RESEARCH PROTOCOL

EUMAEUS: Evaluating Use of Methods for Adverse Event Under Surveillance (for vaccines)

Version: 1.0.0

Contents

1 List of Abbreviations

AUC	Area Under the receiver-operator Curve
CCAE	IBM MarketScan Commercial Claims and Encounters
CDM	Common Data Model
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	COronaVIrus Disease 2019
CPRD	Clinical Practice Research Datalink
CRAN	Comprehensive R Archive Network
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
H1N1	Hemagglutinin Type 1 and Neuraminidase Type 1 (influenza strain, aka swine flu)
HPV	Human PapillomaVirus
IRB	Institutional review board
JMDC	Japan Medical Data Center
LLR	Log Likelihood Ratio
MDCR	IBM MarketScan Medicare Supplemental Database
MDCD	IBM MarketScan Multi-State Medicaid Database
MSE	Mean Squared Error
OHDSI	Observational Health Data Science and Informatics
OMOP	Observational Medical Outcomes Partnership
MaxSPRT	MAXimized Sequential Probability Ratio Test
PS	Propensity score
RCT	Randomized controlled trial
SCCS	Self-Controlled Case Series
SCRI	Self-Controlled Risk Interval
WHO	World Health Organization

2 Responsible Parties

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2.2 Disclosures

This study is undertaken within Observational Health Data Sciences and Informatics (OHDSI), an open collaboration. **GH** receives grant funding from the US National Institutes of Health and the US Food & Drug Administration. **PBR** and **MJS** are employees of Janssen Research and Development and shareholders in John & Johnson. **DPA** reports grants and other from Amgen, grants, non-financial support and other from UCB Biopharma, grants from Les Laboratoires Servier, outside the submitted work; and Janssen, on behalf of IMI-funded EHDEN and EMIF consortiums, and Synapse Management Partners have supported training programmes organised by DPA's department and open for external participants. **MAS** receives grant funding from the US National Institutes of Health and the US Food & Drug Administration and contracts from the US Department of Veterans Affairs and Janssen Research and Development.

3 Abstract

Background and Significance

As recently approved COVID-19 vaccines are rolled out globally, it is likely that safety signals will be identified from spontaneous reports and other data sources. Although some work has been done on the best methods for vaccine safety surveillance, there is a scarcity of information on how these perform in analyses of real-world data.

Study Aims

To study the comparative performance (bias, precision, and timeliness) of different analytical methods for the study of comparative vaccine safety.

Study Description

- Design: Cohort, self-controlled, and case-control studies
- Exposures: previous viral vaccines including 2017-2018 flu, H1N1 flu, Human Papillomavirus (HPV), and Varicella-Zoster.
- Outcomes: selected adverse events of special interest; negative control outcomes; synthetic positive control outcomes
- Analyses:
    1) Historical rate comparisons.
    2) Cohort analyses using a contemporary non-user comparator, with large-scale propensity score matching
    3) Self-controlled case series with variations
    4) Case-control analyses
- Metrics:

- Area Under the receiver-operator Curve (AUC). The ability to discriminate between positive controls and negative controls based on the point estimate of the effect size. Will be stratified by true effect size of the positive controls.
- Coverage. How often the true effect size is within the 95% confidence interval.
- Mean precision, computed as 1 / (standard error)2
- Mean squared error (MSE). Mean squared error between the log of the effect size point-estimate and the log of the true effect size.
- Type 1 error. For negative controls, how often was the null rejected (at alpha = 0.05). This is equivalent to the false positive rate and 1 - specificity.
- Type 2 error. For positive controls, how often was the null not rejected (at alpha = 0.05). This is equivalent to the false negative rate and 1 - sensitivity. Will be stratified by true effect size of the positive controls.
- Non-estimable. Measure for how many of the controls was the method unable to produce an estimate
- Sensitivity and specificity based on the MaxSPRT decision rule
- Detection time: the number of months until 80% of positive controls exceeds the critical value. Will be stratified by true effect size of the positive controls.

4 Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
None				

5 Milestones

Milestone	Planned / actual date
EU PAS Registration	
Start of analysis	
End of analysis	
Results presentation	

6 Rationale and Background

A total of 3 COVID-19 vaccines have been approved for clinical use in Europe, and 4 in the USA. Many more are in pipeline, and at least two more have reported to date on phase 3 efficacy data. Although safe and effective based on large randomised controlled trials, COVID-19 vaccines will be subject to post-marketing safety studies, including both

analyses of spontaneous reports (pharmacovigilance) as well as longitudinal analyses in the form of post-authorisation safety studies.

