

Vaccine safety surveillance with self-controlled study designs

Tuomo A. Nieminen

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University of Helsinki
Faculty of Social sciences, statistics
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Abstract:

All pharmaceutical products, including vaccines, can increase the risk of some undesired medical occurrences (adverse events). Evaluating these risks post-licensure is essential for evaluating the safety of vaccines, since rare adverse events might go undetected in pre-licensure studies. This thesis introduces the BmaxSPRT method for vaccine safety surveillance, suitable for monitoring the safety of vaccines in real-time, utilizing electronic health care records.

Vaccine safety surveillance (VSU) can be used to study a suspected, biologically plausible causal relationships between a vaccine and an adverse event. Information regarding such relationships are called safety signals. VSU methods considered in this thesis address specified hypothesis about suspected vaccine-event pairs and therefore belong to the refinement stage of drug safety studies.

VSU can be seen as an observational study for which different study designs could be used. Popularity of vaccination, self-selection and changes in diagnosis coding practises, along with other possible sources of bias present challenges for popular cohort designs. Self-controlled study designs such as the self-controlled case series (SCCS), eliminate time-invariant confounders and are therefore often more suitable for evaluating vaccine risks. This thesis introduces both a simple and a more general version of SCCS and explicitly describes the assumptions related to the method.

A VSU method involves a decision rule for generating safety signals. Natural goals of a VSU method are to control the rates of false positive and false negative signals, as well as generate a signal as soon as possible when an association between the vaccine and the adverse event exists. Statistical hypothesis testing can be used to derive the decision rules. Since observations arrive sequentially with the object of minimizing the expected sample size, methods designed for sequential analysis should be used.

This thesis describes the maxSPRT, a sequential hypothesis testing method designed for vaccine safety surveillance. The thesis then introduces in detail the BmaxSPRT, a variant of maxSPRT based on a self-controlled study design such as the SCCS. The derivation of the decision rules for BmaxSPRT, including the computation of the critical values, is described in detail both mathematically and algorithmically.

The BmaxSPRT addresses hypotheses concerning the relative incidence of adverse events during specified risk and control periods. The sensitivity of the method to these choices is studied in this thesis. The analysis

highlights the importance of careful consideration of the risk and control periods by quantifying the loss of power due to poor choices.

As a proof-of-concept, the BmaxSPRT method was retrospectively applied to Finnish register data. The relationship between the incidence of febrile seizures and three childhood vaccines; Measles-Mumps-Rubella (MMR), Pneumococcal- (PCV) and the Rota virus vaccination (Rota) was studied. The BmaxSPRT generated an expected safety signal related to MMR and concluded that the relative incidence of febrile seizures is higher during a period 0-13 days following vaccination compared to a period 14-41 days following vaccination. The experiment also highlighted the need for more in depth analysis regarding PCV and febrile seizures.

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1 Introduction

1.1 Safety surveillance

Pharmaceutical products (drugs) can have unintended side effects. An untoward medical occurrence in a patient administered a drug is called an adverse event. Rare adverse events related to drugs are often impossible to detect in pre-licensure studies and therefore there is an incentive to monitor the safety of a drug post-licensure [Kulldorff et al., 2011]. Monitoring the safety of drugs post-licensure is called safety surveillance.

The information related to a possible causal relationship between a drug and an adverse event is called a safety signal (signal). Safety surveillance is interested in finding these signals. According to Nelson et al. [2015, p. 179], post-licensure safety aims related to drugs can be classified into three stages:

1. **Signal identification:** Considers a large number of events and involves detecting signals related to unexpected adverse events.
2. **Signal refinement:** Considers drug-event pairs suspected to have a causal relationship, based on biological plausibility or a previously identified signal. Addresses specified hypotheses related to the pairs.
3. **Signal confirmation:** Involves a one-time, more in depth study of a previously generated signal.

An assumption to the type of safety surveillance considered in this thesis is that a biologically plausible exposure-event pair has been previously identified. The method to be introduced requires that the relationship between the exposure and the adverse event can be characterized by defining a time interval of possibly increased risk. This places the safety surveillance considered in this work to the refinement stage.

In this thesis the drug of interest is a vaccine product (vaccine). The goal is to introduce and utilize a vaccine safety surveillance method to make decisions related to the generation of safety signals, utilizing electronic medical records.

1.2 Vaccine safety surveillance

In vaccine safety surveillance the researcher or an automated system monitors the safety of vaccines and generates a safety signal if an unexpectedly large number of adverse events are observed. After a signal has been generated, further action can be taken, for example a confirmation analysis can be performed.

Assuming that there is random variation in the numbers of events, the observations might not always correspond to the true state of association between the vaccine and the event, leading to false positive or false negative signals. Natural goals of vaccine safety surveillance are to control the expected rates of false positive and false negative signals. It is also desirable to generate a signal as soon as possible, if an association between the vaccine and an adverse event exists.

Statistical methods designed specifically for vaccine safety surveillance exist. This thesis will focus on the maximized sequential probability ratio test (maxSPRT), which is a statistical hypothesis testing method designed for vaccine safety surveillance [Kulldorff et al., 2011]. Vaccine safety surveillance based on maxSPRT has been utilized between 2005 - 2015 in many countries such as in USA, UK, Taiwan and New Zealand. The main focus has been on studying the effects of influenza vaccines. [Leite et al., 2016]

Statistical hypothesis tests such as the maxSPRT aim to control the expected rate of errors when making decisions under uncertainty. In statistical theory the false positive signals are called type I errors, and the false negative signals are called type II errors. The expected true positive signal rate is called the power.

There are multiple variants of the maxSPRT method such as the Poisson maxSPRT (PmaxSPRT), binomial maxSPRT (BmaxSPRT) and conditional PmaxSPRT, along with further versions designed for handling grouped observations. According to Leite et al. [2016], the most popular variant of maxSPRT has been PmaxSPRT followed by BmaxSPRT. In this work the focus will be on the BmaxSPRT variant.

One situation when a safety surveillance method such as the BmaxSPRT could be applied, would be an introduction of a new vaccine to a national vaccination program, such as the introduction of chicken pox vaccination starting in 1.9.2017 in Finland. If there are previously identified safety signals (any reasons to suspect a possible causal relation between the vaccine and some rare adverse event), safety surveillance could be initialized to refine these signals, utilizing accumulating data from electronic health records.

1.3 Elements of safety surveillance

In this work I will generally view a safety surveillance method as consisting of three elements: (1) data accumulation (2) study design and (3) decision rule for generating signals. Table 1.1 describes options for the elements. A unique combination of the three elements can be thought to define a unique safety surveillance method. The different variants of maxSPRT can therefore be viewed as unique safety surveillance methods which vary in terms of the underlying study design and assumptions related to data accumulation. They all use (sequential) hypothesis testing as the decision element.

For any reasonably rare adverse events, daily collected data can be considered as continuous observations. In this work I will mainly consider situations where observations (electronic health care data) accumulates daily and therefore the focus will be on continuous observations. I will utilize a case-only design – and specifically the self-controlled case series (SCCS) – as the design element and I will use maxSPRT sequential hypothesis testing as the decision element of a vaccine safety surveillance method.

These choices (continuous observations, a case-only design and maxSPRT) lead to the continuous binomial variant of maxSPRT, BmaxSPRT.

Table 1.1: Elements of Vaccine safety surveillance and options related to them.

Element	Options
Data accumulation	Continuous observations, grouped observations
Study design	Case-only design, cohort design, case-control design
Decision rule	Hypothesis testing

1.4 The operationalization of exposure and outcome

The starting point of vaccine safety surveillance is the definition of one or several vaccine - adverse event pairs. In this thesis the biological condition of interest (the adverse event) is operationalized by a group of medical diagnoses related to hospital visits. The medical diagnoses are identified based on a diagnosis code recorded in an electronic medical record data base. Vaccinations are operationalized similarly from medical records, identified using the vaccines name or an identification code.

Utilizing register data for vaccine safety research is both economical and powerful, because the data collection is practically free and the registers allow for near population level studies. However, it is important to note that registers are secondary data sources - the data are originally collected for other reasons than the research question at hand - and therefore the selection, quality and methods of the data collection are not controlled by the researcher [Sørensen et al., 1996]. The visit to a hospital resulting in a certain diagnosis code might not directly relate to the biological condition of interest.

In Finland, medical diagnoses data are available from electronic health record data bases such as The National Hospital Discharge Register (HILMO) and The Register of Primary Health Care Visits (AvoHILMO). Vaccination data are available from the National Vaccination Register (NVR). AvoHILMO, HILMO and NVR all contain time-stamped patient-level information and the data from the registers can be linked using a personal identification code, unique to all individuals in Finland. Diagnoses and vaccinations can thus be linked on an individual level and the relative timing of vaccinations to medical diagnoses can be asserted.

There are two diagnosis classifications used in Finland: the International Classification of Diseases and Related Health Problems, 10th edition (ICD-10) and to lesser extent the International Classification of Primary Care, 2nd edition (ICPC-2). The ICD-10 is much broader than the ICPC-2, but the ICPC-2 can be used alongside the ICD-10 due to cross-tabulation provided by the World Health Organisation [THL, 2011].

Data from AvoHILMO and NVR are available as daily collections and at the time of writing this thesis (2017), data from HILMO are available three times a year. Near real-time vaccine safety surveillance considered in this thesis is a possibility in Finland, utilizing data from AvoHILMO and NVR.

1.5 Outline

This thesis will introduce the vaccine safety surveillance method BmaxSPRT in detail by breaking it down to its elements. The study design and decision rules for signal generation are the main focus of this work and are given thorough treatment. The outline of the thesis is as follows.

- Chapter 2 offers discussion related to the design elements in vaccine safety surveillance, focusing on case-only study designs.
- Chapter 3 offers discussion related to the decision elements in vaccine safety surveillance and focuses on sequential hypothesis testing. Dealing with grouped observations (data accumulation) is briefly discussed in section 3.4.
- Chapter 4 offers a proof of concept application of the BmaxSPRT method, utilizing three different vaccine exposures and a single outcome of interest.

The thesis ends with conclusions.

2 Study designs for vaccine safety

In vaccine safety surveillance the researcher (or a defined automated system) observes, but does not intervene, with the events that occur. Therefore safety surveillance falls under observational studies. The researcher observes accumulating data related to vaccinations and medical diagnoses, and attempts to answer the question: has the rate of adverse events for a vaccinated individual increased due to the exposure.

A natural follow-up question is: increased as compared to what? To answer this question, the researcher needs a *study design* which defines the groups of individuals to be compared. Ideally, the defined groups would only differ with respect to their exposure status, so that observed changes in the rates of events could be directly assigned to the exposure. In practise this is difficult to achieve.

Electronic health care data bases such as the hospital discharge register (HILMO) can be utilized as sources of data for the medical diagnoses, used to operationalize the biological condition of interest (adverse event). However, the visit to a hospital resulting in a certain diagnosis code might not directly relate to the adverse event. This can introduce biases when comparing observations from different time periods, due to for example changes in diagnosis coding practises, which are then observed as changes in event rates. The chosen study design should be as robust to these changes as possible.

If the study design is poor and the chosen groups are not comparable, the studied sample can be biased: the observed effect of the exposure can be caused by some other differences between the groups. This means that the rate of false positive or false negative signals generated by the safety surveillance method may be inflated.

In their systematic review of vaccine safety surveillance applications, Leite et al. [2016] found that from 11 recently generated signals, only 3 were confirmed as true signals. The false positive signals were assigned to

1. Confounding factors that have not been considered.

2. Misclassification of the outcome.
3. Changes in the true incidence or coding practises.
4. Inappropriate comparison groups.
5. Uncertainty in background rates.
6. Type I errors. [Leite et al., 2016, p. 234].

All the above reasons except the 2nd one are affected by the study design.

In vaccine safety surveillance, the study design should make it unlikely to introduce biases while enabling the generation of a true signal as reliably as possible. In the following sections, I will first compare possible observational study designs for safety surveillance: Cohort designs, case-control designs and case-only designs. The rest of the chapter will then focus on the two most popular case-only study designs in pharmagovigilance (drug safety): the self-controlled case series (SCCS) and the case-crossover (CCO) designs.

2.1 Observational epidemiological study designs

Ultimately all epidemiological study designs share the same goal: compare some group of individuals (cases or exposed) to another group of individuals (controls or unexposed). In vaccine safety surveillance, the question of interest is if and how the exposure to the vaccine causes an increased risk of an adverse event. The main observations of interest relate to medical diagnoses which occur after exposure. I will consider the following three observational study designs for safety surveillance:

1. **Cohort design:** Time is viewed from the point of view of exposure. Groups of exposed and non-exposed individuals are followed forward in time. The incidences of events are compared between the groups.
2. **Case-control design:** Time is viewed from the point of view of the event. Individuals with events (i.e. cases) are matched to one or more individuals without events (i.e. controls). The proportions of having been exposed are compared between the cases and controls.
3. **Case-only designs:** Only individuals with events are sampled and are self-matched, using for example risk and control periods to define the events as either cases or controls. Event incidences or exposure rates are compared.

The designs have different strengths and weaknesses, which are listed in Table 2.1.

Table 2.1: Strengths and weaknesses of different epidemiological study designs.

Design	Strengths	Weaknesses
Cohort design	<ul style="list-style-type: none"> • Can provide an estimate of the baseline incidence • Utilizes all available data resulting in high power 	<ul style="list-style-type: none"> • If the exposure rate is high, the unexposed group from the same time period will be small • Confounders can affect the distribution of exposure, possibly resulting in bias
Case-control design	<ul style="list-style-type: none"> • If matched by age and time , controls for time-varying confounders such as age and seasonality • Needs little data specially with rare events 	<ul style="list-style-type: none"> • The unexposed group can be small • Finding suitable matches might be difficult • Confounders can affect the distribution of exposure, possibly resulting in bias
Case-only design	<ul style="list-style-type: none"> • Self-controlled: eliminates selection biases and confounding related to control subjects and time-invariant characteristics. • Does not need a baseline incidence estimate • Needs only data on cases 	<ul style="list-style-type: none"> • The choice of the risk and control periods plays a crucial role • Time-dependent confounders such as age and seasonality must be explicitly included in the model

2.1.1 Cohort and case-control designs

The cohort design utilizes all available data and is therefore often a preferred choice if data from the whole population is available. However, the nature of the exposure-event pairs considered here poses a problem to cohort designs. One problem is that the exposure to vaccination is optional, possibly resulting in selection bias. The second problem relates to using medical diagnoses as proxies for the underlying biological condition

of interest. I will provide two examples to clarify.

