RESEARCH PROTOCOL

BETTER: Bayesian Evaluation of Time-To-Event and Reliability (for vaccine surveillance)

Version: 1.0.0

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1 List of Abbreviations

2 Responsible Parties

2.1 Investigators

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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 is an employee of Janssen Research and Development and shareholders in Johnson & Johnson. **FB** and **MAS** receive 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.

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
CRAN	Comprehensive R Archive Network
EHR	Electronic Health Record
H1N1pdm	Hemagglutinin Type 1 and Neuraminidase Type 1 (2009 pandemic influenza)
HPV	Human PapillomaVirus
IRB	Institutional review board
LLR	Log Likelihood Ratio
MAP	Maximum A Posteriori
MaxSPRT	MAXimized Sequential Probability Ratio Test
MCMC	Markov Chain Monte Carlo
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
RCT	Randomized controlled trial
SCCS	Self-Controlled Case Series
SCRI	Self-Controlled Risk Interval
WHO	World Health Organization

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3 Abstract

Background and Significance

As various approved COVID-19 vaccines are rolled out globally, safety signals have been identified from spontaneous reports and other data sources. The current standard method of safety surveillance adopted by the FDA is MaxSPRT, which suffers from the inflexibility of a pre-specified sequential analysis schedule. We hope to develop and implement a more flexible Bayesian surveillance framework and compare its performance with MaxSPRT in real-world data.

Study Aims

To compare the real-data performance (testing errors, timeliness, precision and bias) of Bayesian and frequentist sequential analysis methods for the study of comparative vaccine safety.

We will also produce a reference table of Type I and II error rates and signal detection times for all combinations of design and threshold choices, as exploration of the operating characteristics of Bayesian sequential methods.

Study Description

- Design: historical comparator & self-controlled studies
- Exposures: previous viral vaccines including 2017-2018 flu, H1N1pdm flu, Human Papillomavirus (HPV), and Varicella-Zoster.
- Outcomes: selected adverse events of special interest (e.g., **Guillain-Barre Syndrome**); negative control outcomes; imputed positive control outcomes
- Analyses:
    1) historical comparator/historical rates (frequentist)
    2) historical comparator/historical rates (Bayesian)
    3) Self-controlled case series with variations (frequentist)
    4) Self-controlled case series with variations (Bayesian)
- Decision rules:
    - Frequentist method: reject null at $\alpha = 0.05$ level, using the MaxSPRT adjustment
    - Bayesian method:
        * Posterior probability of *signal*, $P_1 = P(H_1 \text{ true, signal} \mid \text{data})$; reject null (claim signal) when $P_1 > \delta_1$, with $\delta_1 = 0.80, 0.90, 0.95$;
        * Posterior probability of *futility*, $P_0 = P(H_0 \text{ true, safety} \mid \text{data})$; accept null (claim safety) when $P_0 > \delta_0$, with $\delta_0 = 0.90, 0.95, 0.99$.
- Metrics:

1. Hypothesis testing related metrics

- Type 1 error. For negative controls, how often was the null rejected using the various decision rules. This is equivalent to the false positive rate and 1 - specificity.
- Type 2 error. For positive controls, how often was the null **not** rejected using the various decision rules. This is equivalent to the false negative rate and 1 - sensitivity. Will be stratified by true effect size of the positive controls.
- Posterior probability of futility (H_0 true) at final analysis; only reported for Bayesian methods.
- Sensitivity and specificity based on the various decision rules
- Detection time: the number of analyses (months) until signals are claimed for 80% of positive controls. Will be stratified by true effect size of the positive controls.
- Rate of contradictory early decisions. For all controls, how often did an earlier signal/futility decision contradict the decision based on full analysis of all data.
- Rate of "undetermined'' decisions. At each analysis stage, for all controls, how often are the decisions"undetermined" (i.e., neither decision threshold is crossed). For most analyses, we would expect this rate to be high at earlier stages when there isn't enough data evidence but gradually lower as more data accrue.

