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Exact conditional maximized sequential probability ratio test adjusted for covariates

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Abstract

Sequential analysis is now commonly used for post-market drug and vaccine safety surveillance, and a Poisson stochastic process is typically used for rare adverse events. The conditional maximized sequential probability ratio test, CMaxSPRT, is a powerful tool when there is uncertainty in the estimated expected counts under the null hypothesis. This paper derives exact critical values for CMaxSPRT, as well as statistical power and expected time to signal. This is done for both continuous and group sequential analysis, and for different rejection boundaries. It is also shown how to adjust for covariates in the sequential design. A table of critical values is provided for selected parameters and rejection boundaries, while new functions in the R Sequential package can be used for other calculations. In addition, the method is illustrated for monitoring adverse events after pediarix vaccination data.

Keywords

MaxSPRT; Poisson distribution; Type I error spending

1. Introduction

Post-market drug and vaccine safety surveillance, or simply vaccine safety surveillance, is a system of statistical and computational mechanisms directed to prevent possible threats to the population's health integrity caused by administration of recently approved vaccines. In this context, the number of adverse events following the vaccination is potentially informative to decide, within a short-term monitoring, if a new vaccine is to be kept in or withdrawn from the market. According to Kulldorff et al. (2011), given a predefined postexposure risk window, the random number of adverse events, say C_t, following a vaccine that was administrated in the period $(0, t]$ can be modeled as a Poisson process. Hence, a

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sequential hypothesis testing procedure can be designed in order to monitor adverse events data.

Under the null hypothesis, H_0, the mean of C_t, denoted here by μ_t, is a known function of the population at risk. Usually, μ_t is simply the number of people exposed to the vaccine up to time t times the baseline risk of an adverse event during the postexposure risk window. Under the alternative hypothesis, H_A, C_t is still Poisson but with increased mean ($R \times \mu_t$), where $R > 1$ is the relative risk due to the vaccination. For testing these hypotheses, Kulldorff et al. (2011) proposed to use the maximized sequential probability ratio test (MaxSPRT). MaxSPRT is now widely used for detecting increased risks associated to adverse events followed by post-licensed vaccines (Belongia et al., 2010; Davis, 2013; Klein et al., 2010; Li et al., 2014, 2016; Yih et al., 2009, 2011). But, MaxSPRT is applicable only if μ_t is known or if there is a historical data with sufficient information to provide a reliable estimate of it (Li and Kulldorff, 2009). When μ_t can only be estimated with uncertainty, the conditional maximized sequential probability ratio test (CMaxSPRT) introduced by Li and Kulldorff (2009) is the appropriate tool. CMaxSPRT consists of comparing accruing data with historical data in order to dispense with the knowledge about μ_t. This is the reason why CMaxSPRT has been considered as a very important tool for post-market vaccine safety surveillance (Yih et al., 2011).

Let V denote the person-time in the historical data, which results from the cutoff date for collection of the historical sample, and use c to denote the number of adverse events observed in the $(0, V]$ period. Seeking to offer a realistic model for adverse events data analysis, we suppose that V is defined irrespectively to the number of adverse events that is observed in the historical period.

Let P_k denote the person-time accumulated up to the arrival of the kth adverse event in the surveillance period. For fixed c, V is the sum of a Gamma distribution with shape c and scale $1/\lambda_V$ with a modified exponential distribution with parameter $1/\lambda$. More details on the distribution of V are given in the appendix. For fixed k, P_k follows a Gamma distribution with shape k and scale $1/\lambda_P$. With CMaxSPRT, the hypotheses are of the form:

$$H_0: \lambda_P = \lambda_V \text{ against } H_1: \lambda_P = R \times \lambda_V,\ R > 1. \tag{1.1}$$

Based on the likelihood ratio test method, Li and Kulldorff (2009) derived the CMaxSPRT test statistic:

$$U_k = I\left(\frac{k}{c} > \frac{P_k}{V}\right)\left[c\log\frac{c(1 + P_k/V)}{c + k} + k\log\frac{k(1 + P_k/V)}{(P_k/V)(c + k)}\right]. \tag{1.2}$$

The null hypothesis is rejected for the first k such that $U_k \geq CV$, where $k = 1, \ldots, K$, CV is a flat signaling threshold (critical value), and K is a predefined maximum length of surveillance. It merits reinforce that the notation "CV," for critical value, should not be confounded with the notation "V." While the former is a user-defined fixed number, the last is a random variable measuring the person-time in the historical data. Calculation of CV

demands a computable probability distribution of the statistic $\max_k U_k$, which is hard to obtain in practice. Thus, because the exact test is infeasible, Li and Kulldorff (2009) suggest to use Monte Carlo testing. But, this limitation can be transcended. The main contribution of the present work is the derivation of analytical expressions to perform CMaxSPRT. Therefore, Monte Carlo is no longer needed to find CV. The derived expressions enabled us to introduce six new features in the sequential design:

- **i.** Management of a minimal number of events before allowing a signal, which can be advantageous in terms of surveillance time.
- **ii.** Exact calculation of statistical power, expected length of surveillance and expected time to signal.
- **iii.** New option to define the maximum length of surveillance. The maximum length of surveillance of CMaxSPRT was defined by Li and Kulldorff (2009) in terms of the maximum observed number of events (K), which is a bit awkward as it is hard for investigators to project how many events they would observe during a x-year surveillance study. As a convenient alternative, in this article, we show how the maximum length of surveillance can be defined by the cumulative person-time instead of observed number of events. The former is much more natural and easy to use for planning purpose. Before the start of a surveillance, it is much more meaningful to plan the end of the surveillance once we reach, say, 2 million doses and each dose has a follow-up time of x number of days.
- **iv.** Usage of type I error probability spending functions in place of flat CV's.
- **v.** The conventional CMaxSPRT was developed solely to continuous sequential analysis. But the new derivations of the present article allow application of group sequential analysis.
- **vi.** Incorporation of co-variates in the statistical model.

This article is organized in the following way: next section introduces the calculation of the exact CMaxSPRT critical value. Note that the exact solution for the critical value calculation is the key for solutions (i)–(vi). Then, this material is organized in a way that after reading Sections 2–4, the reader can jump to read each of the other sections independently of the others. That way, the person, e.g., interested in the adjustment for co-variates, can quickly read what it is interested in, without having to struggle though other parts of the manuscript. With this in mind, the other features are organized as follows: Section 3 develops the new strategy of selecting the maximum length of surveillance in terms of the cumulative person–time ratio. Section 4 talks about how to consider a minimum number of events before allowing for rejection of the null hypothesis. Section 5 shows how to consider adjustments for covariates. Section 6 describes the arbitrary management of the type I error spending. Section 7 details the calculation of power, expected length of surveillance and expected time to signal. Section 8 gives further mathematical insights for saving computation time in the critical value calculation. Section 9 illustrates the usage of the method for a real data of adverse events following a Pediarix vaccination. Section 10 closes the article with a brief discussion on the main results.