One way to utilize a cohort or a case-control design would be to compare the rates of events between the vaccinated and the not vaccinated populations of selected birth cohorts. This would provide a comparison which utilizes all available data from a single time period. The problem with this approach is that vaccination is both optional and usually very popular. Therefore, the group of unvaccinated individuals is often small and possibly biased due to selection. The latter may mean that the observed differences in the rates of events are due to the same reasons that cause individuals to become or not become vaccinated.

A second example of a cohort design would be a comparison of full birth cohorts from the pre- and post eras of introduction of a new vaccine to a vaccination program. The pre-vaccination era could be used to estimate the baseline incidence and the incidence during the post era could then be compared against the baseline. This approach utilizes a lot of data and provides a seemingly unbiased comparison, assuming that exposure to vaccination is the only significant change between the different birth cohorts. The problem with this approach is that diagnosis coding practises can change over time due to changes in recommendations or practises. The observed differences in event rates in electronic health care data bases can therefore be simply due to these changes.

2.1.2 Case-only designs

Case-only designs are designs which utilize data only from cases (persons with the events of interest). In case-only designs, each individual with an event acts as his/her own control and hence the designs are also called self-controlled designs. The designs considered here are based on comparison of event or exposure rates between defined risk and nonrisk periods.

In self-controlled designs, comparisons are made within the individuals such that all time-invariant confounders are eliminated [Nordmann et al., 2012]. Simulation studies by both McClure et al. [2008] and Glanz et al. [2006] have found that the self-controlled designs retain relatively high power compared to the cohort and case-control designs despite utilizing less data.

In their systematic review of case-only designs, Nordmann et al. [2012] found that the two most popular case-only designs utilized in pharmacovigilance are the case-crossover design (CCO) and the self-controlled case series design (SCCS). They also remark that “With the development of health care information technology .. these designs seem particularly appropriate to analyze pharmacovigilance data”, assuming that the exposure is transient rather than chronic, such as vaccination.

According to Farrington [2004], both CCO and SCCS can and have been used for vaccine safety analysis. According to Maclure et al. [2012], they are better than cohort designs for investigating transient effects of vaccines. In the following sections, I will present the CCO and SCCS. The main focus will be on the SCCS design which is developed for (but not limited to) vaccine safety analysis. CCO and SCCS are both suitable for studying rare adverse events.

2.1.3 CCO and SCCS

The case-crossover design (CCO) and the self-controlled case series design (SCCS) are two of the most popular case-only designs. Both designs implicitly or explicitly define risk and control periods during which rates of events are of interest. The risk period is a time interval following exposure during which the incidence rate of the adverse event can be thought of being potentially related to the exposure. A control period consists of one or more time intervals during which the incidence rate is assumed to be according to the normal background (baseline) rate of the individuals

- **The case-crossover design (CCO):** A case-only study design derived from a case-control design logic. Time is viewed from the point of view of the event. The random variables analysed are retrospectively ascertained exposures.
- **The self-controlled case series design (SCCS)** A case-only study design derived from a cohort design logic. Time is viewed from the point of view of the exposure. The ages at vaccination are regarded as fixed, and the random variable of interest is age at event, conditionally on its occurrence within a pre-determined observation period. [Farrington, 2004]

In CCO and SCCS, events occurring during the risk period can be labeled as “cases” and events during the control period as “controls.” Both designs aim at comparing the incidence rates of adverse events between the different periods, “within individuals”. Individuals act as both cases and controls in the study because the person time of the individuals is used to define both the cases and the controls.

From a statistical inference point of view, incidence rates can be compared with their ratio, called the *rate ratio*, denoted by RR . The rate ratio between two constant incidence rates λ_1 and λ_0 is

$$RR = \frac{\lambda_1}{\lambda_0}. \quad (1)$$

The rate ratio is the parameter of interest in both the CCO and SCCS. The SCCS approaches the problem by directly considering the rates of events during different periods of risk. CCO approaches the problem “backwards” by considering the rates of exposure instead. What follows is a detailed description of the SCCS method followed by a description of CCO.

2.2 The self-controlled case-series design: SCCS

In the self-controlled case series design (SCCS) developed by Farrington [1995], the goal is to compare the relative rates of adverse events during disjoint risk and control time periods, specified in relation to the time of vaccination. The observation period in SCCS is the calendar period and a specified age interval during which individuals can be sampled as cases. The effect of the vaccination is estimated via the rate ratio $RR = \lambda_1/\lambda_0$, where in a simple case

A simple Self Controlled Case Series design

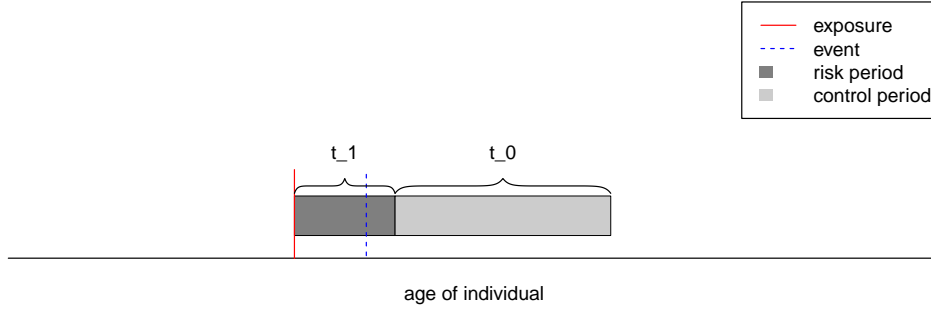


Figure 2.1: A simple example of a SCCS design where the period immediately following exposure is defined as the risk period with length t_1 and a time period following the risk period is defined as the control period with length t_0 .

- λ_1 : event incidence during a period when the exposure to vaccination is assumed to have an effect (risk period)
- λ_0 : event incidence during a period when the vaccination is assumed to not have an effect (control period).

If there is a significant change in the incidence during the risk period, the rate ratio will significantly differ from 1, with values greater than 1 indicating a positive association between the exposure and the event. The risk period could be a period of two weeks immediately following vaccination. A control period can also be explicitly defined, or alternatively all other time during the observation period can be considered as the control period. See Figure 2.1 for an illustration of the former.

The general idea of SCCS is to describe the event incidence as a function of the (constant) individual baseline incidence, effects due to vaccine exposure and other possible time-dependent factors such as age. Statistical inference in SCCS is based on a conditional likelihood which removes the individual incidence nuisance parameter. Inference concerning relative incidences (rate ratios) can therefore be done “within individuals” so that the individual baseline incidences have no effect on the inference.

In what follows is a mathematical description of SCCS largely inspired by the description of the general SCCS given in the case series tutorial by Whitaker et al. [2006, pp. 9-10] with influences from the description of SCCS by Bernardo et al. [2011, pp. 10-12]. I will first give a general framework for the SCCS method by introducing the concepts of a Poisson process and incidence rate function and then describe the conditional likelihood for the parameters of that function.

2.2.1 Poisson process

An underlying assumption in the SCCS method is that adverse events occur as a Poisson process. A Poisson process describes the probabilities for the numbers of events during some time interval(s). An important assumption related to the Poisson process is that the random variables corresponding to these numbers of events are independent between all disjoint time intervals. This implies that an occurrence of an adverse

event should not influence the probabilities of future adverse events. This assumption is likely to be violated in practise, but if the event is rare (relative to the length of the observation period), then this violation is unlikely to have practical consequences.

Definition (Poisson process). *A counting process $\{Y(t), t \geq 0\}$ is a Poisson process with rate λ if*

1. $Y(0) = 0$
2. $Y(t)$ has independent increments
3. The probabilities for the number of events during an interval of length t are given by the Poisson distribution with $E[Y(t)] = \lambda t$:

$$y_t \sim \text{Poisson}(\lambda t) \Leftrightarrow P(Y(t) = y_t) = \frac{(\lambda t)^{y_t} \cdot e^{-\lambda t}}{y_t!}$$

2.2.2 Incidence rate function

In this work the smallest measurable unit for time is a day, since data in electronic health care data bases such as AvoHILMO is collected daily. Remember that the observation period in SCCS is the calendar period and age interval during which individuals can be sampled as cases. For each individual, I will index the observation period by age in days denoted by d . A single day has a time unit of 1.

An assumption is made that during the observation period, adverse events for individuals $i = 1, 2, \dots, N$ arrive as a non-homogenous piecewise-constant Poisson process. The expected number of events (the incidence rate) for each individual is constant within each day, but can vary between days.

The incidence rate during day d for individual i is given by the incidence rate function λ_{id} , which depends on a constant individual effect ϕ_i and a time-dependent effect θ . The latter captures exposures to vaccination and changes in age. The effect of each θ_d is assumed to be multiplicative, so that the incidence rate for individual i during day d is given by

$$\lambda_{id} = \exp(\phi_i + \theta_d). \quad (2)$$

Due to the properties of the Poisson process the cumulative incidence over a number of days during the observation period is a sum of the daily incidences. If the incidence stays constant for a period of consequent, say, t_q days, the incidence during that period is given by the number of days times the daily incidence. Assuming that the observation period consists of such disjoint periods, the incidence rates are then given by

$$\lambda_{iq} = t_q \cdot \exp(\phi_i + \theta_q), \quad (3)$$

where θ_q is the constant θ_d , for the all d days in period q .

For example in a simple case as in Figure 2.1, where $q \in \{\text{risk period, control period}\}$, the incidence rate (3) takes on two different values.

2.2.3 Likelihood

Assume now that events of $i = 1, 2, \dots, N$ individuals are sampled, with $n_i \geq 1$ events for each i for a total of n events. Assume that events during the observation period arrive as a Poisson process with an incidence rate as defined in (3). Denote the number of events for individual i during period q as y_{iq} . The probabilities for the numbers of events during the disjoint intervals q are given by the Poisson distribution: $y_{iq} \sim \text{Poisson}(\lambda_{iq})$. The individual contribution to the likelihood for the observations is therefore

$$L_i(\boldsymbol{\theta}) = P(\mathbf{y}_i \mid \phi_i, \boldsymbol{\theta}) = \prod_q P(y_{iq} \mid \phi_i, \theta_q) \propto \exp\left\{-\sum_q \lambda_{iq}\right\} \prod_q (\lambda_{iq})^{y_{iq}}, \quad (4)$$

where $\lambda_{iq} = t_q \cdot \exp(\phi_i + \theta_q)$ as in (3). The likelihood contains the individual baseline incidence ϕ_i which is a nuisance parameter, since the real interest is in the effect of the vaccination and/or age, captured by $\boldsymbol{\theta}$.

The total number of events for the individual, $n_i = \sum_q y_{iq}$, turns out to be a sufficient statistic for ϕ_i , meaning that conditioning on n_i removes the dependency on ϕ_i . It is therefore convenient to operate with the conditional likelihood instead. Since the random variable corresponding to the total number of events is a sum of Poisson random variables, it is also Poisson distributed: $n_i \sim \text{Poisson}(\sum_q \lambda_{iq})$. The individual contribution to the conditional likelihood is

$$L_i(\boldsymbol{\theta} \mid n_i) = P(\mathbf{y}_i \mid n_i, \phi_i, \boldsymbol{\theta}) = \frac{P(\mathbf{y}_i \mid \phi_i, \boldsymbol{\theta})}{P(n_i \mid \phi_i, \boldsymbol{\theta})} \propto \frac{\prod_q \lambda_{iq}^{y_{iq}}}{\left(\sum_q \lambda_{iq}\right)^{\sum_q y_{iq}}} = \prod_q \left(\frac{\lambda_{iq}}{\sum_{q'} \lambda_{iq'}}\right)^{y_{iq}}. \quad (5)$$

Now, plugging in the incidence rate defined by (3), the conditional likelihood is

$$L_i(\boldsymbol{\theta} \mid n_i) \propto \prod_q \left(\frac{t_q \cdot e^{\phi_i} \cdot e^{\theta_q}}{\sum_{q'} t_{q'} \cdot e^{\phi_i} \cdot e^{\theta_{q'}}}\right)^{y_{iq}} = \prod_q \left(\frac{t_q \cdot e^{\theta_q}}{\sum_{q'} t_{q'} \cdot e^{\theta_{q'}}}\right)^{y_{iq}}, \quad (6)$$

which is a multinomial likelihood where the individual baseline incidences have been canceled out. This means that using the conditional likelihood, the inference concerning the parameter $\boldsymbol{\theta}$ cannot be influenced by the individual incidences ϕ_i . In that sense the SCCS design is self-controlled. However, it should be noted that all factors which depend on the time period q , such as age, remain. The effect of age can be separately included in the model in the general version of SCCS.

Next I will present the simple and the general SCCS which are both based on the assumptions of a piecewise-constant Poisson process and a conditional likelihood. The simple SCCS is particularly useful for the safety surveillance method BmaxSPRT, to be introduced later. The general SCCS is relevant for future research in developing safety surveillance methods.

2.2.4 Simple SCCS

Consider a SCCS with a simple incidence rate function where there are two periods of interest: a risk period and a reference control period. Denote these periods by the indicator $k \in \{0, 1\}$ where 1 indicates a risk period and 0 indicates a control period.

The risk and control periods are disjoint and of lengths t_1 and t_0 respectively, and are defined in relation to the time of exposure to vaccination. For example, a time period immediately following vaccination can be defined as a risk period and a time period following the risk period can be defined as a control period, as illustrated in Figure 2.1. The incidence rate function (3) takes the form

$$\lambda_{ik} = t_k \cdot \exp(\phi_i + \psi_k), \quad k = 0, 1. \quad (7)$$

Assume that during the control period $\psi_0 = 0$ and the incidence is simply determined by the baseline incidence of the individual and by (7) is given by $t_0 \cdot e^{\phi_i}$. The incidence during the risk period is given by $t_1 \cdot e^{\phi_i} e^{\psi_1}$. The parameter of interest is ψ_1 which quantifies the multiplicative effect that the risk period has on the incidence, as now $RR = \lambda_{i1}/\lambda_{i0} = e^{\psi_1}$ is the common rate ratio of the incidence between the risk and control periods.

