Use of the self-controlled case series method in vaccine safety studies: review and recommendations for best practice.

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SUMMARY

The self-controlled case series method is now commonly used to investigate potential associations between vaccines and adverse events. The present paper reviews applications of the method to vaccine safety investigations in the period 1995 - 2010. In total, 40 studies were reviewed. Some of the key features of these studies are described, with the emphasis on promoting good practice.

INTRODUCTION

Evaluation of vaccine safety is an important aspect of any vaccination programme [1]. Although vaccines are tested extensively for relatively common adverse events in clinical trials before they are licensed for use, not enough people are usually included in such trials to detect adverse reactions that happen only rarely. Post-licensure studies also enable the evaluation of vaccine safety within groups such as the elderly, those with chronic medical conditions, and pregnant women, who might be deliberately excluded from clinical vaccine trials. Finally, by providing accumulating evidence of safety, they can help to maintain the public confidence needed to keep vaccination uptake high enough to prevent disease outbreaks.

Cohort and case-control study designs are commonly used to investigate vaccine safety, but confounding by variables related both to avoidance of vaccination and to the outcome of interest is a potential problem [2]. An alternative study design, the self-controlled case series (SCCS) method, often combines the power and simplicity of the cohort design and the economy of the case-control method, while eliminating confounding by all time-independent variables [3,4]. This method, which uses only information from cases, that is, individuals with an adverse event, was developed specifically for use in vaccine safety studies, but has since been applied in non-vaccine pharmacoepidemiology and in other areas of epidemiology [5]. The method is briefly described at the end of this introduction.

The purpose of this paper is to review how the SCCS method has been used in vaccine studies since its publication in 1995. Our aim is to highlight good practice, and, based on experience accumulated over the past 15 years, to attempt to give some clear direction on how the method should be used and reported. We also seek, briefly, to clarify some misconceptions about the SCCS method and how it relates to other case-only study designs. Our aims, however, fall short of developing fully-fledged guidelines on reporting SCCS studies, which require detailed consideration of other applications in pharmacoepidemiology. Nevertheless, we hope that this review will contribute towards the eventual elaboration of such guidelines.

The paper has four sections. In section 2 our review criteria and methods are described. In section 3 we present the results of our review, including specific

discussion on: data description and accuracy, choice of observation and risk periods, potential biases, comparison of SCCS with other methods such as cohort and case control, methodological issues and good practice. Section 4 is a brief discussion of our findings and areas for further research on the SCCS method. First, we set the scene with a brief description of the self-controlled case series method.

The self-controlled case series method

The self controlled case series method was originally developed to estimate the relative incidence of an acute event in a pre-defined post-vaccination risk period, compared to other times, which constitute the control period [3]. It is a conditional, retrospective, risk-interval cohort method and is applied as follows.

An overall study time-window, usually defined by age and calendar time boundaries (but also, sometimes, in terms of vaccination date), is chosen, ideally such that the chance that individuals experience both risk and control periods is maximized. Then, all or a random sample of individuals with at least one event (independent recurrences are permitted) within this study time-window are identified: these are the cases. The study time-window also determines individual observation periods for each case, namely the time spent by each individual within the study time-window (the observation periods generally differ between individuals). Next, the vaccination histories of the cases are collected: as in other epidemiological designs, ascertainment of cases must be independent of vaccination histories. The vaccination dates of each case are used to define one or more risk periods, during which individuals are hypothesized to be at increased (or reduced) risk of the event of interest after (or, for reasons to be discussed later, before) vaccination. All other time within an individual's observation period, that does not fall within a risk period, is included in that individual's control period, which form the study baseline.

Justification for using only cases stems from the analytical strategy, which conditions on the number of events each individual experiences within the observation period: this number is regarded as a fixed quantity. A consequence is that non-cases contribute no information, and therefore need not be sampled. Estimation of parameters in the SCCS method is achieved by fitting a conditional Poisson regression model (it is essential that it should be a conditional model, in order to

justify sampling only cases). The parameter of interest is the relative incidence, that is, the incidence in a risk period relative to the control or baseline periods. A tutorial is available with full practical details and worked examples [5].