2. Estimation related 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 (or credible) interval.
- Mean precision, computed as $1/(\text{standard error})^2$ (for the Bayesian method, "standard error'' is taken as the square root of the posterior distribution variance)
- Mean squared error (MSE). Mean squared error between the log of the effect size point-estimate (MAP estimate for Bayesian method) and the log of the true effect size.
- Non-estimable. Measure for how many of the controls was the method unable to produce an estimate

4 Amendments and Updates

Table 1 lists any protocol amendments made over time.

Table 1: Protocol amendments

Number	Date	Section of study protocol	Amendment or update	Reason

Table 2: Study milestones

Milestone	Planned / actual date
Start of analysis	02/01/2022
End of analysis	08/31/2022
Results presentation	09/30/2022

5 Milestones

Table 2 lists the study milestones.

6 Rationale and Background

Mass vaccination against SARS-CoV-2 is critical to ending the current COVID-19 global pandemic. By the beginning of 2022, 9 vaccines have been approved under the WHO Emergency Use List, and more than 10 billion doses have been administered globally by February 2022 [1]. With the large-scale usage of vaccines under emergency approval, it is essential to ensure their safety and effectiveness through post-market surveillance, as rare but serious adverse events may not be identified in phase 3 clinical trials. In the US, messenger RNA (mRNA) vaccines (BNT162b2, Pfizer-BioNTech; and mRNA-1273, Moderna) were the first SARS-CoV-2 vaccines authorized and as of February 2022, more than 500 million doses of mRNA vaccines have been administered. [2] And yet, there is limited experience with mRNA platforms previous to SARS-CoV-2, and therefore safety surveillance is particularly important to inform public health policy and maintain public trust.

The design of a rapid and reliable vaccine safety surveillance system requires an efficient and robust statistical monitoring approach. The current standard approach used by regulatory agencies in the US is a frequentist sequential analysis method, MaxSPRT [3]. It is designed to control the overall analysis Type I error rate of a sequential analysis by allocating the allowed false positive error over sequential analysis stages. This method has long suffered from its inflexibility as it requires a pre-specified analysis schedule, and does *not* allow extended analysis after the pre-chosen analysis endpoint.

A more flexible sequential analysis method is, therefore, much desired. A promising candidate is a Bayesian sequential testing framework. Under a Bayesian framework, multiplicity of sequential analyses can be handled more elegantly, without the need for a rigid, pre-specified analysis schedule while allowing continued analyses beyond anticipated endpoints. It is also easier to incorporate historical information into current analyses using a

prior distribution through Bayesian inference. With all its theoretical advantages, however, the performance and operating characteristics of Bayesian sequential testing methods have not yet been extensively studied on large-scale real-world data. In particular, with observational health data, Bayesian methods can potentially adjust for unmeasured confounding and sampling bias, but the performance and behavior have not been evaluated in a systematic manner.

The goal of this study is to compare the performance of a Bayesian testing framework with that of MaxSPRT (the current standard approach), in terms of both the hypothesis testing errors (sensitivity and specificity) and estimation accuracy (in estimating the relative risks of adverse events of interest). This study will be conducted on various large-scale health claims databases, in order to understand the operating characteristics in a real-world data-intensive setting. At the initial stage of the study, all analyses will be performed *retrospectively* using historical vaccines with more regular roll-out schedules. We believe the results of our comprehensive evaluations will help us better understand the performance and behavior of a Bayesian sequential testing framework and facilitate the design of a more flexible and reliable safety surveillance system for COVID-19 vaccines.

7 Study Objectives

The overarching aim is to compare the performance of frequentist and Bayesian sequential analysis methods for the generation of evidence of vaccine safety in observational, real-world data. Specific aims:

- To evaluate and compare the operating characteristics (Type I and II errors, sensitivity and specificity, etc.) of frequentist and Bayesian sequential testing methods
- To compare the 'timeliness' of these methods for the identification of vaccine safety signals
- To estimate the bias and precision associated with the use of frequentist and Bayesian methods with self-controlled or historical rates designs for the study of vaccine safety
- To gain a deeper understanding of the behavior of Bayesian sequential methods; specifically, the relationship between threshold choices, Type I and II errors, and time-to-signal – the study will produce **a reference table of estimated Type I and II errors and time-to-signal** for each combination of Bayesian sequential testing choices

8 Research Methods

8.1 Exposure-outcome pairs

Table 3: Exposures of interest.

Exposure Name	Start Date	End Date	History Start Date	History End Date
H1N1pdm 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

8.1.1 Exposures

The evaluation will center on six existing (groups of) vaccines, for specific time periods (start date to end date), as shown in Table 3.

For some methods the period between historical start and historical 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 Imputed 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.[4] Instead, here we will rely on imputed positive controls, created by shifting the estimated effect sizes for the negative controls. We assume the negative controls have a true effect size of 1, so to simulate the estimated

effect size when the true effect size is θ we multiply the estimate by θ. For example, if for a negative control a method produces an effect size estimate of 1.1, for a positive control with true effect size of 2 the estimated effect size becomes 1.1 x 2 = 2.2. This approach makes strong assumptions on the nature of the systematic error, most importantly that systematic error does not change as a function of the true effect size. Although this assumption is likely not to hold in the real world, imputing positive controls allows us to provide some indication of what type 2 error to expect for various true effect sizes. For each negative control we will impute positive controls with true effect sizes of 1.5, 2, and 4, so using the 93 negative controls we are able to construct 93 $\times$ 3 = 279 positive control outcomes. This increased true effect is applied both for the first and second injection of multi-dose vaccines.

8.1.4 Outcome of special interest — Guillain-Barre Syndrome

In addition to the negative control and imputed positive control outcomes, we will further investigate the risk of Guillain-Barre Syndrome (GBS) following the zoster vaccine, as comparison to previous study findings [5]. The previous study by Goud et al. used the self-controlled case series design to analyze Medicare claims data, and found a significant elevated risk (risk ratio 2.34, 95% CI, 1.01-5.41). We will use both the historical comparator and self-controlled designs, apply both frequentist and Bayesian sequential testing methods, and run analyses on a variety of large-scale databases, in the hope of a more comprehensive analysis of the risk of GBS post zoster vaccination.

8.2 Data sources

We will execute BETTER 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 4 lists the potential data sources for BETTER; 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 BETTER.

8.3 Methods to evaluate

Vaccine safety surveillance methods can be broken down into four components: construction of a *counterfactual* (often referred to as the 'expected count'), a *time-at-risk*, the esti-

Table 4: BETTER data sources and the populations they cover.

Data source	Population	Patients	History	Data capture process and short description
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.
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.

mation outcome (an *estimate* or *posterior distribution* for the effect size), and a *decision rule* based on the estimation outcome to differentiate signals from non-signals.

8.3.1 Counterfactual construction

In this study, we mainly focus on two designs for counterfactual construction: historical comparator and self-controlled case series. The former design is currently the standard design adopted by various regulatory agencies such as FDA and CDC in the US and the CDC in the EU, while the latter is a design of rising popularity that has shown satisfactory performance according to numerous recent studies.

8.3.1.1 Historical Comparator (HC) Traditionally, vaccine surveillance methods compute an expected count based on an incidence rate estimated during some historic time period, for example, in the years prior to the initiation of the surveillance study. [6][7] We will use the historical period indicated in Table 8.1 and evaluate **four** variations:

- 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 stratified by age (in 10 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 stratified by age and sex, computed during the time-at-risk relative to a random outpatient visit in the historic year.

8.3.1.2 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. [8] The SCRI design uses a pre-specified control interval relative to the vaccination date as the control time. [9] This unexposed time can be both before or after the time at risk.

We will evaluate **five** variations:

- 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.
- A simple SCCS discarding all time prior to vaccination.
- 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.

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 Estimation Outcome

The effect-size of interest for both the HC and SCCS designs is the (log) relative incidence rate ratio. We obtain slightly different estimation outcomes for the frequentist (i.e., MaxSPRT) and Bayesian methods.

For frequentist MaxSPRT, we obtain:

- Effect-size estimate. This is typically a maximum likelihood estimate (MLE) obtained from the analysis.
- Log likelihood ratio (LLR). 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 and commonly used statistic when performing sequential testing, where the LLR can be compared to a pre-computed critical value, as is done in the MaxSPRT method. [3] Although typically MaxSPRT uses a historic rate as counterfactual, any counterfactual can be used to compute the LLR and can be used in MaxSPRT; our use of either the HC or SCCS/SCRI design does not affect the validity of using the LLR as the test statistic.

