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A Bayesian method for risk window estimation with application to HPV vaccine trial

Tian Fang [a], William Mackillop [a], Wenyu Jiang [b], Allan Hildesheim [c], Sholom Wacholder [c], Bingshu E. Chen [a,*]

[a] Department of Public Health Sciences, Queens University, Kingston, Ontario, Canada
[b] Department of Mathematics and Statistics, Queens University, Kingston, Ontario, Canada
[c] Division of Cancer Epidemiology and Genetics, National Cancer Institute. Bethesda, MD, USA

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ABSTRACT

In biomedical studies, it is often of interest to estimate how the risk profile of an adverse event is related to the timing of an intervention. For example, in randomized controlled clinical trials of bivalent human papillomavirus (HPV) vaccine, investigators are interested to know how miscarriage rate relates to the timing of HPV vaccination. A risk window is defined as an interval for the covariate where the risk of adverse event is elevated. Existing methods cannot make simultaneous inference on both the risk window and the magnitude of the risk. A hierarchical Bayesian logistic regression model is developed to estimate the risk window of miscarriage on the time of conception with respect to vaccination. Hierarchical priors are proposed and used in Markov Chain Monte Carlo for statistical inference. The performance of the Bayesian model and two existing methods is evaluated in simulation settings with varying risk windows and relative risks. The proposed model provides both point and interval estimates for the risk window regarding to vaccination, and captures its effect modification on miscarriage risk in pregnancy. Analysis of the vaccine trial using the proposed model shows no significant evidence of an association between the HPV vaccine and miscarriage risk. The hierarchical Bayesian model is useful in general in analyzing a randomized trial or an epidemiological study in which the effect of an agent is potentially modified by a temporal factor.

1. Introduction

In the safety evaluation of the bivalent vaccine against human papillomavirus (HPV), a higher rate of miscarriage was observed in the HPV-vaccine arm (13.7%) than in the reference hepatitis A vaccine (HAV) arm (9.2%) among pregnancies with conception around vaccination (Wacholder et al., 2010) in a pooled analysis of pregnancy outcomes in two large scale phase III trials. In response, Wacholder et al. (2010) conducted a detailed evaluation of miscarriage. Without precise knowledge of the subset of pregnancies that might be affected by the vaccine, they used a permutation test based on the lowest p-value for testing the equalities of miscarriage rates among overlapping subsets of pregnancies defined on risk window between days of estimated conception and vaccination. The permutation test had more power than the test method based on a pre-specified window unless the window was almost correctly specified. Although the permutation test failed to reject the null

* Correspondence to: Canadian Cancer Trials Group and Department of Public Health Sciences, Queens University, Kingston, Ontario, Canada.
E-mail address: bechen@ctg.queensu.ca (B.E. Chen).

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hypothesis of no higher adverse effect of the bivalent HPV vaccine ($p = 0.16$), it remained a concern that a small effect might exist in pregnancies conceived within a certain time period after vaccination. In this paper, we investigate whether the vaccine associates with any risk, and if so, we proceed to find the particular risk window. The risk window is defined as a particular block of the time between the vaccination and the conception during which the miscarriage risk is elevated. In other words, the goal of this study is to find out whether administration of the bivalent HPV vaccine during a prospectively identified risk window modifies the miscarriage risk in pregnancies.

We intend to provide point estimates and measures of uncertainty for the location and width of the risk window and the magnitude of relative risk (RR). The permutation test used in previous analysis was limited for providing only a p-value, which contains information of the test statistics under the null hypothesis. However, it did not provide point or interval estimates for the window or the magnitude of RR under the alternative hypothesis.

The case-series report used for adverse event following hepatitis B vaccine (Geier and Geier, 2004) provided a descriptive analysis but did not offer information on the strength of the association. In Thomas' comprehensive review of methods for modeling dose–response relationships in environmental epidemiology (Thomas, 2009), he remarked that simultaneously addressing the location of risk threshold and the magnitude of risk was difficult. Langholz et al. (1999) used grid searching for modeling time-delayed latency effects, they provided point estimates for both the minimum and maximum latency as well as the effect magnitude, but they did not provide methods for interval estimation or uncertainty evaluation. Chen et al. (2014) introduced a hierarchical Bayesian method for a threshold model for survival data with a single cut point. In this study, we are interested in capturing a risk window defined by two cut points. Existing statistical approaches are inadequate for assessing the impact of an intervention or an exposure when the effect is restricted to an unknown subset of the study population. This gives us strong motivation to develop an alternative Bayesian approach for the risk window problem.

In this paper, we introduce a Bayesian logistic model to provide posterior distributions for the location of the risk window and the magnitude of the risk. We propose a logistic regression model for the relationship between the occurrence of miscarriage and the treatment and the risk window and develop the Bayesian inference procedures using Markov Chain Monte Carlo (Casella and George, 1992; Gilks et al., 1996). We then evaluate the performance of the Bayesian model in a series of simulations by studying the model's ability to estimate true values of the risk window and magnitude of the risk, and comparing its power with existing methods. Finally, we illustrate the Bayesian model using data from the Costa Rica Vaccine Trial (CVT), a community-based double-blind randomized controlled phase III study of Cervarix sponsored by the US. National Cancer Institute (NCI) (Herrero et al., 2008). Women enrolled in CVT were healthy young adults 18–25 years of age residing in Costa Rica, who received either HPV vaccine as intervention group or HAV vaccine as control group (Herrero et al., 2008). The null hypothesis is that the bivalent HPV vaccine does not associate with additional miscarriage risk for pregnancies during any risk windows. The proposed method initiates simultaneous statistical inference on the location and width of the unknown risk window and the effect modification on the identified window. The method turns out to outperform the existing analytical approaches in situations where the effect of an agent is restricted to a temporal interval or risk window. The method is generally applicable to handle this kind of risk-window problems, which are common in safety analysis of randomized trials and in environmental/occupational epidemiology.

