseline rates may be estimated from full years to maximize power
 - Anchoring
 - Start time at risk at an arbitrary date or at an event (visit, well visit, vaccination)
 - COVID-19 vaccination may be anchored or not
 - Year (secular trend), season, COVID-19 affect on health care
- **Protocol written, edited by FDA, executed**

CIOMS 'Common' Events, Incidence rate by age and gender



The trend of Incidence Rate P100Py as an attribute for Age Group broken down by Outcome Name. Color shows details about Database Name. Details are shown for Gender. The data is filtered on Target Name, Time At Risk Id and Num Outcomes as an attribute. The Target Name filter keeps persons at risk at start of year 2017-2020 with ≥ 365 d prior observation. The Time At Risk Id filter keeps 5. The Num Outcomes as an attribute filter includes values greater than or equal to 5. The view is filtered on Outcome Name, Age Group, Database Name and Gender. The Outcome Name filter keeps Acute myocardial infarction IP, Deep vein thrombosis, Hemorrhagic stroke IP, Non-hemorrhagic stroke IP and Pulmonary embolism. The Age Group filter keeps 8 members. The Database Name filter has multiple members selected. The Gender filter keeps All.

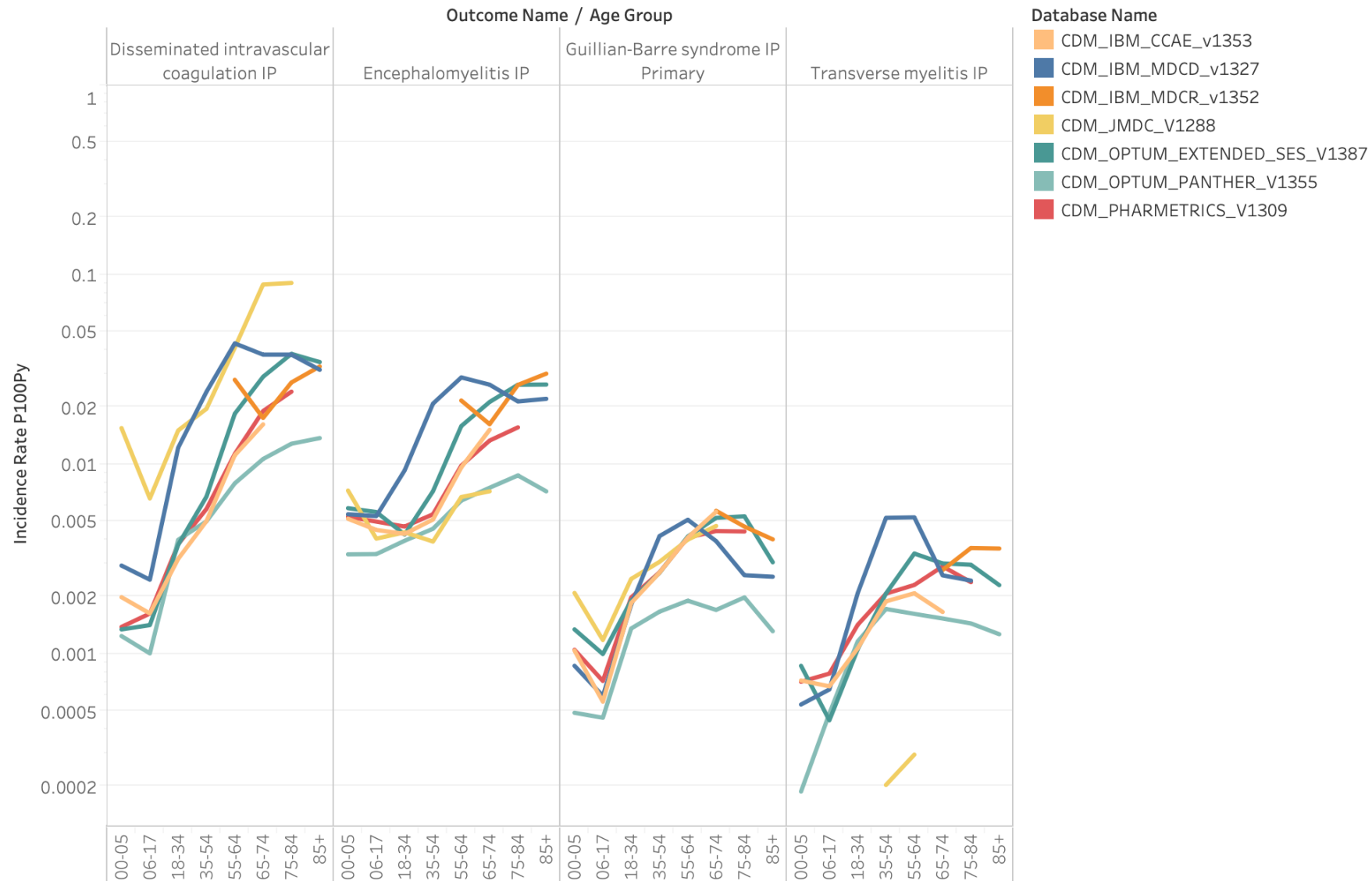
CIOMS 'Rare' Events, Incidence rate by age and gender