2. Exact critical values for cmaxsprt

For each $k = 1, \ldots, K$, define the random variable:

$$\tau_k = P_k / V, \tag{2.1}$$

and take the CMaxSPRT statistic as a function of τ_k, i.e., replace U_k by $U(\tau_k)$ in (1.2). For a fixed critical value CV, and given that $U(\tau_k)$ is downward monotone with τ_k, there always exists $t_k \in (0, \infty)$ such that $U(\tau_k) \geq \text{CV}$ iff $\tau_k \leq t_k$, that is:

$$t_k = \sup\left\{t \in \Re^+ : U(t) \geq \text{CV}\right\}. \tag{2.2}$$

Thus, for a fixed relative risk R, the probability of rejecting the null hypothesis at the kth adverse event is given by

$$\begin{aligned} \pi_k(R, \text{CV}) &= \Pr[\text{rej}.\, H_0 \ \text{ rej}.\ \ k\text{th event} \,|\, R] \\ &= \Pr[\tau_k \leq t_k \,|\, R, \tau_{k^*} > t_{k^*} \ \text{ for each } \ k^* < k]. \end{aligned} \tag{2.3}$$

For fixed t_k and observed $V = v$, the event $\{\tau_k \leq t_k\}$ implies that $\{P_k \leq v t_k\}$. But note that P_k follows a Gamma distribution; hence, the continuous stochastic process P_k can be rewritten in terms of a new process, say C_k, where $C_k \sim \text{Pois}(R v t_k)$. Therefore, for $k = 2, \ldots, K$, the probability in (2.3) can be rewritten as

$$\pi_k(R, \text{CV}) = \int_0^\infty \Pr[C_k \geq k \,|\, R, V = v, C_{k^*} < k^* \ \text{ for each } \ k^* < k] f_V(v) \mathrm{d}v. \tag{2.4}$$

where $f_V(v)$ is the probability density function of V. The probability of rejecting the null hypothesis at the very first event, i.e., for $k = 1$, is given by

$$\int_0^\infty \Pr[C_1 \geq 1 \,|\, R, V = v] f_V(v) \mathrm{d}v. \tag{2.5}$$

In practice, the total person-time, V, observed in the historical data will usually be greater than the actual summation of person-time from the c events. Therefore, the distribution of V is not exactly Gamma because V incorporates the extra person-time observed after the arrival of the cth event. Following the same reasoning proposed by Li and Kulldorff (2009), we can assume that the cutoff date for the historical data is established irrespectively to the number of observed adverse events. Also, it seems reasonable to suppose $c \geq 1$. With this, we can write

$$V = \sum_{i=1}^{c} Y_i + Z Y_{c+1}, \tag{2.6}$$

where $Y_i : i = 1, \ldots, (c + 1)$ are i.i.d. with common density

$$f_Y(y) = \lambda_V e^{-\lambda_V y}, \tag{2.7}$$

and Z, independent of each Y_i, follows an uniform distribution in the (0, 1) interval. The demonstration that V can be written as in (2.6) is left to the appendix.

Define the auxiliary random variables

$$W_c = \sum_{i=1}^{c} Y_i, \text{ and } W^* = W_c/\lambda_V.$$

Note that W^* follows a Gamma distribution with rate 1 and shape c. Now take the transformation

$$Y^* = Y_{c+1}/\lambda_V,$$

which by its turn has density $e^{-y}I(y>0)$. For fixed $W^* = w$, $Z = z$, and $Y^* = y$, we have

$$V = v = (w + zy),$$

in which case $C_k \sim \text{Pois}(Rvt_k)$. Therefore, the conditional probability of rejecting H_0 at the kth event given realized $W^* = w$, $Z = z$, and $Y^* = y$ is calculated as

$$\begin{aligned}
\pi_k(R, \text{CV}, w, z, y) &= \Pr\left[\cap_{j=1}^{k-1}\{C_j < j\}, C_k \geq k \middle| V = v\right] \\
&= \sum_{c_2=0}^{1}\sum_{c_3=c_2}^{2}\cdots\sum_{c_{k-1}=c_{k-2}}^{k-2} \Pr[C_k \geq k | C_{k-1} = c_{k-1}, V = v \\
&] \times \\
&\times \prod_{j=1}^{k-1} \Pr[C_j = c_j | C_{j-1} = c_{j-1}, V = v] \\
&= \sum_{c_2=0}^{1}\sum_{c_3=c_2}^{2}\cdots\sum_{c_{k-1}=c_{k-2}}^{k-2} \\
&\left[1 - \sum_{c_k=c_{k-1}}^{k-1} \Pr[C_k = c_k | C_{k-1} = c_{k-1}, V = v]\right] \\
&\times \prod_{j=1}^{k-1} \Pr[C_j = c_j | C_{j-1} = c_{j-1}, V = v] \\
&= \sum_{c_2=0}^{1}\sum_{c_3=c_2}^{2}\cdots\sum_{c_{k-1}=c_{k-2}}^{k-2} \\
&\left[a(c_{k-1})\prod_{j=1}^{k-1}\frac{\mu_j^{c_j^*}}{c_j^*!} - \sum_{c_k=c_{k-1}}^{k-1} a(c_k)\prod_{j=1}^{k}\frac{\mu_j^{c_j^*}}{c_j^*!}\right],
\end{aligned} \tag{2.8}$$

where

$$a(c_j) = \mathrm{e}^{-Rvt_j}(Rv)^{c_j} = \mathrm{e}^{-R(w+zy)t_j}[R(w+zy)]^{c_j},$$

$c_j^* = c_j - c_{j-1}$, $\mu_j = (t_j - t_{j-1})$, and $c_0 = t_0 = 0$.

Thus, the probability of rejecting the null hypothesis at the kth event, adjusted for the extra person-time, is given by

$$\begin{aligned}\pi_k(R,\mathrm{CV}) &= \Pr\left[C_k \geq k \,\middle|\, R, C_{k^*} < k^* : k^* < k\right] \\ &= \int_0^1\int_0^\infty\int_0^\infty \pi_k(R,\mathrm{CV},w,z,y) f_{W^*}(w) f_{Y^*}(y) f_Z(z)\mathrm{d}w\mathrm{d}y\mathrm{d}z \\ &= \int_0^1\int_0^\infty\int_0^\infty \pi_k(R,\mathrm{CV},w,z,y)\frac{\mathrm{e}^{-w}w^{c-1}}{(c-1)!}e^{-y}\mathrm{d}w\mathrm{d}y\mathrm{d}z \\ &= \sum_{c_2=0}^{1}\sum_{c_3=c_2}^{2}\cdots\sum_{c_{k-1}=c_{k-2}}^{k-2}\left[\prod_{j=1}^{k-1}\frac{\mu_j^{c_j^*}}{c_j^*!}\times A(c_{k-1})\right. \\ &\left. - \sum_{c_k=c_{k-1}}^{k-1}\prod_{j=1}^{k}\frac{\mu_j^{c_j^*}}{c_j^*!}\times A(c_k)\right],\end{aligned} \tag{2.9}$$