2. Hierarchical Bayesian model

Let Y_i denote the binary outcome status for individual $i = 1, 2, \ldots, n$ (that is, $Y_i = 1$ if miscarriage, and $Y_i = 0$ otherwise). Let x_{1i} represent the treatment/control that individual i receives (that is, $x_{1i} = 1$ if HPV vaccine is administered as treatment, and $x_{1i} = 0$ if HAV vaccine is administered as control). Let x_{2i} be a continuous covariate representing the marker factor that may potentially interact with treatment (for example, the number of days between the vaccination and conception). Let $\boldsymbol{z}_i$ be a $1 \times p$ vector of potential confounding variables such as age, race and body mass index. In many clinical and epidemiological studies, the marker factor effect may not be a simple linear function. In this paper, we consider an indicator function for the marker factor effect. Assuming a starting point c_1 and an end point c_2 defining the risk window (c_1, c_2), we introduce an indicator variable $w(x_{2i})$ in the model that describes whether the value of the marker factor (or time from vaccination to conception in the context) is within the hypothesized risk window,

$$w(x_{2i}) = \begin{cases} 1 & \text{if } c_1 < x_{2i} < c_2, \\ 0 & \text{otherwise.} \end{cases}$$

The effect of risk window for covariate x_2 are illustrated in Fig. 1. Given the covariate vector $(x_{1i}, x_{2i}, \boldsymbol{z}_i)^T$, we assume that the binary outcome Y_i follows a Bernoulli distribution with $P(Y_i = 1|x_{1i}, x_{2i}, \boldsymbol{z}_i) = \pi_i$. The logistic regression model for Y_i takes the following form

$$\text{logit}(\pi_i) = \beta_0 + \beta_1 x_{1i} + \beta_2 w(x_{2i}) + \beta_3 x_{1i} w(x_{2i}) + \boldsymbol{\beta}_4^T \boldsymbol{z}_i. \tag{1}$$

In biomedical research, the covariate x_{2i} is often called as a surrogate marker or a biomarker (Cox, 1999). Model (1) addresses the marker factor x_{2i} (duration between vaccination and conception) as an effect modifier via the interaction term β_3. That is, the model allows the association between the types of vaccination and miscarriage (called "the risk" henceforth) to vary for individuals within and outside the risk window. The probability of the outcome $\pi_i = \Pr\{Y_i = 1\}$ can be expressed as

$$\pi_i = \frac{\exp(\boldsymbol{\beta}^T \boldsymbol{x}_i)}{1 + \exp(\boldsymbol{\beta}^T \boldsymbol{x}_i)},$$

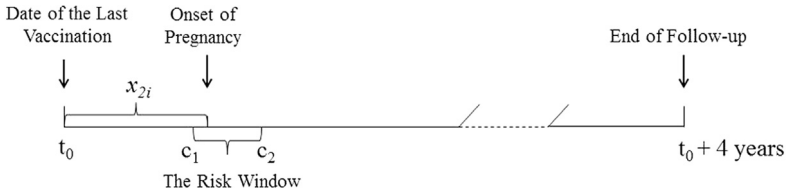

Fig. 1. Illustration of the definitions of risk window and marker factor with regard to the date of last vaccination and onset of pregnancy in the Costa Rica vaccine trial. Specifically, (1) x_{2i} is the marker factor, e.g., the time between the vaccination and the onset of pregnancy, with c_1 and c_2 representing the beginning and end of the risk window respectively; (2) the risk window is an unknown period of time of conception for the pregnancies with increased risk of miscarriage due to the vaccination.

where $\boldsymbol{x}_i = \{1, x_{1i}, w(x_{2i}), x_{1i}w(x_{2i}), \boldsymbol{z}_i\}^T$ is the covariate vector of interest for individual i, and $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_3, \boldsymbol{\beta}_4)^T$ is the vector of regression coefficients. Given the observed data, the likelihood function is

$$f(\boldsymbol{y}; c_1, c_2, \boldsymbol{\beta}) = \prod_{i=1}^{n} \{\pi_i^{y_i}(1-\pi_i)^{1-y_i}\} \tag{2}$$

where $\boldsymbol{y} = (y_1, y_2, \ldots, y_n)^T$ and y_i indicates the observed outcome status for individual $i = 1, 2, \ldots, n$. We further assume that c_1, c_2 and x_{2i} take values between 0 and 1, although the method can be generalized easily to x_{2i} of different scales. When analyzing CVT trial data, the values of x_{2i} can be converted to the interval (0, 1) using the percentile transformation as described by Gentle (2009). That is, each of x_{2i} will be replaced by it's sample percentile of $(x_{21}, x_{21}, \ldots, x_{2n})$. Once the interval (c_1, c_2) is estimated, it can be mapped back to the original scale of x_{2i} according the sample quantile. All transformations will be automatically done by the software package for this paper described in Section 3.

Because the likelihood function (2) is not a smooth function with respect to the parameters c_1 and c_2, there is no straightforward way to obtain the maximum likelihood estimates and their asymptotic distributions. We develop a Bayesian approach for the model inference by treating the regression coefficients $\boldsymbol{\beta}$ and the cut points of the risk window (c_1 and c_2) as random variables with probability distributions.

We start with prior distributions for c_1, c_2 and $\boldsymbol{\beta}$, then multiply them to the observed data likelihood function to obtain the posterior distributions (Bolstad, 2008). Due to the restriction $0 < c_1 < c_2 < 1$ for the risk window, we propose a prior distribution for c_1 given c_2 first. We have $0 < \frac{c_1}{c_2} < 1$, therefore, the prior distribution for c_1 is given by $\frac{c_1}{c_2}\Big| c_2 \sim Beta(2, q_1)$ with probability density function

$$b_1(c_1|c_2) = q_1(q_1+1)\frac{c_1}{c_2}\left(1-\frac{c_1}{c_2}\right)^{q_1-1} \times \frac{1}{c_2},$$

where $q_1 > 0$. For c_2 we assume that $c_2 \sim Beta(2, q_2)$, with probability density function

$$b_2(c_2) = q_2(q_2+1)c_2(1-c_2)^{q_2-1},$$

where $q_2 > 0$. The Beta prior here is flexible enough to accommodate the risk window restricted between 0 and 1. It is possible to replace the priors $Beta(2, q_1)$ and $Beta(2, q_2)$ by the more general form of $Beta(q_{11}, q_{12})$ and $Beta(q_{21}, q_{22})$, respectively. To reduce the influence of prior parameters q_1 and q_2 on the posterior of c_1 and c_2, we propose hyper prior distributions for q_1 and q_2 in the form of $g_j(q_j) \propto \frac{1}{q_j(q_j+1)}$ for $j = 1, 2$. We use this form of $g_j(q_j)$ to simplify the expression of posterior distribution of c_1, c_2 and $\boldsymbol{\beta}$. However, our experience in numerical simulation shows that the impact of prior and hyper prior on the posterior distribution is very minor.