A further consequence of the conditioning is that the analysis is within-individuals, and, as a result, in the SCCS method all fixed confounding factors, known and unknown, are controlled for implicitly. Temporal confounding factors, such as age can be accounted for by subdividing each individual's observation period into age categories, which are modelled explicitly. Alternatively, a semi-parametric approach, for which the age groups do not need to be specified, is available, though it is not suitable for large studies [4].

Three key assumptions are made by the SCCS method: these are (1) that events arise either in a non-homogeneous Poisson process, or are unique and uncommon over the observation periods; (2) that the occurrence of an event must not alter the probability of subsequent exposure; and (3) that the occurrence of the event of interest must not censor or affect the observation period [3 - 6]. Elaborations of the method to weaken these assumptions are mentioned in the Discussion.

METHODS

We identified self-controlled case series studies which included a vaccine as an exposure, first published (in print or electronically) between 1995, when the SCCS method was first introduced, and end 2010. We identified papers by searching for those citing references 1 – 8 in the following databases: Scopus, JSTOR, Science Direct, British Library and all those within the ISI Web of Knowledge.

We excluded all methodological papers published in statistics journals. We also excluded methodological papers published in epidemiology journals, unless they included a specific application using SCCS not reported elsewhere, and sufficient detail of this application was provided.

Each paper was reviewed against a standard form which was piloted on 13 papers. The form included details on: vaccines and adverse events studied, data collection and description, study population, sample size, observation period, age groups, the

allowance for any other temporal confounders, risk periods and their rationale, sensitivity analyses undertaken, statistical features, reporting of results, whether key SCCS assumptions were met, any good, bad or unusual practice, and comparison with other study methods used in addition to SCCS.

RESULTS

We identified 40 studies which met our selection criteria [9 – 48]. Four of these [9, 14, 17 and 20] were papers with a methodological flavour, aimed at validating a surveillance system, but including a specific SCCS application.

Figure 1 presents the distribution by year of publication of these 40 studies (references [10] and [38] appeared in 2002, even though the journals are dated 2001; reference [21] was published electronically in 2010). Thirty-eight of the 40 papers appeared in 2000 – 2010; Figure 1 suggests a moderate increase over this period. All but three studies were undertaken in high median income countries; the three outliers hail from Vietnam [9], Brazil [16] and Cuba [38].

Insert Figure 1

Vaccines and adverse events studied

Table 1 presents the vaccines and the adverse events studied. For ease of presentation, adverse events have been grouped, as for example purpura (which includes ITP, allergic purpura, and other purpura). Similarly, vaccine types (for example, intranasal and parenteral influenza vaccines) have been listed under the same heading. MMR and other measles-containing vaccines were the most frequently studied (17 studies), followed by influenza vaccines (13 studies) and vaccines containing pertussis antigens (8 studies). The sample sizes (cases or numbers of events) included in SCCS analyses ranged from the very small (7 events in one analysis in [17], 8 in one analysis in [17]) to the very large (8180 cases in [21], 22400 in [39]).

Typically, several vaccines and/or adverse events were studied at the same time. One study [37] investigated concurrency of vaccination (administration of at least two

vaccines on the same or adjacent days) as a risk factor. When several vaccines potentially related to the same outcome are administered at similar ages, their effects should be studied within the same model, as was done in [12]. This also applies to non-vaccine exposures, as with influenza vaccination and influenza-like illness in Guillain-Barré Syndrome [42]. In 22 studies, vaccines were given in multiple doses; in 12 of these, dose-specific effects were investigated.

The SCCS method can only cope with a single outcome variable at a time. The most frequently studied events were convulsion (including febrile convulsion and aseptic meningitis) and purpura (6 studies each). There were four studies of intussusception, and three each of autism and Guillain-Barré Syndrome.

Data description and data accuracy

In common with other epidemiological methods, it is essential that ascertainment of events should be independent of vaccination history; in SCCS studies, this also applies to the timing of events in relation to vaccination. A clear description of how the data were obtained is therefore important in order for the reader to be able to assess any possible dependence. All 40 studies were felt to provide sufficient detail in this respect. Sixteen obtained data on vaccinations and outcomes from a single database (of these, 7 studies used the UK General Practice Research Database and 6 the US Vaccine Safety Datalink), 14 linked two or more databases, and in 10 data were obtained from other sources.