where

$$\begin{aligned}A(c_k) &= \int_0^1\int_0^\infty\int_0^\infty \mathrm{e}^{-R(w+zy)t_k}[R(w+zy)]^{c_k}\frac{\mathrm{e}^{-w}w^{c-1}}{(c-1)!}\mathrm{e}^{-y}\mathrm{d}w\mathrm{d}y\mathrm{d}z \\ &= \int_0^1\int_0^\infty \mathrm{e}^{-y(Rzt_k+1)}\left\{\int_0^\infty e^{-Rwt_k}[R(w+zy)]^{c_k}\frac{\mathrm{e}^{-w}w^{c-1}}{(c-1)!}\mathrm{d}w\mathrm{d}y\right\}\mathrm{d}z \\ &= R^{c_k}\int_0^1\int_0^\infty \mathrm{e}^{-y(Rzt_k+1)}\left\{\int_0^\infty e^{-Rwt_k}\left[\sum_{l=0}^{c_k}D_l^{c_k}w^l(zy)^{c_k-l}\right.\right. \\ &\left.\left.\frac{\mathrm{e}^{-w}w^{c-1}}{(c-1)!}\mathrm{d}w\mathrm{d}y\right\}\mathrm{d}z \\ &= R^{c_k}\int_0^1\int_0^\infty \mathrm{e}^{-y(Rzt_k+1)} \\ &\left\{\sum_{l=0}^{c_k}D_l^{c_k}(zy)^{c_k-l}\int_0^\infty \mathrm{e}^{-Rwt_k}w^l\frac{\mathrm{e}^{-w}w^{c-1}}{(c-1)!}\mathrm{d}w\mathrm{d}y\right\}\mathrm{d}z \\ &= R^{c_k}\sum_{l=0}^{c_k}D_l^{c_k}\frac{(l+c-1)!}{(Rt_k+1)^{l+c}(c-1)!}\int_0^1 z^{c_k-l}\int_0^\infty e^{-y(Rzt_k+1)}y^{c_k-l}\mathrm{d}y\mathrm{d}z \\ &= R^{c_k}\sum_{l=0}^{c_k}D_l^{c_k}\frac{(l+c-1)!}{(Rt_k+1)^{l+c}(c-1)!}(c_k-l) \\ &!\underbrace{\int_0^1\frac{z^{c_k-l}}{(Rzt_k+1)^{c_k-l+1}}\mathrm{d}z}_{B(c_k,l)},\end{aligned} \tag{2.10}$$

and $D_l^{c_k} = c_k!/[l!(c_k-l)!]$.

For $c_k = l$, we have

$$B(c_k, l) = [\log(Rt_k + 1)]/(Rt_k).$$

Otherwise, make $G = Rzt_k$, and then:

$$\begin{aligned} B(c_k, l) &= \int_0^{Rt_k} (Rt_k)^{l - c_k - 1} \frac{G^{c_k - l}}{(G+1)^{c_k - l + 1}} \mathrm{d}G \\ &= (Rt_k)^{l - c_k - 1} \int_1^{Rt_k + 1} \frac{(u-1)^{c_k - l}}{u^{c_k - l + 1}} \mathrm{d}u \\ &= (Rt_k)^{l - c_k - 1} \int_1^{Rt_k + 1} \frac{\sum_{g=0}^{c_k - l} D_g^{c_k - l} u^g (-1)^{c_k - l - g}}{u^{c_k - l + 1}} \mathrm{d}u \\ &= (Rt_k)^{l - c_k - 1} \sum_{g=0}^{c_k - l} D_g^{c_k - l} (-1)^{c_k - l - g} \underbrace{\int_1^{Rt_k + 1} \frac{u^g}{u^{c_k - l + 1}} \mathrm{d}u}_{E(g, c_k, l)}, \end{aligned} \tag{2.11}$$

where

$$E(g, c_k, l) = \begin{cases} \log(Rt_k + 1) & \text{for } g = c_k - l, \\ \dfrac{(Rt_k + 1)^{g - c_k + l} - 1}{g - c_k + l} & \text{for } g < c_k - l. \end{cases} \tag{2.12}$$

Hence,

$$\begin{aligned} B(c_k, l) = (Rt_k)^{l - c_k - 1} \Bigg\{ &\log(Rt_k + 1) + \sum_{g=0}^{c_k - l - 1} \frac{(-1)^{c_k - l - g} D_g^{c_k - l}}{g - c_k + l} \\ &\left[(Rt_k + 1)^{g - c_k + l} - 1 \right] \Bigg\}. \end{aligned} \tag{2.13}$$

Finally, the overall statistical power under $R > 1$ of the CMaxSPRT test, say $\pi(R, CV)$, is given by:

$$\pi(R, \mathrm{CV}) = \sum_{k=1}^{K} \pi_k(R, \mathrm{CV}), \tag{2.14}$$

and the overall size of the test, which is the type I error probability under R=1, is given by

$$\pi(1, CV) = \sum_{k=1}^{K} \pi_k(1, \mathrm{CV}), \tag{2.15}$$

with $\pi_k(1, \mathrm{CV})$ calculated according to (2.9).

As (2.15) is downward monotone with CV, the bisection method can be applied in order to find CV attaining with a desired significance level. The bisection method is a well-known numerical procedure extensively used for finding roots of equations (Autar et al., Autar et al. 2011).

Because $\pi(R, \text{CV})$ is increasing with R, CMaxSPRT can be used under flexible hypotheses forms such as $H_0 : R \leq r_0$ versus $H_1 : R > r_0$, with $r_0 > 0$ arbitrary.

2.1. The algorithm

Consider to find CV under a significance level of $\alpha = (0, 1)$. Also, define a precision parameter, say ϵ, such that $|\alpha - \pi(1, \text{CV})| \leq \epsilon$. The bisection method is then based on the following six steps:

- Step (i)—set $\text{CV}_1 := 0$ and $\text{CV}_2 := 50$.
- Step (ii)—set $\text{CV}_{med} := (\text{CV}_1 + \text{CV}_2)/2$. Set $k = 0$ and $t_k = 0$.
- Step (iii)—while $k \leq K$, update $k := k + 1$ and find t_k such that $t_k = \sup\{t_{k*} : U(t_{k*}) \geq \text{CV}_{\text{med}}\}$. Then, set $t_1 = \cdots = t_M$.
- Step (iv)—Using expression (2.15), calculate $\pi(1, \text{CV}_{\text{med}})$. If $|\alpha - \pi(1, \text{CV}_{\text{med}})| \leq \epsilon$, stop and take CV_{med} as the critical value solution. Otherwise, proceed to Step (v).
- Step (v)—if $\pi(1, \text{CV}_{\text{med}}) > \alpha$, then update $\text{CV}_1 := \text{CV}_{\text{med}}$, otherwise, update $\text{CV}_2 := \text{CV}_{\text{med}}$. Go to Step (ii).

The number of iterations needed to reach the CV solution is equal to $\ln(1/\epsilon)/\ln(2)$. For example, a precision of $\epsilon = 0.00000001$ leads to $\lceil \ln(1/0.00000001)/\ln(2) \rceil = 27$ iterations.

Table 1 brings critical values for common values of α, K, and c. Solutions were obtained through direct application of the algorithm described above. This algorithm was programed and executed in **R** language and the code is now part of the **R** *Sequential* package, which can be run with the function "CV.CondPoisson." Unfortunately, due to space limitations, we can offer only a few variety of values for c and K, but any other tuning parameters configurations can be easily obtained through the function "CV.CondPoisson."