The ENCEPP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) methodological guidelines, in their 8th revision,[1] mention a few documents that set out standards for the conducting of vaccine safety studies. Specific aspects related to vaccine safety research are discussed in detail in different materials, including the Report of the CIOMS/WHO Working Group on Definition and Application of Terms for Vaccine Pharmacovigilance (2012), the CIOMS Guide to Active Vaccine Safety Surveillance (2017), the CIOMS Guide to Vaccine Safety Communication (2018), the Brighton Collaboration resources, the Module 4 (Surveillance) of the e-learning training course Vaccine Safety Basics by the World Health Organization (WHO), or the recommendations on vaccine-specific aspects of the EU pharmacovigilance system outlined in the Module P.I: Vaccines for prophylaxis against infectious diseases of the Good pharmacovigilance practices (GVP). Additionally, the Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE) project has summarized methods for vaccine safety in a bespoke report [2] covering multiple study designs, both experimental and observational in nature. The EMA (European Medicines Agency) has also issued guidances [3] and a plan [4] for pharmacovigilance of COVID-19 vaccines. Despite this plethora of literature and guidance, there is a scarcity of methodological studies on the performance of different methods for vaccine safety.

Given the quick and increasingly global rollout of COVID-19 vaccines internationally, it is highly likely that potential safety signals will emerge, which will need a timely but robust evaluation in 'real world' observational studies. It is therefore urgent that we conduct large-scale evaluations of methods for vaccine safety, similar to previous work on methods for drug safety. [5] The results of this evaluation will help us understand how these methods will perform when applied to COVID-19 vaccines.

7 Study Objectives

The overarching aim is to identify the best methods for the generation of evidence of vaccine safety in observational, real-world data. Specific aims:

- To estimate the bias and precision associated with the use of different methods (historic rate, cohort, self-controlled, and case-control) for the study of vaccine safety compared
- To compare the 'timeliness' of these methods for the identification of vaccine safety signals

Table 1: Exposures of interest.

Exposure Name	Start Date	End Date	History Start Date	History End Date
H1N1 vaccination	01-09-2009	31-05-2010	01-09-2008	31-05-2009
Seasonal flu vaccination (Fluvirin)	01-09-2017	31-05-2018	01-09-2016	31-05-2017
Seasonal flu vaccination (Fluzone)	01-09-2017	31-05-2018	01-09-2016	31-05-2017
Seasonal flu vaccination (All)	01-09-2017	31-05-2018	01-09-2016	31-05-2017
Zoster vaccination (Shingrix)	01-01-2018	31-12-2018	01-01-2017	31-12-2017
HPV vaccination (Gardasil 9)	01-01-2018	31-12-2018	01-01-2017	31-12-2017

8 Research Methods

8.1 Exposure-outcome pairs

8.1.1 Exposures

The evaluation will center on six existing (groups of) vaccines, for specific time periods (start date to end date), as shown in Table 1.

For some methods the period between historic start and historic end date will be used to estimate the historic incidence rate. For analyses executed on data in the southern hemisphere (if any) the flu seasons are different, and the study periods will need to be adjusted accordingly. The formal cohort definitions of each exposure can be found in Appendix A.

8.1.2 Negative control outcomes

Negative controls are outcomes believed not to be caused by any of the vaccines, and therefore ideally would not be flagged as a signal by a safety surveillance system. Any effect size estimates for negative control ideally should be close to the null.

A single set of negative control outcomes is defined for all four vaccine groups. To identify negative control outcomes that match the severity and prevalence of suspected vaccine adverse effects, a candidate list of negative controls was generated based on similarity of prevalence and percent of diagnoses that were recorded in an inpatient setting (as a proxy for severity). Manual review of this list by clinical experts created the final list of 93 negative control outcomes. The full list of negative control outcomes can be found in Appendix B

Negative control outcomes are defined as the first occurrence of the negative control concept or any of its descendants.