Now assume again that events of $i = 1, 2, \dots, N$ individuals are sampled, with $n_i \geq 1$ events for each i for a total of n events. Denote the number of events for individual i during the risk period as y_{i1} and during the control period as y_{i0} . The individual contribution to the conditional likelihood (5) for the parameter ψ_1 is

$$L_i(\psi_1 | n_i) \propto \prod_{k=0,1} \left(\frac{t_k \cdot e^{\psi_k}}{\sum_{k'} t_{k'} \cdot e^{\psi_{k'}}} \right)^{y_{ik}} = \left(\frac{e^{\psi_1}}{e^{\psi_1} + t_0/t_1} \right)^{y_{i1}} \left(\frac{t_0/t_1}{e^{\psi_1} + t_0/t_1} \right)^{n_i - y_{i1}}. \quad (8)$$

which is the binomial likelihood, where the only unknown parameter is the common rate ratio $RR = e^{\psi_1}$. If one labels the events that occurred during the risk period as “cases”, and the events that occurred during the control period as “controls”, the probability of an event labeled as a case depends only on RR and the ratio of the lengths of the two periods $z = t_0/t_1$. The probabilities of a “case” (“success”) and “control” (“failure”) are given by

$$P(\text{"case"}) = p = \frac{RR}{RR + z}, \quad P(\text{"control"}) = 1 - p = \frac{z}{RR + z}. \quad (9)$$

Assuming that individuals are independent, the total conditional likelihood can be seen as independent binomial trials with a homogenous probability of success, $p = RR/(RR + z)$. Given that observations included $y_1 = \sum_i y_{i1}$ “cases”, the total conditional likelihood for the parameter RR is

$$L(RR | n) = P(y_1 | RR, n) \propto \left(\frac{RR}{RR + z} \right)^{y_1} \left(\frac{z}{RR + z} \right)^{n - y_1}. \quad (10)$$

2.2.5 General SCCS

I will now present a more general version of SCCS, including an age effect parameter and multiple risk periods with varying risks. Varying risks can be motivated by for example the desire to include the effects of different doses of a vaccine. The inclusion of an age effect is motivated by the fact that many biological conditions are age-dependent.

Consider an observation period as described earlier and assume that adverse events arrive as a piecewise-constant Poisson process with an incidence rate function similar to (3). The observation period for each individual is split into disjoint intervals by age groups indexed by j and disjoint risk periods indexed by k . The number of days in an interval where i is in age group j and risk period k is denoted by t_{ijk} . The incidence rate function for i can then be written as

$$\lambda_{ijk} = t_{ijk} \cdot \exp(\phi_i + \gamma_j + \psi_k), \quad (11)$$

where for the reference age group $\gamma_0 = 0$ and for the reference risk period (control period) $\psi_0 = 0$. Now denote the number of events observed during each interval by y_{ijk} . The individual contribution to the conditional likelihood (5) is

$$L_i(\psi, \gamma \mid n_i) \propto \prod_{jk} \left(\frac{t_{ijk} \cdot e^{\gamma_j} \cdot e^{\psi_k}}{\sum_{j'k'} t_{ij'k'} \cdot e^{\gamma_{j'}} \cdot e^{\psi_{k'}}} \right)^{y_{ijk}}. \quad (12)$$

Assuming that individuals are independent, the total conditional likelihood is

$$L(\psi, \gamma \mid n_i) \propto \prod_i \prod_{jk} \left(\frac{t_{ijk} \cdot e^{\gamma_j} \cdot e^{\psi_k}}{\sum_{j'k'} t_{ij'k'} \cdot e^{\gamma_{j'}} \cdot e^{\psi_{k'}}} \right)^{y_{ijk}}, \quad (13)$$

which, again, is the multinomial likelihood where all the individual baseline incidences have been cancelled out.

2.3 The case-crossover design: CCO

The most popular case-only design utilised in pharmacovigilance is the case-crossover design (CCO). CCO is a modification of a case-control design, originally developed by Maclure [1991] to study the effect of transient exposures to acute events. Its use in drug safety studies has increased during 2000-2010 [Nordmann et al., 2012]. CCO has also been used for vaccine safety analysis [Farrington, 2004, p. 2066].

A simple Case–crossover design

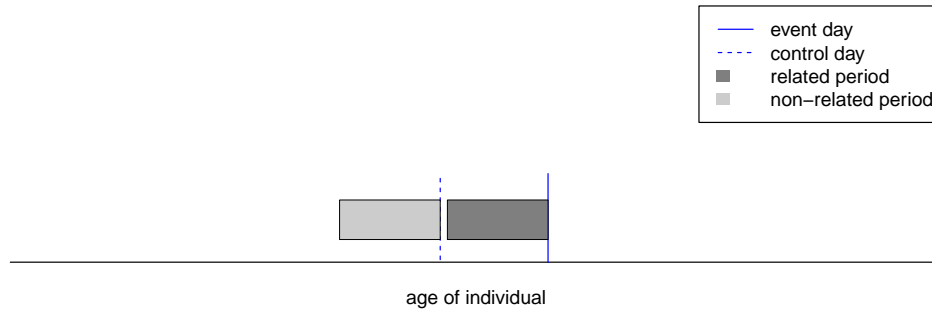


Figure 2.2: A graphical illustration of the CCO design. Exposures occurring immediately before the event day are considered as related to the event and exposures occurring immediately before the control day are considered as not related to the event.

2.3.1 Description of CCO

Following Maclure et al. [2012, pp. 50-51], one way to describe the CCO design is as follows: Assume that rare events are observed for individuals $i = 1, \dots, n$. Each event occurs during some *event day* and a *control day* is defined as the day that was d time units (e.g. days) before the event day. The control day could for example be the day two weeks (14 days) before the event day. For each sampled individual i , exposure status is retrospectively examined. Exposures during a time interval of length t immediately preceding the event day are considered as related to the event. Exposures occurring during a time interval of the same length (t) immediately preceding the control day are considered as not related to the event.

The periods where the exposure status is of interest are sometimes called risk and control periods in CCO literature. I will call these periods the *related period* and the *non-related period*, respectively. The idea of the CCO design is to compare the rates of exposure between the related and the non-related periods. This description of CCO is illustrated in Figure 2.2.

2.3.2 Prospective and retrospective arguments

The description of CCO given above follows the so-called retrospective conditional argument of case-control studies. In the retrospective probability model, the exposures are conditioned by the case or control status and the odds ratio of exposure between different event status (“case” or “control”) is the parameter of interest. However, the estimation of disease-exposure relationship in case-control studies may also be approached using a prospective conditional argument. In the prospective probability model, the event status is conditioned on the exposure and the odds ratio of the event status between levels of exposure is estimated [Clayton and Hills, 1993, ch. 16].

From a prospective point of view, a time interval following exposure is called the *effect period* in CCO literature, during which the rate of events for the exposed individuals is possibly increased. The effect period corresponds to the related period and is of identical length. The effect period in CCO is comparable to the

risk period in SCCS. I will therefore use the term risk period to refer to the effect period. Similarly, a control period of identical length to the non-related period can be defined.

For example, the risk period could be a period of two weeks following vaccination, in which case the related period is the period two weeks prior to the event day. A control period could be defined as the period of 2 weeks following the risk period, in which case the control day would be the day two weeks prior to the event day and the non-related period would be the period two weeks prior to the control day. See again Figure 2.2 for an illustration.

CCO is interested in the same question as SCCS, which is to infer if the rate of events is affected by exposure. Even though the method is based on the idea of exposures as the random variable, the parameter of interest can be defined as any of the prospective relative risk parameters: the odds ratio, relative risk or the incidence rate ratio [Nordmann et al., 2012, p.8].

2.3.3 CCO in the literature

The literature concerning the CCO approach can be confusing, since it must be interpreted from context if the author has chosen to treat the design from a prospective or retrospective point of view and sometimes both views are used simultaneously. For example, Nordmann et al. [2012, p. 2] describe the method using phrasing “*With this design, the probability of exposure in the risk period is compared to the probability of exposure in control period(s).*”. They however then go on to state that “*same probability of event occurrence during case and control periods*” is a major assumption of the method.

When discussing CCO, Farrington [2004] instead writes that “*the underlying probability of vaccination should be the same in all intervals*”, which is inline with treating exposure as the random variable of interest. Farrington [2004, p. 2066] then adds that this assumption “*is unlikely to hold for paediatric vaccines administered according to stricter schedules*”.

To estimate the relative risk in the CCO setting, Maclure [1991] suggests using the Mantel-Haenzel estimator to approximate the rate ratio parameter. Further discussion of maximum likelihood estimation in the CCO setting is provided by Marshall and Jackson [1993].

2.4 Study design conclusions

Cohort designs are problematic for vaccine safety studies due to many possible sources of bias. Case-only designs are attractive because they implicitly control for time-invariant confounders.

Of the two most popular case only designs, the SCCS compares somewhat favourably to CCO. Farrington [2004, p. 2066] has pointed out that in the case of paediatric vaccines there is a conceptual problem with the CCO design, where vaccination times are treated as random variables. It is more natural to view event times as the random variables of interest, since vaccinations often occur according to a strict schedule.

SCCS assumes that the vaccination time is fixed and the time of the adverse event is a random variable. SCCS allows for direct inference concerning the population parameter of interest, which is the relative rate of adverse event incidences between specified risk and control time periods. The simple SCCS introduced in 2.2.4 offers a statistical model where the rate ratio RR is the only unknown parameter and fixed individual covariates have no effect on the inference.

The following chapter continues discussion of safety surveillance from the point of view of the decision element. The simple SCCS is adopted as the design element.

3 Decision rules for vaccine safety surveillance

One of the key elements of a safety surveillance method is a decision rule for generating safety signals. In safety surveillance, the observations are medical diagnoses used as proxies for the biological condition of interest (adverse event). The goal is to stop observing and take some further action if an unexpectedly high number of adverse events are observed. Dynamically determining what exactly is “unexpectedly high”, is a problem that this chapter aims to solve.

Gradually accumulating diagnoses form the sample to be analysed and decisions related to safety signal generation are made based on the sample. The sample never represents the total study population of interest, which can be thought to include also unborn individuals, possibly experiencing adverse events in the future. Furthermore, there is presumably random variation in the occurrence of adverse events in the population.

The decision making process in safety surveillance involves uncertainty. Inevitably, some amount of errors are expected to be made. A desirable quality of a safety surveillance method is to control the expected rate of false positive and false negative signals. When a true association between a vaccination and an adverse event exists, another desirable quality is to generate a safety signal as soon as possible. In other words, a natural goal is to minimize the number of adverse events needed to generate a signal, for some fixed rate of false positive and false negative signals.

In this chapter, the focus will be on sequential hypothesis testing, which can be used to control the expected rate of errors and minimize the time to signal generation. The BmaxSPRT safety surveillance method is described in detail, including the derivation of decision rules for safety signal generation.

3.1 Hypothesis tests in vaccine safety surveillance

Statistical hypothesis testing is a method of statistical inference for decision making under uncertainty. Uncertainty usually arises from the fact that available observations do not cover the whole population of interest, but rather are a sample from that population. In a regular hypothesis testing scenario, there is a single fixed sample and a single hypothesis test is performed to reach a conclusion. The setting in safety surveillance is different, since observations arrive sequentially.

In the following sections, I will discuss the use of sequential hypothesis testing for deriving decision rules for vaccine safety signal generation. I will first describe hypothesis testing in general and then discuss testing with sequential observations. I will introduce the sequential probability ratio test (SPRT), which was the first hypothesis testing method developed for sequential analysis. I will then describe in detail the maximized sequential probability ratio test (maxSPRT), which is a sequential hypothesis testing method designed for (but not limited to) vaccine safety surveillance.

3.1.1 Statistical hypotheses

Statistical inference is based on a family of probability models $P(Y|\boldsymbol{\theta})$ for the observations Y , indexed by the parameters $\boldsymbol{\theta}$. A statistical hypothesis is a proposition which assigns restrictions for the parameter of a statistical model. Usually there are two hypotheses: the null hypothesis H_0 and the alternative hypothesis H_1 . These are expressed by

$$H_0 : \boldsymbol{\theta} \in \Theta_0 \quad H_1 : \boldsymbol{\theta} \in \Theta_1,$$

where Θ_0 and Θ_1 are disjoint and usually $\Theta_0 \cup \Theta_1 = \Theta$, so that the two hypothesis together cover the whole parameter space (all possible values of the parameter). For short I will denote $\boldsymbol{\theta} \in \Theta_0$ as $\boldsymbol{\theta}_0$ and similarly for $\boldsymbol{\theta}_1$.

A hypothesis is called simple if it addresses only a single point in the parameter space. In many applications such as in vaccine safety, the most interesting alternative hypothesis is of the form $H_1 : \theta > \theta_0$. This type of hypothesis – which addresses more than a single point in the parameter space – is called a composite hypothesis.

When the objective is to find evidence of an association between an exposure and an event (for example that the rate ratio for exposed and not exposed is positive), the null proposition (hypothesis) is a state of no association. The alternative hypothesis is composite: some positive association. Using the rate ratio parameter RR , this can be stated as two competing hypotheses as follows:

$$H_0 : RR = 1 \quad H_1 : RR > 1 \tag{14}$$

3.1.2 Hypothesis testing

In statistical hypothesis testing, two statistical models $P(\mathbf{Y} | \boldsymbol{\theta}_0)$ and $P(\mathbf{Y} | \boldsymbol{\theta}_1)$, defined by the competing hypotheses H_0 and H_1 , are compared. Usually the comparison is done by defining a test statistic $T = T(\mathbf{y})$ for which high values are critical to the null hypothesis and the probability distribution of T is known under H_0 . If the observed value for T is very unlikely when H_0 were true, then one chooses to reject H_0 .

The test statistic can be for example the likelihood ratio:

$$LR = \frac{L(\boldsymbol{\theta}_1; \mathbf{y})}{L(\boldsymbol{\theta}_0; \mathbf{y})} = \frac{P(\mathbf{y} | \boldsymbol{\theta}_1)}{P(\mathbf{y} | \boldsymbol{\theta}_0)}. \quad (15)$$

Values of (15) greater than 1 mean that the observations are more likely under the alternative hypothesis ($P(\mathbf{y} | \boldsymbol{\theta}_1) > P(\mathbf{y} | \boldsymbol{\theta}_0)$).

3.1.3 Errors and power

When a decision is made between two competing hypothesis, two types of errors can be made:

- Type I error: H_1 is chosen (H_0 rejected) when the H_0 is true.
- Type II error: H_0 is chosen (H_0 accepted) when the H_1 is true.

The probabilities of type I and II errors are usually denoted by α and β , respectively. Terminology related to hypothesis testing is displayed in Table 3.1.

The complement of β is called the power of the hypothesis test: the probability of choosing H_1 (rejecting H_0) when the H_1 is true. If the hypotheses are as in (14), and the parameter of interest is RR , the power of a hypothesis test is usually a function of RR , meaning that higher values of RR make it more likely for the test to reject the null hypothesis. This also means that the actual type II error rate is a decreasing function of RR .

In the context of vaccine safety surveillance the above means that one would be more likely to conclude that there is a difference in the rate of events between two groups, the bigger that difference is. This is important because it leads to the following observation: when the alternative hypothesis is composite, knowing the type II error rate or the power of a test before collecting observations is impossible without fixing the value of RR .