Case note reviews were undertaken in 18 studies, and in two of these the review was commendably reported as blinded to vaccine history. In one study [12], case notes were used to identify vaccinations. This may bias results towards a positive association, in as much as vaccinations prior to event are more likely to be ascertained by case note review than vaccinations after the event. However, in this study the association was not significant, and so the ascertainment procedure in this instance leant further weight to the conclusions reached.

Most studies had full information on the day of vaccination and the day of event (studies [18] and [45] used month as the time unit for analysis, but with long risk periods). In [14] and [16], dates of vaccination were imputed rather than observed

exactly. The sensitivity to imputation errors will depend on the lengths of the risk periods used, and it would be advisable to study this by sensitivity analyses, though none were reported. In [13], vaccination dates were known exactly, but the types of vaccines used at different times were derived indirectly.

Observation periods and risk periods

A well-conducted SCCS study requires great rigour in the definition of observation periods and risk periods for each case. The observation period, in particular, must be defined so that, had an event occurred at any point within it, the case would have been ascertained. Often, the observation period is determined by a combination of calendar time and age constraints, defined precisely in the time units of the study. Risk periods are defined in terms of time since vaccination (with, preferably, a stated convention to describe the day of vaccination, for example day 0). A similarly rigorous report of these choices provides confidence that care was taken in the analysis, and enables the reader, in theory at least, to reconstruct the study exactly.

In all 40 studies, observation periods were defined with sufficient detail to reconstruct the study. The idiosyncracies of specific databases need to be allowed for appropriately in defining observation periods. Thus, some studies excluded day of vaccination (or allocated it a special parameter) owing to the fact that, in some information systems, past events are retrospectively recorded on day of vaccination; left uncorrected, this would induce spurious associations on day of vaccination. This effect is illustrated graphically in dramatic fashion in [44]. In one study in the GPRD [13], events on day of vaccination were validated by case-note review.

The risk periods were defined explicitly in all 40 studies. The choice of risk periods should be made a priori and its rationale explained. Typically, the choice will be motivated by reference to previous studies or hypotheses, as in [19] for example; by biologically plausible mechanisms [17]; or by expert opinion [30]. Inevitably, in some circumstances the choice is arbitrary, and if so this should be stated [18]. Three studies [18, 23, 28] used indefinite post-vaccination risk periods. In several studies (for example, [26]) a sensitivity analysis was undertaken by varying the risk period.

Confounders

SCCS studies adjust automatically for time-invariant multiplicative confounders. However, effect modification by fixed covariates can be investigated through interactions with the vaccine effect: for example in [21] such effects were investigated, for sex and age at start of observation.

In vaccine studies, particularly those undertaken in children, age (or in some cases season, or both) is likely to be the major confounder, and should, as a rule, be adjusted for in the analysis, unless observation periods are extremely short. Seven studies did not report using any kind of temporal adjustment; in four of these, the observation period was less than a year. Of the remaining 33 studies, 19 adjusted for age only, 3 for season only, 1 for calendar time only, 6 for age and season, 1 for age and calendar time, and 2 for age, season and calendar time (for example [24]).

Only one study [23] used the semi-parametric model [4], in which it is not necessary to specify age classes. If a parametric method of age adjustment is used, it is good practice to check that the age model used is adequate, by varying the number of age classes used. Two studies reported such sensitivity analyses [23, 39]. One study [25] controlled for age as a continuous covariate, though no details of how this was achieved were given; such a method of control is not straightforward owing to the conditioning.

Discussion of potential biases

The SCCS method makes a number of key assumptions that should be checked, as far as possible, and discussed. The main assumption, as it affects vaccine studies, is that the event should not affect the subsequent probability of vaccination. This assumption fails if the event is a contra-indication for vaccination (as with intussusception and rotavirus vaccination since the publication of [34]), or if vaccination after the event is more or less likely (as with Guillain-Barré Syndrome and influenza vaccination). A third possibility is that vaccination is deferred after (or more rarely, precipitated by) an event, so that the impact of the event on vaccination is short-lived. Nevertheless, an important feature of such biases is that their direction is predictable: if the event reduces the probability of subsequent vaccination, then the relative incidence associated with vaccination will be biased upwards.