8.1.3 Synthetic positive control outcomes

Positive controls are outcomes known to be caused by vaccines, and ideally would be detected as signals by a safety surveillance system as early as possible. For various reasons, real positive controls are problematic.[6] Instead, here we will rely on synthetic positive controls,[5,7] created by modifying a negative control through injection of additional, simulated occurrences of the outcome. To preserve (measured) confounding, simulated outcome occurrences are sampled from the probability distribution derived from a predictive model fitted on the data. Target true hazard ratios for the positive control synthesis are 1.5, 2, and 4, so using the 93 negative controls we are able to construct 93 $\times$ 3 = 279 positive control outcomes. The hazard for the outcome is simulated to be increased by the target ratio for the period starting 1 day after vaccination until 28 days after vaccinations, with a constant hazard ratio during that time. This increased risk is applied both for the first and second injection of multi-dose vaccines.

8.2 Data sources

We will execute EUMAEUS as an OHDSI network study. All data partners within OHDSI are encouraged to participate voluntarily and can do so conveniently, because of the community's shared Observational Medical Outcomes Partnership (OMOP) common data model (CDM) and OHDSI tool-stack. Many OHDSI community data partners have already committed to participate and we will recruit further data partners through OHDSI's standard recruitment process, which includes protocol publication on OHDSI's GitHub, an announcement in OHDSI's research forum, presentation at the weekly OHDSI all-hands-on meeting and direct requests to data holders.

Table 2 lists the 5 already committed data sources for EUMAEUS; these sources encompass a large variety of practice types and populations. For each data source, we report a brief description and size of the population it represents. All data sources will receive institutional review board approval or exemption for their participation before executing EUMAEUS.

8.3 Methods to evaluate

Vaccine safety surveillance methods can be broken down in to four components: construction of a *counterfactual* (often referred to as the 'expected count'), a *time-at-risk*, the *statistic* to estimate, and potentially a *decision rule* on the estimate to classify signals from non-signals.

Table 2: Committed EUMAEUS data sources and the populations they cover.

Data source	Population	Patients	History	Data capture process and short description
Administrative claims				
IBM MarketScan Commercial Claims and Encounters (CCAE)	Commercially insured, < 65 years	142M	2000 –	Adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) from large employers and health plans who provide private healthcare coverage to employees, their spouses and dependents.
IBM MarketScan Medicare Supplemental Database (MDCR)	Commercially insured, 65$+$ years	10M	2000 –	Adjudicated health insurance claims of retirees with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitated health plans.
IBM MarketScan Multi-State Medicaid Database (MDCD)	Medicaid enrollees, racially diverse	26M	2006 –	Adjudicated health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims.
Optum Clinformatics Data Mart (Optum)	Commercially or Medicare insured	85M	2000 –	Inpatient and outpatient healthcare insurance claims.
Electronic health records (EHRs)				
Optum Electronic Health Records (OptumEHR)	US, general	93M	2006 –	Clinical information, prescriptions, lab results, vital signs, body measurements, diagnoses and procedures derived from clinical notes using natural language processing.

8.3.1 Counterfactual construction

Historic rates

Traditionally, vaccine surveillance methods compute an expected count based an incidence rate estimated during some historic time period, for example in the years prior to the initiation of the surveillance study. We will use the historic period indicated in Table 1. We will evaluate two variants:

- Unadjusted, entire year. Using a single rate computed across the entire historic year for the entire population.
- Age and sex adjusted, entire year. Using a rate stratifying by age (in 5 year increments) and sex, computed across the entire historic year. This allows the expected rate to be adjusted for the demographics of the vaccinated.
- Unadjusted, time-at-risk relative to outpatient visit. Using a single rate computed during the time-at-risk relative to a random outpatient visit in the historic year.
- Age and sex adjusted, time-at-risk relative to outpatient visit. Using a rate stratifying by age and sex, computed during the time-at-risk relative to a random outpatient visit in the historic year.

