論文の内容の要旨

Estimation of the relative incidence of adverse events in disseminated intravascular coagulation patients using the self-controlled case series method

セルフ・コントロールド・ケースシリーズ法を用いた
播種性血管内凝固症候群(DIC)患者における副作用発現リスクの推定

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1. Introduction

The self-controlled case series (SCCS) method was initially proposed to estimate the relative incidence (RI) of rare adverse events after some transient time-varying exposures following vaccination. This method provides an alternative to the more common cohort and case-control methods to investigate the association of rare adverse event and treatment exposure of which pre-marketing clinical trials usually have insufficient power to detect. Like the case-crossover design, the SCCS method requires only information on cases. Both methods share the same advantage as being self-matched, thereby providing control implicitly for all time-invariant multiplicative confounders, measured and unmeasured. However, the SCCS method is based on the cohort logic, not the case-control logic as in the case of a case-crossover study. Estimates of the RIs obtained via the SCCS method have been shown to be more efficient than those derived from a case-control study, when compared to cohort design as a standard. The design is also appealing as it is smaller, faster and cheaper than the more established cohort and case-control design.

Nonetheless, it only provides estimates of RI, not absolute incidence. A key assumption that is often an issue in SCCS analysis is that exposures should be independent of the adverse event. In recent years, a growing number of causal studies of non-vaccine exposure and adverse drug reaction that utilized the SCCS method have been reported.

The motivation of this study is to understand the feasibility and potential utility of a modified SCCS method in a particular clinical scenario with two key differences that differs from conventional SCCS study. First, the adverse outcomes are common and highly associated with the underlying disease being treated. Second, there are two competing treatment options for a disease that is critical. This scenario is unlike published studies of adverse drug reaction (ADR) using the standard SCCS method in which these ADRs are often unrelated to the disease. For the case of vaccine, the disease prevented is often absent and therefore, unrelated to the ADR. In this study, because the adverse outcomes are assumed common, there might be very few, if any, patients for control in a case-control study or outcome comparison in a cohort study. Moreover, because disease is critical, all patients are treated with either competing treatments; hence, no untreated patients for baseline comparison. The disseminated intravascular coagulation (DIC) disorder fits this scenario and is used to demonstrate the scenario. Modification to the standard SCCS method is attempted to accommodate the aforementioned differences so as to compare the risk of adverse events between two treatments – thrombomodulin ART-123 and low-dose heparin – otherwise not possible with the standard SCCS approach. Estimates from the modified SCCS approach were compared to the results of the randomized trial, as well as those obtained under the cohort and matched case-control assumption. The proposed modification can be an alternative for comparing drug safety in situation where adverse outcome is common and all patients are treated with competing treatment options.

2. Study Objective

This study aims to extend the standard SCCS method to accommodate the following limitations of the original design:

(i) the adverse outcome of interest is associated with the disease being studied;

(ii) there are two competing treatment options.

Specifically, the objective of the study is to modify the SCCS method in order to estimate the relative incidence of common adverse events associated with an underlying critical disease for the purpose of comparing the safety of two treatment options.

3. Data and Method

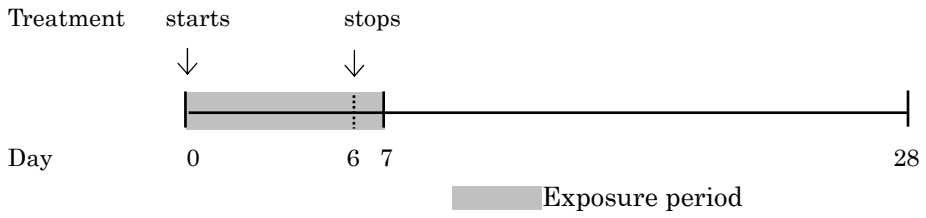
Data for this study come from a completed phase III randomized trial of ART-123 versus low-dose heparin. The use of randomized data allows the assessment of the proposed modification to the SCCS method without any bias or confounding issues. A total of 231 patients were included; 116 and 115 patients in the ART-123 and heparin treatment group, respectively. Study variables include anonymous patient identification, start and stop date of treatment, reason for early stopping of treatment, start and stop date of observation period, reason for early stopping of observation, DIC admission score, treatment type, incidence of bleeding adverse event and serious adverse event, discontinuation of treatment and its reason, severe thombocytopenia at admission, underlying disease characteristics, and basic patient demographics. While age can be adjusted in SCCS analysis, it is not in this study by virtue of the randomized data.

