COVID-19 Vaccine Adverse Events of Special Interest Background Rates

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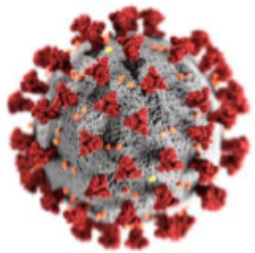
Framework

- COVID-19 is important, as is COVID-19 vaccine safety
  - Risks and lack thereof
- “Adverse events of special interest” (AESI) but may not be adverse events
- One approach: compare COVID-19 vaccine incidence rates to baseline rates
  - European protocol - overall rates
  - FDA protocols - database rates
- Phenotyping
- Produce real rates
- Methods sensitivity
- Also comparing methods (Martijn Schuemie PLE/PLP WG)

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 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
- 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

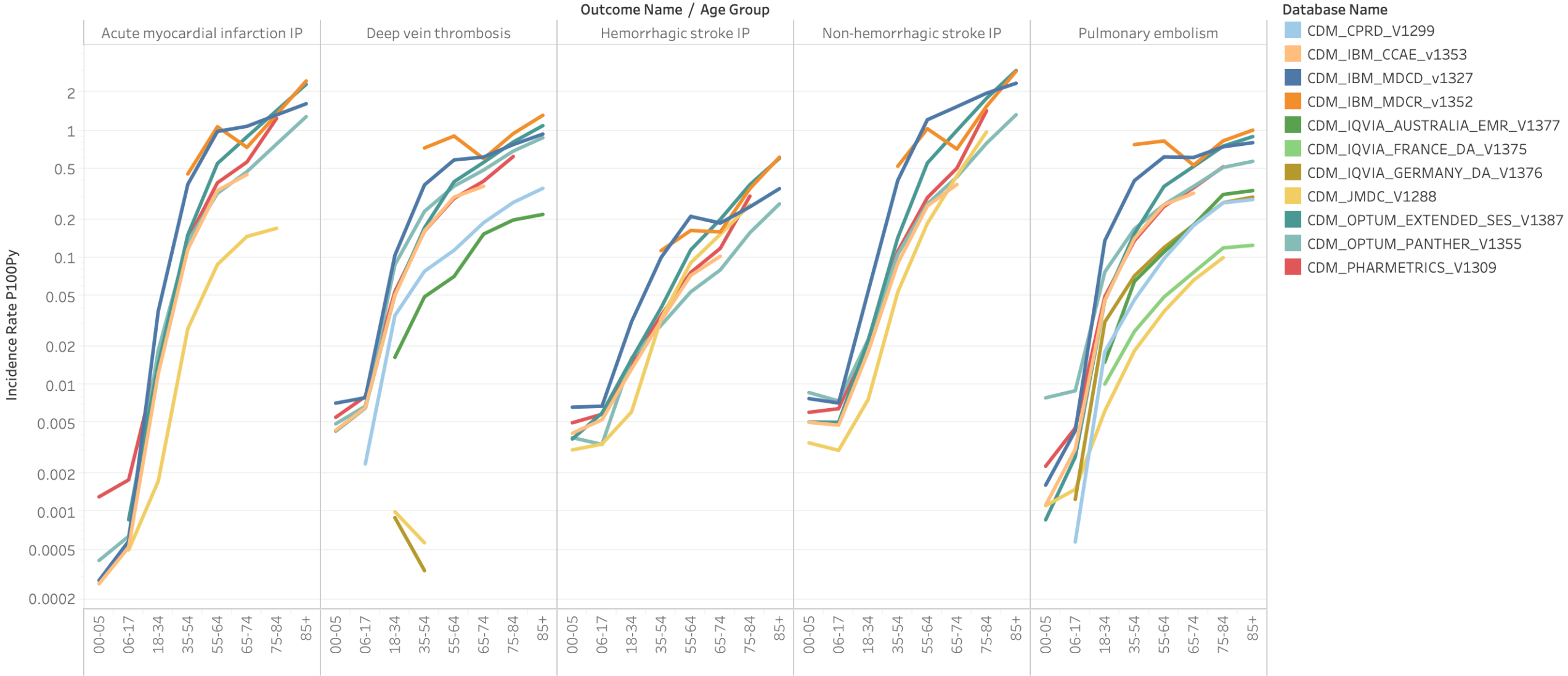
- Xintong Li, lead
- Best estimate of background incidence rates from 2017 to 2019
- 8 claims, 5 EHR databases from 7 countries (4 continents)
- Estimates stratified by age, sex, database
- 310,522,149 total person-years of follow up (largest ever)
- Incidence per 100 person years from 0.002 (transverse myelitis in JMDC) to 1.38 (non-hemorrhagic stroke in MDCR)