Since there are no restrictions on the regression coefficient $\beta_j \in (-\infty, +\infty)$, we assume a multivariate normal prior of the form $N(\boldsymbol{\beta}^*, \Sigma^*)$ for the regression coefficient vector $\boldsymbol{\beta}$, where the prior knowledge can be incorporated through $\boldsymbol{\beta}^*$ and Σ^*. For example, if historical knowledge can provide an estimate of the disease or adverse event incidence for response variable $\boldsymbol{y}$, this information can be reflected in the prior distribution for the intercept parameter β_0^*. The variance Σ^* reflects the uncertainty about the prior knowledge of $\boldsymbol{\beta}$, in general, a large variance Σ^* can be used if there is little or no prior information about $\boldsymbol{\beta}$. Let $\boldsymbol{\theta} = (c_1, c_2, \boldsymbol{\beta}, q_1, q_2)^T$ be the parameter vector. By simple algebra, the prior density function for $\boldsymbol{\theta}$ can be expressed as

$$\begin{aligned} g(\boldsymbol{\theta}) &\propto b_1(c_1|c_2)b_2(c_2)\phi(\boldsymbol{\beta})g_1(q_1)g_2(q_2) \\ &= q_1(q_1+1)\frac{c_1}{c_2^2}\left(1-\frac{c_1}{c_2}\right)^{q_1-1} q_2(q_2+1)c_2(1-c_2)^{q_2-1}\phi(\boldsymbol{\beta})\prod_{j=1}^{2}\frac{1}{q_j(q_j+1)} \\ &= c_1(c_2-c_1)^{q_1-1}c_2^{-q_1}(1-c_2)^{q_2-1}\phi(\boldsymbol{\beta}), \end{aligned}$$

where $\phi(\boldsymbol{\beta})$ is the probability density function of a multivariate normal distribution $N(\boldsymbol{\beta}^*, \Sigma^*)$.

Based on the Bayes' theorem, we derive the joint posterior distribution $g(\boldsymbol{\theta}|\boldsymbol{y})$ by multiplying the prior distribution $g(\boldsymbol{\theta})$ to the likelihood function (1). This is further expressed as

$$\begin{aligned} g(\boldsymbol{\theta}|\boldsymbol{y}) &\propto g(\boldsymbol{\theta}) \times f(\boldsymbol{y}; c_1, c_2, \boldsymbol{\beta}) \\ &= c_1(c_2 - c_1)^{q_1-1} c_2^{-q_1} (1 - c_2)^{q_2-1} \phi(\boldsymbol{\beta}) f(\boldsymbol{y}; c_1, c_2, \boldsymbol{\beta}). \end{aligned}$$

We then propose using the Gibbs sampling techniques iteratively to draw random samples from the conditional distributions of all parameters (Gilks et al., 1996). This provides random samples that approximate the marginal posterior distributions. The point and interval estimates can be obtained from the posterior distribution samples accordingly. The sampling algorithm proceeds as follows.

1. We start with initial values of the unknown parameters for regression coefficients and hyper parameters. The initial values for the regression coefficient vector $\boldsymbol{\beta}^{(0)}$ are set to be $\boldsymbol{\beta}^{(0)} = \mathbf{0}$. The initial values for q_1 and q_2 are taken to be $q_1^{(0)} = 2$ and $q_2^{(0)} = 2$.
2. Conditional on $\boldsymbol{\beta}^{(k)}$, $q_1^{(k)}$ and $q_2^{(k)}$, one sample of the threshold parameter $(c_1^{(k+1)}, c_2^{(k+1)})$ is drawn from the conditional distribution of
$$f_1(c_1, c_2|\boldsymbol{y}, \boldsymbol{\beta}^{(k)}, q_1^{(k)}, q_2^{(k)}).$$
3. Conditional on the risk window endpoints $c_1^{(k+1)}$ and $c_2^{(k+1)}$, one sample of the regression coefficients $\boldsymbol{\beta}^{(k+1)}$ is drawn from the conditional distribution $f_2(\boldsymbol{\beta}|\boldsymbol{y}, c_1^{(k+1)}, c_2^{(k+1)})$.
4. Samples of $q_1^{(k+1)}$, $q_2^{(k+1)}$ are drawn from $f_3(q_1|\boldsymbol{y}, \boldsymbol{\beta}^{(k+1)}, c_1^{(k+1)}, c_2^{(k+1)})$ and $f_4(q_2|\boldsymbol{y}, \boldsymbol{\beta}^{(k+1)}, c_1^{(k+1)}, c_2^{(k+1)})$ respectively.
5. Steps $2-4$ are repeated until the random samples for all parameters reach stationarity.

While the procedures are similar to the algorithm proposed by Chen et al. (2014), methods in this paper are complicated for using multiple cut points c_1, c_2. Below we provide more details on how to sample from the conditional distributions in Steps 2, 3, and Step 4 of the above algorithm.