Exposure variables are the recombinant thrombomodulin ART-123 and low-dose heparin sodium treatments, both of which were administered for 6 consecutive days via drip infusion. The ART-123 has an *in vivo* half-life of about 20 hours. In consideration of this, and to be consistent with the ART-123 randomized trial, the exposure period for both drugs was set at 7 days unless infusion was stopped prematurely due to adverse event, aggravation of complication or DIC, change of treatment or patient's request.

The primary endpoints for this study are the bleeding related adverse events and serious adverse events exactly as defined in the original randomized trial. Adverse events were observed for 14 days from the start of infusion. They include new or exacerbated bleeding and organ symptoms, and abnormal changes in the clinical laboratory test findings. Serious adverse events were documented throughout the entire 28-day observation period. They include death, life-threatening events, prolonged hospitalization, permanent or significant disorder or dysfunction, or other severe medical events. Serious adverse events can also be bleeding related and vice versa. These primary endpoints were chosen because they are important for the safety assessment of ART-123 treatment in comparison with the low-dose heparin therapy in DIC patients.

The timeline of a typical DIC patient undergoing treatment is illustrated in Figure 1. Adverse events are assumed to be recurrent and occur randomly as a non-homogenous Poisson process.

Figure 1 Timeline of a DIC patient during the trial



In the SCCS analysis of this study, the multiplicative model for the incidence function, $\lambda_{ij} = \exp(\phi_i + \beta_j)$, with i denoting patient, j=1 denoting exposure period, as the baseline incidence of adverse event for patient i, and the RI for exposure j=1. The general form of the multinomial log-likelihood, conditioning on the number of events n_i observed for individual i during the observation period is then derived as

$$l(\beta) = \sum_{ij} n_{ij} \log \left[\frac{\exp(\beta_j) t_{ij}}{\sum_r \exp(\beta_r) t_{ir}} \right]$$

This multinomial model can be fitted as an associated Poisson model with a log link function. The response variable is the number of adverse events in each interval, n_{ij}, and the natural log of time period ln(t_{ij}) is included as an offset. The associated Poisson main effects model is n_{ij} ~ Poisson (λ_{ij} t_{ij}) .

In the first part of the analysis, standard SCCS method was performed separately for the two treatment arms, using 7-day and daily exposure period (Analysis 1). In the second part, modifications to the SCCS method were attempted. In the first attempt, the 7-day exposure period of a heparin patient was conjoined to the exposed period of the ART-123 patient (Analysis 2). The exposure period to heparin was taken as the control period for the ART-123 patient to adjust the baseline incidence. Such modification is based on the rationale that heparin is the conventional treatment for DIC disorder. A similar procedure was attempted using the entire observation period for bleeding-related adverse events (14 days) and the serious adverse event (28 days) (Analysis 3). Because there are many ways to match the subjects, matching was done randomly

using sampling with and without replacement. Once the time periods from both treatment arms were conjoined, time periods without adverse events were then dropped before proceeding to the SCCS analysis. The process was repeated for 300 iterations, separately for sampling with and without replacement.

As there were some patients whose treatment was terminated prematurely due to adversity, these cases violate the key assumption of independence between adverse events and probability of exposure. In addition, the adverse events could possibly be related to one another, i.e., similar episode. Analysis is possible by restricting outcome to the first cases of adverse event in each patient, ignoring subsequent events and assuming full exposure and observation period (Analysis 4). Since there is no second treatment exposure in this study, adverse events such as death can only curtail the observation period. But by considering only the first events, the said assumption of the SCCS method remains valid. It is also noted that the RI estimates from the first-case only analyses should approximate the relative risk (RR) estimates which consider patient as the unit of analysis instead of the frequency of adverse outcome.