For the Bayesian method, we obtain:

- Posterior distribution for the effect-size, approximated by MCMC posterior samples. This is obtained using the Bayes Rule by combining the likelihood function and the prior distribution. The end result is not a single point estimate but rather a *distribution profile* about our knowledge of the effect-size given accrued data.
- Maximum A Posteriori (MAP) estimate for the effect-size. This is a point estimate obtained by extracting the maxima of the posterior density; this estimate can be regarded as a Bayesian counterpart of the frequentist effect-size estimate.
- Posterior mean for the effect-size. This is a commonly adopted Bayesian estimate, and is, in fact, the optimal Bayesian estimate with squared loss.

- Posterior median for the effect-size. This is another commonly adopted Bayesian estimate, and is also the optimal Bayesian estimate with absolute error loss.

For the Bayesian method, we also evaluate different prior distribution choices for the effect-size:

- A log-normal prior with mean $= 0$ and SD $= 1.5$ (a **conservative** prior with >90% mass below 2)
- A log-normal prior with mean $= 0$ and SD $= 4$ (a **weakly informed** prior with ~70% mass below 2)
- A log-normal prior with mean $= 0$ and SD $= 10$ (a **diffuse** prior)

We choose to use log-normal priors for their simplicity and wide use, in order to focus mainly on comparison between Bayesian and frequentist testing methods. We will consider adopting other prior distributions (e.g., Laplace priors) in subsequent studies.

For the frequentist method (MaxSPRT), analyses will be conducted *with* and *without* empirical calibration. [10,11]. 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.

For the Bayesian method, inference will be conducted *with* and *without* Bayesian bias adjustment using negative control analyses. Similarly, bias adjustment will be done using leave-one-out.

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, for the frequentist surveillance method, we will consider a decision rule using the critical value cv computed for the LLR at the $\alpha = 0.05$ level. That is, we will reject the null and claim a signal when $LLR > cv$. Here all critical values will be computed using the `Sequential` package in CRAN.

For the Bayesian method, we will implement two sets of decision rules, one for signal (rejecting null) and one for futility/safety (accepting null), by examining the posterior probabilities of the null and alternative hypotheses simultaneously:

- If the posterior probability of signal, $P_1 = P(H_1 \text{ true } \mid \text{data}) > \delta_1$, we claim a signal;
- If the posterior probability of futility/safety, $P_0 = P(H_0 \text{ true } \mid \text{data}) > \delta_0$, we claim safety (non-signal).

We will evaluate three choices of δ_1: $0.80, 0.90, 0.95$; and also three choices of δ_0:$0.90, 0.95, 0.99$.

8.4 Metrics

As we will conduct both estimation and testing tasks at the same time, we will compute two sets of metrics based on the study outcomes: (1) metrics for testing, and (2) metrics for estimation. (Some of the following metrics are adapted from previous work [12].)

1. Testing-related metrics:

   - Type 1 error. For negative controls, how often was the null rejected using the various decision rules. This is equivalent to the false positive rate and 1 - specificity.
   - Type 2 error. For positive controls, how often was the null **not** rejected using the various decision rules. This is equivalent to the false negative rate and 1 - sensitivity. Will be stratified by true effect size of the positive controls.
   - Posterior probability of futility (H_0 true) at final analysis; only reported for Bayesian methods.
   - Sensitivity and specificity based on the various decision rules, as well as prior choices in the Bayesian method.
   - Detection time: the number of analyses (months) until signals are claimed for 80% of positive controls. This will be stratified by true effect size of the positive controls.
   - Rate of contradictory early decisions. For all controls, how often did an earlier signal/futility decision contradict the decision based on full analysis of all data. This can serve as a measure of temporal stationarity of the sequential process — if such contradictory rate is high, then there may be time-varying confounding factors left unadjusted for.
   - Rate of "undetermined'' decisions. At each analysis stage, for all controls, how often are the decisions"undetermined" (neither decision thresholds crossed). For most analyses, we would expect this rate to be high at earlier stages when there isn't enough data evidence but gradually lower as more data accrue.