In Step 2, we draw a pair of sample $\{(c_1, c_2) : c_1 < c_2\}$ with the following conditional distribution

$$f_1(c_1, c_2|\boldsymbol{y}, \boldsymbol{\beta}^{(k)}, q_1^{(k)}, q_2^{(k)}) \propto c_1(c_2 - c_1)^{q_1^{(k)}-1} c_2^{-q_1^{(k)}} (1 - c_2)^{q_2^{(k)}-1} f(\boldsymbol{y}; c_1, c_2, \boldsymbol{\beta}^{(k)}).$$

More specifically, the conditional distribution of $f_1(c_1, c_2|\cdot)$ can be obtained by applying Metropolis–Hastings algorithms (Metropolis et al., 1953; Hastings, 1970). For a small constant δ_0, let $\delta_1 = \min\{\delta_0, c_1^{(k)}/2, (c_2^{(k)} - c_1^{(k)})/2\}$ and $\delta_2 = \min\{\delta_0, (c_2^{(k)} - c_1^{(k)})/2, (1 - c_2^{(k)})/2\}$. A candidate sample $\tilde{c}_j$ for c_j is generated from the uniform distribution $U(c_j^{(k)} - \delta_j, c_j^{(k)} + \delta_j)$, for $j = 1$ and 2. Let

$$\alpha_1 = \min\left(\frac{f_1(\tilde{c}_1, \tilde{c}_2|\boldsymbol{y}, \boldsymbol{\beta}^{(k)}, q_1^{(k)}, q_2^{(k)})}{f_1(c_1^{(k)}, c_2^{(k)}|\boldsymbol{y}, \boldsymbol{\beta}^{(k)}, q_1^{(k)}, q_2^{(k)})}, 1\right),$$

and $u \sim U(0, 1)$. If $u \le \alpha_1$, then let $c_1^{(k+1)} = \tilde{c}_1$ and $c_2^{(k+1)} = \tilde{c}_2$, otherwise, let $c_1^{(k+1)} = c_1^{(k)}$ and $c_2^{(k+1)} = c_2^{(k)}$.

In Step 3, we take

$$f_2(\boldsymbol{\beta}|\boldsymbol{y}, c_1^{(k+1)}, c_2^{(k+1)}) \propto \phi(\boldsymbol{\beta}) f(\boldsymbol{y}; c_1^{(k+1)}, c_2^{(k+1)}, \boldsymbol{\beta}).$$

Similar to Step 2, the conditional distribution of $f_2(\boldsymbol{\beta}|\cdot)$ can be obtained by applying Metropolis–Hastings algorithms (Metropolis et al., 1953; Hastings, 1970). The candidate sample $\tilde{\boldsymbol{\beta}}$ for $\boldsymbol{\beta}$ is generated from a conditional normal distribution $\phi(\tilde{\boldsymbol{\beta}}|\boldsymbol{\beta}^{(k)})$ with the mean $\boldsymbol{\beta}^{(k)}$ and variance–covariance matrix obtained by fitting a regular logistic regression model with threshold parameters given by $c_1^{(k+1)}, c_2^{(k+1)}$. Then let $\boldsymbol{\beta}^{(k+1)} = \tilde{\boldsymbol{\beta}}$ with probability

$$\alpha_2 = \min\left(\frac{\phi(\tilde{\boldsymbol{\beta}}) f(\boldsymbol{y}; c_1^{(k+1)}, c_2^{(k+1)}, \tilde{\boldsymbol{\beta}})}{\phi(\boldsymbol{\beta}^{(k)}) f(\boldsymbol{y}; c_1^{(k+1)}, c_2^{(k+1)}, \boldsymbol{\beta}^{(k)})}, 1\right).$$

Note that $\phi(\tilde{\boldsymbol{\beta}}|\boldsymbol{\beta}^{(k)}) = \phi(\boldsymbol{\beta}^{(k)}|\tilde{\boldsymbol{\beta}})$ are the probability density functions for the candidate sample and they cancel out in the formula for α_2.

In Step 4, we take

$$\begin{aligned} f_3(q_1|c_1^{(k+1)}, c_2^{(k+1)}) &\propto \{c_2^{(k+1)} - c_1^{(k+1)}\}^{q_1} (c_2^{(k+1)})^{-q_1} = \exp(-q_1 \lambda_1^{(k)}), \\ f_4(q_2|c_1^{(k+1)}, c_2^{(k+1)}) &\propto \{1 - c_2^{(k+1)}\}^{q_2} = \exp(-q_2 \lambda_2^{(k)}), \end{aligned}$$

where $\lambda_1^{(k)} = -\log\left\{1 - \frac{c_1^{(k+1)}}{c_2^{(k+1)}}\right\}$ and $\lambda_2^{(k)} = -\log\left\{1 - c_2^{(k+1)}\right\}$, respectively. It is obvious that both conditional distributions of $(q_1|c_1^{(k+1)}, c_2^{(k+1)})$ and $(q_2|c_1^{(k+1)}, c_2^{(k+1)})$ follow an exponential distribution with parameters $\lambda_1^{(k)}$ and $\lambda_2^{(k)}$, respectively.

Eventually, we generate the Markov Chain Monte Carlo (MCMC) sample sequence with B_0 steps of burn-in and additional B steps of iterations. The random samples obtained from MCMC sampling approximate the marginal posterior distributions, after excluding the initial burn-in period (the first B_0 iterations). To make sure that the MCMC samples converge to a stationary distribution, we recommend users analyze the posterior samples using a standard statistics output analysis and diagnostics tool such as *CODA* package for R (Plummer et al., 2006) for Markov Chain Monte Carlo.

The posterior means and $100 \times (1-\alpha)\%$ credible intervals can be calculated from the sample means and percentiles of the posterior distributions respectively. By taking the iteration number B large enough, we have

$$\hat{c}_j = \frac{1}{R}\sum_{k=B_0+1}^{B_0+B} c_j^{(k)}, \quad \text{for } j = 1, 2$$

and

$$\hat{\boldsymbol{\beta}} = \frac{1}{R}\sum_{k=B_0+1}^{B_0+B} \boldsymbol{\beta}^{(k)}.$$

We can then carry out hypothesis testing for regression coefficients $\boldsymbol{\beta}$. For example, when testing the hypothesis that $H_0 : \beta_3 = 0$ versus $H_a : \beta_3 \neq 0$ at significance level α, we will reject H_0 if zero lies outside the $100 \times (1-\alpha)\%$ credible interval of β_3. More details regarding to hypothesis testing will be discussed in simulation studies (Section 4).