For comparison purpose, the randomized data were also analyzed as a 1:1 matched case-control as well as cohort study design for both count and binary response. As there were many combinations or ways to match subjects, uniform random number generator without seed was used for random matching. The procedure was repeated for 100 iterations for different endpoints observed over different time periods.

All analyses were performed in SAS 9.1.

4. Results

The results of 7-day and daily RI estimates using the standard SCCS method (Analysis 1) are presented in Figure 2 and 3. The downward trend of the daily estimates of RIs after the second or third day show that both ART-123 and low-dose heparin treatments are able to reduce risk of adverse events over time. The results suggest that patients receiving ART-123 were at relatively lower risk of adverse events.

The results of modification via conjoining of exposure periods (Analysis 2 in Table 2) reveal that the mean RI and the corresponding confidence interval (CI) obtained via sampling without replacement (RI: 0.638; 95% CI: 0.469, 0.863) are very comparable to the 7-day RR obtained in the cohort design (RR: 0.637; 95% CI: 0.448, 0.905). Both estimates are statistically significant, implying the lower risk of bleeding related adverse events in patients treated with ART-123 during the first 7 days of therapy. The mean estimates of RI of Analysis 3 (0.795 and 0.750) are very comparable to the 14-day RR obtained using the cohort design (0.789). Both modifications in Analysis 1 and 2 produce rather similar bound of error.

Analysis 4 is the first-case only reanalysis of Analysis 2 and 3. Referring to the reanalysis of Analysis 2, the modified SCCS method using sampling without replacement produce a mean RI of 0.765 (95% CI: 0.513, 1.136), which is comparable to the 7-day RR of 0.763 (95% CI: 0.586, 0.993). The estimate of the modified method is not statistically significant, and its confidence intervals are slightly wider. The same is observed in the first-case reanalysis of Analysis 3,

wherein the mean RIs of 0.846 and 0.798 are fairly comparable to the 14-day RR of 0.806.

The matched case-control and binary-response cohort method appear to underestimate RR (0.763 and 0.806 for 7-day and 14-day respectively), despite the larger sample size compared to the modified SCCS approach. Nonetheless, both methods detected significant lower risk of bleeding related adverse events in ART-123 patients during the first 7 days (OR: 0.575; 95% CI: 0.334, 0.984 for the matched case-control, and OR: 0.583; 95% CI: 0.346, 0.981 for the binary-response cohort method). In terms of point estimates and confidence intervals, the results from the modified SCCS method in Analysis 4 seem to fare better.

The aforementioned observations for bleeding related adverse events are mostly true for the case of serious adverse events in Table 3. The main difference is the lower number of severe adverse event cases available for analysis despite the longer observation period. However, when compared to the cohort design, the RI estimate of the SCCS method in Analysis 2 using sampling without replacement (RI: 0.772; 95% CI: 0.446, 1.314) is still very close to the 7-day RR estimates achieved via the cohort method (RR: 0.765; 95% CI: 0.418, 1.401). The same was observed for the RI estimate in Analysis 3 using sampling without replacement (RI: 0.961; 95% CI: 0.653, 1.402) which was comparable to the 28-day RR estimated with cohort method (RI: 0.959; 95%: 0.621, 1.483). The bounds of error are fairly alike as well. In Analysis 4 using only the first cases, the RI estimates consistently underestimated the RRs for the corresponding time period (RI: 0.723 and 0.585 versus RR: 0.828; RI: 0.896 and 0.776 versus RR: 0.920). The confidence intervals are wider, possibly due to the small number of cases available for SCCS analysis, hence, smaller overall sample sizes. It is noted that the RI estimates obtained by sampling without replacement are closer to the RR than those using sampling with replacement.