There are three main ways of coping with such bias: including pre-vaccination 'risk' periods to allow for short-term deferral of vaccination (or indeed to investigate the presence of longer term effects); exclusion of all pre-vaccination time (so that the observation period begins with vaccination), which works provided the vaccine can only be given at most once during the projected observation period; and the use of more complex analytic techniques [49]. Of the studies reviewed, 16 used pre-vaccination 'risk' periods (see, for example [10] and [38]), and three [26, 39, 48] started observation at vaccination for some analyses.

Further sources of bias are the healthy vaccine effect, which is a form of confounding by an uncontrolled time-varying factor, and event-dependent censoring of observation periods, which occurs with events carrying high mortality – an unusual occurrence for vaccine studies. Potential biases of these and other types were discussed in several of the studies reviewed (for example, [19]).

Comparisons with other statistical methods

In addition to implementing the self-controlled case series method, 12 studies used or reported results obtained on the same data using other study designs. These included cohort, case control, and ecological methods. Table 2 presents the results obtained using SCCS and other methods, for a selection of analyses.

The results obtained using SCCS were broadly similar to those obtained by other methods, with the exception of studies of influenza vaccine and asthma exacerbation [27, 28] where the SCCS method found a protective or null effect, but a cohort analysis found a positive association. In a study of HBV vaccine and wheezing onset [33], the point estimates from SCCS and a case-control study were of the same order, but the greater precision of the SCCS method produced a statistically significant effect. The better precision of the SCCS method was also noted in another study of HBV [23], where it was pointed out that some cases cannot be used in matched case-control studies owing to lack of matching controls; the SCCS method does not suffer from this problem.

In one study [22] the alternative method was incorrectly described as a case-crossover design, when in fact it was another SCCS with a 'before and after vaccination' observation period. The distinction between SCCS and case-crossover methods [50] stems from the key fact that, in an SCCS study, exposures (in this case, vaccination) are fixed and event times random, whereas for case-crossover designs the converse is the case. The use of case-crossover methods for vaccine safety studies is discussed briefly in [1].

Methodological issues

An unusual feature of the SCCS method is that post-event time is included in the analysis. This is a consequence of the fact that the method works by conditioning, for each individual, on that person's vaccination history over the entire observation period, and on the number of events arising within that period. It follows that observation time should not be censored at the event. One study [25] did censor observation at the event, in this instance Guillain-Barré Syndrome, because patients who have had GBS may be advised not to have further immunizations. If this were the case, a standard SCCS analysis would have resulted in an overestimate of the relative incidence. Censoring at event, however, produces bias of unpredictable direction. It is not recommended unless undertaken as a secondary sensitivity analysis.

Several studies of potentially recurrent events, such as convulsions [24], ITP [32] or GBS [42], considered repeat events to be part of the same episode if separated by less than some minimum time period τ. This presents the methodological problem that, after an event, no other event can then occur for a time interval τ: an instance of immortal time, which, if included in the analysis, may result in bias [51]. Generally τ is short and repeat events are relatively uncommon, so any such bias is likely to be small. A simple approach is to do a sensitivity analysis restricted to first events, which also sidesteps the requirement for repeat episodes to be independent. One interesting study [19] excluded person-time for a period τ after each episode; however, the performance of such a strategy requires further investigation.

Several SCCS studies defined observation periods relative to the day of vaccination, either starting with vaccination and ending a fixed number of days after vaccination

[26, 48], or starting and ending some fixed number of days before and after vaccination [9, 14]. For some studies this was done for convenience of data collection. While not invalid, this approach results in short observation periods, which is not optimal, as information from events occurring at other times is not used. For a given number of events, the SCCS method is most efficient when risk periods are short in comparison to the observation period. In addition, short observation periods may include times when the risk of temporal bias is high. For example, in the case of 'before and after' studies, bias from delayed vaccination following an event may artificially depress the incidence in the period immediately preceding vaccination. This effect is very apparent on the plots of intervals between vaccination and events in [14], which shows a marked trough of hospitalizations in the week preceding vaccination (this week was, rightly, excluded from the analysis).