3. Software for the proposed method

We implemented the proposed hierarchical Bayesian method as a part of the R software package for biomarker threshold models (the *bhm* package) developed and maintained by the corresponding author of this manuscript (BEC). The most recent version of *bhm* package for R can be installed in two simple steps.

1. Load the *devtools* package.

   library(*devtools*).

   This package allows users to install other R packages from a wide range of repositories. If you do not have 'devtools' in your R system, invoke R and then type *install.packages*("*devtools*") to install it.
2. Install *bhm* package using the R command

   install_github("*statapps*/*bhm*").

A stable version of *bhm* package is also available from the *Comprehensive R Archive Network* (https://CRAN.R-project.org/package=bhm) and can be installed using R command

install.packages("*bhm*").

Once the *bhm* package is installed in R, users can fit Hierarchical Bayesian Model for binary data through the following syntax

$$fit = bhm(y \sim x_1 + x_2 + x_3 \ldots, family = \text{'}binomial\text{'}, data = data, c.n = 2),$$

where *family* specifies the distribution of response variable y and $c.n$ specifies number of cut points to be used in the model. Both *summary*(*fit*) and *print*(*fit*) can be used to summary and display the results. More details on how to use the *bhm* package can be found from R command *help*(*bhm*).

4. Simulation studies

To evaluate the performance of the proposed method and make comparison to existing methods, we conducted a series of simulation studies with different sample sizes, and varying risk windows and magnitudes of risk. Data were generated based on Model (1) using different parameter combinations. A sample size of $n = 2000$ and 4000 was used because in epidemiology and population based observational studies, researchers often use thousands of observations to detect a small effect. Treatment covariate x_{1i} was generated from a Bernoulli distribution with $P(x_{1i} = 1) = 0.5$. Covariate x_{2i} was a continuous variable with uniform distribution in interval (0, 1). For the main effects of Model (1), we take $\beta_0 = \log(0.1)$ as the intercept, $\beta_1 = \log(1.5)$ and $\beta_2 = \log(2.5)$ as the true values of the parameters to generate the simulated data. We used $\beta_3 = \log(1.5)$, $\log(2.5)$ and $\log(3.5)$ for small, moderate and large risk window and treatment interaction effect. The threshold parameters c_1 and c_2 take a set of pre-specified values between 0.1 and 0.9 such that the length of risk window $\Delta c = c_2 - c_1 = 0.1, 0.2, 0.3, 0.4, 0.5$ and 0.6. For any given covariates $\boldsymbol{x}_i$ and parameters $c_1, c_2, \boldsymbol{\beta}$, the response variable Y_i was generated from a Bernoulli distribution with π_i given by model (1).

A chain of $B_0 + B = 5500$ iterations including $B_0 = 500$ burn-in and $B = 5000$ iterations was run for each MCMC sampling procedure. In order to reduce auto correlations among interactions, a thinning parameter of 10 was applied to the MCMC samplers. All measurements in simulations were based on $R = 500$ replications of simulated data sets. It took several days

Table 1
Empirical bias of the estimation for risk window $(\hat{c}_1, \hat{c}_2)$ and the relative risk $(\hat{\beta}_3)$ using the Bayesian method. The true values for $\beta_0 = \log(0.1)$, $\beta_1 = \log(1.5)$ and $\beta_2 = \log(2.5)$ in all simulations. Results are based on $B = 5000$ MCMC iterations and $R = 500$ simulation replications.

(c_1, c_2)	Δc	$\beta_3 = \log(1.5)$			$\beta_3 = \log(2.5)$			$\beta_3 = \log(3.5)$		
		$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$
$n = 2000$										
(0.1, 0.2)	0.1	0.002	0.001	0.085	0.001	0.003	0.021	0.001	0.002	0.041
(0.2, 0.4)	0.2	0.001	0.003	0.083	0.001	0.003	0.028	0.002	0.005	−0.031
(0.2, 0.5)	0.3	0.002	0.004	−0.004	0.002	0.004	−0.002	0.003	0.003	−0.011
(0.3, 0.7)	0.4	0.004	0.002	0.008	0.001	−0.001	0.006	0.003	0.001	−0.030
(0.2, 0.7)	0.5	0.002	−0.001	0.006	0.003	−0.001	−0.007	0.007	−0.001	−0.048
(0.3, 0.9)	0.6	0.001	−0.001	−0.011	−0.001	−0.003	−0.019	−0.001	−0.002	−0.023
$n = 4000$										
(0.1, 0.2)	0.1	0.001	0.003	−0.002	0.001	0.006	−0.010	0.001	0.008	−0.009
(0.2, 0.4)	0.2	0.001	0.001	0.010	0.001	0.001	−0.010	−0.001	0.001	0.006
(0.2, 0.5)	0.3	−0.001	−0.001	−0.012	0.002	0.002	−0.020	−0.003	0.001	0.003
(0.3, 0.7)	0.4	0.001	−0.001	0.008	−0.001	−0.006	−0.032	0.002	0.001	−0.010
(0.2, 0.7)	0.5	0.002	−0.001	−0.009	0.002	−0.001	−0.020	0.001	−0.002	−0.006
(0.3, 0.9)	0.6	−0.001	−0.001	−0.002	−0.001	−0.002	−0.012	0.001	−0.001	−0.011

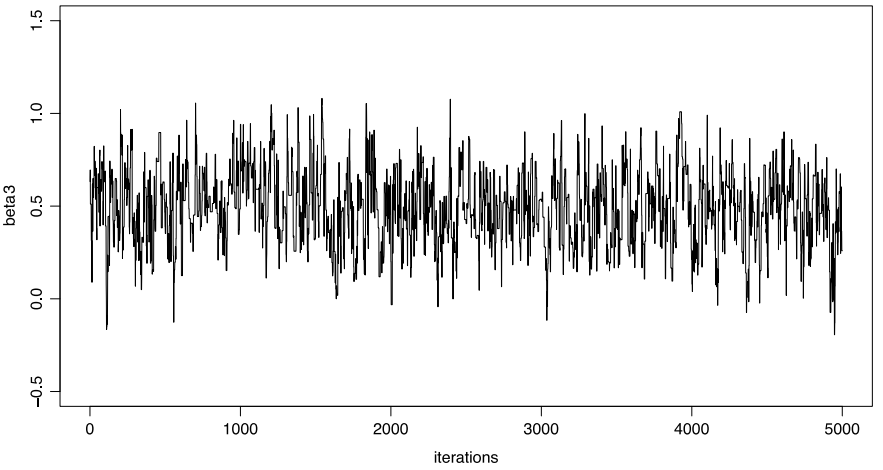

Fig. 2. Time series trace plots for β_3 from the stimulations. The parameters for this simulation were set at $n = 4000$, $(c_1, c_2) = (0.2, 0.4)$, $\beta_0 = \log(0.1)$, $\beta_1 = \log(1.5)$, $\beta_2 = \log(2.5)$, and $\beta_3 = \log(1.5)$.