2. Estimation-related metrics:

   - Mean precision, computed as $1/(\text{standard error})^2$ (for the Bayesian method, "standard error'' is taken as the square root of the posterior distribution variance)
   - Mean squared error (MSE). Mean squared error between the log of the effect size point-estimate (MAP estimate for Bayesian method) and the log of the true effect size.
   - 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 (or credible) interval.
   - Non-estimable. Measure for how many of the controls was the method unable to produce an estimate

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:

- 9 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
- 1 outcome of special interest
- 3 dose definitions (both, first, second) for the zoster and HPV vaccines, 1 for H1N1pdm and seasonal flu.
- 4 prior distribution choices (Bayesian only)
- $3 \times 3 = 9$ decision rule thresholds (Bayesian only)

For the frequentist MaxSPRT method, this will result in a total of 9 $\times$ 3 $\times$ [(9 + 9 + 9 + 9) $\times$ 1 + (12 + 12) $\times$ 3] $\times$ (93 + 279 + 1) = 1,087,668 effect-size estimates, where each estimate will contain:

- The effect-size estimate with 95% confidence interval and p-value.
- The empirically calibrated effect-size estimate and p-value
- The LLR

For the Bayesian method, this will result in a total of 9 $\times$ 3 $\times$ [(9 + 9 + 9 + 9) $\times$ 1 + (12 + 12) $\times$ 3] $\times$ (93 + 279 + 1) $\times$ 4 = 4,350,672 estimation outcomes, where each outcome will include:

- The posterior distribution profile of effect-size with MAP estimate
- The empirically calibrated effect-size posterior distribution profile with MAP estimate

- The decision (signal or safety) made based on the $3 \times 3 = 9$ different decision rule thresholds

These analysis results will be computed for each database.

9 Strengths and Limitations

9.1 Strengths

- Use and comprehensive evaluation of Bayesian sequential analysis methods for vaccine safety surveillance on large-scale real-world data.
- Use of self-controlled case series in addition to historical comparator methods, as the former method is less subject to unmeasured confounding and systematic error.
- 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, and we (at this stage) do not investigate time-varying confounding.
- We only adopt two commonly used study designs (at this stage) which may not be the most suitable design for vaccine safety surveillance situations with complex roll-out schedules (e.g., COVID-19 vaccines).

Table 5: 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.
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.

- 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.

10 Protection of Human Subjects

BETTER 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 BETTER 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 5). BETTER 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

BETTER 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 [13] and is a governing principle of BETTER. Open science delivers reproducible, transparent and reliable evidence. All aspects of BETTER (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 [12]. We will publicly host BETTER source code at **URL TBD**, allowing public contribution and review, and free re-use for anyone's future research.

12.2 Continous sharing of results

BETTER 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 [4]. 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 BETTER 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. BETTER 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.

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A Exposure Cohort Definitions

A.1 H1N1pdm 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 12: 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

C Additional investigated outcome cohort

C.1 Adverse Event Outcome - Guillain Barre Syndrome

C.1.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Guillian-Barre syndrome.'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or Inpatient/ER visit,' starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

C.1.2 Inclusion Criteria

C.1.2.1 1. has no events in prior 'clean window' Entry events having no condition occurrences of 'Guillian-Barre syndrome,' starting in the 365 days prior to cohort entry start date; allow events outside observation period; having at least 1 visit occurrence of 'Inpatient or Inpatient/ER visit,' starting anytime on or before 'Guillian-Barre syndrome' start date and ending between 0 days before and all days after 'Guillian-Barre syndrome' start date.

C.1.3 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

C.1.4 Cohort Eras

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

C.1.5 Concept set: Guillian-Barre syndrome

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
374925	Acute infective polyneuritis	129131007	SNOMED	NO	YES	NO|
4164770	Guillain-Barre syndrome	40956001	SNOMED	NO	YES	NO|
4070552	Fisher's syndrome	1767005	SNOMED	NO	YES	NO|

C.1.6 Concept set: Inpatient or Inpatient/ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO|
9201	Inpatient Visit	IP	Visit	NO	YES	NO|