3. Maximum length of surveillance by doses/person-time

Although Li and Kulldorff (2009) have defined the maximum sample size, K, in the scale of the expected number of events, in this section, we show that it can also be settled in terms of the person-time ratio, P_k/V, under the null hypothesis. The critical value can still be calculated through the algorithm of Section 2.1, which demands a simple adjustment on Step (iii) as explained in the following remark.

Remark

The upper limit on the surveillance can be defined in terms of a constant, T, at which the surveillance is interrupted and the null is not rejected at the first k*th event such that $P_{k*}/V > T$. This alternative setting for the maximum length of surveillance can be easily

implemented by replacing the constraint "while $k \leq K$" by "while $t_k \leq T$" in Step (iii) of the algorithm presented in Section 2.1. Likewise, when convenient, one can also use both constraints, T and K, in that algorithm simultaneously.

Some practitioners might prefer to define the maximum length of surveillance in terms of K, but others will prefer to use T. In both cases, the final choice will probably be made in such a way that target statistical powers are satisfied for fixed overall significance levels. For example, one may want to find T such that the statistical power is surely greater than 0.9 for $R = 2$ and $\alpha = 0.05$. The same can be done by those analysts that prefer to establish the maximum length of surveillance by K. Naturally, when one defines the maximum length of surveillance in terms of T, it is involuntarily establishing a K-value that corresponds to that T choice and vice versa.

Table 2 illustrates the correspondence between K and T. For $\alpha = 0.05$ and $R = 2$, and historic information scenarios of $c = 50, 60, \ldots, 200$, this table brings lower bounds T_0 of T, and correspondent lower bounds K_0 of K, required to accomplish with target statistical powers of 0.9 and 0.99. All solutions were obtained through the function "SampleSize.CondPoisson" of the **R** package *Sequential.*

4. Requiring a minimum number of events before signaling

Unsafe drugs/vaccines should not endure in the market. Hence, the expected time to signal, defined as the expected number of events when the null hypothesis is rejected, is the meaningful design criterion for post-market safety surveillance. According to Kulldorff and Silva (2017), the expected time to signal can be substantially reduced by requiring a minimum number M of events before allowing the rejection of H_0. In this direction, Kulldorff and Silva (2017) show that values of M in between 3 and 6 are typically advantageous in the sense of reducing expected time to signal under the same power magnitude.

If one desires to permit the H_0 rejection only after a certain minimum number M of events, the unconditional probability of rejecting H_0 at the Mth event is given by

$$Pr[C_M \geq M \mid R] = 1 - \sum_{m=0}^{M-1} A(m) \times t_M^m / m!, \tag{4.1}$$

with $A(.)$ calculated according to (2.10), then the numerical calculation of CV described in Section 2.1 must be adjusted by replacing "Set $k = 0$" by "Set $k = M-1$" in Step (ii).

5. Adjusting for covariates

CMaxSPRT is now adapted for categorical covariates (e.g., age groups, sex). Suppose that there are N covariate strata from a set of strata levels $n = 1, \ldots, N$. Without loss of generality, let $n = 1$ denote the reference group. If we know the relative risks between the other strata compared to the reference group under the null hypothesis, we can easily transform the person-times from other strata to the reference scale to adjust for confounding. Specifically, for $n = 1, \ldots, N$, let r_n denote the ratio between the baseline risks for stratum n vs. stratum 1

($r_1 = 1$) and ($P_{n,k}$, V_n) denote the stratum-specific person-times ($P_k = \sum_{n=1}^{N} P_{n,k}, V = \sum_{n=1}^{N} V_n$), then the revised test statistic is given by

$$\widetilde{U}_k = I\left(\frac{k}{c} > \widetilde{P}_k\widetilde{V}\right)\left[c\log\frac{c\left(1+\widetilde{P}_k/\widetilde{V}\right)}{c+k} + k\log\frac{k\left(1+\widetilde{P}_k/\widetilde{V}\right)}{\left(\widetilde{P}_k/\widetilde{V}\right)(c+k)}\right], \tag{5.1}$$

where $\widetilde{P}_k = \sum_{n=1}^{N} r_n P_{n,k}$ and $\widetilde{V} = \sum_{n=1}^{N} r_n V_n$.

Unfortunately, the relative risks r_n, $n = 1, \ldots, N$, are typically unknown in real applications and thus we need to estimate them using observed data. Let c_n denote the number of events in stratum n in the historical cohort, i.e., $\sum_{n=1}^{N} c_n = c$, then the relative risk r_n can be estimated using

$$\frac{c_n/V_n}{c_1/V_1}.$$

With the estimated relative risks, the transformed person-times are given by

$$\widehat{V} = \sum_{n=1}^{N} \frac{c_n/V_n}{c_1/V_1} V_n = \frac{V_1}{c_1} c$$

and

$$\widehat{P}_k = \sum_{n=1}^{N} \frac{c_n/V_n}{c_1/V_1} P_{n,k} = \frac{V_1}{c_1} \sum_{n=1}^{N} \frac{c_n P_{n,k}}{V_n}.$$

In consequence, the ratio $\widehat{P}_k/\widehat{V}$ is simplified to

$$\widehat{P}_k/\widehat{V} = \frac{1}{c} \sum_{n=1}^{N} \frac{c_n P_{n,k}}{V_n} = \mu_k/c,$$

where

$$\mu_k = \sum_{n=1}^{N} \frac{c_n P_{n,k}}{V_n}$$

is the expected number of events, under the null hypothesis, in the surveillance population at interim test k. Thus, the adjusted test statistic for covariates is

$$\widehat{U}_k = I\left(\frac{k}{c} > \frac{\widehat{P}_k}{\widehat{V}}\right)\left[c\log\frac{c\left(1+\widehat{P}_k/\widehat{V}\right)}{c+k} + k\log\frac{k\left(1+\widehat{P}_k/V\right)}{\left(\widehat{P}_k/\widehat{V}\right)(c+k)}\right] = I(k > \mu_k)\left[c\log\frac{c(1+\mu_k/c)}{c+k} + k\log\frac{k(1+\mu_k/c)}{(\mu_k/c)(c+k)}\right]. \quad (5.2)$$

Note that $\mu_k = \sum_{n=1}^{N} \frac{c_n P_{n,k}}{V_n}$, given observed $V_n = v_n$, $n = 1, \ldots, N$, follows a gamma distribution. Hence, all reasoning used in Section 2 to derive exact critical values hold under the same steps (i)–(v).

6. Group sequential analysis: the type I error probability function spending aproach

In practice, data can arrive not only in continuous but also in a near-continuous manner or even in grouped chunks of data (Nelson et al., 2012; Zhao et al., 2012). Therefore, sometimes even the exact calculations of Section 2 will produce conservative critical values since the number of sequential tests can be smaller than K. To solve this limitation, instead of using a flat critical value in the scale of the likelihood ratio, one can define the sequential decision rule through a type I error spending approach. Doing so, we can arbitrate the amount of type I error probability to be spent at each test no matter if the cases arrive one by one or in groups of unpredictable lengths.

Following the definition of Jennison and Turnbull (2000), the type I error spending is a nondecreasing function taking values in the $(0, \alpha)$ interval. Here denoted by $S(k)$, the type I error spending is meant to establish the rate at which the type I error probability shall be spent along the sequential tests. With this, the signaling threshold for the kth event can be settled to take in account the actual amount of person-time contribution observed with that particular adverse event.