to analyze the 500 simulated data sets for each set of parameter combination. Iteration series trace showed that a burn-in period of 500 interactions was sufficient (Fig. 2). The procedures were implemented in R software programs (R Core Team, 2016) on the Shared Hierarchical Academic Research Computing Network in Canada (Compute Canada, 2016).

We first assessed the finite sample performance of the model in estimating the true values of the risk window (c_1, c_2) and the regression coefficient β_3 in terms of empirical bias and coverage probability. We further studied the statistical power of the proposed test in detecting a non-zero coefficient β_3.

Table 1 presents the empirical bias for $\hat{c}_1$, $\hat{c}_2$ and $\hat{\beta}_3$ under different simulated scenarios. The empirical bias is defined as the average difference between the estimates and the true value. In all the settings that we considered, the absolute bias values for both c_1 and c_2 are less than 0.008, with most of the bias values being ± 0.001 or ± 0.002. The empirical bias for regression coefficient β_3 is also very small, regardless the value of sample size $n = 2000$ or 4000 and the true parameter value of $\beta_3 = \log(1.5)$, $\log(2.5)$, or $\log(3.5)$. The excellent finite sample performance is due to the fact that there is a non-zero main effects for the risk window $I(c_1, c_2)$. When the risk window main effects have the same cut points as the interaction term, it provides additional information for estimating the risk window parameters c_1 and c_2.

Table 2 shows the empirical coverage probabilities (C.P. in percentage) of the 95% credible intervals for $\hat{c}_1$, $\hat{c}_2$ and $\hat{\beta}_3$. The empirical coverage probability (C.P.) is defined as the proportion that the 95% credible interval contains the true value. In all the 108 coverage probabilities that we calculated, most of the coverage probabilities were close to 95%, with about two-third of them (72 out of 108) around 93% to 96%, and the other one-third around 90% to 92%. This suggests that the proposed Bayesian method provides excellent point estimates and the accurate 95% credible intervals, correspondingly.

Table 2
Coverage probabilities (C.P. in percentage) for 95% credible intervals using the Bayesian method. The true values for $\beta_0 = \log(0.1)$, $\beta_1 = \log(1.5)$ and $\beta_2 = \log(2.5)$ in all simulations. Results are based on $B = 5000$ MCMC iterations and $R = 500$ simulation replications.

(c_1, c_2)	Δc	$\beta_3 = \log(1.5)$			$\beta_3 = \log(2.5)$			$\beta_3 = \log(3.5)$		
		$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$
$n = 2000$										
(0.1, 0.2)	0.1	95.0	92.6	90.4	91.4	93.0	94.0	92.6	93.0	93.4
(0.2, 0.4)	0.2	93.6	95.8	92.6	93.0	94.2	91.2	91.6	90.4	94.0
(0.2, 0.5)	0.3	91.6	93.6	96.2	93.2	93.4	94.2	92.2	93.2	92.2
(0.3, 0.7)	0.4	93.4	94.0	93.8	92.8	94.6	92.4	92.8	92.4	92.8
(0.2, 0.7)	0.5	93.6	94.8	92.4	93.4	93.6	93.2	92.0	91.4	92.0
(0.3, 0.9)	0.6	93.6	94.6	93.0	94.0	92.4	92.0	93.2	92.8	94.8
$n = 4000$										
(0.1, 0.2)	0.1	93.8	95.0	93.8	92.4	91.8	93.4	93.4	92.2	92.8
(0.2, 0.4)	0.2	93.6	93.8	94.0	94.8	92.0	93.2	93.4	93.6	93.0
(0.2, 0.5)	0.3	94.8	92.4	94.0	93.4	91.4	91.2	90.2	91.8	94.4
(0.3, 0.7)	0.4	93.2	94.6	95.8	92.0	90.6	92.0	94.0	90.8	93.6
(0.2, 0.7)	0.5	95.0	91.8	94.4	93.4	94.2	93.6	91.2	92.6	94.6
(0.3, 0.9)	0.6	94.6	93.8	91.6	94.0	93.0	94.2	94.0	92.2	94.8

Table 3
Empirical test size and power (in percentage) of the Bayesian method in testing the null hypothesis $H_0 : \beta_3 = 0$. The true values for $\beta_0 = \log(0.1)$, $\beta_1 = \log(1.5)$ and $\beta_2 = \log(2.5)$ in all simulations. Results are based on $B = 5000$ MCMC iterations and $R = 500$ simulation replications.