Cohort method using a contemporary non-user comparator

A comparator cohort study most closely emulates a randomized clinical trial, comparing the target cohort (those vaccinated) to some comparator cohort. We define two types of non-user comparator cohort, one having an outpatient visit on the index date, and another having a random date as the index date. For both comparator variants we exclude subjects

having a vaccinations for the same disease as the target vaccine on or before the index date. We will evaluate four method variants:

- Unadjusted comparison to random outpatient visit. The comparator cohort will be a random sample (of outpatient visits) of equal size as the target cohort.
- 1-on-1 propensity score (PS) matched outpatient visit. The comparator cohort before PS matching will be a stratified (by age and sex) random sample of four times the size as the target cohort. (two times for the Seasonal Flu Vaccination (all) target cohort for computational reasons). Propensity models will use a large generic set of covariates, including demographics and covariates per drug, condition, procedure, measurement, etc., and will be fitted using large-scale regularized regression as described previously. [8]
- Unadjusted comparison to random date. The comparator cohort will be a random sample (of random dates) of equal size as the target cohort.
- 1-on-1 propensity score (PS) matched random date. The comparator cohort before PS matching will be a stratified (by age and sex) random sample of four times the size as the target cohort. (two times for the Seasonal Flu Vaccination (all) target cohort for computational reasons). Propensity models will use a large generic set of covariates, including demographics and covariates per drug, condition, procedure, measurement, etc., and will be fitted using large-scale regularized regression as described previously. [8]

Self-Controlled Case Series (SCCS) / Self-Controlled Risk Interval (SCRI)

The SCCS and SCRI designs are self-controlled, comparing the time-at-risk (the time shortly following the vaccination) to some other time in the same patient's record. The SCCS design uses all patient time when not at risk as the control time. [9] The SCRI design uses a pre-specified control interval relative to the vaccination date as the control time. [10] This unexposed time can be both before or after the time at risk. We will evaluate four variants:

- A simple SCCS, using all patient time when not at risk as the control time, with the exception of the 30 days prior to vaccination which is excluded from the analysis to avoid bias due to contra-indications.
- An SCCS adjusting for age and season. Age and season will be modeled to be constant within each calendar month, and vary across months as bicubic splines.
- An SCRI, using a control interval of 43 to 15 days prior to vaccination.
- An SCRI, using a control interval of 43 to 71 days after to vaccination.

Case-control

The case-control design compares cases (those with the outcome) to controls (those that do not have the outcome), and looks back in time for exposures to a vaccine. We will evaluate two variants:

- Using up to four age and sex matched controls per case. For age we will use a

two-year caliper.
- By sampling controls from the general non-case population, and adjusting for age and sex in the outcome model. The control sample will be four times the number of controls. Age will be modeled as one variable per 5-year age category.

8.3.2 Time-at-risk

The time-at-risk is the time window, relative to the vaccination date, when outcomes will potentially be attributed to the vaccine. We define three time-at-risk windows: 1-28 days, 1-42 days, and 0-1 days after vaccination. Time-at-risk windows will be constructed both for the first and second dose. The time-at-risk for one dose will be censored at the time of the next dose.

8.3.3 Statistic

- Effect-size estimate. Each method can be used to produce an effect-size estimates such as a hazard ratio, incidence rate ratio, or odds ratio. For example, when using a historic rate we can compute the observed to expected ratio, which can be interpreted as the incidence rate ratio.
- Log likelihood ratio (LLR). A common practice in vaccine safety surveillance is to computer the LLR, which is the log of the ratio between the likelihood of the alternative hypothesis (that there is an effect) and the likelihood of the null hypothesis (of no effect). The LLR is a convenient statistic when performing sequential testing, where the LLR can be compared to a pre-computed critical value, as is done in the MaxSPRT method. [11] Although typically MaxSPRT uses a historic rate as counterfactual, any counterfactual can be used to compute the LLR and can be used in MaxSPRT.

Effect-size estimates will be computed both with and without empirical calibration. [7,12] Empirical calibration will be done using leave-one-out: when calibrating the estimate for a control, the systematic error distribution will be fitted uses all controls except the one being calibrated.

8.3.4 Decision rule

To identify 'signals' we need a decision rule, for example in the shape of a threshold value on one of the estimates statistics. In our experiment we will consider one decision rule, which is the critical value computed for the LLR at an alpha of 0.05. For the historical rates method we will use a Poisson model assuming the counterfactual is known without

uncertainty. For all other methods we will use a binomial model. All critical values will be computed using the `Sequential` package in CRAN.