As explained in the Introduction, the SCCS method is derived from a Poisson cohort model by conditioning on the number of events observed, as well as on vaccination history. Thus, a conditional Poisson model must be used to estimate the parameters. Fewer than half of the 40 studies indicated that a conditional Poisson regression model was used, either explicitly (for example, [19, 21, 22]) or with words to that effect (as in [20, 48]). In a few studies it was unclear whether a conditional or unconditional model was fitted (for example [37]). The only circumstance in which an unconditional Poisson model may be used in an SCCS analysis is when all individuals have identical observation periods and vaccination histories. In this case, the conditional and unconditional methods give the same results. In two instances the method of analysis appeared somewhat idiosyncratic [14, 25].

Some further good practice

Many instances of good practice have already been mentioned and documented, such as careful reporting of risk and observation periods, clear statements of modelling choices, sensitivity analyses relating, for example, to the choice of age adjustment and the choice of risk periods, allowance (where possible) for concurrent exposures, testing for relevant interactions, analysis using contrasting methods (if possible), and the evaluation and discussion of possible biases, possibly including the use of pre-vaccination risk periods and sensitivity analyses.

Several studies (for example [16, 43, 44]) included plots showing the intervals between events and vaccination; these are useful for visualising the association between exposure and event (though they are also prone to censoring effects), and for identifying pre-vaccination troughs. Such plots are trickier to draw for multi-dose vaccines, but are useful nonetheless [34]. Other studies (for example [19, 36]) illustrated the case ascertainment procedure using a flow diagram, which presents clearly the inclusions and exclusions applied to assemble the cases, and hence can help the reader assess any biases that may have arisen in the process. Further useful plots include those illustrating the risk periods used [21, 39], of estimated age or season effects [23] and, for complex analyses with many endpoints, graphical representation of the relative incidences [13].

In some cases, power calculations may be important [8]. One study [21] reported checking the sample size required to achieve 90% power to detect at least a doubling of risk.

DISCUSSION

We identified and reviewed 40 papers which applied the self controlled case series method to vaccine studies. In general the method was applied appropriately. All 40 studies provided sufficient detail of how their data were collected, which enabled the reader to make sure that events are identified independently of vaccinations. Also, observation and risk periods were generally carefully specified. Most studies adjusted for age and/or season as appropriate.

The following key issues emerge when using the SCCS method. Ascertainment of cases and collection of data on exposure history should be independent, as bias may result if case ascertainment was influenced by knowledge of exposure status. The observation and risk periods should be clearly defined, and the choice of risk period should be justified. Where necessary, age and season effects should be allowed for, and when using the parametric model, sensitivity to the choice of age and seasonal groups should be checked. Other relevant time varying covariates (such as concurrent vaccinations and other exposures) which may be associated with both the exposure and outcome should be identified and, if possible, taken into account in the analysis. The validity of the assumptions required by the SCCS method should be carefully

considered and appropriate supplementary sensitivity analyses undertaken where these come into question.

A few papers suggest there remains a degree of confusion about what an SCCS study entails, in particular how it differs from a 'before and after vaccination' analysis or from the case-crossover paradigm. This is wholly unsurprising, owing to the somewhat abstruse and technical, yet fundamental, distinction between conditional and unconditional analyses. Nevertheless, the picture that emerges is dominated by the numerous impressive and often imaginative applications of the method.

The SCCS method has witnessed considerable methodological development aimed at weakening the assumptions it requires. Thus, methods have been developed to handle event-dependent exposures and deaths [49, 52], dependent recurrences [53], event-dependent observation periods [54]. The method has also been extended to the prospective monitoring of vaccine safety [55, 56]. This review has raised some further methodological issues worthy of further study. One such is how best to handle the 'immortal time' after an event, during which recurrences are classified as part of the same episode, and whether ignoring this effect has any substantive bearing on the results. Another is to study and quantify the bias that results from censoring observation periods at events. Sensitivity analyses may be indicated in both circumstances. Also, while the SCCS method is only applicable with a single outcome variable at a time, it may be desirable to study several outcomes jointly. A bivariate SCCS method has been suggested for the analysis of antibiotic resistance [57]; perhaps similar ideas can be used for a multivariate SCCS applied to vaccine safety, in which several possibly dependent outcomes could be studied at the same time.

Self-controlled case series analysis is a relatively new statistical methodology, and the issues that require particular emphasis and care in reporting have, therefore, only become apparent over time. The development of suitable guidelines for reporting such studies, in vaccine safety and pharmacoepidemiology more widely, may perhaps now be indicated.

DECLARATION OF INTERESTS

No financial support was received for this work. None of the authors have any financial involvement with or affiliation to any organisation whose financial interests may be affected by material in the manuscript, or which might potentially bias it.

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Table 1 *Vaccines and adverse events studied*

Vaccine	Adverse effect	Reference
Any concurrent	Hospitalization	37
DT, Td	Convulsion	12
	Myocardial infraction, stroke	39
DTP, DTaP	Convulsion	12, 17, 20, 24
	Encephalitis	47
	Immune haemolytic anaemia	36
	Wheeze onset	33
DTP/Hib, DTP/HIB/IPV	Apnoea, convulsion, crying, diarrhoea, feeding problem, fever	13
HBV	Demyelination onset	23
	Immune haemolytic anaemia	36
	Wheeze onset	33
Hib	Wheeze onset	33
Influenza	Asthma exacerbation	27, 28, 44
	Bell's palsy	35, 41
	Cellulitis or abscess, UTI	14
	COPD exacerbation	44
	Gastritis/duodenitis	22
	Guillain-Barré syndrome	25, 26, 42
	Myasthenia gravis	48
	Myocardial infraction, stroke	21, 39
MCCV	Convulsions, purpura	12
	Encephalitis	47
	Nephritic syndrome relapse	46
Measles	Acute respiratory tract infection, arthropod-borne viral fever, gastroenteritis, pneumonia, tonsillitis	9
	Autism	18, 45
MMR	Aseptic meningitis	16, 17, 31
	Autism	11, 18, 45
	Bacterial or viral infection	29, 43
	Convulsion	12, 17, 20, 31
	Encephalitis	47
	Gait disturbance	30
	Purpura	12, 17, 19, 20, 32, 40
	Wheeze onset	33
OPV	Intussusception	10, 15, 38
	Wheeze onset	33
Pneumococcal	Bell's palsy	41
	Cellulitis or abscess, UTI	14
	Guillain-Barré Syndrome	42
	Myocardial infarction, stroke	39
Rotavirus	Intussusception	34

Table 2 *Selected relative incidence (RI) estimates from self-controlled case series method and RI or odds ratio (OR) from other study designs applied to the same case data, and 95% confidence interval (CI)*

Vaccine	**SCCS**	**Other Study type**	
(adverse effect) [Reference]	**RI (95% CI)**	**Study type**	**RI or OR (95% CI)**
MMR (aseptic meningitis) [16]	30.4 (11.5 – 80.8)	Before/after ecological analysis	14.3 (7.9 – 25.7)
MMR (ITP) [19]	5.38 (2.72 – 10.62)	Cohort	3.94 (2.01 – 7.69)
Influenza (gastritis/ duodenitis) [22]	4.54 (1.90 – 10.86)	'Case crossover'*	4.33 (1.23– 15.21)
HBV (first demyelination) [23]	1.68 (0.77 – 3.68)	Case-control	1.8 (0.7 – 4.6)
DTaP (seizure) [24]	0.91 (0.75 – 1.10)	Cohort	0.87 (0.72 – 1.05)
Influenza (asthma exacerbation) [27]	0.98 (0.76 – 1.27)	Cohort	1.39 (1.08 – 1.77)
Influenza (asthma exacerbation) [28]	0.65 (0.52, 0.80)	Cohort	1.4 (1.2 – 1.5)
HBV (wheezing onset) [33]	0.41 (0.24 – 0.70)	Case-control	0.59 (0.22 – 1.59)
Oral rotavirus (intussusception) [34]	29.4 (16.1 – 53.6)	Case-control	21.7 (9.6 – 48.9)
Intranasal flu vaccine (Bell's palsy) [35]	35.6 (14.1 – 89.8)	Case-control	84.0 (20.1 – 351.9)
Concurrent vaccines (hospitalization) [37]	'identical'	Cox regression	0.90 (0.75 – 1.09)
MCCV (nephritic syndrome relapse) [46]	0.95 (0.61 – 1.47)	Before/after ecological analysis	1.05 (0.95 – 1.15)

* This description is incorrect: it is actually another SCCS (see text)

Figure Legend

Fig. 1. Distribution of vaccine studies using SCCS by year of publication.