Aiming a more suggestive notation, instead of a function of R and CV, redefine the notation for the type I error probability associated to the kth event so that it turns out as a function of R and t_k given the fixed previous time thresholds, i.e., for $k > 1$, the type I error probability is now denoted by $\pi_k(R, t_k|t_1, \ldots, t_{k-1})$. Hence, one can always establish a target type I error spending $S(k)$ for monitoring the kth event by solving $\pi_k(R, t_k|t_1, \ldots, t_{k-1})$ for t_k as follows:

$$t_k = \sup\left\{t_{k*} : \pi_k\left(R, t_k^* \middle| t_1, \ldots, t_{k-1}\right) \le S(k)\right\}. \quad (6.1)$$

A well-known choice for $S(k)$ is the power-type form:

$$S(k) = \alpha \times \left(\frac{k}{K}\right)^{\rho}, \rho > 0.$$

Jennison and Turnbull (2000) suggest that, if the design criteria are expected sample size, then ρ values around 2 are recommended. Studies devoted to explore suitable choices of ρ

having the expected time to signal as the main design criteria are just emerging. An example is the work of Silva (2018) suggesting that values of ρ around 0.5 are appropriate choices if the design criterion is the minimization of the expected time to signal.

7. Statistical performance

As already mentioned, the three key performance measures for post-market vaccine safety surveillance are the statistical power, the expected time of surveillance, and the expected time to signal.

7.1. Power

Remind that the overall statistical power of the test, evaluated for $R > 1$, can be calculated using (2.14). Statistical powers for the scenarios of Table 1, and assuming a true relative risk of $R = 2$, are placed in Table 3. All values were obtained with the function "Performance.CondPoisson" of the R *Sequential* package.

7.2 Expected length of surveillance and expected time to signal

Because in post-market safety surveillance the vaccine is already administrated at the population, maximum sample sizes can be easily administrated. But, for a fixed power, one might want to calculate, previously to the beginning of the surveillance, the expected length of surveillance, and the expected time to signal. The expected length of surveillance evaluated for $R > 1$, and denoted by EL(R, CV), is given by

$$\mathrm{EL}(R, \mathrm{CV}) = \sum_{k=1}^{K} k \times \pi_k(R, \mathrm{CV}) + K \times [1 - \pi(R, \mathrm{CV})], \tag{7.1}$$

and the expected time to signal, denoted by ETS(R, CV), is given by

$$\mathrm{ETS}(R, \mathrm{CV}) = \frac{\sum_{k=1}^{K} k \times \pi_k(R, \mathrm{CV})}{\pi(R, \mathrm{CV})}, \tag{7.2}$$

with $\pi_k(R, \mathrm{CV})$ obtained according to (2.9) and $\pi(R, CV)$ obtained from (2.14). Table 4 presents expected time to signal for a true relative risk of $R = 2$ under the same tuning parameters of Table 1.

8. Conservative and liberal tests

The exact calculation of CV can take a long time to run in high-level programing languages such as e.g., the software **R** (Team 2014). This is so because of the double sum implied by the terms $A(c_k)$ and $B(c_k, l)$. To circumvent this limitation, conservative and liberal approximations for CV are offered as alternatives for a faster computation.

8.1. Conservative tests

A conservative critical value solution, say $\mathrm{CV}_{\mathrm{cons}}$, can be defined in such a way that, if CV is the exact solution obtained according to Section 2, then $\pi(1, \mathrm{CV}) \geq \pi(1, \mathrm{CV}_{\mathrm{cons}})$. To do so, note that:

$$B(c_k, l) = \int_0^1 \frac{z^{c_k - l}}{(Rzt_k + 1)^{c_k - l + 1}} \mathrm{d}z \le \left. \frac{z^{c_k - l}}{(Rzt_k + 1)^{c_k - l + 1}} \right|_{z=1} = (t_k + 1)^{l - c_k - 1}. \tag{8.1}$$

The last inequality holds because the integrand in (8.1) is increasing with z. Thus, define the modified $A(c_k)$, denoted by $A^*(c_k)$, obtained by replacing $B(c_k, l)$ by

$$B^*(c_k, l) = (t_k + 1)^{l - c_k - 1}. \tag{8.2}$$

Since $B(c_k, l)$ always contributes with a positive value, it holds that $A^*(c_k) \ge A(c_k)$. Let $\pi^*(R, \mathrm{CV})$ denote the probability in (2.9) calculated after replacing $A(c_k)$ by $A^*(c_k)$. Hence, the probability $\pi^*(R, \mathrm{CV})$ overestimates the actual size $\pi(R, \mathrm{CV})$, and then a solution $\mathrm{CV}_{\mathrm{cons}}$ that returns $\pi^*(R, \mathrm{CV}_{\mathrm{cons}}) = \alpha + \epsilon$ is always greater than or equal to the exact critical value CV, but this conservative critical value requires much less computational effort than the computation of the exact CV. Another option to deal with the long run time of the exact solution is to discard the extra person-time.

8.2. Discarding the extra person-time: liberal tests

Consider two Poisson processes, $X[W^*t_k]$ and $X[(W^* + ZY^*)t_k]$, i.e., for fixed positive constants $W^* = w$, $Z = z$, and $Y^* = y$, the random variables $X[wt_k]$ and $X[(w + zy)t_k]$ have means Rwt_k and $R(w + zy)t_k$, respectively. Thus, it holds that

$$\Pr[X[wt_k] \ge k \mid R] \le \Pr[X[(w + zy)t_k] \ge k \mid R] \tag{8.3}$$

for any positive constants w, z and y. The exact critical value of Section 2 is based on the critical value given in the scale of C_k, which has the same distribution as $X[(W^* + ZY^*)t_k]$. If we neglect the extra person-time information ZY, then C_k turns to behave as $X[W^*t_k]$. From (8.3), the resultant critical value, say CV_{lib}, will be slightly larger than the exact CV. This is the same as assuming that the distribution of $V = \mathrm{W} + \mathrm{ZY}$ is approximately equal to the distribution of the random variable W. Under this assumption, the probability of rejecting the null hypothesis at the kth test becomes far simpler:

$$\pi_k(R, \mathrm{CV}_{lib}) = \sum_{c_2 = 0}^{1} \cdots \sum_{c_{k-1} = c_{k-2}}^{k-2} \left[\prod_{j=1}^{k-1} \frac{\mu_j^{c_j^*}}{c_j^*!} \times A^*(c_{k-1}) - \sum_{c_k = c_{k-1}}^{k-1} \prod_{j=1}^{k} \frac{\mu_j^{c_j^*}}{c_j^*!} \times A^*(c_k) \right], \tag{8.4}$$

where:

$$A^*(c_j) = \frac{(c + c_j - 1)!}{(1 + t_j)^{c + c_j}(c - 1)!},$$

$c_j^* = c_j - c_{j-1}$, $\mu_j = (t_j - t_{j-1})$, and $c_0 = t_0 = 0$.

Therefore, critical values calculated using (8.4) will produce tests with actual significant levels slightly greater than the desired α.

8.3. When should we adopt exact, conservative or liberal calculations?

One may wonder if the gains, in terms of computation time, from conservative or liberal approaches would pay back the decrease, or the overshoot, on the test size. To formulate an answer for this question, we offer Table 5 with actual test sizes for each approach, and Table 6, which presents computation times, expressed in hours (h), minutes (m) and seconds (s), taken for calculating the critical values associated to the same tuning parameters (α, K, c) of Table 5.