8.4 Metrics

Similar to our previous study, we will compute the following metrics based on the effect size estimates: [13]

- Area Under the receiver-operator Curve (AUC). The ability to discriminate between positive controls and negative controls based on the point estimate of the effect size. This will be stratified by true effect size of the positive controls.
- Coverage. How often the true effect size is within the 95% confidence interval.
- Mean precision. Precision is computed as 1 / (standard error)2, higher precision means narrower confidence intervals. We use the geometric mean to account for the skewed distribution of the precision.
- Mean squared error (MSE). Mean squared error between the log of the effect size point-estimate and the log of the true effect size.
- Type 1 error. For negative controls, how often was the null rejected (at alpha = 0.05). This is equivalent to the false positive rate and 1 - specificity.
- Type 2 error. For positive controls, how often was the null not rejected (at alpha = 0.05). This is equivalent to the false negative rate and 1 - sensitivity. This will be stratified by true effect size of the positive controls.
- Non-estimable. For how many of the controls was the method unable to produce an estimate? There can be various reasons why an estimate cannot be produced, for example because there were no subjects left after propensity score matching, or because no subjects remained having the outcome.

In addition, based on the MaxSPRT decision rule, we will compute sensitivity, specificity, as well as the number of months until 80% of all positive controls exceeds the critical value (detection time). These will be stratified by true effect size of the positive controls.

8.4.1 Timeliness

To understand the time it takes for a method the identify signals, the study period for each vaccine will be divided into calendar months. For each month the methods will be executed using the data that had accumulated up to the end of that month, and the performance metrics will be reported for each month.

8.4.2 Multiple doses

For those vaccines requiring multiple doses (zoster, HPV), metrics will be computed three times:

- Treating all doses the same, so computing statistics using both doses without distinguishing between first and second.
- Using the first dose only
- Using the second dose only

8.5 Overview of analyses

In total, we will evaluate:

- 14 counterfactuals
- 3 times at risk (0-1, 1-28, and 1-42 days)
- 6 vaccines, with a total of 9 + 9 + 9 + 9 + 12 + 12 = 60 time periods
- 93 negative controls
- 3 $\times$ 93 = 279 positive controls
- 3 dose definitions (both, first, second) for the zoster and HPV vaccines, 1 for H1N1 and seasonal flu.

Resulting in a total of 14 $\times$ 3 $\times$ [(9 + 9 + 9 + 9) $\times$ 1 + (12 + 12) $\times$ 3] $\times$ (93 + 279) = 117,695,592 effect-size estimates. Each estimate will contain:

- The effect-size estimate (e.g. hazard ratio, odds ratio) with 95% confidence interval and p-value.
- The empirically calibrated effect-size estimate and p-value
- The LLR

This will be computed for each database.

9 Strengths and Limitations

9.1 Strengths

- Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects; new use allows for a clear exposure index date.

- Large-scale propensity score matching and stratification create balance on a large number of baseline potential confounders and have been found in the past to balance unmeasured confounders.
- Systematic processes including a pre-specified selection of covariates avoids investigator-specific biases in variable selection.
- Use of real negative and synthetic positive control outcomes provides an independent estimate of residual bias in the experiment.
- The fully specified study protocol is being published before analysis begins.
- Dissemination of the results will not depend on estimated effects, avoiding publication bias.
- All analytic methods have previously been verified on real data.
- All software is freely available as open source.
- Use of a common data model allows extension of the experiment to future databases and allows replication of these results on licensable databases that were used in this experiment, while still maintaining patient privacy on patient-level data.
- Use of multiple databases allows estimating consistency to add credibility and supports generalizability.

9.2 Limitations

- Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders, such as confounding by indication, differences in physician characteristics that may be associated with drug choice, concomitant use of other drugs started after the index date, and informative censoring at the end of the on-treatment periods. To minimize this risk, we used methods to detect residual bias through our negative and positive controls.
- Our follow-up times are limited and variable, potentially reducing power to detect differences in effectiveness and safety.
- We assume hazards are not time varying.
- Misclassification of study variables is unavoidable in secondary use of health data, so it is possible to misclassify treatments, covariates, and outcomes; we do not expect differential misclassification, so bias will most likely be towards the null.
- The electronic health record databases may be missing care episodes for patients due to care outside the respective health systems; bias will most likely be towards the null.

Table 3: IRB approval or waiver statement from partners.

Data source	Statement
IBM MarketScan Commercial Claims and Encounters (CCAE)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IBM MarketScan Medicare Supplemental Database (MDCR)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IBM MarketScan Multi-State Medicaid Database (MDCD)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Japan Medical Data Center (JMDC)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Optum Clinformatics Data Mart (Optum)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Optum Electronic Health Records (OptumEHR)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Clinical Practice Research Datalink (CPRD) GOLD	Independent Scientific Advisory Committee will review the protocol prior to study execution.