(c_1, c_2)	Δc	$\beta_3 = 0$	$\beta_3 = \log(1.5)$	$\beta_3 = \log(2.5)$	$\beta_3 = \log(3.5)$
$n = 2000$					
(0.1, 0.2)	0.1	7.0	20.0	74.6	92.6
(0.2, 0.4)	0.2	6.8	32.6	87.6	96.4
(0.2, 0.5)	0.3	4.8	32.6	94.0	98.2
(0.3, 0.7)	0.4	5.4	37.2	95.4	98.2
(0.2, 0.7)	0.5	4.0	35.0	93.4	97.4
(0.3, 0.9)	0.6	5.8	33.4	91.6	98.8
$n = 4000$					
(0.1, 0.2)	0.1	7.2	33.4	95.0	98.0
(0.2, 0.4)	0.2	6.2	55.8	98.4	100.0
(0.2, 0.5)	0.3	4.8	83.0	98.0	100.0
(0.3, 0.7)	0.4	5.6	65.0	97.0	99.6
(0.2, 0.7)	0.5	4.4	62.2	99.0	99.4
(0.3, 0.9)	0.6	4.4	53.0	99.2	100.0

Table 3 displays the empirical test size and power for testing the hypothesis $H_0 : \beta_3 = 0$ versus $H_1 : \beta_3 \neq 0$ with different sample sizes n, various risk windows (c_1, c_2) and effects β_3. At the nominal significant level alpha $= 0.05$, the null hypothesis H_0 will be rejected if the 95% credible interval for β_3 does not contain 0. The column under $\beta_3 = 0$ shows the empirical test size under H_0. We observed that most of the test size values are between 4% and 7%, which suggested that the test procedure controls the type I error rate. There is a consistent trend that the power increases as the sample size increases across different risk windows. Specifically, when $\beta_3 \geq \log(2.5)$, the power was mostly over 80% for both $n = 2000$ and 4000, for all risk windows (c_1, c_2) that we considered (except the risk window (0.1, 0.2), which has an empirical power of 74.6%). However, with a smaller effect of $\beta_3 = \log(1.5)$ and narrower risk window $(c_1, c_2) = (0.1,\ 0.2)$, the empirical powers are low (20.0% and 33.4% for $n = 2000$ and $n = 4000$, respectively). Our simulations showed a larger sample size is required to have reasonable power for testing $H_0 : \beta_3 = 0$ versus $H_1 : \beta_3 \neq 0$.

We also compared the proposed method with two existing methods in terms of the statistical power to detect a risk window at the 0.05 significance level, using simulated data with three sets of parameter combinations (Table 4). A sample size of $n = 2000$ was used in the simulated data, with the risk window defined by $\boldsymbol{c}_0 = (0.2, 0.4)$. A standard test is to assume a single arbitrarily pre-specified risk window (c_{10}, c_{20}) for testing the null hypothesis $H_0 : \beta_3 = 0$. The given risk window (c_{10}, c_{20}) may or may not be close to the true risk window (c_1, c_2), as we usually do not know the true risk window values when analyzing data in a real application. The permutation test of Wacholder et al. (2010) assessed the statistical significance of a series of potential risk windows without compromising type I error.

For comparing empirical test size, we studied each method by obtaining the probability of rejecting the null hypothesis $H_0 : \beta_3 = 0$ when in fact $\beta_3 = 0$. We observed acceptable test size for each method (see Table 4, with $\beta_3 = 0$ for details). In terms of empirical power, we consider the scenario with $\beta_3 = \log(2.5)$ and $\log(3.5)$, in which case a sample size of $n = 2000$ provides reasonable statistical power for the null hypothesis $H_0 : \beta_3 = 0$. The proposed Bayesian method showed greater power than the standard hypothesis testing in the settings when the risk window was badly mis-specified. For example if

Table 4
Comparison of the statistical power to detect the risk window using the Bayesian method, the standard test with pre-specified risk window, and the permutation test in simulation studies, with sample size $n = 2000$.

β_3	Bayesian Method	Test with pre-specified risk window		Permutation
	Power	(c_1, c_2)	Power	Power
log(1.0)	6.4	(0.20, 0.40)	7.4	7.2
		(0.20, 0.50)	3.0	
		(0.25, 0.35)	4.4	
		(0.10, 0.60)	5.0	
		(0.60, 0.80)	5.2	
log(2.5)	87.6	(0.20, 0.40)	98.8	66.6
		(0.20, 0.50)	94.4	
		(0.25, 0.35)	84.8	
		(0.10, 0.60)	76.6	
		(0.60, 0.80)	9.4	
log(3.5)	96.4	(0.20, 0.40)	100.0	97.0
		(0.20, 0.50)	100.0	
		(0.25, 0.35)	99.0	
		(0.10, 0.60)	98.2	
		(0.60, 0.80)	12.6	

1. True values for $\beta_0 = \log(0.1)$ and $\beta_1 = \log(1.5)$, $\beta_2 = \log(2.5)$.
2. True values for $c_1 = 0.2$, $c_2 = 0.4$.
3. Simulation replications $R = 500$.
4. Numbers in brackets in the standard test columns indicate the values of (c_1, c_2) that we arbitrarily specified for the test.

the true risk window was (0.2, 0.4) while a window of (0.1, 0.6) was used. In general, a correct guess is unlikely when there is limited knowledge about the risk window. The permutation tests showed comparable power to the Bayesian method, but it provided only a p-value without estimating the magnitude of the effect and cannot be generalized to adjust for additional covariates.

5. Application

We illustrate our method on the data from the CVT trial to evaluate miscarriage risk from the Bivalent HPV Vaccine. Detailed information on the trial was discussed by Herrero et al. (2008). In the CVT trial data, some women might have more than one pregnancies. To simplify the analysis, we analyzed the data on first-time pregnancy after vaccination only. Additional exclusion criteria followed Wacholder et al. (2010). The date of conception was estimated as two weeks after the last menstrual period (LMP). We defined the events of miscarriage as loss of pregnancies that occurred within 20 weeks after LMP. Since both the HPV and HAV vaccines were administrated in three doses, the marker factor x_{2i} was calculated as the number of days between the date of the last vaccination and the date of conception. Note that we excluded the few pregnancies that had conceptions before vaccination. Since the incidence of miscarriage in the control arm was about 10%, we assigned β_0 a prior distribution of $N(\log(0.1), 1)$.

We analyzed 3309 women (median age at enrollment 23 years old, range 18 to 30) with their first-time pregnancies after the enrollment of the trial out of the 4252 pregnancies (which included the second or higher number of pregnancies of the same woman). For the 3309 women included in this analysis, 1649 of them received HPV vaccination and 1660 of them received HAV vaccination. The time interval between last vaccination date and conception date varies between 0 and 5.57 years, with median time 1.45 years and interquartile range IQR $=$ 0.56–2.48 years. Results of the analysis are displayed in Table 5. Maternal age was included in the model because of its possible influence on miscarriage rate (Belloc et al., 2008; de la Rochebrochard and Thonneau, 2002). Other factors considered were treatment arms, body mass index (BMI), education, income, marital status and smoking status. But these factors were eventually excluded as corresponding credible intervals of the coefficients were found to contain the value 0.0, indicating that they were not significantly associated with the miscarriage outcomes. We forced the main effects and the interaction terms between the treatment and vaccination risk window (marker factor) to be included in the model even though they are not significant.