Observe that, as it should be, the test size of the exact approach attains exactly equal to α value in all scenarios. In contrast, usage of conservative and liberal solutions requires prudence. Their actual test sizes can differ in more than 10% in comparison to the exact solution for small c, like 10 for example. But, this difference is less than 1% in all scenarios when c is equal to 200. Hence, as a general rule, conservative and liberal solutions should not be used if K and c are of moderate magnitudes. In such cases, the liberal approach can lead to test sizes greater than α, and the conservative approach can lead to substantial power losses. Furthermore, under situations of small K, the exact approach takes only a few seconds to run, then there is no need for using liberal or conservative approximations.

In terms of computation time, the liberal approach is far faster. It requires just few seconds to run in all scenarios, which contrasts with the several hours taken by the exact for large K, like for example $K = 50$.

The conservative approach is also fast. It presents an intermediate execution time, reaching some minutes on its worse performances.

Considering these results, we suggest the following rule of thumb: use the exact calculation for small K, like in the scale of dozens, for example. If K is of moderate or intermediate magnitude, like 50 for example, use the conservative approach. Finally, use the liberal approach for large K like those with magnitudes of hundreds.

9. Monitoring adverse events for pediarix vaccination

This section illustrates the usage of CMaxSPRT for a time series of health insurance claims from the CDC-sponsored VSD project. The data are composed by 82 weekly entries, each representing the number of adverse events related to neurological symptoms within 28 days after Pediarix vaccination, which summed up to 31 adverse events. Pediarix, manufactured by GlaxoSmithKline, is a vaccine that, with a single injection, can protect children from five

different diseases: diphtheria, tetanus, whooping cough, hepatitis B, and Polio. The adverse events counts are shown in Figure 1.

As CMaxSPRT demands historical information, this data was divided in two subsamples, each with 41 entries. This way, the first 41 observations are treated as the historical sample, then the second sub-sample is taken by surveillance data. Although this division is artificial as the entire series is composed by surveillance information, this exercise might be useful for exemplifying how the exact CMaxSPRT works in practice. The part representing the surveillance data is highlighted with the dark down triangles shown in Figure 1.

Note that there is an abrupt change in the cumulative cases after week 42, then, analyzing this data indeed has practical and interesting appeals. Because both samples belong to the same population exposed to the same vaccine, one should apply a formal test for checking the evidence of a possible change on the relative risk, for some reason and irrespective to the vaccine itself, after that point in time.

9.1. Tuning parameters settings

For this application, we used $\alpha = 0.05$ and $\rho = 1.5$. Because the number of adverse events in the historical period was $c = 11$, for a historical person-time information of $v = 61.603$, we iterated expression (2.9) for different K values to find out the minimum sample size required for a power of at least 0.9 under target $R = 2$, and the resulting sample size was 40. Hence, $K = 40$ was adopted for the present example.

9.2. Data analysis results

The overall relative risk estimate for this hypothetical data is

$$\widehat{R} = \frac{k \times v}{c \times p_k} = \frac{20 \times 61.603}{11 \times 69.037} = 1.62,$$

with $k = 20$ adverse events observed after an amount of $p_k = 69.037$ person-time accrued in the surveillance period. This suggests an elevation on the relative risk after week 41. But, a formal sequential test should be applied in order to take in account the sample variability in drawing a definitive decision in favor or against H_0. Figure 2 presents the observed CMaxSPRT statistic, dotted line, test by test. The exact critical value is shown with a solid flat line. The observed CMaxSPRT test statistic remained below the critical value throughout the monitoring period. Hence, there are no strong evidences against H_0, leading to the conclusion that the relative risk was likely the same for the entire time series of 82 observations.

10. Discussion

Coding computational programs to implement the exact CMaxSPRT test can be a troublesome work. To make things easier, we have implemented the results of this paper in the **R** "Sequential" package. *Sequential* was designed for continuous/group sequential analysis and to analyze either Poisson type data or binomial 0/1 type data. With the package, one can easily reproduce tables and any other calculations shown in this article.

Concerning the decision on when/why to use CMaxSPRT, as already emphasized in the Introduction, CMaxSPRT has been developed as an alternative to MaxSPRT in cases where μ_t under H_0 is either unknown or when trustful estimates of it are not available. But, as demonstrated by Li and Kulldorff (2009), the bias caused by usage of MaxSPRT in such circumstances is only relevant for $K \geq c/5$. Therefore, CMaxSPRT is needed instead of MaxSPRT when approximately $K \geq c/5$, while it is unusual to have $K \geq c$. Hence, besides the suggested rule of thumb of Section 8.3 about when to choose among the exact, conservative or liberal solutions, one can instead choose the regular MaxSPRT when $K<c/5$ because it involves simpler and faster computations. For example, consider the sample size calculation in order to attend a power of 0.99 under a target relative risk of $R = 2$ with $c = 50$. Using the *Sequential* package, and a PC(Windows 7, Intel(R) Core(TM) i7–2675QM CPU, 2.20GHz), the execution time of CMaxSPRT is around 98 seconds, which is contrasted by the 18 seconds observed with the regular MaxSPRT.

Another important feature developed in this article is the possibility of managing the type I error probability spending for CMaxSPRT, which favors to design appropriate signaling thresholds for a given design criterion. For example, in clinical trials it is expensive to expose many patients to the experiment, hence expected sample size is the meaningful design criterion. In this case, a convex shape for the type I error spending is indicated since it usually leads to reduced sample sizes (Silva 2018). However, in post-market vaccine safety surveillance, the costs of increasing the sample size is negligible (Silva and Kulldorff 2015). But, as stressed in details by Silva and Kulldorff (2015), the expected time to signal is a very important design criterion. A delayed signalization of elevated risks can lead to a large number of affected individuals. In this scenario, a concave shape for the type I error spending is the recommended choice (Silva 2018).

Construction of confidence intervals for the relative risk is a direct result as the power function, expression 2.14, is increasing with R. But, due to space limitations, we prefer to let this discussion for future works since it would demand further mathematical demonstrations and proper examples.

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References

Autar DK, Egwu K, and Nguyen D (2011). Numerical Methods with Applications, Textbooks Collection: University of South Florida.

Belongia EA, Irving SA, Shui IM, Kulldorff M, Lewis E, Yin R, Lieu TA, Weintraub E, Yih WK, Li R, Baggs J, and the Vaccine Safety Datalink Investigation Group (2010). Real-time Surveillance to Assess Risk of Intussusception and Other Adverse Events after Pentavalent, bovine-derived Rotavirus Vaccine, Pediatric Infectious Disease Journal 29: 1–5. [PubMed: 19907356]

Davis RL (2013). Vaccine Safety Surveillance Systems: Critical Elements and Lessons Learned in the Development of the US Vaccine Safety Datalink's Rapid Cycle Analysis Capabilities, Pharmaceutics 5: 168–178. [PubMed: 24300403]

Jennison C and Turnbull BW (2000). Group Sequential Methods with Applications to Clinical Trials, London: CRC.

Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, Baxter R, Hambidge S, Nordin J, Naleway A, Belongia EA, Lieu T, Baggs J, Weintraub E, and the Vaccine Safety Datalink (2010). Measles-Mumps-Rubella-Varicella Combination Vaccine and Risk of Febrile Seizures, Pediatrics 126: e1–e8. [PubMed: 20587679]

Kulldorff M, Davis RL, Kolczak M, Lewis E, Lieu T, and Platt R (2011). A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance, Sequential Analysis 30: 58–78.

Kulldorff M and Silva IR (2017). Continuous Post-Market Sequential Safety Surveillance with Minimum Events to Signal, Revstat Statistical Journal 15: 373–394.

Leite A, Andrews NJ, and Thomas SL (2016). Near Real-time Vaccine Safety Surveillance Using Electronic Health Records a Systematic Review of the Application of Statistical Methods, Pharmacoepidemiology and Drug Safety 25: 225–237. [PubMed: 26817940]

Li L, and Kulldorff M (2009). A Conditional Maximized Sequential Probability Ratio Test for Pharmacovigilance, Statistics in Medicine 29: 284–295.

Li R, Stewart B, Weintraub E, and McNeil MM (2014). Continuous Sequential Boundaries for Vaccine Safety Surveillance, Statistics in Medicine 33(19): 3387–3397. [PubMed: 24691986]

Nelson J, Cook A, Yu O, Dominguez C, Zhao S, Greene S, Fireman B, Jacobsen S, Weintraub E, and Jackson L (2012). Challenges in the Design and Analysis of Sequentially Monitored Postmarket Safety Surveillance Evaluations Using Eletronic Observational Health Care Data, Pharmacoepidemiology and Drug Safety 21: 62–71. [PubMed: 22262594]

Silva IR (2018). Type I Error Probability Spending for Post-market Drug and Vaccine Safety Surveillance with Binomial Data, Statistics in Medicine 37: 107–118. [PubMed: 28948642]

Silva IR and Kulldorff M (2013). Sequential-package, Vienna: R Foundation for Statistical Computing, http://www.R-project.org.

Silva IR and Kulldorff M (2015). Continuous Versus Group Sequential Analysis for Post-Market Drug and Vaccine Safety Surveillance, Biometrics 71: 851–858. [PubMed: 26011024]

Team RC (2014). (2015). A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna: http://www.R-project.org.

Yih WK, Kulldorff M, Fireman BH, Shui IM, Lewis EM, Klein NP, Baggs J, Weintraub ES, Belongia EA, Naleway A, Gee J, Platt R, and Lieu TA (2011). Active Surveillance for Adverse Events: The Experience of the Vaccine Safety Datalink Project, Pediatrics 127: 54–64.

Yih WK, Nordin JD, Kulldorff M, Lewis E, Lieu TA, Shi P, and Weintraub ES (2009). An Assessment of the Aafety Datalink of Adolescent and Adult Tetanus-diphteria-acellular Pertussis (Tdap) Vaccine, Using Active Surveillance for Adverse Events in the Vaccine Safety Datalink, Vaccine 27: 4257–4262. [PubMed: 19486957]

Zhao S, Cook A, Jackson L, and Nelson J (2012). Statistical Performance of Group Sequential Methods for Observational Post-Licensure Medical Product Safety Surveillance: A Simulation Study, Statistics and Its Interface 5: 381–390.

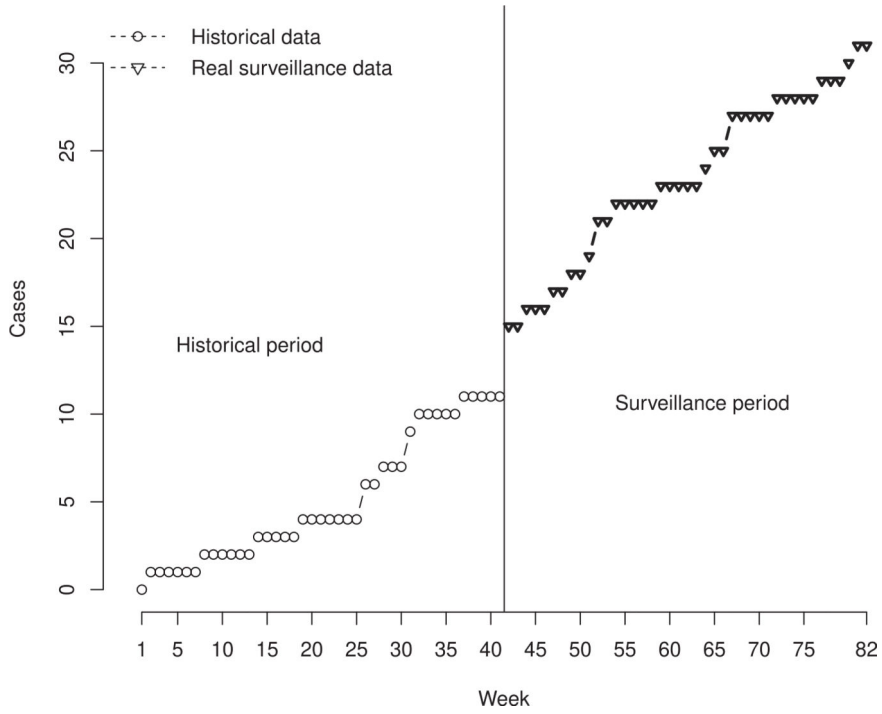

Figure 1.

Time series formed by 82 observed counts of adverse events after Pediarix vaccination indexed by week.

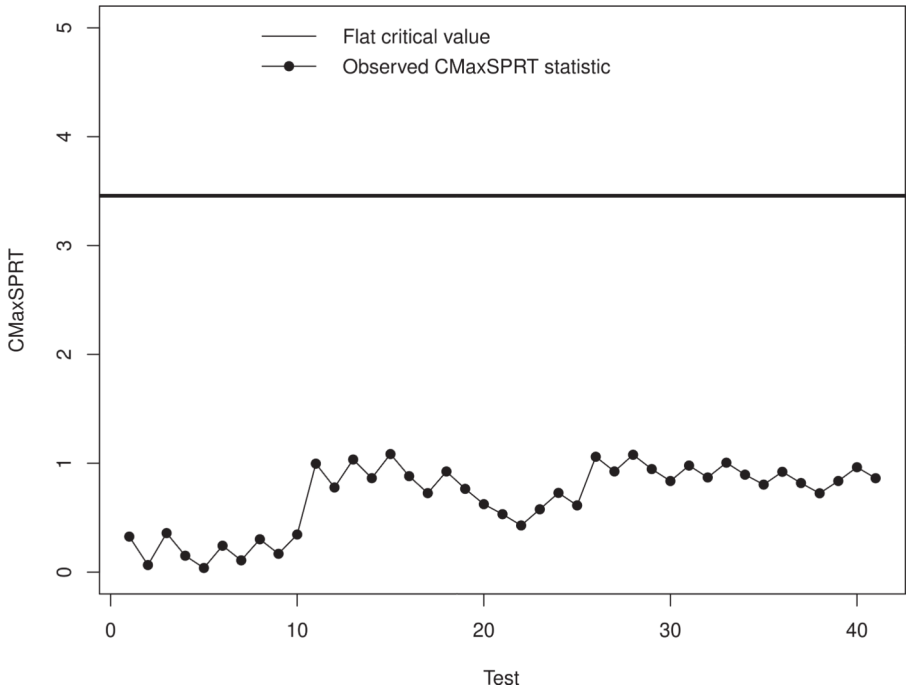

Figure 2.