In contrast to the RR (0.828 and 0.920 for 7-day and 28-day period respectively), the odds ratios from both the matched case-control and cohort method with binary response underestimated the RR. The CIs were wider. The first-case only reanalysis of Analysis 2 for 7-day and Analysis 3 for 28-day period seem to have closer estimates to the RRs, even though the CIs are almost as wide as the matched case-control and binary cohort method. The same was observed in the estimates for bleeding related adverse events.

5. Discussion

In the standard SCCS analysis, the downward trend of RI estimates starting from the second or third day of treatment suggests that both drugs were able to reduce the risk of adverse events over time. These daily RIs also imply that patients treated with thrombomodulin ART-123 had lower risk of bleeding related adverse events than those treated with low-dose heparin, during the first 7 days of therapy, the period during which DIC was critical. This observation is consistent with the findings from the randomized trial that reported significantly higher resolution rate for DIC in the ART-123 treatment group, as well as significantly better improvement in the clinical course of bleeding (Saito et al, 2007). Nonetheless, the standard SCCS analysis does not produce estimate of RI that directly compares the risk of adverse events between two treatments, which leads to the modification attempt.

The modified SCCS method can produce estimates that are very comparable to the relative risks from the cohort method and experimental trial, while requiring smaller sample size. Such proximity of the estimates obtained from the SCCS and cohort method can be explained by the same Poisson regression method used to model count response.

To circumvent the issue of certain adverse events altering the probability of subsequent exposure, as well as the possibility these events may be related to one another, the SCCS analysis is restricted to only the first cases of adverse events. The results are mixed. The RIs of modified SCCS method are found to be comparable to the RRs obtained from randomized trial for the bleeding related adverse events. However, the RIs for serious adverse events were underestimated with wider confidence intervals, possibly due to the smaller number of cases available for multiple random matching. The modified SCCS approach of using only the first cases of adverse events might produce better results in studies with larger sample size. Further study is required to validate this.

From the results, the ORs obtained from the 1-to-1 matched case-control and binary-response cohort design fare poorly in comparison to the proposed modified SCCS approach. This is probably due to the departure from the rare disease assumption, since in this study the adverse outcome is common and recurrent in DIC patients. It could also be due to the reason that when event rates are high, the relative reduction in odds ratio can be larger than the equivalent reduction in relative risk (Deeks, 1998).

Estimates achieved via random sampling without replacement are almost always closer to the relative risk of the cohort method and randomized trial, than when using random sampling with replacement in this study. It is suspected that when the number of patients with adverse events increases, both sampling methods should approximate each other. Validation should be attempted using a larger sample.

The proposed modification of the SCCS method by conjoining time periods from different patients essentially remove the key advantage of this method – self-controlling which adjusts for all

measured and unmeasured fixed confounders. This modification of the baseline period is necessary for treatment comparison when the adverse outcome is common. The original SCCS method does not produce estimates directly comparable to the RR for two competing treatment options (Analysis 1). Despite the lack of self-control, results using the modified approach appear promising. This could partly be explained by the choice of randomized data used in this study. Nevertheless, the use of randomized data is crucial, so that the feasibility of the modified SCCS approach can be ascertained without the issues of potential confounding. For application using non-randomized data, the limitation of not having self-control can be overcome by (i) prior matching of patients on all known confounders to ensure homogeneity between treatment groups; (ii) the modified SCCS method that includes multiple random matching of time periods to reduce potential bias due to mismatch. Results of this study suggest that in the comparison of treatments for a disease that has an identical causal system to the DIC disorder, the modified SCCS method with repeated random matching mechanism can be used to obtain estimates comparable to the cohort method. Yet, the choice of control period from the alternative treatment group is crucial and should be matched on all known and measured confounders before proceeding to the proposed modified SCCS analysis.

Potential studies with the objective of treatment comparison using the modified SCCS design proposed in this paper should have a causal system similar to the DIC example demonstrated here. The outcome of interest should be associated with the underlying disease being treated. Patients diagnosed with the disease should only receive one of the two competing treatment options. The key differences between the standard and modified SCCS methods are shown in Table 1.

Table 1 Characteristics of the standard and modified SCCS methods.

	Standard SCCS	Modified SCCS
Outcome	Unrelated to underlying disease being treated or prevented.	Related to underlying disease being treated
Disease	Usually absent for vaccine, present for some studies.	Must be present
Exposure	Single or multiple within individual.	Single within individual with exposure to either one of two competing treatment options.
Control	Self-control; derived from similar individual timeline. (All fixed confounders adjusted for)	Exposure period of patient receiving competing treatment. (Confounding issue presents, but can be minimized with the modification)
Sample size	Like the original SCCS method, the modified version may possibly require smaller than cohort and case control, but further validation recommended	

For the post-marketing safety surveillance of the thrombomodulin ART-123 drug, the RI of adverse events in DIC patients receiving ART-123 in comparison to other treatments can be computed using the similar idea proposed in this paper. That is, the baseline period of the ART-123 patients can be modified via repeat random matching of the exposure periods with matching patients receiving alternative drug. Although this implies that during the surveillance period, data of patients receiving other treatments are needed as well, only the information of those who reported the adverse events needs to be collected. Definition of endpoint should be in relation to the drug of interest and objective of the study. Subgroup analysis on homogeneous patients can also be attempted. Repeat exposures to similar drug, multiple drug exposures, and interaction of

drugs can also be analyzed.

This study acknowledges the limit of the small sample size (i.e., low cases of adverse events). The proposed modification should be further studied in a larger cohort for better understanding of the implication of sample size and study power. Large sample studies that employed SCCS method using prescription databases and primary care data have been reported. In Japan, study using databases such as the Diagnosis Procedure Combination (DPC) system, with linkage to the adverse drug reaction (ADR) system is likely possible. It should be noted that unlike the scenario presented in this study, in many common ADR situations, the underlying disease targeted by the drug is usually not associated with the adverse reaction reported. In such situations, the usual SCCS method can be applied with acceptable results.

6. Conclusion

A modification to the SCCS method was proposed to estimate the RI of adverse events in a context of two competing treatments wherein the adverse events are common and highly associated with an underlying disease that is critical. Results using the proposed modification are very encouraging and highly comparable to the corresponding relative risk estimates of the cohort method and randomized trial. In comparison to results of the 1-to-1 matched case-control and binary response cohort method, the results of the modified SCCS method using random matching without replacement are closer to the results of the randomized trial. Although further validation using large cohort is recommended, the study shows that with choice of proper control period and adequate number of cases, the proposed modified SCCS approach can be a viable alternative to study the association of treatment and adverse events related to the disease being treated.

Figure 2 Estimated relative incidences of bleeding related adverse events by day

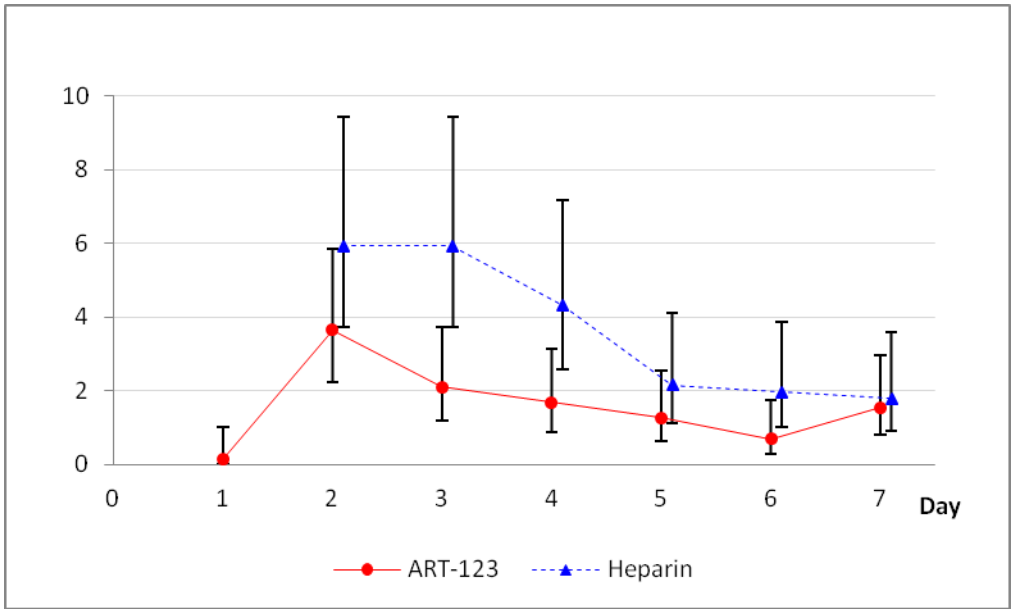


Figure 3 Estimated relative incidences of serious adverse events by day

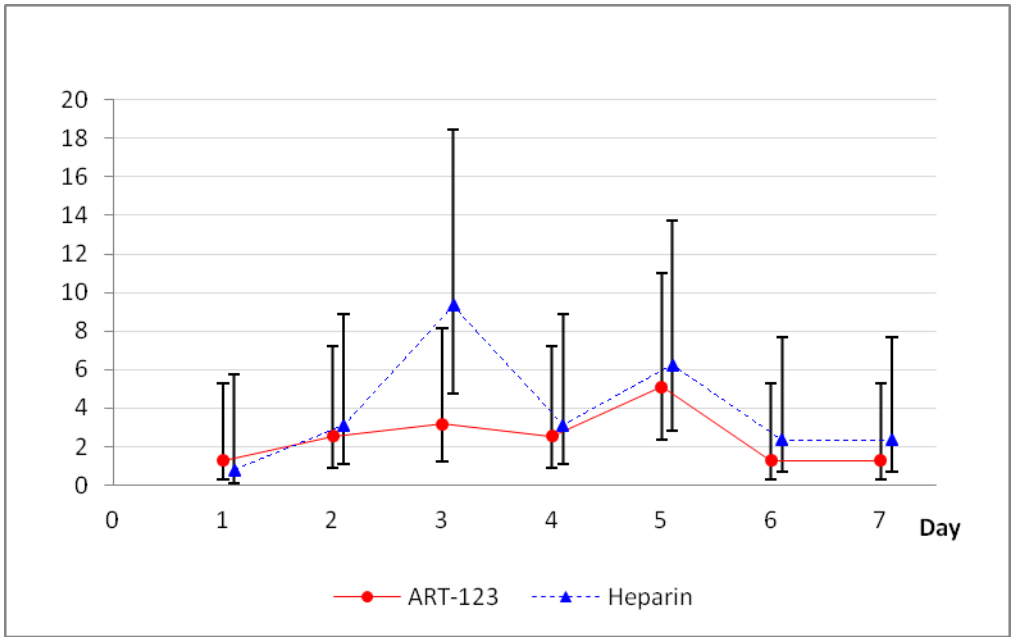


Table 2 Estimated relative risks and relative incidences of bleeding related adverse events in DIC patients.