The estimated starting and end points of the risk window were 0.62 years (95% credible interval: 0.16–1.14) and 1.27 years (95% C.I.: 0.54–2.01) from the last vaccination date and the conception date, respectively. The point estimate for the odds ratio $\exp(\beta_3)$ was 1.06 with a 95% credible interval of (0.38, 2.69). These results do not provide supporting evidence for a significant association between the bivalent HPV vaccine and the miscarriage risk, which was consistent with previous analysis (Wacholder et al., 2010; VRBPAC, 2009). This confirms the safety of the HPV vaccination regarding the risk of miscarriage.

It is worth noting that this Bayesian analysis cannot completely rule out the possibility of miscarriage risk, as it may be underpowered because of the sample size of the study. We conducted numerical simulation with parameters given by those estimates from the HPV trial data and found that the empirical power of rejecting $H_0 : \beta_3 = 0$ is only 10.2%.

Table 5
Summary of the parameter estimates and 95% credible intervals using the Bayesian model on the Costa Vaccine trial ($n = 3433$).

Risk window	Parameter c_1, c_2		Cut points (years)	
	Estimates	95% CI	Estimates	95% CI
c_1	0.28	(0.09, 0.42)	0.62	(0.16, 1.14)
c_2	0.45	(0.25, 0.65)	1.27	(0.54, 2.01)
Coefficients	Parameter $\boldsymbol{\beta}$		exp($\boldsymbol{\beta}$)	
	Estimates	95% CI	Estimates	95% CI
β_0: Intercept	−3.05	(−3.97, −2.12)	0.05	(0.02, 0.12)
β_1: HPV effect	0.08	(−0.15, 0.31)	1.08	(0.86, 1.36)
β_2: Risk window effect	−0.40	(−1.13, 0.35)	0.67	(0.32, 1.42)
β_3: Interaction effect	0.06	(−0.98, 0.99)	1.06	(0.38, 2.69)
β_4: Age effect:	0.05	(0.01, 0.09)	1.05	(1.01, 1.09)
Prior parameters	Parameter			
	Estimates	95% CI		
q_1	2.05	(1.02, 5.40)		
q_2	1.60	(1.01, 3.37)		

The risk window estimation was based on the transformed scale in interval (0, 1). The estimated window was then transformed back to the original scale in years. Results were based on posterior distribution from $B = 5000$ MCMC iterations.

6. Discussion

In this paper, we use a Bayesian hierarchical model to assess the risk window of a potential vaccine-related side effect following administration of the bivalent HPV vaccine. The main contribution of this study is to make statistical inference simultaneously on both the risk effect and the risk window by using a Bayesian approach and Markov Chain Monte Carlo method. It provides an alternative test method that takes the uncertainty of the risk window into account.

The proposed Bayesian approach estimates the risk window and the corresponding risk from the data. When the true risk window is known, the standard test method with pre-specified risk window should be used. However, when the true risk window is unknown, the proposed method has outperformed the standard test method using a misspecified risk window. Also, prior knowledge can be incorporated into analysis when specifying the prior distributions. The use of hierarchical priors in the proposed method allows for more flexibility than fixed priors (Chen et al., 2014; Gelman et al., 2009). The Bayesian method provides point estimates for the risk window and the risk effect simultaneously, and provides the corresponding credible intervals capturing the uncertainty in these estimations (Goodman, 1993; Rothman, 1998; Walker, 1986). In contrast, the permutation procedure used in previous analysis of the HPV trials provided only a p-value. The model may become non-identifiable when the lower bound of the risk window is very close to 0 (e.g., $\boldsymbol{c} = (0.01, 0.2)$), or the upper bound is very close to 1 (e.g., $\boldsymbol{c} = (0.7, 0.99)$), in which case the proposed method may produce unstable results. In these situations, we suggest users try the model with a single cut point by specifying $c.n = 1$ in the "*bhm*" R package discussed in Section 3.

The proposed Bayes method can be extended to a wide scope of application scenarios. First, the outcome of interest can also be a continuous variable such as duration of efficacy measurement, or a time to event (survival) variable such as gestational age of fetuses affected. These situations can be handled by the "*bhm*" R package by using *family* = '*Gaussian*' for continuous outcome variable and *family* = '*Surv*' for survival outcome variable, respectively. For example, when studies have demonstrated long-term temporal trends of cancer risk among atomic-bomb survivors (Furukawa et al., 2013), the proposed method can be used to identify the actual risk window of age-at-exposure. Another example arises when investigating a time-dependent effect, an exposure at time $t_0 = 0$ may affect the risk between time $t_0 + L$ (latency) and $t_0 + R$ (recency), where (L, R) is the risk window. In addition, this model may apply more generally when the effect of an exposure is restricted to an uncertain class of individuals, as in many situations in occupational or environmental epidemiology. The restriction can be temporal, as we assumed here that the effect was likely restricted to fetuses conceived within an unknown risk window defined by days between conception and vaccination. The restriction can also be spatial, for example, when the only individuals having elevated risk are those who lived within an unknown distance of a place of exposure, such as a pollution source.

In Bayesian applications, choices of the appropriate prior distributions are usually subjective. The corresponding frequentist analysis ignores the component of uncertainty due to standard but unverifiable model assumptions. In general, statistical models may be underpowered when the sample size is not large enough for detecting a small effect. However, the Bayesian model can be empowering if proper prior knowledge is incorporated in the model. When explicit assumptions about priors and hyper-priors are realistic, our approach produces joint point and interval estimates and measures of uncertainty on the risk window and the risk. These may lead to better appreciation of etiologic and public health implications than existing approaches when an exposure alters the risk of disease only within a particular risk window.

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