Observed CMaxSPRT after Pediarix vaccination indexed by the test order. The signaling threshold was obtained under $\alpha = 0.05$ with power of 0.9 for relative risk of at least 2.

Table 1.

Exact critical values for CMaxSPRT using $\alpha = 0.01, 0.05$, $c = 5, 10, 20, 30, 40, 50, 60, 80, 100, 150, 200$, and $K = 20, 30, 50$. All solutions were obtained by running the "CV.CondPoisson" function of the **R** *Sequential* package. (Silva and Kulldorff 2013).

	$\alpha = 0.01$			$\alpha = 0.05$		
c	$K = 20$	$K = 30$	$K = 50$	$K = 20$	$K = 30$	$K = 50$
5	5.045802	5.110297	5.164204	3.270508	3.325895	3.372863
10	5.107656	5.185651	5.254975	3.340221	3.40892	3.469784
20	5.15563	5.247806	5.333842	3.394381	3.477358	3.55485
30	5.176597	5.276471	5.372742	3.418073	3.508914	3.596611
40	5.188503	5.293283	5.396597	3.431531	3.508914	3.62216
50	5.196208	5.304405	5.412835	3.440244	3.539671	3.639593
60	5.201612	5.312331	5.424701	3.446356	3.548400	3.652315
80	5.208702	5.322900	5.440909	3.454375	3.560043	3.669717
100	5.21315	5.329638	5.451537	3.459408	3.567469	3.681107
150	5.219332	5.339152	5.466938	3.466402	3.577955	3.697632
200	5.222538	5.344160	5.475263	3.470031	3.583476	3.706563

Table 2.

Lower bounds, T_0 and K_0, for the maximum length of surveillance by doses/person-time (T) and by observed cases in the surveillace period (K), respectively, for reaching an actual target statistical powers of 0.9 and 0.99 under a level $\alpha = 0.05$, historical number of events $c = 50, 60, \ldots, 200$, and a true relative risk $R = 2$.

	Target power = 0.9		Target power = 0.99	
c	K_0	T_0	K_0	T_0
50	66	0.79	290	3.89
60	56	0.56	244	2.78
70	50	0.43	157	1.53
80	47	0.35	126	1.07
90	44	0.29	107	0.80
100	43	0.25	96	0.65
110	41	0.22	89	0.55
120	40	0.20	83	0.47
130	39	0.18	79	0.41
140	39	0.16	76	0.36
150	38	0.15	73	0.33
160	37	0.14	71	0.30
170	37	0.13	69	0.27
180	37	0.12	68	0.25
190	36	0.11	67	0.24
200	36	0.11	64	0.21

Table 3.

Statistical powers of CMaxSPRT for a true relative risk of 2, with $\alpha = 0.01, 0.05$, $c = 5, 10, 20, 30, 40, 50, 60, 80, 100, 150, 200$, and $K = 20, 30, 50$. All solutions were obtained by running the "Performance.CondPoisson" function of the **R** *Sequential* package.

	$\alpha = 0.01$			$\alpha = 0.05$		
c	***K* = 20**	***K* = 30**	***K* = 50**	***K* = 20**	***K* = 30**	***K* = 50**
5	0.127	0.150	0.174	0.312	0.340	0.367
10	0.175	0.223	0.276	0.396	0.451	0.504
20	0.234	0.323	0.432	0.489	0.581	0.673
30	0.268	0.388	0.539	0.539	0.654	0.768
40	0.291	0.434	0.614	0.570	0.700	0.825
50	0.308	0.467	0.669	0.592	0.732	0.860
60	0.320	0.492	0.709	0.607	0.755	0.888
80	0.337	0.528	0.765	0.629	0.785	0.919
100	0.348	0.552	0.800	0.642	0.805	0.937
150	0.364	0.587	0.850	0.662	0.832	0.959
200	0.373	0.606	0.875	0.672	0.846	0.969

Table 4.

Expected time to signal of CMaxSPRT for a true relative risk of 2, with $\alpha = 0.01, 0.05$, $c = 5, 10, 20, 30, 40, 50, 60, 80, 100, 150, 200$, and $K = 20, 30, 50$. All solutions were obtained by running the "Performance.CondPoisson" function of the **R** *Sequential* package.

	$\alpha = 0.01$			$\alpha = 0.05$		
c	***K* = 20**	***K* = 30**	***K* = 50**	***K* = 20**	***K* = 30**	***K* = 50**
5	9.39	12.30	16.60	7.34	9.30	12.08
10	10.52	14.14	19.63	8.38	10.89	14.53
20	11.47	15.75	22.34	9.26	12.26	16.60
30	11.90	16.49	23.53	9.65	12.86	17.40
40	12.14	19.92	24.16	9.87	13.19	17.75
50	12.30	17.19	24.51	10.02	13.39	17.90
60	12.42	17.38	24.73	10.11	13.53	17.96
80	12.56	17.63	24.96	10.24	13.69	17.97
100	12.66	17.78	25.05	10.32	13.79	17.92
150	12.78	17.98	25.11	10.43	13.91	17.78
200	12.85	18.09	25.09	10.49	13.96	17.66

Table 5.

Comparing actual test sizes among exact, conservative, and liberal approaches for CMaxSPRT.

α	*K*	*c*	Exact	Conservative	Liberal
0.01	10	10	0.01	0.009	0.011
0.01	10	50	0.01	0.01	0.01
0.01	10	200	0.01	0.01	0.01
0.01	50	10	0.01	0.008	0.012
0.01	50	50	0.01	0.01	0.011
0.01	50	200	0.01	0.01	0.01
0.05	10	10	0.05	0.045	0.055
0.05	10	50	0.05	0.049	0.051
0.05	10	200	0.05	0.05	0.05
0.05	50	10	0.05	0.043	0.058
0.05	50	50	0.05	0.048	0.052
0.05	50	200	0.05	0.049	0.051

Table 6.

Computation Time when finding critical values based on exact, conservative and liberal approaches for CMaxSPRT. The calculations were executed in **R** language using a PC(Windows 7, Intel(R) Core(TM) i7–2675QM CPU, 2.20GHz).

α	*K*	*c*	Exact	Conservative	Liberal
0.01	10	10	3 s	<1 s	<1 s
0.01	10	50	3 s	<1 s	<1 s
0.01	10	200	3 s	<1 s	<1 s
0.01	50	10	4 h 26 m 11s	5m 20s	11 s
0.01	50	50	4 h 23 m 53s	5m 54s	13 s
0.01	50	200	4 h 24 m 4 7s	5 m 30 s	13 s
0.05	10	10	3s	1 s	<1 s
0.05	10	50	3s	1 s	<1 s
0.05	10	200	3s	1 s	<1 s
0.05	50	10	4 h 15 m 11 s	6 m	14 s
0.05	50	50	2 h 23 m 43 s	5 m 40 s	14 s
0.05	50	200	2 h 29 m 50 s	5 m 52 s	14 s