10 Protection of Human Subjects

EUMAEUS does not involve human subjects research. The project does, however, use de-identified human data collected during routine healthcare provision. All data partners executing the EUMAEUS studies within their data sources will have received institutional review board (IRB) approval or waiver for participation in accordance to their institutional governance prior to execution (see Table 3). EUMAEUS executes across a federated and distributed data network, where analysis code is sent to participating data partners and only aggregate summary statistics are returned, with no sharing of patient-level data between organizations.

11 Management and Reporting of Adverse Events and Adverse Reactions

EUMAEUS uses coded data that already exist in electronic databases. In these types of databases, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any specific individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product and event) are not available and adverse events are not reportable as individual adverse event reports. The study results will be assessed for medically important findings.

12 Plans for Disseminating and Communicating Study Results

Open science aims to make scientific research, including its data process and software, and its dissemination, through publication and presentation, accessible to all levels of an inquiring society, amateur or professional [14] and is a governing principle of EUMAEUS. Open science delivers reproducible, transparent and reliable evidence. All aspects of EUMAEUS (except private patient data) will be open and we will actively encourage other interested researchers, clinicians and patients to participate. This differs fundamentally from traditional studies that rarely open their analytic tools or share all result artifacts, and inform the community about hard-to-verify conclusions at completion.

12.1 Transparent and re-usable research tools

We will publicly register this protocol and announce its availability for feedback from stakeholders, the OHDSI community and within clinical professional societies. This protocol will link to open source code for all steps to generating diagnostics, effect estimates, figures and tables. Such transparency is possible because we will construct our studies on top of the OHDSI toolstack of open source software tools that are community developed and rigorously tested [13]. We will publicly host EUMAEUS source code at (https://github.com/ohdsi-studies/Eumaeus), allowing public contribution and review, and free re-use for anyone's future research.

12.2 Continous sharing of results

EUMAEUS embodies a new approach to generating evidence from healthcare data that overcome weaknesses in the current process of answering and publishing (or not) one question at a time. Generating evidence for thousands of research and control questions using a systematic process enables us to not only evaluate that process and the coherence and consistency of the evidence, but also to avoid p-hacking and publication bias [6]. We will store and openly communicate all of these results as they become available using a user-friendly web-based app that serves up all descriptive statistics, study diagnostics and effect estimates for each cohort comparison and outcome. Open access to this app will be through a general public facing EUMAEUS web-page.

12.3 Scientific meetings and publications

We will deliver multiple presentations at scientific venues and will also prepare multiple scientific publications for clinical, informatics and statistical journals.

12.4 General public

We believe in sharing our findings that will guide clinical care with the general public. EU-MAEUS will use social-media (Twitter) to facilitate this. With dedicated support from the OHDSI communications specialist, we will deliver regular press releases at key project stages, distributed via the extensive media networks of UCLA and Columbia.

References

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A Exposure Cohort Definitions

A.1 H1N1 Vaccines

A.1.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. drug exposures of 'H1N1 vaccine', starting between September 1, 2009 and May 31, 2010.

Limit cohort entry events to the earliest event per person.

A.1.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 0 days.

A.1.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.1.4 Concept set: H1N1 vaccine

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40213187	Novel influenza-H1N1-09, all formulations	128	CVX	NO	YES	NO
40166607	influenza A-California-7-2009-(H1N1)v-like virus vaccine 0.03 MG/ML Injectable Suspension	864704	RxNorm	NO	YES	NO
40166130	0.25 ML influenza A-California-7-2009-(H1N1)v-like virus vaccine 0.03 MG/ML Prefilled Syringe	864781	RxNorm	NO	YES	NO
40166144	0.5 ML influenza A-California-7-2009-(H1N1)v-like virus vaccine 0.03 MG/ML Prefilled Syringe	864797	RxNorm	NO	YES	NO
42902936	influenza A-California-7-2009-(H1N1)v-like virus vaccine 0.03 MG/ML Prefilled Syringe	1360049	RxNorm	NO	YES	NO
40240135	influenza A-California-7-2009-(H1N1)v-like virus vaccine 0.09 MG/ML	1111367	RxNorm	NO	YES	NO
40225009	influenza A-California-7-2009-(H1N1)v-like virus vaccine 0.12 MG/ML	1005949	RxNorm	NO	YES	NO
40166608	influenza A-California-7-2009-(H1N1)v-like virus vaccine 158000000 UNT/ML	864812	RxNorm	NO	YES	NO
45776785	influenza A-California-7-2009-(H1N1)v-like virus vaccine 50000000 MG/ML	1543758	RxNorm	NO	YES	NO
40166609	influenza A-California-7-2009-(H1N1)v-like virus vaccine Injectable Suspension	864703	RxNorm	NO	YES	NO
40166611	influenza A-California-7-2009-(H1N1)v-like virus vaccine Prefilled Syringe	864780	RxNorm	NO	YES	NO