Table 3.1: Terminology related to statistical hypothesis testing

Term	Description
H_0	The null hypothesis ($H_0 : \boldsymbol{\theta} \in \Theta_0$)
H_1	The alternative hypothesis ($H_1 : \boldsymbol{\theta} \in \Theta_1$)
Composite hypothesis	A hypothesis which addresses more than a single point in the parameter space. For example $H_1 : \theta > 1$
α	$P(\text{reject } H_0 H_0)$. The type I error rate (false positive rate)
β	$P(\text{accept } H_0 H_1)$. The type II error rate (false negative rate)
Power	$1 - \beta$

3.2 Sequential analysis

From a statistical inference point of view, a situation where observations accumulate gradually is different from a more common situation with a fixed number of observations. With a fixed number of observations,

one can perform a single statistical hypothesis test and make a single decision. With accumulating data, multiple such tests could be done. Sequential analysis focuses on situations where there is a need to perform an analysis whenever new observations arrive. Sequential hypothesis tests can be used to derive decision rules for each new observation.

A naive approach to sequential analysis would be to perform a standard hypothesis test on the accumulating data set each time new observations become available. Hypothesis testing is based on the general idea that if observations are unlikely under a statistical model defined by H_0 , then some assumptions of that model can be questioned. However, if an experiment is repeated multiple times, then even very unlikely outcomes of the experiment are likely to be observed during at least one of the trials. Repeated analysis of accumulating data creates a problem, since repetition introduces multiple chances to reject the H_0 . The naive approach needs adjustment: in a situation of accumulating data, methods designed specifically for sequential analysis are needed.

Sequential analysis was developed by Wald [1945] during the second world war and it addresses the problem of hypothesis testing in a situation where observations arrive sequentially. Wald defined a sequential test of a statistical hypothesis as a test procedure which gives a rule of making one of three possible decisions at a single trial of the experiment:

1. Accept the null hypothesis.
2. Reject the null hypothesis.
3. Continue the experiment by making an additional observation.

Wald [1945] developed the sequential probability ratio test (SPRT), which is the optimal sequential hypothesis test between two simple hypotheses [Wald and Wolfowitz, 1948].

SPRT has since been extended to address composite hypotheses with so called sequential generalized probability ratio tests. Kulldorff et al. [2011] introduced a version of such a test, called the maxSPRT, designed for vaccine safety surveillance. In the following sections I will first briefly introduce SPRT and then describe the maxSPRT and its self-controlled binomial variant BmaxSPRT in detail.

3.2.1 Sequential probability ratio test: SPRT

Wald's [1945] sequential probability ratio test (SPRT) is a sequential hypothesis test designed for testing two simple hypotheses. SPRT is based on the likelihood ratio:

$$LR_n = \frac{L(\boldsymbol{\theta}_1; \mathbf{y}_n)}{L(\boldsymbol{\theta}_0; \mathbf{y}_n)} = \frac{P(\mathbf{y}_n | \boldsymbol{\theta}_1)}{P(\mathbf{y}_n | \boldsymbol{\theta}_0)}, \quad (16)$$

where \mathbf{y}_n are the current observations for $n = 1, 2, \dots$. The SPRT procedure is described in Algorithm 3.2.1. Even though there is no defined upper limit to the number of observations, Wald [1945, p. 128] proved that the SPRT experiment will eventually terminate with probability 1. He also later showed that SPRT is the

optimal sequential test for testing a simple null hypothesis against a simple alternative, in the sense that it has the lowest expected sample size among tests of equal power [Wald and Wolfowitz, 1948].

Algorithm 3.2.1: SPRT

Input: Desired Type I and Type II error rates α and β , test statistic function LR_n as in (16)

1. Compute critical upper and lower boundaries $A = (1 - \beta)/\alpha$ and $B = (1 - \alpha)/\beta$.
2. After observation $n = 1, 2, \dots$ do
 - if $LR_n \geq A$ stop, reject H_0
 - if $LR_n \leq B$ stop, reject H_1
 - otherwise draw an additional observation.

3.2.2 Critical values of SPRT

The SPRT test has two critical regions: $Q_0 = \{LR_n \mid LR_n \geq A, B < LR_{n-1} < A\}$ for rejecting H_0 and $Q_1 = \{LR_n \mid LR_n \leq B, B < LR_{n-1} < A\}$ for rejecting H_1 , defined by the two critical values A and B . These regions define the stopping criteria for the test for all observations $n = 1, 2, \dots$. The SPRT procedure and the critical regions are illustrated in Figure 3.1.

Note that the probability of rejecting the null hypothesis when it is true (type I error) is given by $P(Q_0 \mid H_0) = \alpha$ and the probability of rejecting the alternative hypothesis when it is true (type II error) is given by $P(Q_1 \mid H_1) = \beta$. The critical values A and B should be chosen to match the desired (low) error rates.

In order to determine the values A and B , Wald considered the entire sample space consisting of all possible realisations in the sequential test. He showed that the critical values A and B can be approximated by functions of the desired α and β regardless of the statistical model by setting $A = (1 - \beta)/\alpha$ and $B = (1 - \alpha)/\beta$. He also remarked that this procedure will guarantee that the actual type I and II errors will not exceed α and β and will only differ from them slightly [Wald, 1945, 127-133].

The above is a beautiful and simple result, but the solution requires a fixed α and β . To give the type II error a proper meaning, however, requires fixing the parameter of interest (RR), which can be considered a weakness. In what follows I will introduce Wald's suggested solution for dealing with a composite alternative hypothesis and then illustrate the weakness related to the solution.

3.2.3 SPRT and a composite alternative hypothesis

SPRT was designed for testing two simple hypotheses. Wald did however propose a solution to a situation of a composite alternative hypothesis. In this section I will introduce this solution and then illustrate a weakness related to it.

SPRT illustration

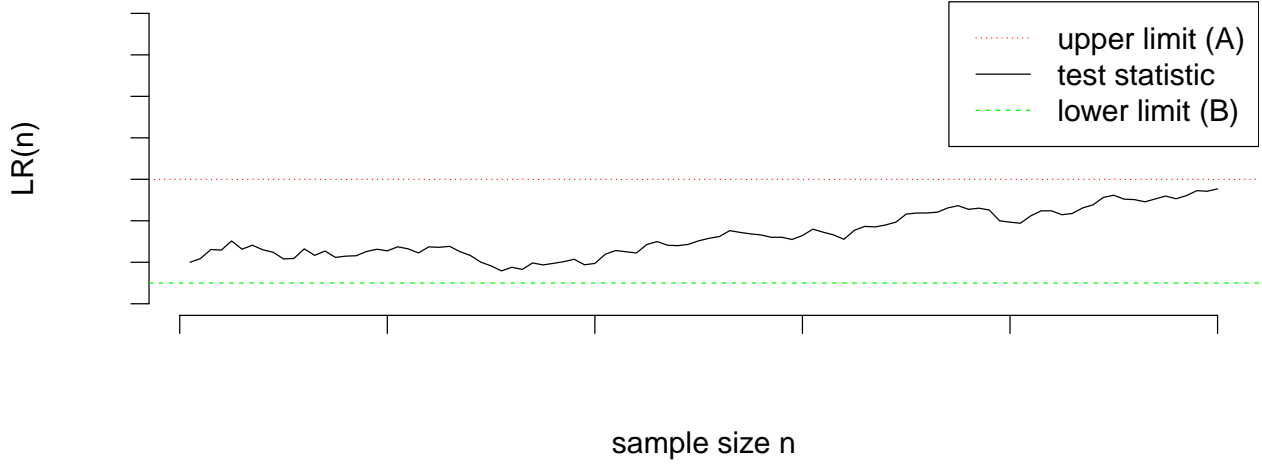


Figure 3.1: A graphical illustration of the critical boundaries of the sequential probability ratio test (SPRT) where the test statistic is the likelihood ratio (LR). If the numerator of LR is the likelihood according to the alternative hypothesis, then high values of LR mean that the alternative model fits the data better and are thus critical to the null hypothesis. The upper limit A (dashed red line) then defines the critical region to the null hypothesis. Similarly, the lower limit B (dashed green line) defines the critical region for the alternative hypothesis.

Wald [1945, p. 158] remarked that in common statistical models the power of the SPRT test is an increasing function of the parameter of interest θ . He therefore suggested dealing with a composite alternative hypothesis by simply defining a value θ_1 such that the difference $\theta_1 - \theta_0$ would be of significant interest in the application and then setting a point alternative hypothesis $H_1 : \theta = \theta_1$. Then one could simply utilize SPRT as described in algorithm 3.2.1 and test a simple null hypothesis against a simple alternative.

When the parameter of interest is the rate ratio, one example of the strategy above would be to view rate ratios $1 \leq RR < 1.2$ as of no interest and therefore for example set $H_1 : RR = 1.2$. Kulldorff et al. [2011] remarked that an unfortunate relation between the choice of RR_1 and the actual (i.e. true) RR_a can either

1. delay the rejection of H_0 when the observed rate of events is higher than the specified alternative hypothesis would expect (delayed signal generation)
2. increase the type II error when the actual rate of events is closer to the rate suggested by H_0 , than the rate suggested by H_1 (decreased power).

In other words, scenario (1) can happen when $RR_0 < RR_1 \ll RR_a$ and scenario (2) when $RR_0 < RR_a \ll RR_1$.

The intuition leading to (1) is that if RR_a is far from both RR_0 and RR_1 , then both models, defined by H_0 and H_1 , are “bad” models and therefore $P(\mathbf{y} | RR_1)$ and $P(\mathbf{y} | RR_0)$ will on average be close to each other. For example, if one specifies $RR_0 = 1$ and $RR_1 = 1.2$ when in reality $RR_a = 6$, then both H_0 and H_1 specify bad models. In such a case the high number of adverse events expected to be observed would be given low probability by both models. The likelihoods would remain close to each other and the likelihood ratio would

remain close to one. It might take a large number of samples to reach a point where $LR \geq A$ and H_0 is rejected.

The above is clearly undesirable especially with serious adverse events, where it is desirable that an unexpectedly high number of adverse events would lead to a quick decision to reject H_0 .

To see the intuition behind scenario (2), assume again that we are interested to find if $RR > 1$. Following Wald's suggestion one might for example choose $RR_0 = 1$ and $RR_1 = 2$, when $RR_a = 1.4$. In this case the model specified by H_0 is closer to the real value of RR and it is thus expected that $P(\mathbf{y} | RR_0) > P(\mathbf{y} | RR_1)$, making it more likely that $LR \leq B$ (H_1 rejected). Thus the type II error is increased. See Figure 3.2 for an illustration.

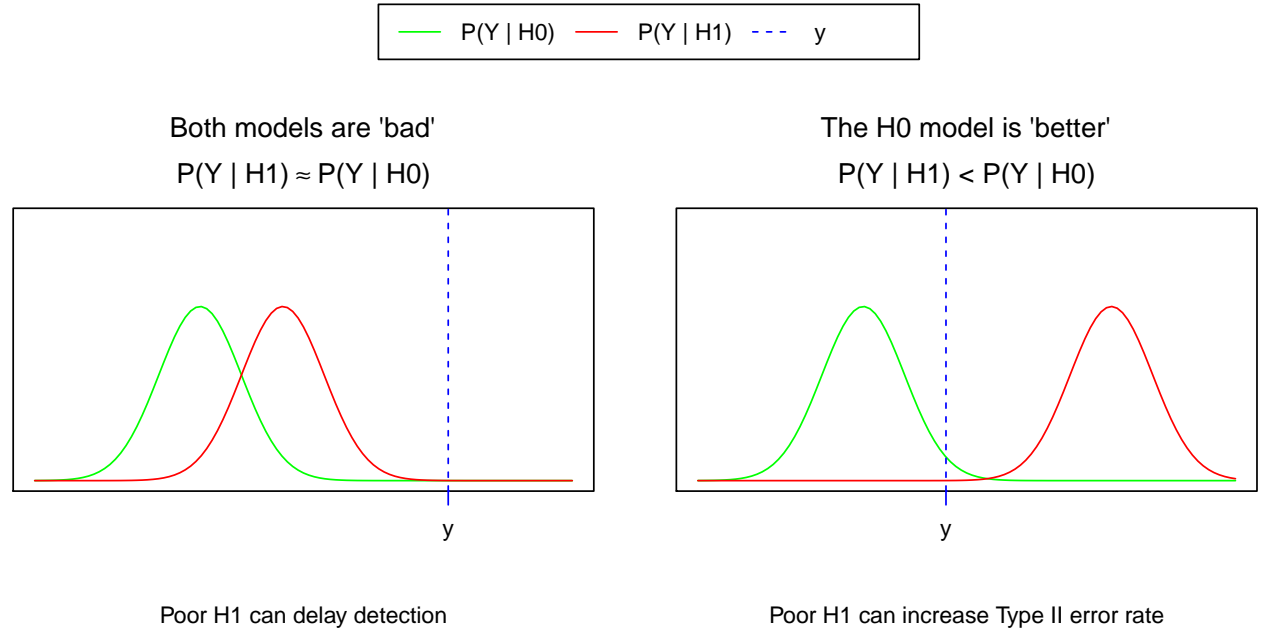


Figure 3.2: A graphical illustration of a weakness of Wald's SPRT. The blue line describes the number of observations and the green and red lines describe the statistical model for the observations under the null and alternative hypothesis, respectively. Left: A choice of point alternative hypothesis close to the null hypothesis and far from the actual observations can delay the rejection of H_0 , because the (high number of) observations are unlikely under both hypotheses. Right: A choice of point alternative hypothesis that is 'too aggressive' compared to the actual observations can increase the type II error rate, because the data is more likely under the null hypothesis.

3.3 Maximized sequential probability ratio test: maxSPRT

A solution suggested by Kulldorff et al. [2011] to the weakness of SPRT described above is to modify the test in two ways:

1. Maximize the likelihood ratio in the space of the alternative hypothesis Θ_1
2. Instead of setting a lower bound B to reject H_1 , define a maximum number of observations N and reject H_1 if $n \geq N$.

The modified sequential test is called the maximized sequential probability ratio test (maxSPRT). The maxSPRT is a general sequential hypothesis testing method, which can be used on any statistical model.

Kulldorff et al. [2011] introduce two versions of the maxSPRT method: one based on Poisson likelihood and the other on Binomial likelihood. The binomial model arises when the study design is a simple self-controlled design such as the simple SCCS introduced in section 2.2.4.