The trend of Incidence Rate P100Py as an attribute for Age Group broken down by Outcome Name. Color shows details about Database Name. Details are shown for Gender. The data is filtered on Target Name, Time At Risk Id and Num Outcomes as an attribute. The Target Name filter keeps persons at risk at start of year 2017-2020 with ≥ 365 d prior observation. The Time At Risk Id filter keeps 5. The Num Outcomes as an attribute filter includes values greater than or equal to 5. The view is filtered on Outcome Name, Age Group and Gender. The Outcome Name filter keeps 6 of 26 members. The Age Group filter keeps 8 members. The Gender filter keeps All.



CIOMS 'Very Rare' Events, Incidence rate by age and gender



The trend of Incidence Rate P100Py as an attribute for Age Group broken down by Outcome Name. Color shows details about Database Name. Details are shown for Gender. The data is filtered on Target Name, Time At Risk Id and Num Outcomes as an attribute. The Target Name filter keeps persons at risk at start of year 2017-2020 with ≥ 365 d prior observation. The Time At Risk Id filter keeps 5. The Num Outcomes as an attribute filter includes values greater than or equal to 5. The view is filtered on Outcome Name, Age Group and Gender. The Outcome Name filter keeps Disseminated intravascular coagulation IP, Encephalomyelitis IP, Guillain-Barre syndrome IP Primary and Transverse myelitis IP. The Age Group filter keeps 8 members. The Gender filter keeps All.



Incidence rate (per 100,000 person-years) by age group

Outcome	Sex	1 - 5	6 - 17	18 - 34	35 - 54	55 - 64	65 - 74	75 - 84	85+
Non-hemorrhagic stroke	Female	4 (2-9)	4 (1-12)	18 (4-86)	83 (11-617)	217 (25-1882)	413 (77-2198)	874 (197-3884)	1523 (320-7239)
	Male	6 (2-20)	5 (2-10)	17 (4-75)	119 (21-664)	370 (67-2046)	612 (145-2578)	1063 (242-4662)	1495 (260-8607)
Acute myocardial infarction	Female	<1 (<1-1)	<1 (<1-1)	6 (1-49)	54 (7-430)	171 (24-1235)	312 (76-1280)	617 (184-2069)	1144 (313-4184)
	Male	<1 (<1-1)	1 (1-1)	16 (4-72)	172 (40-740)	467 (135-1611)	653 (214-1994)	934 (290-3013)	1514 (356-6432)
Deep vein thrombosis	Female	12 (3-50)	18 (8-40)	140 (66-298)	306 (117-797)	428 (150-1224)	683 (257-1820)	975 (360-2642)	1206 (407-3572)
	Male	14 (4-55)	14 (6-32)	80 (28-228)	272 (88-836)	499 (194-1289)	695 (250-1931)	831 (254-2720)	1003 (278-3616)
Hemorrhagic stroke	Female	7 (2-28)	5 (2-16)	13 (4-47)	36 (7-175)	77 (15-389)	124 (29-527)	249 (56-1108)	412 (85-1986)
	Male	8 (2-43)	8 (3-24)	19 (5-76)	51 (10-268)	115 (23-562)	178 (49-650)	312 (73-1340)	506 (86-2961)
Pulmonary embolism	Female	1 (<1-36)	3 (1-13)	38 (11-124)	81 (21-309)	125 (33-470)	217 (77-611)	358 (135-951)	427 (154-1184)
	Male	1 (<1-24)	2 (<1-12)	20 (5-80)	80 (20-318)	171 (59-497)	256 (96-683)	349 (119-1030)	398 (124-1277)
Appendicitis	Female	32 (12-84)	154 (55-430)	134 (69-260)	85 (42-172)	66 (28-156)	53 (20-143)	40 (13-124)	35 (12-98)
	Male	38 (17-85)	194 (101-372)	146 (81-266)	88 (49-159)	65 (32-132)	57 (23-144)	47 (15-152)	45 (14-143)
Bells palsy	Female	15 (9-27)	25 (12-51)	44 (23-84)	61 (26-140)	76 (31-184)	86 (29-256)	101 (31-330)	92 (31-274)
	Male	15 (10-24)	21 (13-34)	43 (29-64)	68 (37-125)	86 (43-172)	94 (35-252)	92 (29-291)	100 (34-292)
Anaphylaxis	Female	49 (16-150)	50 (16-154)	39 (16-95)	34 (13-91)	35 (14-85)	29 (11-76)	23 (7-73)	12 (4-36)
	Male	74 (26-209)	56 (18-175)	29 (14-63)	24 (11-53)	25 (11-53)	24 (9-68)	18 (7-49)	10 (2-50)
Immune thrombocytopenia	Female	12 (8-19)	9 (4-21)	14 (6-36)	15 (5-43)	18 (6-53)	25 (8-82)	30 (8-110)	36 (11-118)
	Male	17 (12-23)	8 (3-19)	8 (2-23)	10 (3-35)	19 (6-57)	30 (9-105)	41 (10-170)	56 (15-210)
Myocarditis pericarditis	Female	6 (1-25)	7 (2-21)	16 (8-32)	22 (9-53)	31 (13-72)	35 (12-97)	39 (11-138)	34 (8-143)
	Male	7 (1-32)	11 (5-24)	37 (16-88)	37 (16-87)	45 (20-102)	49 (17-139)	54 (15-193)	41 (9-193)
Disseminated intravascular coagulation	Female	2 (<1-104)	2 (<1-48)	4 (<1-99)	5 (<1-75)	10 (1-89)	14 (2-97)	19 (4-94)	16 (3-82)
	Male	3 (<1-137)	2 (<1-44)	4 (<1-31)	5 (1-56)	12 (1-120)	17 (2-154)	23 (4-152)	24 (5-126)
Encephalomyelitis	Female	5 (2-15)	5 (2-16)	5 (2-19)	6 (1-44)	9 (1-61)	11 (2-62)	12 (2-77)	14 (2-100)
	Male	5 (2-12)	5 (2-14)	5 (2-17)	7 (1-55)	12 (3-58)	16 (3-73)	18 (3-101)	16 (1-180)
Narcolepsy	Female	1 (<1-5)	7 (3-17)	15 (4-52)	11 (2-55)	9 (2-42)	10 (2-46)	8 (1-49)	9 (2-42)
	Male	1 (<1-5)	6 (2-18)	13 (4-40)	10 (2-47)	11 (3-44)	10 (2-50)	10 (2-68)	10 (2-60)
Guillain-Barre syndrome	Female	1 (<1-8)	1 (<1-2)	3 (1-5)	3 (1-11)	5 (1-18)	6 (2-19)	6 (3-16)	7 (2-22)
	Male	2 (<1-18)	1 (<1-3)	2 (1-4)	4 (2-7)	7 (4-14)	8 (3-25)	11 (3-40)	12 (2-68)
Transverse myelitis	Female	1 (<1-3)	1 (<1-3)	3 (1-8)	4 (1-12)	4 (2-13)	4 (2-13)	4 (1-11)	2 (1-9)
	Male	1 (<1-2)	1 (<1-3)	2 (1-6)	3 (1-10)	4 (1-10)	4 (1-11)	4 (1-13)	4 (1-11)

CIOMS Frequency classification

Very rare: <1/10,000
Rare: >1/10,000 AND <1/1,000
Uncommon: >1/1,000 AND <1/100
Common: >1/100 AND <1/10
Very common: >1/10

Li X, et al.



Hypotheses

- Sex IRR(male/female) = 1.13 (1.03-1.23)
 - Female: transverse myelitis > anaphylaxis, narcolepsy
 - Male: acute myocardial infarction, myocarditis-pericarditis, hemorrhagic stroke, non-hemorrhagic stroke > Guillian-Barre, deep vein thrombosis, encephalomyelitis, pulmonary embolism, DIC, appendicitis
- *Anchoring IRR(random event/date) = 1.62 (1.48-1.78)
 - Consistent across databases and outcomes
- Time at risk IRR(2 days/365 days) = 0.98 (0.93-1.02)
 - Germany database with low IRR
- All of the above are age (and sex) adjusted
- I^2 high for all combinations



Conclusions and impact

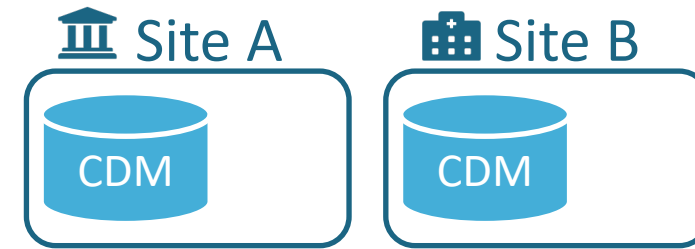
- Age effect is strong enough that **must** adjust for it
 - Small differences in age distribution can produce large effects
- **Anchoring is also strong**
 - We do not yet know how COVID-19 vaccine will behave
- Databases differ (beyond age and sex) so consider within-database comparisons
- Adjust for sex, moderate but present
- **Rates supplied to EMA last week in midst of AZ analysis**



Meta-analysis for rare events

- Motivation

- Vaccine safety events are rare
 - Need large populations or long follow-up
- Many data sources are federated
 - e.g., BEST partners, OHDSI Network
 - Limited individual patient data (IPD)



- Current limitations

- Standard meta-analysis relies on simple summary statistics
 - Often measure slightly different quantities across sources
 - Restricted to:
 - Asymptotic normality (often violated), or
 - Simple outcome models ($K \times 2$ tables)



Distributed Research Network

- Any site can lead a study





Distributed Research Network

- Any site can lead a study
- Analysis code is developed locally





Distributed Research Network

- Any site can lead a study
- Analysis code is developed locally
- Code is distributed to study participants





Distributed Research Network

- Any site can lead a study
- Analysis code is developed locally
- Code is distributed to study participants
- Results are generated (aggregated statistics)





Distributed Research Network

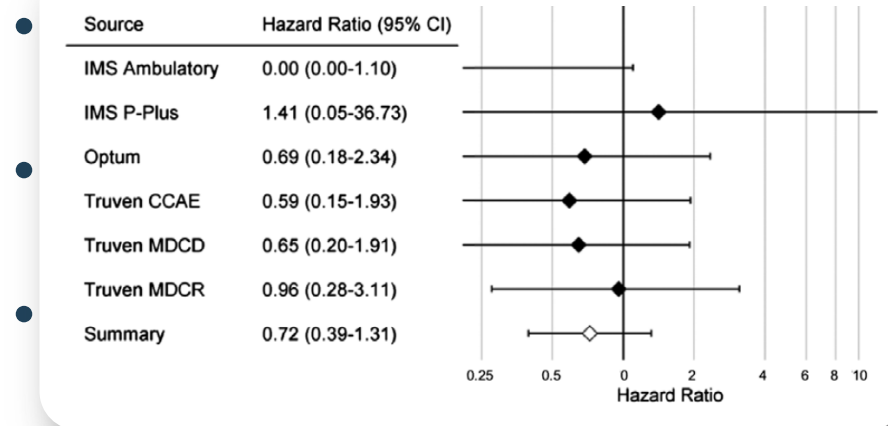
- Any site can lead a study
- Analysis code is developed locally
- Code is distributed to study participants
- Results are generated (aggregated statistics)
- Results are sent back to coordinating site



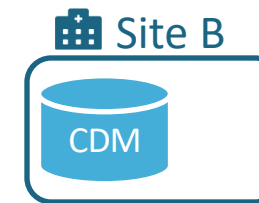


Distributed Research Network

- Any site can lead a study
- Analysis code is developed locally



Study lead



Site C

Site D

BRIEF COMMUNICATION

Risk of angioedema associated with levetiracetam compared with phenytoin: Findings of the observational health data sciences and informatics research network

*Jon D. Duke, *Patrick B. Ryan, *Marc A. Suchard, *George Hripcsak, *Peng Jin, *Christian Reich, *Marie-Sophie Schwalm, ***Yuriy Khoma, *Yonghui Wu, *Hua Xu, *Nigam H. Shah, *Juan M. Banda, and *Martijn J. Schuemie

Epilepsia, **():1-6, 2017
doi: 10.1111/epi.13828

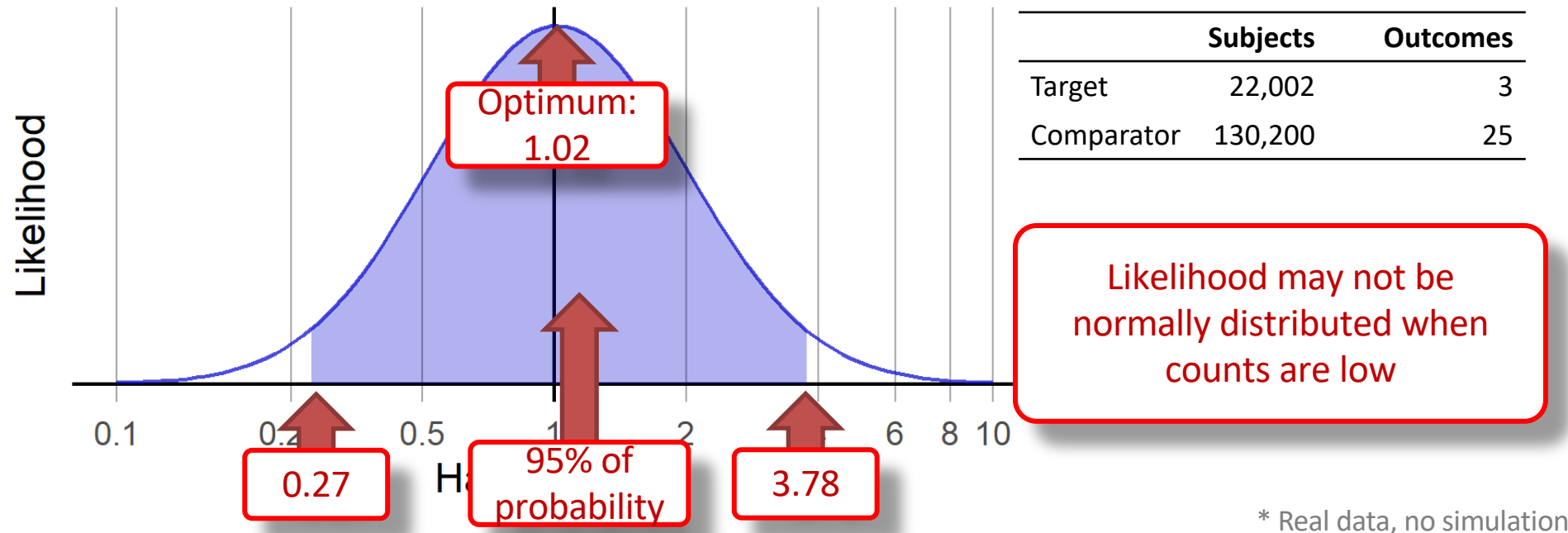
SUMMARY

Recent adverse event reports have raised the question of increased angioedema risk