A.2 Seasonal Flu Vaccines (Fluvirin)

A.2.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. drug exposures of 'Fluvirin', starting between September 1, 2017 and May 31, 2018.

Limit cohort entry events to the earliest event per person.

A.2.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 0 days.

A.2.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.2.4 Concept set: Fluvirin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1593906	influenza A virus A/Hong Kong/4801/2014 (H3N2) antigen 0.03 MG/ML / influenza A virus A/Singapore/GP1908/2015 (H1N1) antigen 0.03 MG/ML / influenza B virus B/Brisbane/60/2008 antigen 0.03 MG/ML [Fluvirin 2017-2018]	1928971	RxNorm	NO	YES	NO

A.3 Seasonal Flu Vaccines (Fluzone)

A.3.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. drug exposures of 'Fluzone', starting between September 1, 2017 and May 31, 2018.

Limit cohort entry events to the earliest event per person.

A.3.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 0 days.

A.3.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.3.4 Concept set: Fluzone

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1593354	influenza A virus A/Hong Kong/4801/2014 (H3N2) antigen 0.12 MG/ML / influenza A virus A/Michigan/45/2015 (H1N1) antigen 0.12 MG/ML / influenza B virus B/Brisbane/60/2008 antigen 0.12 MG/ML [Fluzone 2017-2018]	1928341	RxNorm	NO	YES	NO

A.4 Seasonal Flu Vaccines (All)

A.4.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. drug exposures of 'Seasonal flu vaccine', starting between September 1, 2017 and May 31, 2018.

Limit cohort entry events to the earliest event per person.

A.4.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 0 days.

A.4.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.4.4 Concept set: Seasonal flu vaccine

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40213145	influenza, injectable, quadrivalent, contains preservative	158	CVX	NO	YES	NO
42903442	influenza B virus	1312376	RxNorm	NO	YES	NO
40213150	influenza, live, intranasal, quadrivalent	149	CVX	NO	YES	NO
40213159	influenza virus vaccine, whole virus	16	CVX	NO	YES	NO
40225028	influenza virus vaccine, inactivated A-Victoria-210-2009 X-187 (H3N2) (A-Perth-16-2009) strain	1005931	RxNorm	NO	YES	NO
40213156	influenza virus vaccine, split virus (incl. purified surface antigen)-retired CODE	15	CVX	NO	YES	NO
40213151	Seasonal, trivalent, recombinant, injectable influenza vaccine, preservative free	155	CVX	NO	YES	NO
40213327	influenza nasal, unspecified formulation	151	CVX	NO	YES	NO
40213148	influenza, intradermal, quadrivalent, preservative free, injectable	166	CVX	NO	YES	NO
40213158	influenza virus vaccine, unspecified formulation	88	CVX	NO	YES	NO
36878713	Influenza Virus Fragmented, Inactivated, Strain B / Phuket / 3073/2013	OMOP98957	RxNorm Extension	NO	YES	NO
42873961	influenza B virus vaccine, B-Wisconsin-1-2010-like virus	1303855	RxNorm	NO	YES	NO
40225038	influenza virus vaccine, live attenuated, A-Perth-16-2009 (H3N2) strain	1005911	RxNorm	NO	YES	NO
40213146	Influenza, injectable, quadrivalent, preservative free	150	CVX	NO	YES	NO
40213143	Influenza, injectable, Madin Darby Canine Kidney, preservative free, quadrivalent	171	CVX	NO	YES	NO