When the parameter of interest is RR , the maxSPRT test statistic is

$$LR_n = \max_{RR_1} \frac{L(RR_1; \mathbf{y}_n)}{L(RR_0; \mathbf{y}_n)} = \max_{RR_1} \frac{P(\mathbf{y}_n | RR_1)}{P(\mathbf{y}_n | RR_0)}. \quad (17)$$

The maxSPRT procedure is described in Algorithm 3.3. The procedure uses a test statistic such as (17) and requires that the desired type I error rate and the maximum number of observations are chosen before the experiment is carried out. The first step is the computation of the critical value of the test statistic. This computation depends on the statistical model for the observations (i.e. the likelihood function). The following sections discuss the case where the likelihood is binomial.

Algorithm 3.3: MaxSPRT

Input: Desired type I error rate α' , upper boundary for the sample size N , test statistic function LR_n as in (17)

1. Compute the critical value c of the test.
2. After observation $n = 1, \dots, N - 1$ do
 - if $LR_n \geq c$ stop, reject H_0
 - otherwise continue
3. After observation N do
 - if $LR_N \geq c$ stop, reject H_0
 - otherwise reject H_1

3.3.1 Binomial maxSPRT: BmaxSPRT

Let us now adopt the maxSPRT method in the setting of the simple SCCS. Assume that for the sequence of observations $(y_n, n), n = 0, 1, \dots, N$, where y_n denotes the number of “cases” out of n events, the probability distribution for y_n is given by the binomial distribution as described in section 2.2.4. The probability of “success” (i.e. adverse event classified as a “case”), depends on the unknown rate ratio parameter RR and the known ratio between the lengths of the control and risk periods, z and the conditional likelihood is as in (10).

Let the two hypotheses be as in (14). Using equation (17), the maxSPRT test statistic is given by

$$LR_n = \max_{RR > 1} \frac{P(y_n | RR)}{P(y_n | RR = 1)} = \max_{RR > 1} \frac{\left(\frac{RR}{z+RR}\right)^{y_n} \left(\frac{z}{z+RR}\right)^{n-y_n}}{\left(\frac{1}{z+1}\right)^{y_n} \left(\frac{z}{z+1}\right)^{n-y_n}}. \quad (18)$$

Kulldorff et al. [2011] call a sequential test based on the test statistics (18) the binomial maxSPRT. A simple SCCS design combined with the the maxSPRT method is one way to arrive at the BmaxSPRT, which shows that the BmaxSPRT method is self-controlled.

Computation of (18) requires maximization. It is easy to see that maximization in terms of RR depends only on the numerator, which is a likelihood function. Maximizing a likelihood function is a common task in statistics and the value that maximizes the likelihood in terms of the parameter RR is called the maximum likelihood estimate (MLE) for RR , denoted by \hat{RR} .

For computational reasons, it is usually convenient to operate with the log likelihood ratio instead. Since the logarithm is a strictly increasing function, maximizing the log likelihood ratio is equivalent to maximizing the likelihood ratio. The (log) likelihood ratio is maximized by finding the MLE for RR , which is easily seen to be $(y_n \cdot z)/(n - y_n)$. Since we are not interested in situations where $RR < 1$, one should use $\hat{RR} = \max\{1, \frac{z \cdot y_n}{n - y_n}\}$. Then the test statistic becomes

$$LLR_n = \log(LR_n) = \log \left(\frac{\left(\frac{\hat{RR}}{z + \hat{RR}}\right)^{y_n} \cdot \left(\frac{z}{z + \hat{RR}}\right)^{n - y_n}}{\left(\frac{1}{z + 1}\right)^{y_n} \cdot \left(\frac{z}{z + 1}\right)^{n - y_n}} \right). \quad (19)$$

A simplified form of (19) is given by Kulldorff et al. [2011, p. 71].

3.3.2 Computing the critical values of BmaxSPRT

The values of the test statistic (19) are easy to compute. What then remains is the definition of the critical region Q of the test: which values of the test statistic should lead to a decision to reject the null hypothesis. Since higher values of the test statistic are always more critical to the H_0 , it is sufficient to determine a single critical value c , which defines the boundary of the critical region. Values of (19) higher than c then lead to rejection of H_0 . The critical region of BmaxSPRT is

$$Q = \{LLR_n \mid LLR_n \geq c, LLR_{n-1} < c\}, \quad \text{for all } n = 1, 2, \dots, N,$$

where N is the maximum number of observations (adverse events). In order to compute the critical value, one must first choose a desired Type I error rate α' and an upper boundary for the sample size N . The goal is to then define c so that when H_0 is true, Q is only expected to be reached α' proportion of the time.

The upper boundary of the sample size makes it possible to compute the critical value of the maxSPRT test to any desired precision. Kulldorff et al. [2011, pp. 65-67, p. 72] describe how to do this for the Binomial and Poisson likelihoods. In the discrete binomial case the critical value can be computed by using a Markov chain approach.

Next, I will introduce the concept of a Markov chain in the setting of the BmaxSPRT experiment. I will define the state space, the initial probabilities and the transition probabilities, and show that the BmaxSPRT

experiment has the Markov property. I will then proceed to present an algorithm which can be used to compute the critical values of BmaxSPRT.

3.3.2.1 State space

In the BmaxSPRT sequential test, the possible states of the experiment are all the possible combinations of “trials” (n) and “successes” (y_n) during the experiment, bounded by the maximum number of observations N , set at the beginning of the experiment. Therefore the state space S is defined as follows:

$$S = (n, y_n), \quad \text{where } n = 0, 1, \dots, N \quad \text{and} \quad y_n = 0, 1, \dots, n. \quad (20)$$

The experiment always starts at the state $(0, 0)$. Clearly, there are a finite number of states. In fact, there are $M = \sum_{n=0}^N n + 1 = (N + 1)(N + 2)/2$ possible states.

3.3.2.2 Transitions

In the BmaxSPRT experiment, a new observation is either a “success” ($Y = 1$) or a “failure” ($Y = 0$), depending on the outcome of a Bernoulli random variable Y . Possible transitions in the state space S are therefore as follows:

$$\begin{aligned} \text{”success”} : (n, y_n) &\rightarrow (n + 1, y_n + 1) \\ \text{”failure”} : (n, y_n) &\rightarrow (n + 1, y_n). \end{aligned} \quad (21)$$

If the experiment is stopped at some state $s \in S$, then that state is called absorbing: it is impossible to leave the state. Otherwise, a state is called transient. In BmaxSPRT, the set of absorbing states are those for which the value of the test statistic reaches the critical value c and the experiment ends. I will denote the value of the test statistic (19) for a state s by $LLR(s)$. The set of absorbing states in the experiment are then

$$Q = \{s \in S \mid LLR(s) \geq c\}, \quad (22)$$

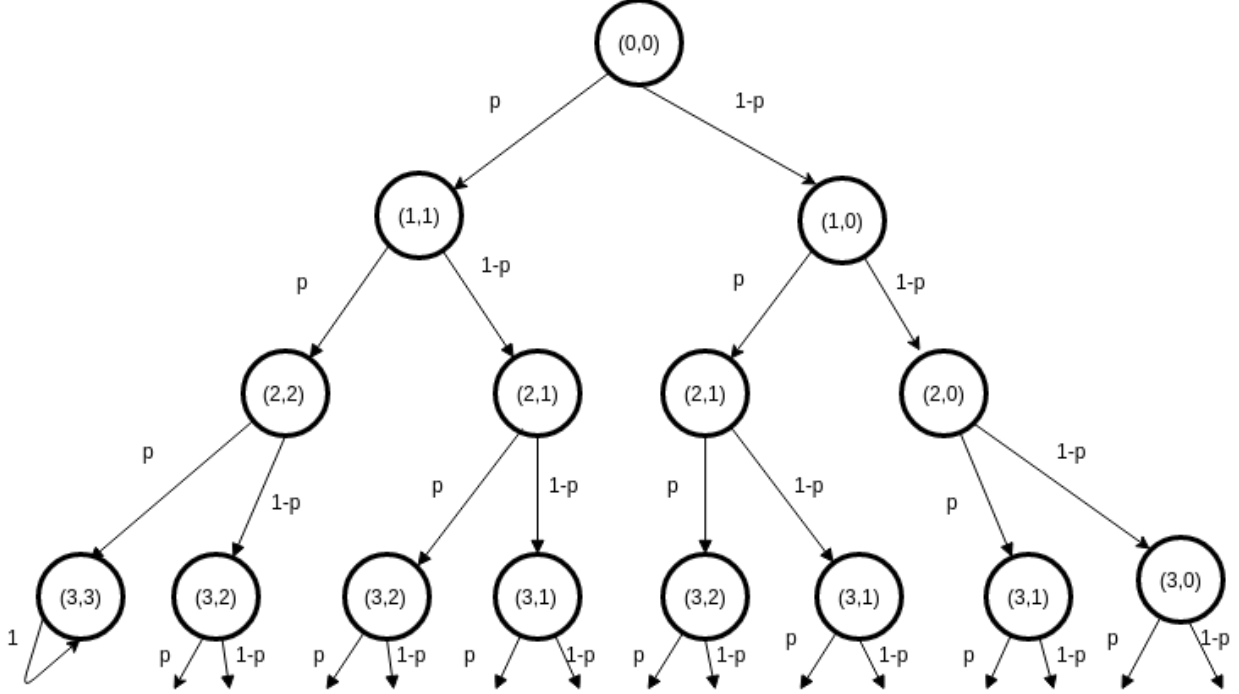
which is the critical region of the test.

3.3.2.3 Transition probabilities

The BmaxSPRT experiment starts at the state $(0, 0)$ with probability 1. Therefore a vector of initial probabilities \mathbf{v} for being in each of the (M number of) states at the beginning of the experiment is given by

$$\mathbf{v}_{1 \times M} = (1, 0, \dots, 0). \quad (23)$$

Figure 3.3: Visualization of the BmaxSPRT Markov Chain. The chain starts from the node (0,0) and a trial with the result "success" or "failure" is performed at each node, with p being the probability for "success". In this example the state (3,3) with 3 successes out of 3 trials is an absorbing state, corresponding to belonging to the critical region of the BmaxSPRT experiment.



A Bernoulli random variable Y determines the transitions. The transition probabilities for the transient states are given by

$$\begin{aligned} P\{(n, y_n) \rightarrow (n+1, y_n+1) \mid LLR(n, y_n) < c\} &= P(Y=1) = p \\ P\{(n, y_n) \rightarrow (n+1, y_n) \mid LLR(n, y_n) < c\} &= P(Y=0) = 1-p, \end{aligned} \quad (24)$$

where p is as in (9). Under the null hypothesis ($RR = 1$) $p = 1/(1+z)$. The probabilities of other transitions from the transient states are zero. The transition probabilities for the absorbing states are

$$P\{(n, y_n) \rightarrow (n, y_n) \mid LLR(n, y_n) \geq c\} = 1, \quad (25)$$

meaning that if such a state is reached, it is never left.

The matrix \mathbf{P} in (26) is a transition matrix which gathers the transition probabilities and defines the probability distribution over all the transitions from state to state in the state space S . Each row and column of \mathbf{P} corresponds to one of the states $s \in S$ and \mathbf{P}_{ij} gives the probability of the transition from s_i to s_j .

The probabilities of being in each of the states after N transitions in the state space are given by

$$\mathbf{P} = \begin{matrix} & \begin{matrix} (0,0) & (1,0) & (1,1) & (2,0) & (2,1) & (2,2) & (3,0) & (3,1) & .. & (N,0) & .. & (N,N) \end{matrix} \\ \begin{matrix} (0,0) \\ (1,0) \\ (1,1) \\ (2,0) \\ (2,1) \\ (2,2) \\ (3,0) \\ (3,1) \\ . \\ . \\ (N,0) \\ . \\ . \\ (N,N) \end{matrix} & \left(\begin{array}{cccccccccccc} 0 & 1-p & p & 0 & 0 & 0 & 0 & 0 & .. & 0 & .. & 0 \\ 0 & 0 & 0 & 1-p & p & 0 & 0 & 0 & .. & 0 & .. & 0 \\ 0 & 0 & 0 & 0 & 1-p & p & 0 & 0 & .. & 0 & .. & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1-p & p & .. & 0 & .. & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1-p & .. & 0 & .. & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & .. & 0 & .. & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & .. & 0 & .. & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & .. & 0 & .. & 0 \\ . & . & . & . & . & . & . & . & .. & . & .. & . \\ . & . & . & . & . & . & . & . & .. & . & .. & . \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & .. & 1 & .. & 0 \\ . & . & . & . & . & . & . & . & .. & . & .. & . \\ . & . & . & . & . & . & . & . & .. & . & .. & . \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & .. & 0 & .. & 1 \end{array} \right) \end{matrix} \quad (26)$$

Figure 3.4: A transition matrix describing the transition probabilities between the states in the state space S of the BmaxSPRT experiment. The rows and columns of the matrix are the possible states and \mathbf{P}_{ij} gives the probability of the transition $s_i \rightarrow s_j$. For example under the null hypothesis of the BmaxSPRT experiment the probability of the transition $(0,0) \rightarrow (1,0)$ ("failure") is given by $1-p = z/(1+z)$ and the probability of the transition $(0,0) \rightarrow (1,1)$ ("success") is given by $p = 1/(1+z)$. The states where the maximum number of observations is reached are all absorbing states.

$$\mathbf{p}_{1 \times M} = \mathbf{v} \mathbf{P}^{(N)} \quad (27)$$

3.3.2.4 Markov property

The Markov property means that the probability of transition to the next state depends only on the current state. It is easy to see that the BmaxSPRT experiment has a Markov property. Since the transitions are defined by independent Bernoulli trials, the probability of moving to the next state depends only on whether the current state is absorbing or not. Gathering the information of (24) and (25), the probability of transition to the next state is given in equation (28).

$$P(S_{i+1} = s_{i+1} \mid S_1, \dots, S_i) = \begin{cases} P(Y_{i+1} = y_{i+1} \mid Y_1, \dots, Y_i) \stackrel{\text{def}}{=} p, & \text{when } LLR(s_i) < c, \\ 0, & \text{when } LLR(s_i) \geq c. \end{cases} \quad (28)$$

3.3.3 Algorithm for BmaxSPRT critical values

Let N now be the chosen maximum number of observations (adverse events) and α' the desired type I error rate in the BmaxSPRT experiment. Using the notation for the absorbing states defined in (22), the goal is to define c such that $P(Q \mid H_0) = \alpha'$, meaning that the overall probability of rejecting the null hypothesis when it is true is α' .

For any given critical value c , the overall probability of reaching the critical region of the BmaxSPRT experiment can be computed by summing over the probabilities of being in each of the absorbing states $s \in Q$ after N transitions in the state space S . Note that a transition from an absorbing state to itself counts as a transition. Using the result introduced in (27), this probability is given by

$$\alpha_{(BmaxSPRT)} = P(Q | H_0) = \sum_{s \in Q} \mathbf{v} \mathbf{P}_0^{(N)}, \quad (29)$$

where \mathbf{P}_0 is the transition matrix (26), where $p = 1/(1+z)$ is according to H_0 . Using this result, it is possible to try out possible values of c until the one is found which best matches the desired α' . One way to execute this procedure is given in algorithm 3.3.3.

It should be noted that for a desired α' , the algorithm finds the value c which corresponds to a type I error α for which the inequality $\alpha \leq \alpha'$ holds. It is unlikely that $\alpha = \alpha'$ exactly. This is due to the discrete nature of the binomial distribution.

Algorithm 3.3.3: BmaxSPRT critical

- Input: States S , initial probabilities \mathbf{v} , transition matrix \mathbf{P}_0 , test statistic function LLR_n as in (19)
1. Compute all possible test statistic values $L = \{LLR(s) \mid s \in S\}$ and sort L from lowest to highest.
 2. Choose $c' = \min\{L\}$ to be the critical value. The absorbing states are $Q = \{s \in S \mid LLR(s) \geq c'\}$.
 3. Compute $P(Q \mid H_0) = \pi'$
 - if $\pi' \leq \alpha'$, stop, choose c' to be the critical value c for the type I error rate $\pi' = \alpha$
 - otherwise remove c' from L and go to 2.

3.3.4 Power of BmaxSPRT

The power of the BmaxSPRT experiment depends on the true value of the rate ratio. When the true rate ratio is RR_a , the probability of an event classified as a “case” is given by $p_a = RR_a/(RR_a + z)$. The true transition matrix of the experiment \mathbf{P}_a is then defined by these probabilities.

From this observation it is easy to see that the power of the BmaxSPRT experiment can be computed for any chosen fixed value of RR , say $RR_1 = 1.5$. One simply needs to define the transition matrix \mathbf{P}_1 , where the probabilities are given by $p_1 = RR_1/(RR_1 + z)$. This value only corresponds to the actual power of the experiment in the case where $RR_1 = RR_a$, which is of course unlikely. However, this procedure can provide a conservative estimate for the power of the experiment for a reasonable (small) choice of fixed RR_1 .

Denoting the critical region corresponding to a desired α' as Q_0 , the power of the BmaxSPRT experiment is given by the overall probability of reaching the critical region:

$$\text{Power}_{(BmaxSPRT)} = P(Q_0|H_1) = \sum_{s \in Q_0} \mathbf{v} \mathbf{P}_1^{(N)}, \quad (30)$$

where \mathbf{v} are the initial probabilities of the states and \mathbf{P}_1 is the transition matrix (26), where $p = RR_1/(RR_1 + z)$ for some fixed choice of RR_1 .

3.4 Grouped observations

The sequential hypothesis testing methods discussed so far in this chapter (SPRT, maxSPRT) assume that the value of the test statistic is evaluated whenever a new observation (a medical diagnosis) arrives. This applies to situations where data are available in near real time and observations arrive individually. This type of analysis is called continuous sequential analysis. Continuous sequential analysis is applicable in situations where the adverse events of interest are reasonably rare and medical diagnoses are collected reasonably often (for example daily).

Due to administrative reasons, sometimes medical diagnoses become available for analysis in groups. For example, the National Health and Welfare Institute (Finland) receives data from the HILMO register three times a year (2016). Unless the adverse events of interest are extremely rare, it can be expected that more than a single observation arrives simultaneously. The methods applicable in these situations are called group sequential methods [Silva and Kulldorff, 2015].

According to Silva and Kulldorff [2015] group sequential and continuous sequential analyses can be formally defined as follows.

Let X_t be a non-negative integer valued stochastic process describing the number of adverse events that occur during a $[0, t]$ time window.

Definition (Group sequential analysis). *For a set of constants A_1, \dots, A_K and a sequence of $\{t_i\}_{i=1}^K$ of times, a group sequential analysis design is any procedure that rejects the null hypothesis if $X_{t_i} \geq A_i$ for some $i \in \{1, \dots, K\}$*

Definition (Continuous sequential analysis). *For a function $B(t)$, a continuous sequential analysis design is any procedure that rejects the null hypothesis if $X_t \geq B(t)$ for some $0 < t \leq L$.*

In the coming sections I will discuss why the grouped nature of the data should affect a sequential hypothesis test and its critical values. I will then discuss possible solutions.

3.4.1 Adjusting for grouped observations

Silva and Kulldorff [2015] discuss the differences between group sequential and continuous sequential analyses. I will present a short overview of that discussion. I will show that the following statements are true.

1. Continuous sequential analysis should not be used if data become available in groups.
2. Any post-market safety surveillance system should attempt to obtain data as frequently as possible.

To see the intuition for statement 1, assume a special case of group sequential analysis with only a single group of observations. The two choices are then to either perform a retrospective continuous sequential analysis or do a single hypothesis test (using the single group of data). Assume that the same test statistic is used in both cases. For the continuous sequential analysis, the critical value of the test statistic must adjust for multiple chances to reject the H_0 . This means that it must be more difficult to reject the H_0 when H_1 is true. Continuous sequential analysis would therefore always have lower power than group sequential analysis if a group of data are already available.

The reason for statement 2 is that a continuous sequential method is always superior to a group sequential method if observations can be made separately. To see the intuition for this, assume a group sequential design that rejects H_0 when the total number of events (after a group of observations) are at least y_c . Now assume a continuous sequential design that looks at the observations separately and rejects H_0 as soon as there are y_c events. The error rates of the designs are identical because the number of events are non-decreasing. However, the continuous method is superior because it can reject the H_0 sooner (with a smaller sample size). Therefore for every group sequential design there is a superior continuous sequential design.

A conclusion can be made that not adjusting for the availability of the data can result in either loss of power or an increase in the expected sample size. Analyses should always be performed as soon as possible, using all the available data.

3.4.2 Group sequential methods

The same statistical model and test statistic that would be utilized in a continuous sequential analysis can be applied for group sequential analysis. However, when analyses are done for groups of data, there are less opportunities to reject the H_0 and therefore the critical values of the sequential hypothesis test should be affected. Unfortunately, if the number of observations per group is unknown, the computation of the critical values becomes difficult. Two assumptions could be made to simplify this computation, but the validity of the assumptions is questionable.

The problem of determining the critical values of a group sequential test would simplify if the number of observations per group were assumed to be fixed (fixed group sizes). Silva and Kulldorff [2017] have implemented this solution for computing critical values of a group sequential BmaxSPRT test in their Sequential R package, available in the Comprehensive R Archive Network (CRAN). This assumption makes the problem very similar to the situation discussed in section 3.3.2. The intuition for the similarity is that continuous BmaxSPRT can be seen as a special case of a group sequential hypothesis test with group sizes fixed at 1.

It is quite obvious that if adverse events are assumed to arrive as a random process in time but are collected during infrequent time intervals, the number of observations per group is by assumption a random variable. Therefore the solution of fixed group sizes does not seem satisfactory if the grouped nature of the data were due to administrative reasons.

The problem would also simplify if the maximum number of groups was fixed. However, assuming that the group sizes are unknown, fixing the number of groups will not fix the number of observations at the end of surveillance. Remember that the goal of safety surveillance is to keep collecting and analyzing data until there is sufficient information regarding a possible association between the exposure and the event. Naturally, the amount of information depends on the amount of observations. Therefore it would clearly be better to fix the number of observations than the number of groups.

A possible solution which needs neither simplifying assumption is to use an error spending approach, as introduced by Jennison and Turnbull [1999] in their book focusing on group sequential methods in clinical trials. Next, I will introduce the concept of error spending functions and maximum information trials, which could be useful approaches for future research regarding vaccine safety surveillance with grouped observations.

3.4.3 Error spending functions

One solution to group sequential analysis for random group sizes is to use an error spending approach (also known as alpha spending) [Jennison and Turnbull, 1999, ch. 7]. The idea of error spending is that for K groups, the type I error α is partitioned into probabilities π_1, \dots, π_K which sum to α . For the test statistics Z_k , critical values c_k are calculated so that

$$P(|Z_1| < c_1, \dots, |Z_{k-1}| < c_{k-1}, |Z_k| \geq c_k) = \pi_k \quad (31)$$

Intuitively this means that for each group k , only a proportion of the desired error probability α is spent.

A practical problem remaining is: how should each π_k be chosen? To solve this problem, Jennison and Turnbull [1999, pp. 148-150] introduce families of error spending functions and compare their properties. An error spending function $f(t)$ is a non-decreasing function which partitions the desired type I error rate and for which $f(0) = 0$ and $f(t) = \alpha$ for $t \geq 1$. Jennison and Turnbull [1999, p. 148] suggest a family of error spending functions defined by

$$f(t) = \min\{\alpha \cdot t^p, \alpha\} \quad (32)$$

where the choices of $p \in \{1, 3\}$ yield similar results to more classical approaches suggested by Pocock and O'brian & Fleming, which belong to the Wang & Tsiatis family of error spending functions.

3.4.4 Maximum information trials

Utilizing the concept of error spending functions, Jennison and Turnbull [1999, pp. 146-148] discuss decision rules in the case of two-sided alternative hypotheses, where the stopping rule for accepting H_0 is defined by a target maximum information level, denoted by I_{max} . Information level for group k is defined as

$$I_k = \{var(\hat{\theta}^{(k)})^{-1}\}, k = 1, 2, .. \quad (33)$$

where $\hat{\theta}$ is the estimator for the parameter of interest θ . A maximum information trial uses an error spending function such as (32), where the value of $f(t)$ indicates the cumulative type I error to be spent when a fraction t of the maximum anticipated information has been obtained. The type I errors allocated to each analyses are

$$\begin{aligned} \pi_1 &= f(I_1/I_{max}) \\ \pi_k &= f(I_k/I_{max}) - f(I_{k-1}/I_{max}). \end{aligned} \quad (34)$$

A decision rule for a maximum information trial is described in Algorithm 3.4.4 [Jennison and Turnbull, 1999, p. 54].

Algorithm 3.4.4: A maximum information trial

Input: target information I_{max} , sequence of groups k , test statistic function Z .

1. Define K as the smallest value k for which the information reaches the target information:

$$K = \min\{k \mid I_k \geq I_{max}\}$$

2. After group $k = 1, \dots, K$

- if $|Z_k| \geq c_k$ stop, reject H_0
- otherwise continue to group $k + 1$

3. After group K

- if $|Z_k| \geq c_k$ stop, reject H_0
- otherwise stop, accept H_0

The target information I_{max} is a very similar idea to the maximum sample size in maxSPRT. In their example utilizing the maximum information trial approach, Jennison and Turnbull [1999, pp. 150-153] assume that the test statistic has a normal distribution and the alternative hypothesis is two-sided. In maxSPRT type surveillance, the alternative hypothesis is one-sided and the test statistic is not assumed to be normal.

Maximum information trials provide a promising approach for grouped observation in vaccine safety surveillance, but further research is needed to adopt the method in the maxSPRT setting.

4 Childhood vaccinations and febrile seizures: application of BmaxSPRT safety surveillance

In this proof-of-concept application, BmaxSPRT vaccine safety surveillance was retrospectively applied to data from the Finnish HILMO register. The exposures of interest are three different childhood vaccinations: Measles-Mumps-Rubella vaccination (MMR), Pneumococcal vaccination (PCV) and the Rota virus vaccination (Rota). The outcome of interest are febrile seizures. The three vaccines are interesting because:

- For MMR there exists a known relationship to increased risk of febrile seizures
- For PCV there exists a suspected relationship to increased risk of febrile seizures
- For Rota there exist a suspected relationship to decreased risk of febrile seizures

MMR, PCV and Rota are all included in the vaccination program in Finland and are free for all children. The main interest of this application was to see if and when the BmaxSPRT method would generate a signal for the MMR and febrile seizure pair, and also to see what the results would be for the two other vaccines.

4.1 Febrile seizures and vaccinations

Fevers can cause a child to experience spasms or jerky movements called seizures. Seizures caused by a fever are called febrile seizures. Febrile seizures usually last for less than one or two minutes and they do not cause any permanent harm or have any lasting effects.

It is established that there is an increased risk of acute fever seizures during the 5-12 days following the first dose vaccination with MMR in children aged from 6 months to 2 years. This relationship has been previously shown by both international studies and using Finnish register data.

A study by the Centers for Disease Control and Prevention (CDC) has indicated that PCV vaccination together with a flu vaccination could be associated with an increased risk of febrile seizures during the 24 hours following exposure. A PCV vaccination alone might also cause a small increased risk of seizures. There is no evidence of Rota vaccination having similar effects and Sheridan et al. [2016] have found that a Rota vaccination can prevent febrile seizures. [CDC]

4.2 Data

In a real application of BmaxSPRT surveillance, data is collected and analyzed until a decision to reject or accept the null hypothesis can be made. In this retrospective proof-of-concept application, the goal was to utilize a limited amount of already existing data.

Finnish children under 2 years of age, born during 2010 - 2014 were considered eligible for this study. For MMR, the 2014 birth cohort was not considered, as due to the higher expected first dose vaccination age, no sufficient data for the 2014 cohort was yet available at the time of the study.

Vaccination data of all the three vaccines (Rota, PCV, MMR) were collected from the National Vaccination Register maintained by THL. Health care data regarding the febrile seizures were collected from the HILMO register.

4.2.1 Vaccinations

One challenge with analysing the effects of vaccines in an observational study is that multiple vaccinations can be given during the same day. For example, the second dose of Rota is recommended to be taken at the same age as the first dose of PCV. The recommended schedule for each of the three vaccines of interest is given in Table 4.1. In an effort to make the vaccines more identifiable, only first doses of each of the vaccines were considered in the experiment.

Sometimes the same vaccination is collected multiple times and there can be duplicate records in the vaccination register. Vaccination records with the same personal identification code and the same date as another record were excluded from analyses.

The three vaccines were analyzed separately by defining vaccination groups. A child belongs to a vaccination group if he/she was vaccinated with the respective vaccine during the observation period. A child can belong to multiple vaccination groups.

4.2.2 Hospitalizations

Febrile seizures were operationalized utilizing medical diagnoses related to hospitalizations. Febrile seizures were identified with the following ICD-10 diagnosis codes:

- A858: *Other specified viral encephalitis*, A86: *Unspecified viral encephalitis*, A87: *Viral meningitis*, A88: *Other viral infections of central nervous system, not elsewhere classified*
- G038: *Meningitis due to other specified causes*, G039: *Meningitis, unspecified*, G04: *Encephalitis, myelitis and encephalomyelitis*, G05: *Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere*
- R291: *Meningismus*, R55: *Syncope and collapse*, R560: *Febrile convulsions*, R568: *Other and unspecified convulsions*

Hospitalization associated with any one of these diagnosis codes was classified as a febrile seizure event. The date of the seizure was taken to be the date of hospitalization. A seizure within 7 days from the previous one for the same child was considered to represent the same event and thus the latter event was not included in the analysis.