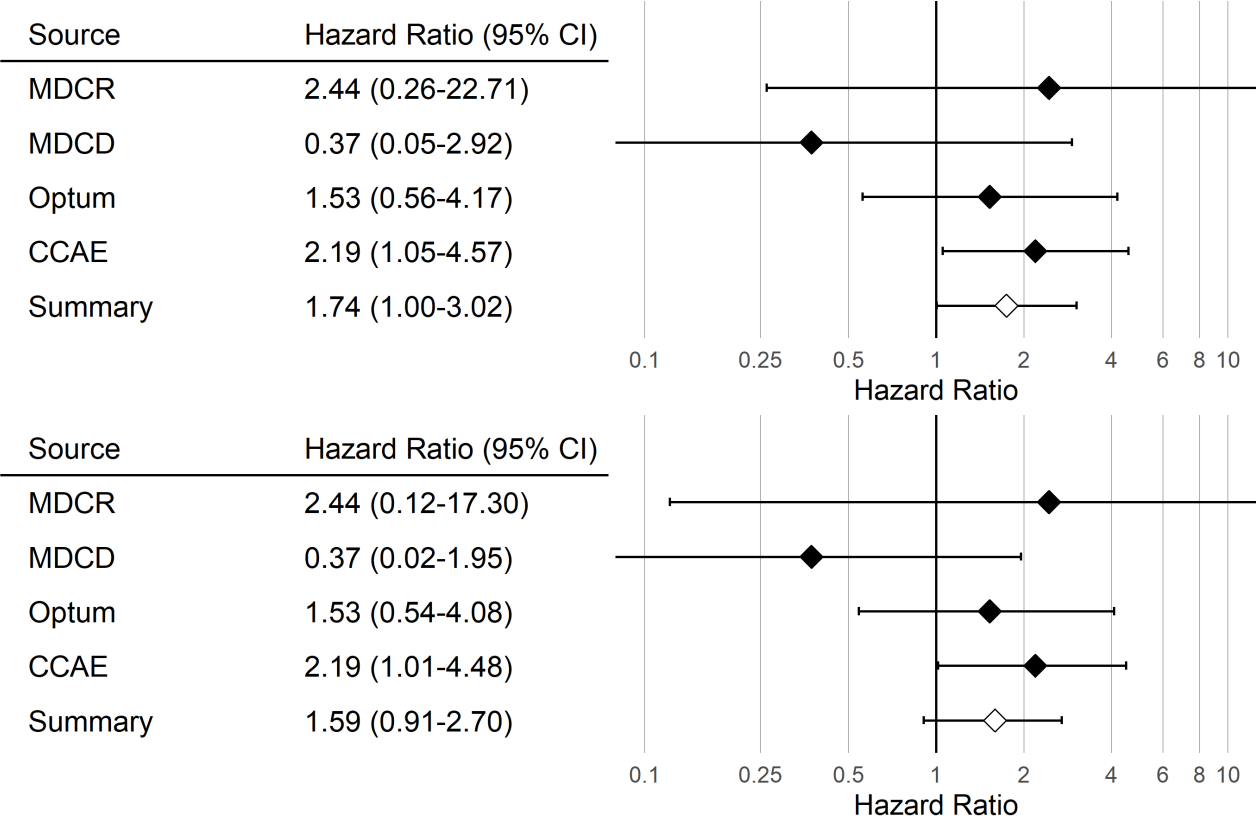
Hazard ratios from small counts

Hazard Ratio = 1.02 (0.27 – 3.78) Assuming normal distribution





Cox meta-analysis with small counts



Assuming
normal distribution

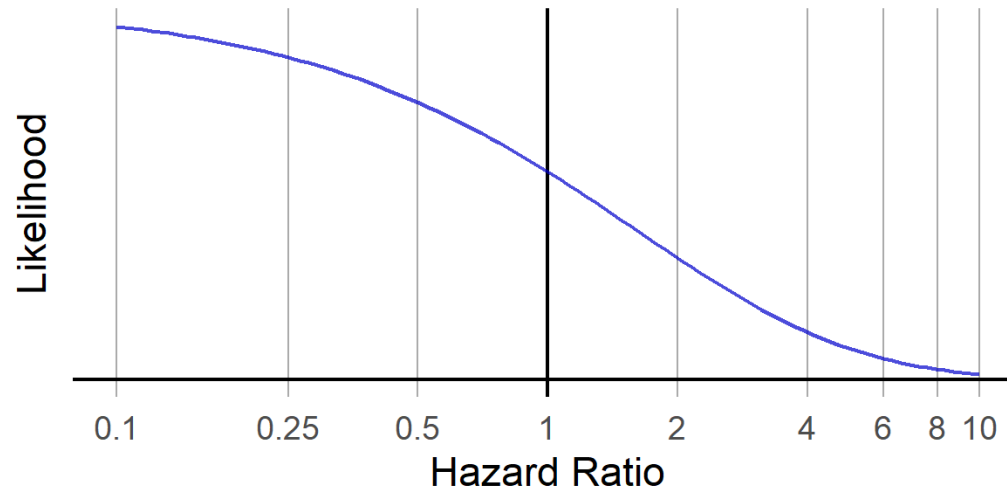
Normality assumption here
leads to statistically
significant summary
estimate

No shape assumption
(Pooling data)

* Real data, no simulation



Hazard ratios from zero counts



No optimum, no
confidence
interval

	Subjects	Outcomes
Target	2,834	0
Comparator	15,168	10

Traditionally, we would ignore
this data source because no
estimate is produced

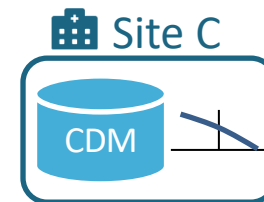
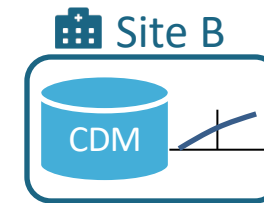
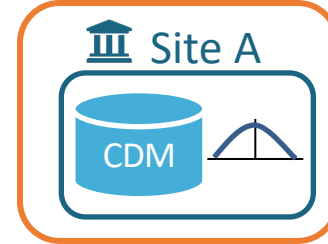
* Real data, no simulation



Solution

Data sites share actual shape of likelihood, instead of just the hazard ratio + confidence interval