36879025	Influenza Virus Surface Antigens, strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain Nib-88	OMOP991645	RxNorm Extension	NO	YES	NO
40213157	Seasonal trivalent influenza vaccine, adjuvanted, preservative free	168	CVX	NO	YES	NO
45776076	influenza A virus vaccine, A-Texas-50-2012 (H3N2)-like virus	1541617	RxNorm	NO	YES	NO
40213149	influenza virus vaccine, live, attenuated, for intranasal use	111	CVX	NO	YES	NO
40213147	Influenza, injectable,quadrivalent, preservative free, pediatric	161	CVX	NO	YES	NO
40213152	Seasonal, quadrivalent, recombinant, injectable influenza vaccine, preservative free	185	CVX	NO	YES	NO
42903441	influenza A virus	1312375	RxNorm	NO	YES	NO
40213141	influenza, high dose seasonal, preservative-free	135	CVX	NO	YES	NO
40213153	Influenza, seasonal, injectable	141	CVX	NO	YES	NO
40213144	Influenza, injectable, Madin Darby Canine Kidney, quadrivalent with preservative	186	CVX	NO	YES	NO
40213142	Influenza, injectable, Madin Darby Canine Kidney, preservative free	153	CVX	NO	YES	NO
40213155	seasonal influenza, intradermal, preservative free	144	CVX	NO	YES	NO
40164828	influenza B virus vaccine B/Brisbane/60/2008 antigen	857921	RxNorm	NO	YES	NO

A.5 HPV Vaccines

A.5.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. drug exposures of ‘Gardasil 9’, starting between January 1, 2018 and December 31, 2018.

A.5.2 Cohort Exit

The cohort end date will be offset from index event’s start date plus 0 days.

A.5.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.5.4 Concept set: Gardasil 9

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
36248866	Gardasil 9 Injectable Product	1597098	RxNorm	NO	YES	NO
45892513	L1 protein, human papillomavirus type 11 vaccine / L1 protein, human papillomavirus type 16 vaccine / L1 protein, human papillomavirus type 18 vaccine / L1 protein, human papillomavirus type 31 vaccine / L1 protein, human papillomavirus type 33 vaccine /	1597102	RxNorm	NO	YES	NO
45892514	0.5 ML L1 protein, human papillomavirus type 11 vaccine 0.08 MG/ML / L1 protein, human papillomavirus type 16 vaccine 0.12 MG/ML / L1 protein, human papillomavirus type 18 vaccine 0.08 MG/ML / L1 protein, human papillomavirus type 31 vaccine 0.04 MG/ML /	1597103	RxNorm	NO	YES	NO
45892510	0.5 ML L1 protein, human papillomavirus type 11 vaccine 0.08 MG/ML / L1 protein, human papillomavirus type 16 vaccine 0.12 MG/ML / L1 protein, human papillomavirus type 18 vaccine 0.08 MG/ML / L1 protein, human papillomavirus type 31 vaccine 0.04 MG/ML /	1597099	RxNorm	NO	YES	NO
40213322	Human Papillomavirus 9-valent vaccine	165	CVX	NO	YES	NO

A.6 Zoster Vaccines

A.6.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. drug exposures of ‘Shingrix’, starting between January 1, 2018 and December 31, 2018.

A.6.2 Cohort Exit

The cohort end date will be offset from index event’s start date plus 0 days.

A.6.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.6.4 Concept set: Shingrix

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
792784	varicella zoster virus glycoprotein E Injection [Shingrix]	1986828	RxNorm	NO	YES	NO
792783	varicella zoster virus glycoprotein E, recombinant 0.1 MG/ML [Shingrix]	1986827	RxNorm	NO	YES	NO
792788	varicella zoster virus glycoprotein E, recombinant 0.1 MG/ML Injection [Shingrix]	1986832	RxNorm	NO	YES	NO
36421491	Varicella-Zoster Virus Vaccine Live (Oka-Merck) strain Injectable Solution [Shingrix]	OMOP4763774	RxNorm Extension	NO	YES	NO
792785	Shingrix Injectable Product	1986829	RxNorm	NO	YES	NO
706103	zoster vaccine recombinant	187	CVX	NO	YES	NO

B Negative controls

Table 10: Negative control outcomes.

Outcome Id	Outcome Name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia

193530	Follicular cyst of ovary
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi
4299408	Gouty tophus
135215	Hashimoto thyroiditis
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung's disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland
194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud's disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor's bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets