Commentary

The self-controlled case series method for evaluating safety of vaccines

Using cases as their own controls potentially provides stronger evidence for analysing adverse events following vaccination

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doi: 10.5694/mja12.11087

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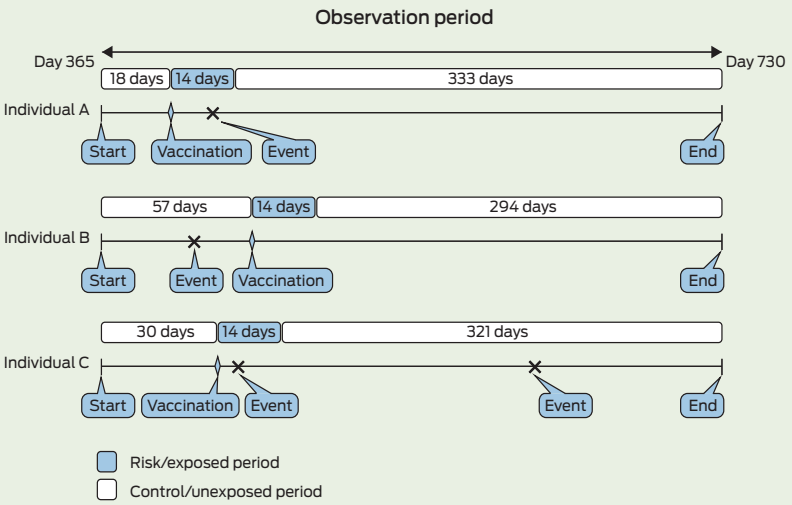
Maintaining public confidence in vaccines requires having effective postmarketing vaccine safety surveillance systems in place to rapidly address emerging concerns about vaccine safety. However, conducting studies of vaccine safety presents several challenges for traditional observational study designs. Important differences may exist between vaccinated and unvaccinated individuals that could confound the true association of interest between vaccination and adverse events. In practice, it is often difficult or impossible to adequately control statistically for these differences, either because confounders are unmeasured or unmeasureable, or because of the scarcity of unvaccinated controls when studying population-wide immunisation programs.

In this issue of the Journal, Crawford and colleagues used the self-controlled case series (SCCS) method to assess the association between pandemic (H1N1) 2009 influenza vaccination and the occurrence of Guillain-Barré syndrome.[1] The SCCS design, which was developed by C Paddy Farrington, has emerged as a gold-standard method for studying adverse events following vaccination.[2-6] In contrast to other designs such as cohort and case–control, the SCCS is a case-only design, requiring information only on individuals who have received the exposure (vaccination) and experienced one or more adverse events of interest, thus avoiding problems related to differences between vaccinated and unvaccinated individuals.

In the SCCS design, the observation time for each person is subdivided into exposed (risk) segments where it is biologically plausible that the exposure (vaccination) could cause the event, and unexposed (control) segments where it is biologically implausible that the exposure could cause the event. Each person is, in essence, compared with him- or herself in exposed versus unexposed time periods. This cancels out fixed individual factors (eg, sex, socioeconomic status) and thus completely adjusts for the effect of these potential confounders.[3,5] The incidence of events in risk and control periods is calculated by determining the number of events per person/time at risk (ie, events/day). An overall relative incidence (RI) is then calculated by obtaining the ratio of incidence levels in the risk period compared with the control period. In order to calculate valid confidence intervals for RI estimates, statistical modelling is required. The SCCS model can be fitted using a

Examples of exposure and event information for three hypothetical individuals observed between 1 and 2 years of age for a self-controlled case series study of febrile seizures following measles–mumps–rubella vaccination



Individual A experienced an event during the postvaccination risk/exposed period.
Individual B experienced an event in the control/unexposed period before the vaccination.
Individual C experienced an event in the postvaccination risk/exposed period, and a second event in the control/unexposed period long after vaccination.

Person ID	Risk or control period	Number of events	Duration of period (days)
A	control	0	18
A	risk	1	14
A	control	0	333
B	control	1	57
B	risk	0	14
B	control	0	294
C	control	0	30
C	risk	1	14
C	control	1	321

Poisson regression model, which is routinely used to model count data. The Poisson regression is stratified by individual, to allow estimation of the association between intraindividual exposure and adverse events, expressed as an RI, and appropriate confidence limits.[5]

The observation period for three individuals from a hypothetical SCCS study of febrile seizures following measles–mumps–rubella (MMR) vaccination after children reach 1 year of age is illustrated in the Box. Each child is observed between their first and second birthday (age 365 to 730 days). Febrile seizures are expected to occur within 1–2 weeks following MMR vaccination. For simplicity, we define one risk period — the 14 days immediately following vaccination. The remainder of the observation period before and after the postvaccination risk period is designated as the control period. This simplistic example illustrates the basic method; however, it is easily generalised to multiple exposures, multiple risk periods and adjustment for age and seasonal effects. This would be necessary, for example, if individuals were to receive a second MMR vaccination at 18 months.

The SCCS design has some important limitations. First, like other observational designs, it is susceptible to confounding from coincident temporal exposures (unmeasured exposures that occur during the same observation period as the exposure of interest; for example, a second vaccine given at the same time as the vaccine of interest). Second, also like other observational vaccine safety designs, the SCCS is susceptible to the healthy vaccinee effect, whereby vaccination is deferred for patients in ill health in the week preceding a scheduled vaccination. This results in vaccinated individuals appearing healthy immediately before and after vaccination, potentially washing out effects within the first few days following vaccination.[4,7,8] Third, the method is not well suited to situations where the occurrence of events truncates or curtails the duration of the exposure period (eg, death). However, extensions to the model have been developed that address these issues.[5,9-11]

The SCCS is an important method for studying adverse events following vaccination. It is well suited to use in linked health administrative data and is quick to implement, allowing safety surveillance studies to be undertaken in a short time frame. In many cases, SCCS studies can provide stronger evidence than even a large cohort study, since they provide complete control of individual-level confounders and often have as much, or more, power.[3] For more detailed information, we recommend the following website: http://statistics.open.ac.uk/sccs.

Competing interests: No relevant disclosures.

Provenance: Commissioned; not externally peer reviewed.

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