Study lead



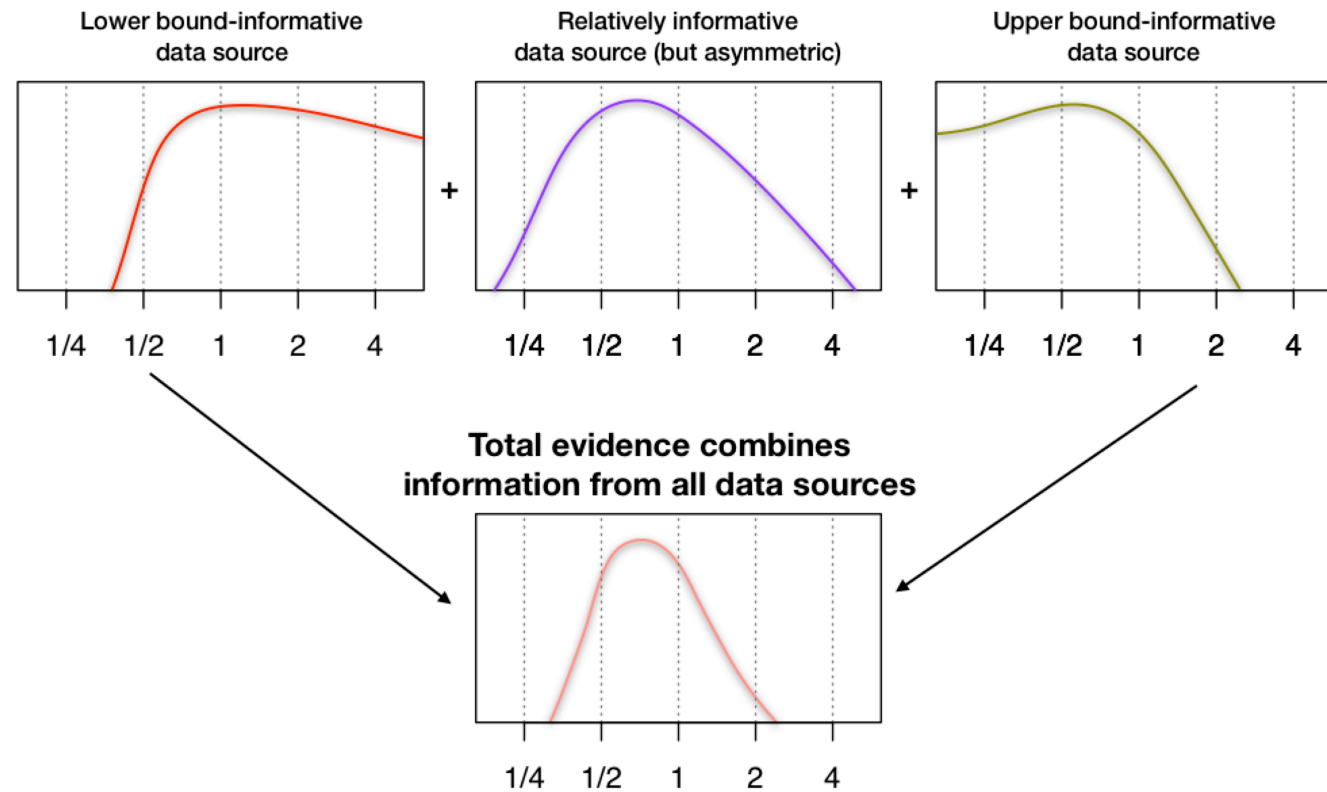
Then use **Bayesian** inference machinery to combine shapes:

- New high-performance MCMC package for OHDSI



Graphical view: total evidence

- Take home perspective:





Status and Moving Forward

- Current progress (w/ Schuemie, Chen, Hripcsak, Madigan)
 - Three choices on how to communicate likelihood function
 - Relative performance metrics with drug safety examples:
 - Bias, coverage, MSE, precision, %-non-estimable
 - arXiv manuscript
- Next steps
 - Models for incidence (relative risk) rates with small counts in vaccine safety, ... or how to avoid 0 / 0. (Punchline: be Bayesian)
 - Methods benchmarking for identifying AEFI after vaccination



Training, Outreach and Engagement



Training, Outreach and Engagement

- Conduct training, outreach and engagement of FDA staff and the BEST stakeholder community to improve and advance BEST as a system that meets the needs of FDA and the community.
 - First through identification, characterization; gathering of stakeholder input and information through methods including interviews, surveys, meetings, and workshops.
 - Results will inform approaches to engage the stakeholder community and foster and encourage use of the BEST infrastructure for safety and effectiveness evaluations and surveillance, real-world evidence generation and other related activities.