4.3 Method

The method used in this experiment is the binomial variant of maxSPRT, BmaxSPRT. In order to deploy the BmaxSPRT, one needs to specify

1. The observation period.
2. The risk and control periods.
3. The desired type I error rate.
4. The maximum number of observations.

The chosen maximum number of observations affects the power of the experiment. Alternatively to directly specifying 4, the desired power corresponding to the choices made for 2-3 and a specified rate ratio could be chosen and the maximum number of events corresponding to that power could then be computed. In this experiment the maximum number of observations was directly chosen. Auxiliary information was used to help define the maximum number of observations.

The choices 1-4 were used to compute the critical value of the BmaxSPRT experiment, which together with the maximum number of observations defines the stopping conditions for the experiment. In what follows I will briefly describe the BmaxSPRT method and the parameters of the experiment. For details on the method please refer to earlier chapters.

4.3.1 Observation period

The observation period in BmaxSPRT for each individual is an age interval during which the individual can be sampled as a case, starting from some determined calendar date. To define the age intervals of interest, distributions of age at first vaccination dose were analyzed for each of the vaccination groups. The observation period for each vaccination group was then defined so that the chosen age interval covers most first dose vaccinations (>95%). The observation periods as ages in days for each of the vaccination groups are displayed in Table 4.1.

Table 4.1: The recommended vaccination schedule and observation ages by vaccination group.

Group	Schedule	Observation.ages
MPR	12 months	250-650 days
Rota	2, 3 and 5 months	30-140 days
PCV	3, 5, and 12 months	60-200 days

The analysis was performed with the assumption that new data might become available each day, starting from 2010-01-01. It should be noted that in reality the first observation is expected to arrive much later, since a person born during 2010 will first have to be vaccinated, then be hospitalized, and then pass through

the risk and control periods in order to contribute to the study.

4.3.2 Risk and control periods

From an epidemiological design standpoint, the study design in BmaxSPRT is a self-controlled, case-only design, such as the simple SCCS design introduced in section 2.2.4. In the simple SCCS, the observation period for each child is divided into risk and control periods following exposure. A febrile seizure during the risk period is classified as a case and a febrile seizure during the control period is classified as a control.

In this application, the risk period was chosen to be 0 - 13 days following vaccination and the control period 14 - 41 days following vaccination, for each of the vaccines. This risk period simultaneously covers the suspected period of increased risk for both PCV (24 hours following exposure) and MMR (5 - 12 days following exposure). The chosen risk and control periods are displayed in Table 4.3.

It should be noted that the chosen risk period is likely to be too long especially for PCV. This could affect the power of the BmaxSPRT experiment for the PCV group. In a real safety surveillance application, specific knowledge of the actual period of increased risk might not be available, which is why in this proof-of-concept application a choice of a conservative common risk period was used. See section 4.5 for a simulation study of how the choice of the risk period affects the power of the experiment.

4.3.3 Maximum number of observations

BmaxSPRT surveillance lasts until a determined maximum number of adverse events is observed or a safety signal is generated. There is no predetermined calendar time for the end of surveillance. In this retrospective proof-of-concept application however, it was desirable to reach a conclusion utilizing the available data. Measures were taken to make this more likely, by utilizing information on the incidence of febrile seizures available in the data. This information wouldn't be available nor would it be needed in a real application of BmaxSPRT.

For each of the age intervals of interest, the incidence of febrile seizures during the observation period, but excluding the risk period, was estimated to aid determining the maximum number of observations. I will call these the baseline incidences. The baseline incidences for each vaccination group are displayed in Table 4.2. For the oldest age group the baseline incidence of febrile seizures is higher than for the two younger groups.

The size of the vaccinated population was estimated using available birth data and vaccination coverage estimates. The expected number of seizures during surveillance, during which each vaccinated individual contributes a total of 42 person days to the experiment, was then computed. These expected numbers of events were then used as the maximum number of observations in the experiment.

Table 4.2: The included birth cohorts, size of the study population and estimated vaccination coverage for each of the observed age groups, along with the baseline event incidence estimates given by 1000 person years. The incidence estimates were used to calculate the expected number of events during surveillance, during which vaccinated individuals contribute 42 person days to the experiment.

Age	Cohorts	Population	Vaccination.coverage	Baseline.incidence	Expected.Events
250-650 days	2010-2013	238 568	95%	14.6	380
30-140 days	2010-2014	295 800	93%	8.1	259
60-200 days	2010-2014	295 800	94%	7.9	252

It should be noted that alternative strategies could have been used. For this retrospective experiment, it would have also been possible to simply count the total number of events during the risk and control periods in the available data for each vaccination group, instead of estimating the expected number of events. One could then choose the smallest of those as the mutual maximum number of observations. It is likely that other plausible solutions exist as well.

4.3.4 Hypotheses and decision rule

For each vaccination group, the hypotheses are

- $H_0 : RR = 1$
- $H_1 : RR > 1$,

where $RR = \lambda_1/\lambda_0$ is the rate ratio of the incidence of febrile seizures during the risk period (λ_1) and control period (λ_0).

Inference in the experiment is based on a conditional likelihood as in (10), which can be thought of as independent binomial trials, where the probability of an adverse event being classified as a “case” is a function of the rate ratio parameter RR . Higher values of RR correspond to a higher probability that an event occurred during the risk period instead of the control period. The test statistic is the maximized log-likelihood ratio as in (19).

The experiment proceeds as described in algorithm 3.3. For each day of surveillance, the value of the test statistic is computed and compared to the critical value to make a decision. If at any day during surveillance the value of the test statistic reaches the critical value, the experiment is stopped for the vaccination group and the H_0 is rejected. If there are no new observations, the value of the test statistic will remain the same and the decision made during the previous day will not change. If the maximum number of observations is reached without rejecting H_0 , the experiment ends and H_0 is accepted.

Auxiliary information was used to help choose the maximum number of observations N for each vaccination group. The maximum number of observations was chosen according to the expected number of seizures during surveillance, computed according to the estimated baseline incidence. The desired type I error rate was chosen to be $\alpha' = 0.05$. The actual type I errors were approximately the desired rates. The power of the BmaxSPRT experiment was calculated for a choice of rate ratio $RR = 1.5$.

The parameters defining the stopping conditions of the maxSPRT experiment for each vaccination group are displayed in Table 4.3, along with the power estimates. It can be seen that power of the experiment is reasonable for each group. However, the actual power of the experiment depends on the actual relative incidence rate and the actual risk period.

Table 4.3: Parameters of the BmaxSPRT experiment. z is the ratio of the lengths of the control and risk periods, p is the expected proportion of cases under the null hypothesis ($p = 1 / (z + 1)$), N is the maximum number of observations. α is the type I error. The power was computed for a rate ratio of 1.5.

	risk	ctrl	z	p	N	c	alpha	power
MMR	0-13	14-41	2	1/3	380	3.78	0.05	0.92
ROTA	0-13	14-41	2	1/3	259	3.69	0.05	0.80
PCV	0-13	14-41	2	1/3	252	3.68	0.05	0.79

4.4 Results

All analyses were carried out using the R program for statistical computing [R Core Team, 2017]. Functions from the Sequential R package were used for parts of the computations [Silva and Kulldorff, 2017], such as computing the critical values and the power of the experiment. In addition to the main results of BmaxSPRT surveillance for the three vaccines, results for continued surveillance are illustrated for MMR and PCV.

4.4.1 Surveillance results

The BmaxSPRT method generated a signal on day 693 of surveillance for PCV and on day 1041 for MMR and the H_0 was rejected. No signal was generated for Rota and the maximum number of observations was reached without rejecting H_0 . Thus the H_0 was accepted for Rota. The values of the test statistic and the rate ratio estimates for each day of surveillance are illustrated in Figure 4.1).

According to the choices of the risk and control periods, the expected proportion of cases under the H_0 is 1/3. For MMR there were 66 cases out of 149 events ($\approx 44\%$) and for PCV there were 29 cases out of 56 events ($\approx 52\%$). For Rota, the proportion of cases ($\approx 34\%$) closely matched the expected proportion. The

rate ratio estimates at the time of signal generation were 1.59 for MMR and 2.15 for PCV. For Rota, the rate ratio estimate at the end of surveillance was 1.01. These results are displayed in Table 4.4.

Table 4.4: Summary of the results of the BmaxSPRT surveillance for the three vaccination groups. A signal was generated for MMR and PCV.

	signal.day	LLR	cases	controls	n	prop.cases	RR
MMR	1041	3.85	66	83	149	44%	1.59
Rota	-	0.00	87	172	259	34%	1.01
PCV	693	4.03	29	27	56	52%	2.15

4.4.2 More results and conclusions

In a real application of BmaxSPRT, the surveillance immediately ends once evidence of an association between the vaccine and the adverse event has been found (a signal is generated) or if the maximum number of observation is reached. In this proof-of-concept application however, it is possible to satisfy ones curiosity and see what would happen if surveillance was instead continued for the two vaccines for which signal was generated and early stopping occurred (MMR, PCV).

The values of the test statistic and the rate ratio estimates for each day of the continued surveillance are illustrated in Figure 4.2. Further surveillance shows that when using all the available data, the estimate of the rate ratio for the PCV group goes down and the value of the test statistic stays below the critical value. The evidence of an association to febrile seizures for the PCV group therefore seems inconclusive. For MMR the evidence of an association becomes stronger with more observations.

It should be noted at this point that there are two reasons for why in this proof-of-concept application the results of the sequential hypothesis test should not be considered as conclusive results, especially for the PCV group. First, since a group of data is already available, the continuous maxSPRT is not the optimal hypothesis test. A regular hypothesis test would have greater power, as discussed in section 3.4. Second, the chosen risk period (0-13 days from vaccination) is possibly too long for PCV, where according to the literature the suspected increased risk of a febrile seizure is within a 24 hour period following vaccination.

The sensitivity of the power of the BmaxSPRT experiment to the choice of the risk period is an important question, which I will consider next.

4.5 Sensitivity analysis of BmaxSPRT

It is clear that the results of the BmaxSPRT experiment depend on the succesful choice of the risk period. Intuitively, if the actual time period of increased risk is shorter or longer than the chosen risk period, that

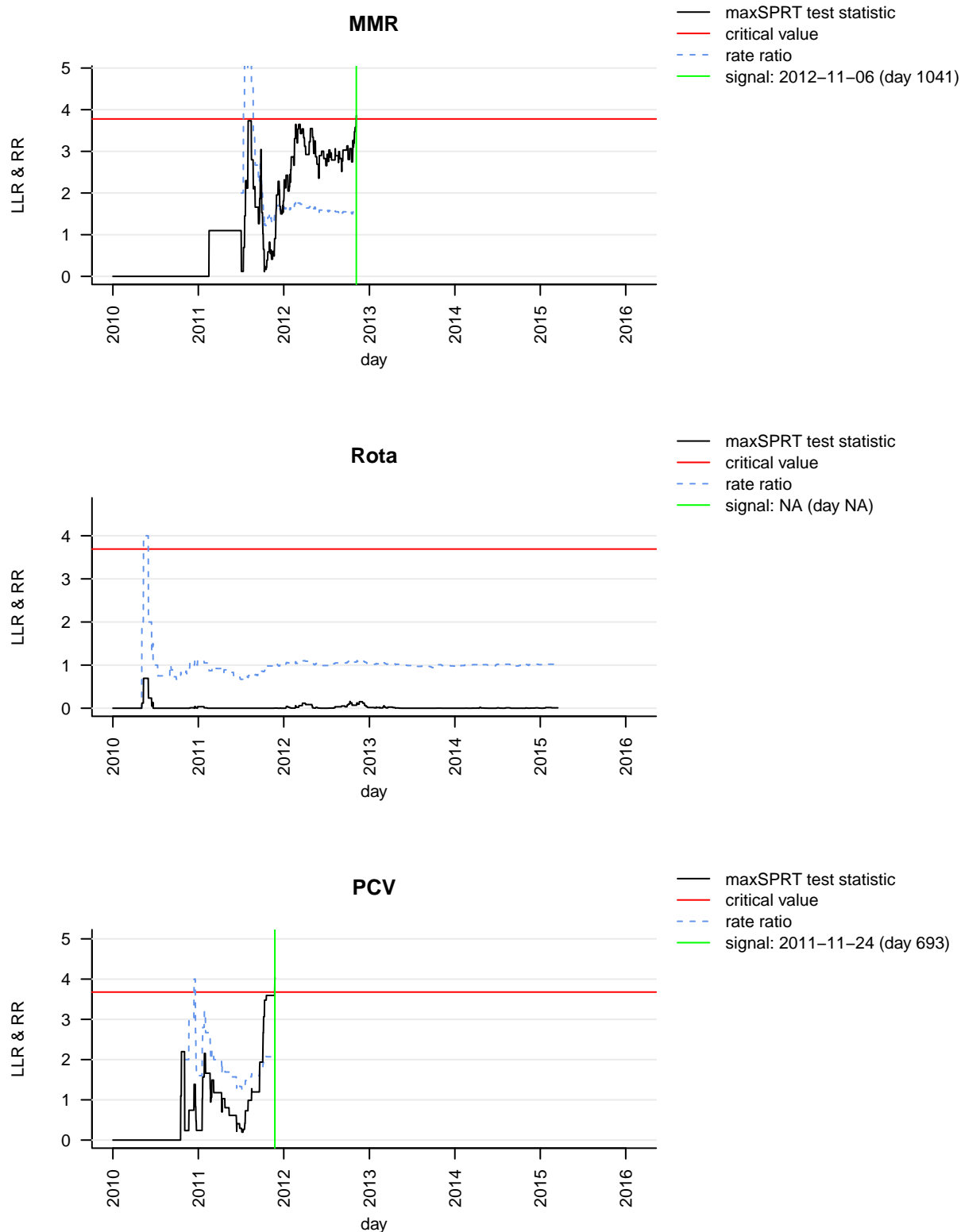


Figure 4.1: Results of BmaxSPRT surveillance for MMR, Rota and PCV. A signal was generated on day 1041 for MMR and on day 694 for PCV as the value of the test statistic (solid black) reached the critical value (solid red). The maximum number of observations (259) was reached for Rota without generating a signal. The running maximum likelihood estimate for the rate ratio is also displayed in the picture (dashed blue).