Method		exp(β)	95% CI*	Median exp(β)	95% CI‡	Min, max	Sample size‡ (min, max)
Relative risk†	7-day	*0.763*	(0.586, 0.993)				231
	14-day	*0.806*	(0.610, 1.065)				231
Analysis 2: conjoined 7-day exposure periods							
no replacement		0.638	(0.469, 0.863)	0.636	(0.466, 0.867)	0.530, 0.806	76+76 (68, 83)
with replacement		0.692	(0.426, 1.102)	0.682	(0.403, 0.812)	0.661, 0.902	77+77 (67, 83)
Analysis 3: conjoined 14-day observation periods							
no replacement		0.795	(0.619, 1.018)	0.795	(0.621, 1.018)	0.671, 0.938	83+83 (78, 92)
with replacement		0.750	(0.548, 1.000)	0.737	(0.554, 0.979)	0.465, 1.185	86+86 (74, 93)
Analysis 4: first case only reanalysis							
for Analysis 2							
no replacement		0.765	(0.513, 1.136)	0.764	(0.511, 1.141)	0.661, 0.902	71+71 (67, 83)
with replacement		0.692	(0.426, 1.102)	0.682	(0.429, 1.084)	0.458, 1.029	74+74 (61, 89)
for Analysis 3							
no replacement		0.846	(0.591, 1.210)	0.846	(0.591, 1.212)	0.746, 0.952	84+84 (77, 90)
with replacement		0.798	(0.514, 1.224)	0.786	(0.505, 1.225)	0.544, 1.098	85+85 (74, 94)
Matched case-control design (1:1)							
7-day		0.575	(0.334, 0.984)	0.571	(0.330, 0.990)	0.448, 0.659	231
14-day		0.664	(0.365, 1.184)	0.667	(0.379, 1.174)	0.444, 0.852	231
Cohort design							
7-day		0.637	(0.448, 0.905)				231
14-day		0.789	(0.578, 1.078)				231
Cohort design with binary response							
7-day		0.583	(0.346, 0.981)				231
14-day		0.656	(0.386, 1.115)				231

* confidence intervals computed using the mean of standard errors from 300 iterations for analysis 2-4 and 100 iterations for matched case-control
‡ the corresponding confidence interval and sample size for median, rounded up whenever necessary
† results from a randomized trial (Saito et al, 2007)

Table 3 Estimated relative risks and relative incidences of serious adverse events in DIC patients.

Method		exp(β)	95% CI*	Median exp(β)	95% CI‡	Min, max	Sample size‡ (min, max)
Relative risk†	7-day	*0.828*	(0.619, 1.108)				231
	28-day	*0.920*	(0.705, 1.202)				231
Analysis 2: conjoined 7-day exposure periods							
no replacement		0.772	(0.446, 1.314)	0.774	(0.454, 1.319)	0.433, 1.174	33+33 (28, 41)
with replacement		0.605	(0.303, 1.091)	0.585	(0.312, 1.097)	0.233, 1.188	35+35 (23, 49)
Analysis 3: conjoined 28-day observation periods							
no replacement		0.961	(0.653, 1.402)	0.948	(0.654, 1.373)	0.717, 1.250	59+59 (49, 63)
with replacement		0.828	(0.513, 1.261)	0.809	(0.526, 1.243)	0.348, 2.045	58+58 (39, 70)
Analysis 4: first case only reanalysis for Analysis 2							
no replacement		0.723	(0.380, 1.361)	0.720	(0.393, 1.320)	0.500, 0.947	40+40 (28, 41)
with replacement		0.585	(0.266, 1.188)	0.563	(0.249, 1.273)	0.259, 1.200	32+32 (22, 52)
for Analysis 3							
no replacement		0.896	(0.553, 1.442)	0.890	(0.555, 1.429)	0.737, 1.097	57+57 (47, 63)
with replacement		0.776	(0.434, 1.343)	0.759	(0.436, 1.320)	0.455, 1.389	57+57 (44, 71)
Matched case-control design (1:1)							
7-day		0.645	(0.265, 1.468)	0.625	(0.284, 1.377)	0.294, 1.182	231
28-day		0.856	(0.446, 1.589)	0.850	(0.445, 1.623)	0.526, 1.375	231
Cohort design							
7-day		0.765	(0.418, 1.401)				231
28-day		0.959	(0.621, 1.483)				231
Cohort design with binary response							
7-day		0.671	(0.347, 1.294)				231
28-day		0.845	(0.490, 1.459)				231

* confidence intervals computed using the mean of standard errors from 300 iterations for analysis 2-4 and 100 iterations for matched case-control

‡ the corresponding confidence interval and sample size for median, rounded up whenever necessary

† results from a randomized trial (Saito et al, 2007)