Training, Outreach and Engagement

- We plan to develop training for stakeholders and the research community to target different groups who may vary in their knowledge and understanding of key areas (e.g., active surveillance):
 - High-level presentation of concepts
 - More technical sessions for epidemiologists, clinicians, informaticists, and scientists from related life and health sciences areas and specialties



Training, Outreach and Engagement

- Delivery of training
 - In person and virtually
 - EHDEN Academy as a platform for delivering training
- We have experience using a case-based format to improve trainee engagement and facilitate relation of content to real-world applications.
 - In the digital environment, stories (case studies) are used to show the application of the content to real situations.



Training, Outreach and Engagement

- We will draw on Design Research Methodology (DRM), which calls for stakeholder assessment (e.g., critical topics), training development, and assessment in order to design, implement, refine and improve the quality of learning resources with stakeholder participation (characteristics of trainees, segmentation of trainees, topics to include)

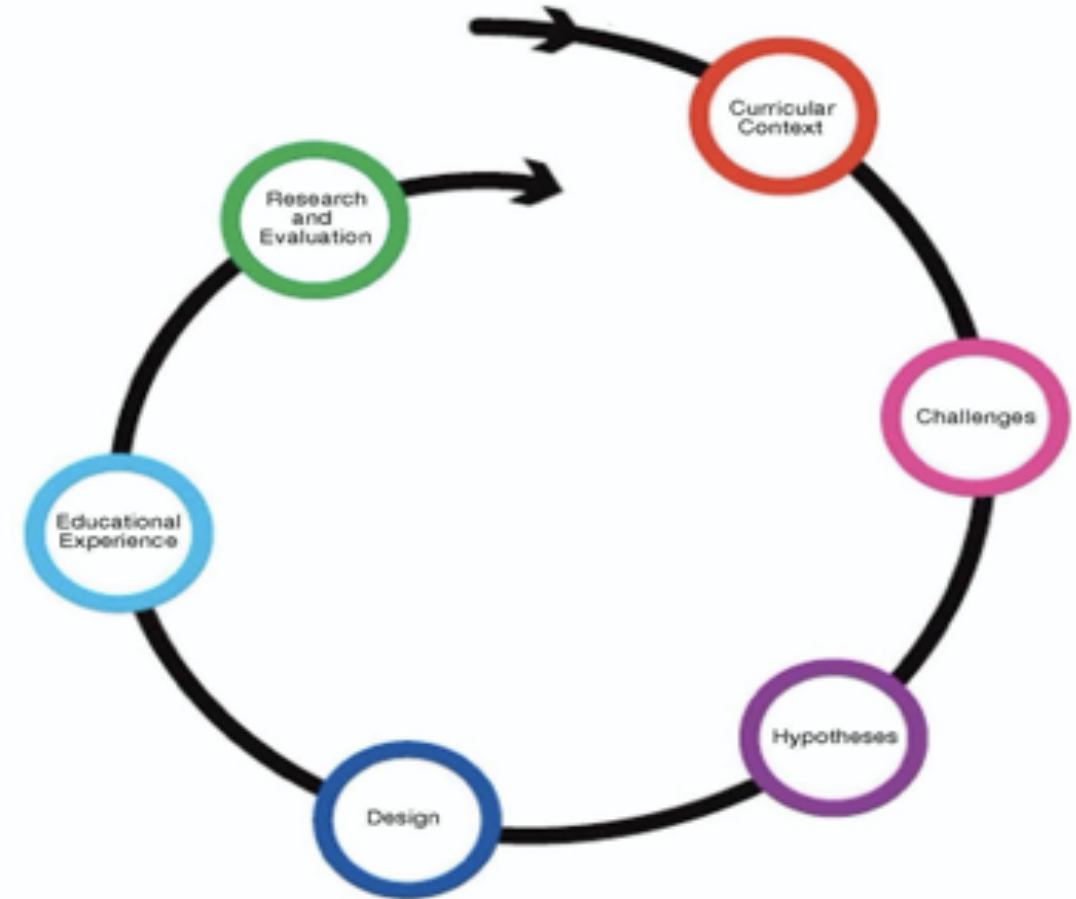


Figure 1. Training stages



Training, Outreach and Engagement

- Following review of findings from the formative data collection, competencies and learning objectives will be defined.
 - Competencies will be matched to different trainee subtypes e.g., high-level, more technical.
- Subject matter experts will be critical in all steps, including defining the competencies and development of materials.
- For all trainings, we will track the number of trainees, types of training, and provide a training assessment.



Training, Outreach and Engagement

- In the current year, we plan to begin the task of training, outreach and engagement by conducting the proposed formative work.
- Surveys, and qualitative interviews are being planned.
- Questions/comments/desire to be involved, please contact me at: Rita Kukafka, Email: rk326@cumc.columbia.edu