Methods study related to estimating incidence rates for AESI

- Anna Ostropolets, lead
- Study factors that affect incidence rates
  - Age, sex, database
  - Target population
    - FDA requires 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

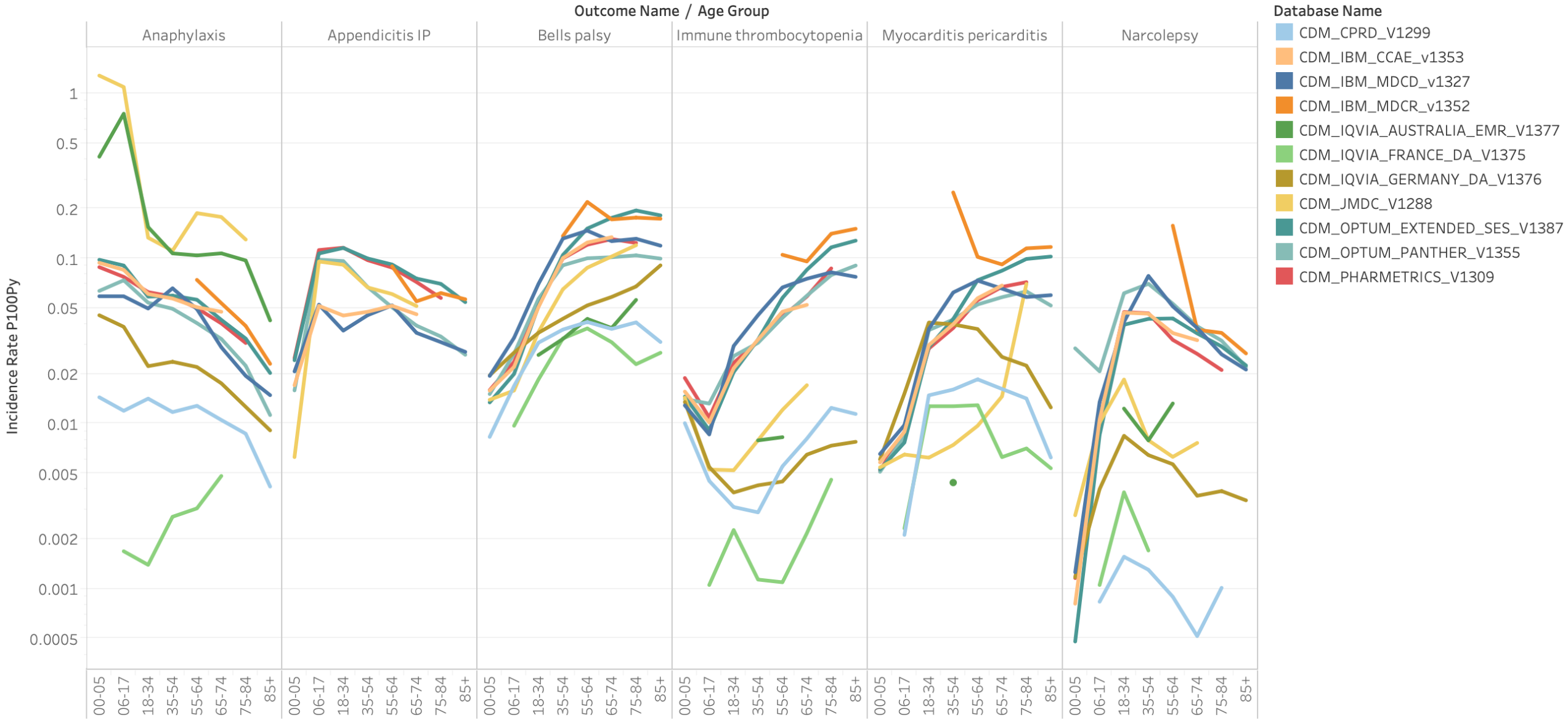
Results

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 >=365d 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 >=365d 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 >=365d 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, Guillian-Barre syndrome IP Primary and Transverse myelitis IP. The Age Group filter keeps 8 members. The Gender filter keeps All.

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 (28d) IRR(random event/date) = 1.62 (1.48-1.78)
  - Consistent across databases and outcomes
- Time at risk (arb date) 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

- 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
- Time at risk matters only when there is anchoring
- Yet to look at year, season, COVID-19