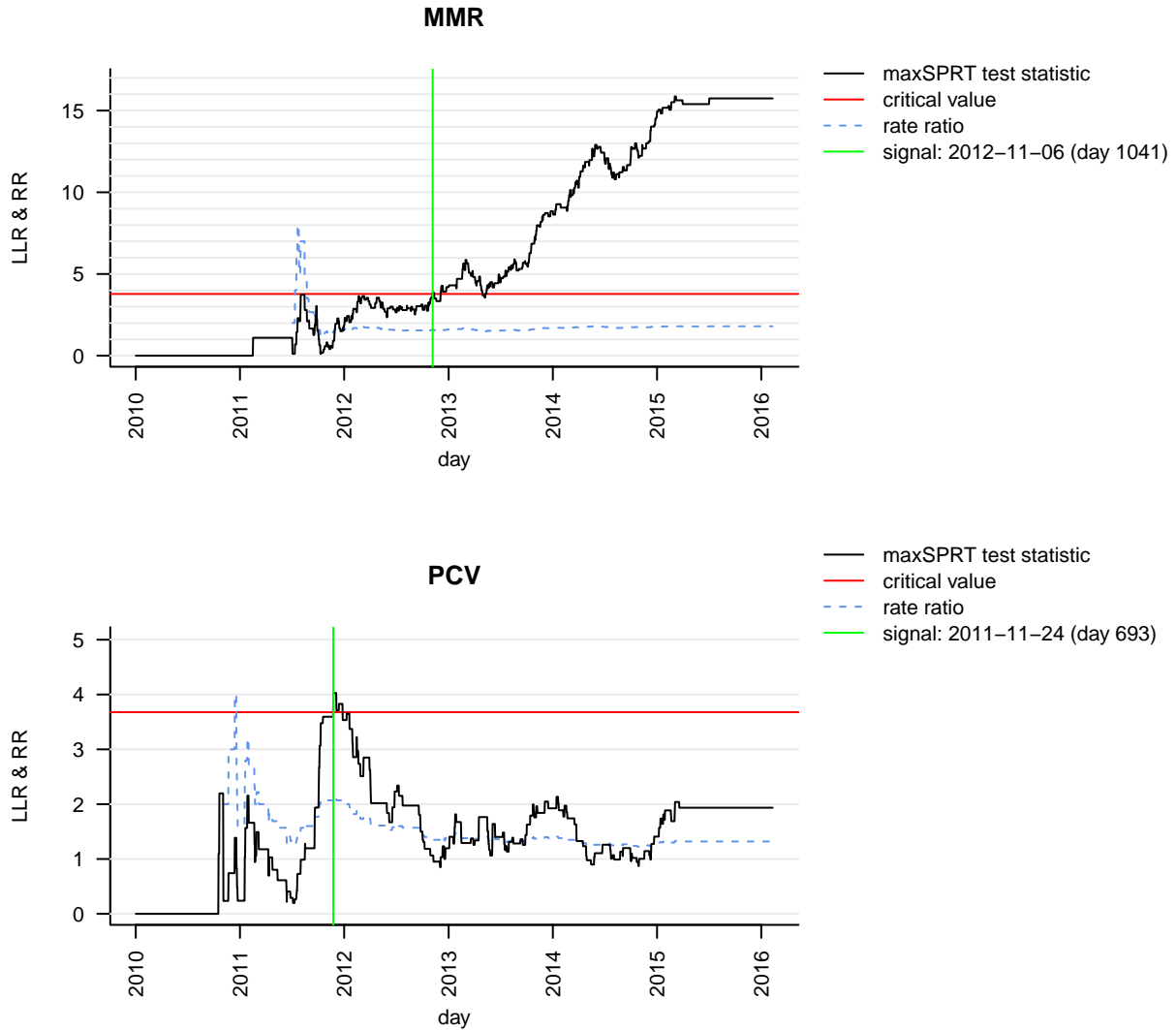


Figure 4.2: Results for continued surveillance for the PCV and MMR groups, both of which a safety signal was generated. Continued surveillance shows that the evidence of an association to febrile seizures for MMR gets stronger when utilizing the complete data set: the value of the test statistic (solid black) gets higher and further away from the critical value (solid red). The estimate for the rate ratio (dashed blue) remains above 1. Results for PCV are inconclusive, as the evidence of an association gets weaker with more observations.

should have a decreasing effect on the power of the test. An interesting question is therefore to quantify this effect for different choices of risk and control periods.

I used simulation to study how the power of BmaxSPRT is affected by the poor choices of risk and control periods. The analysis was carried out by repeatedly simulating adverse events data and applying the BmaxSPRT method to the simulated data with different choices for the risk and control periods. Below I will describe the assumptions of the simulation and then present the results of the analysis.

4.5.1 The studied risk and control periods

Six risk and control periods which differed from the actual risk and baseline time periods of the simulation were chosen, along with a seventh pair of reference choices which matched the actual risk and baseline periods perfectly. Figure 4.3 illustrates the chosen case and control periods. All the chosen periods have a common ratio between the lengths of the risk and control periods, as shown in Table 4.5.

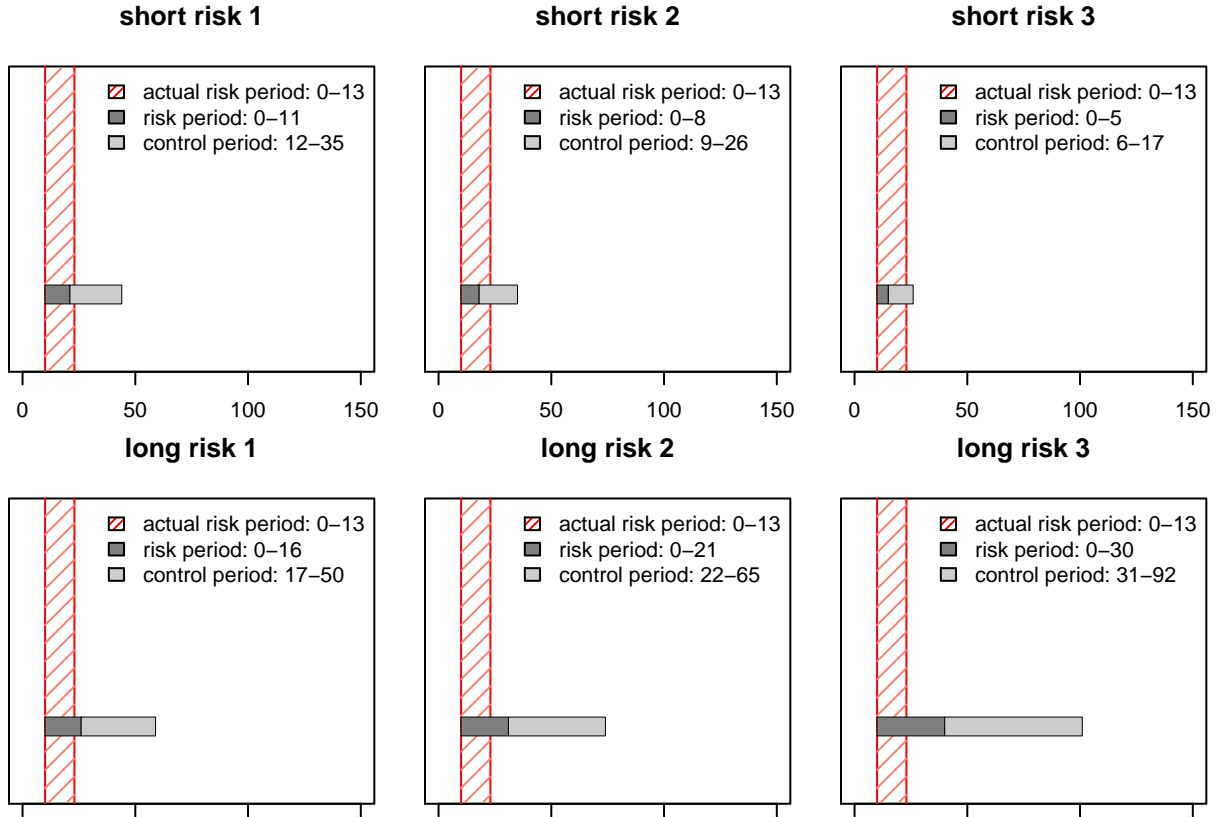


Figure 4.3: The six risk and control periods studied in the experiment. In the top row the risk period is too short and the control period overlaps with the risk period. In the bottom row the risk period is too long and overlaps with the control period.

Table 4.5: The chosen risk and control periods of the simulation experiment. The reference group matches the actual risk period used in the simulation of adverse event data. The relative length (z) of all the risk and control periods is identical.

	risk	control	risk.length	control.length	z
reference	0-13	14-41	14	28	2
short risk 1	0-11	12-35	12	24	2
short risk 2	0-8	9-26	9	18	2
short risk 3	0-5	6-17	6	12	2
long risk 1	0-16	17-50	17	34	2
long risk 2	0-21	22-65	22	44	2
long risk 3	0-30	31-92	31	62	2

4.5.2 Assumptions of the simulation

The following assumptions were made when simulating the adverse events data:

- The baseline rate of an event is 10 events per thousand person years
- The incidence rates are equal (homogenous) for all individuals
- The actual risk period is always 0-13 days after exposure
- For each exposed individual, the rate of events is multiplied by 1.5 during the risk period ($RR_a = 1.5$)
- The number of exposed individuals is 200 000 x 6 during a 6 year period (6 birth cohorts)
- The type I error of the sequential test is 0.05
- When the risk and control periods are chosen correctly, the power of the sequential test is 0.9

Adverse events were simulated for the 6 birth cohorts 10 000 times. For each of these iterations, multiple maxSPRT surveillances (with differing risk and control periods) were carried through. The date of signal generation was saved (if there was a signal).

4.5.3 Results of the simulation

Table 4.6 shows the power for each risk and control period pair in the simulation. Power is the proportion of simulation iterations where the null hypothesis was rejected. When the risk and control periods were chosen perfectly as was done with the reference group, the power in the simulation was 0.9. As expected, the power is lower the more the choices for the risk and control periods differ from the reference period. For example, if the chosen risk period is approximately 2.5 times the size of the actual risk period (0-30 compared to 0-13), the power decreases from 0.9 to 0.35.

If the chosen risk period is shorter than the actual risk period and the control period simultaneously overlaps

with the actual risk period, the situation is even worse. If the actual risk period is 2.5 the size of the chosen risk period and the control period overlaps, the power decreases from 0.9 to 0.16.

Table 4.6: Results of the simulation. The power for the reference group matches the desired power of the experiment. The power is lower the more the choices for the risk and control periods differ from the reference period.

	risk	control	power
reference	0-13	14-41	0.90
short risk 1	0-11	12-35	0.82
short risk 2	0-8	9-26	0.58
short risk 3	0-5	6-17	0.16
long risk 1	0-16	17-50	0.78
long risk 2	0-21	22-65	0.57
long risk 3	0-30	31-92	0.35

5 Conclusions

All pharmaceutical products, including vaccines, can increase the risk of some undesired medical occurrences (adverse events). Evaluating these risks post-licensure is essential for evaluating the safety of the vaccine, since rare adverse events might go undetected in pre-licensure studies.

This thesis has presented vaccine safety surveillance as an observational study where the goal is to evaluate the safety of a vaccine (or vaccines) in real-time. The goal of a safety surveillance method is to generate a safety signal as soon as possible, when an association between a vaccine and an adverse event exists.

Electronic health care data bases (registers) can be utilized as sources of data for safety surveillance. Registers such as AvoHILMO in Finland provide daily data and thus enable near real-time surveillance. Adverse events can be operationalized by one or several medical diagnoses, identified with an ICD code.

An important consideration in vaccine safety studies is that sources of bias such as self-selection and changes in diagnosis coding practises present challenges for which some observational study designs such as the cohort design, are vulnerable to. Case-only designs such as SCCS and CCO eliminate all time invariant confounders and can therefore be considered more suitable for drug safety analysis.

5.1 Contribution to existing literature

This thesis has considered vaccine safety surveillance from the general perspectives of drug safety and epidemiological studies. The type of safety surveillance considered is placed in the refinement stage of drug

safety studies, where the interest is in refining a previously identified, biologically plausible causal relationship between a vaccine and an adverse event. The refinement stage is preceded by an identification stage and possibly followed by a confirmation stage.

A key contribution of this thesis to existing literature is to explicitly link the BmaxSPRT vaccine safety surveillance method to a specific epidemiological study design, the SCCS, therefore showing how and why the BmaxSPRT is a self-controlled method.

More specifically, I have shown how a simple version of SCCS combined with the maximized sequential probability ratio test (maxSPRT) gives the BmaxSPRT method. Additionally I have, both mathematically and algorithmically, presented the computation of the critical values of BmaxSPRT, which are essential elements of the decision rule of BmaxSPRT, also presented in detail in this work.

I have also analyzed the sensitivity of BmaxSPRT to the choice of risk and control periods by simulation, showing how the power of BmaxSPRT is affected by the choices. The analysis highlights the importance of careful selection of the risk and control periods as the loss of power due to poor choices can be considerable.

5.2 Discussion of application results

As a proof-of-concept, I applied the BmaxSPRT method retrospectively to Finnish register data to show how the method performs with real data. The outcome of interest was febrile seizures. Three vaccines, MMR, PCV and Rota, each with a different type of known or suspected relationship to febrile seizures, were the exposures of interest.

The effects of each of the vaccines were studied during a risk period of 0-13 days following vaccination. The results of the experiment were as expected for MMR and Rota, as a safety signal was generated for the former and not generated for the latter. A safety signal was also generated for PCV.

The result of the experiment for PCV raises further questions. Utilizing all the available data, the point estimate for the rate ratio between the chosen risk and control periods stayed consistently, but not considerably, above 1, indicating some increased risk during the risk period. Given that the chosen risk period significantly differed from the suspected risk period for PCV, there are at least two plausible interpretations for this outcome: (i) The actual risk period for PCV is much longer than the suspected period, and the risk of febrile seizures increases only slightly. (ii) The actual risk period for PCV is according to the suspected risk period and the risk of febrile seizures increases substantially.

A confirmation analysis studying the relationship between febrile seizures and PCV vaccinations should be performed.

5.3 Further reasearch

The thesis provides starting points for further reseach in developing the BmaxSPRT method. The general version of SCCS can provide a framework for a more general version of a self-controlled maxSPRT, a multinomial maxSPRT if you will. Maximum information trials provide a promising approach for dealing with grouped observations.

This thesis has argued that the BmaxSPRT method belongs to the refinement stage of drug safety studies and requires that a biologically plausible vaccine-adverse event pair has been previously identified. Electronic medical records could however also be used to identify safety signals. According to Nelson et al. [2015], signal identification has primarily been conducted using spontaneous report databases, which are not considered in this work. Dumouchel [1999] introduces Bayesien data mining methods for detecting adverse drug reactions from such data bases.

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