Institution: The Open University

Unit of Assessment: B10 Mathematical Sciences

Title of case study: The self-controlled case series method in pharmacoepidemiology

1. Summary of the impact

This research has profoundly influenced the practice of pharmacoepidemiology in 2008–13. The self-controlled case series (SCCS) method is particularly well-suited for working with computerised databases, which are increasingly used in epidemiology. The method has been recommended by international agencies (WHO, ECDC) and is now widely used by health practitioners within national public health agencies, including the CDC (USA), Public Health England (UK) and many other national and regional public health bodies. It has influenced practice within the private sector (notably the pharmaceutical and the healthcare industries). Use of the SCCS method has impacted on health by reducing costs, improving timeliness and improving the quality of evidence upon which policy decisions are based.

2. Underpinning research

The SCCS method was published in 1995 by Dr Farrington [3.1], who was then a statistician at the Public Health Laboratory Service, part of what is now Public Health England (PHE). Further methodological developments since 1999 at The Open University, detailed below, have extended the SCCS method's applicability and accessibility, and are central to its impact.

The method is unusual in that it requires only individuals who have experienced the adverse event of interest and thus, unlike case-control studies, does not require separate controls. Instead, each individual is used as their own control. An important consequence of this self-matching is that the method automatically controls for time-invariant confounders, thus overcoming biases associated with the selection of individuals for treatment, known as indication and channelling biases. This is particularly important when analysing data from electronic databases where covariate information is often inadequate, and which are therefore more likely to suffer from confounding biases. Because it requires only cases, the method is also simple, cheap and rapid to apply.

In 1999, the SCCS method was used to provide the first substantive evidence that the claim of an association between MMR and autism was unfounded [3.2]. The method subsequently gained greatly in prominence, generating further research by Dr Farrington, who had moved in 1998 to a Lectureship at The Open University's Department of Statistics (which later merged with the Department of Mathematics). From 1999, a sustained research programme by Dr Farrington (who was appointed Professor of Statistics in 2004) and colleagues at The Open University, including Dr Heather Whitaker (postdoc 2001–06, then Lecturer from 2006), Dr Karen Vines (Lecturer), Dr Patrick Musonda (PhD student then postdoc, 2003–07), Dr Mounia Hocine (postdoc, 2007–09) and Yonas Weldeselassie (PhD student, 2010–present) was undertaken to extend the method's applicability.

A key theme in this research has been to weaken the assumptions required by the method. This was largely in response to interest from the wider pharmacoepidemiology community, who sought to apply the method to life-changing events and in contexts where some of the assumptions may be violated [3.3, 3.5, 3.7]. A second theme of the research, led by Dr Whitaker, has been to increase the accessibility of the method by making it available in standard software, creating a dedicated website (http://statistics.open.ac.uk/sccs) and popularising the method through workshops and publications in leading medical statistics journals [3.4, 3.6].

Since 2003, this research programme at The Open University has been supported by six external research grants, and its outputs have been published in leading statistics journals. As a result, the reach and impact of the SCCS method have been greatly expanded. In 2011, Professor Farrington was awarded a Royal Society Wolfson Research Merit Award, and in 2013 he was awarded the Royal Statistical Society's Bradford Hill medal, partly in recognition of his work on the SCCS method.

Important contextual aspects of the impact are the heightened public profile of vaccine safety issues following the MMR and autism controversy, and the large-scale use of pandemic influenza vaccines. These have focused attention on the need for reliable yet rapid methods of safety evaluation such as provided by the SCCS method.

3. References to the research

3.1. Farrington, C.P. (1995) 'Relative incidence estimation from case series for vaccine safety evaluation-, *Biometrics*, vol. 51, pp. 228–35.

3.2. Taylor, B., Miller, E., Farrington, C.P., Petropoulos, M.-C., Favot-Mayaud, I., Li, J. and Waight, P.A. (1999) 'Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal association', *Lancet*, vol. 353, pp. 202–9.

3.3. Farrington, C.P. and Whitaker, H.J. 'Semiparametric analysis of case series data (with discussion)', *Journal of the Royal Statistical Society, Series C*, vol. 55, pp. 553–94.

3.4. Whitaker, H.J., Farrington, C.P., Spiessens, B. and Musonda, P. (2006) 'Tutorial in biostatistics: the self-controlled case series method', *Statistics in Medicine*, vol. 25, pp. 1768–98.

3.5. Farrington, C.P., Whitaker, H.J. and Hocine, M.N. (2009) 'Case series analysis for censored, perturbed or curtailed post-event exposures', *Biostatistics*, vol. 10, pp. 3–16.

3.6. Whitaker, H.J., Hocine, M.N. and Farrington, C.P. (2009) 'The methodology of self-controlled case series studies', *Statistical Methods in Medical Research*, vol. 18, pp. 7–26.

3.7. Farrington, C.P., Anaya-Izquierdo, K., Whitaker, H.J., Hocine, M.N., Douglas, I. and Smeeth, L. (2011) 'Self-controlled case series analysis with event-dependent observation periods', *Journal of the American Statistical Association*, vol. 106, pp. 417–26.

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4. Details of the impact

The SCCS method was widely used in 2008–2013 by health practitioners, and has been recommended by the World Health Organisation and the European Centre for Disease Prevention and Control [5.1]. Non-academic practitioners using the method include public health officials at national government-funded institutes (notably the US Centers for Disease Control and Prevention (CDC)) and epidemiologists working in the private sector, notably the healthcare and pharmaceutical industries [5.2]. The means by which the research contributed to the impact is primarily the large number of epidemiological studies using the SCCS method, alone or in combination with other methods, and relating to pressing public health issues, which were published in the medical literature over the period 2008–13.

The breadth of applications of the SCCS method demonstrates both its reach and its impact. The following two paragraphs document (non-exhaustively) the range of investigations using the SCCS method that were published in the medical and epidemiological literature in 2008–13 [5.3].

In vaccine safety studies, the SCCS method was used to study the safety of off-label vaccines in elderly populations; epilepsy and influenza vaccine; Guillain-Barré syndrome and influenza vaccines; adverse events after vaccination of premature children; febrile convulsions and childhood vaccinations; multiple sclerosis relapse and influenza vaccination; thrombocytopenic purpura and vaccinations; effectiveness of pandemic 'flu vaccine; emergency admissions and vaccinations; and metabolic disorders and vaccines.

In non-vaccine epidemiology, the SCCS method was used to investigate depression in patients with heart disease or diabetes; fracture and hypertensive drugs; adverse events and proton pump inhibitors; risks associated with antipsychotics; motor vehicle accidents and drugs; motor vehicle accidents and medications; falls and antidepressants; vascular events and invasive dental treatment; oral antibiotic prescribing and pregnancy; fractures and thiazolidinediones; oral

bisphosphonates and heart problems; and antipsychotics and stroke. The method was also used to study vascular events after infections and in chronic respiratory disease.

The benefits of using the SCCS method are:

- the ability to rapidly undertake low-cost, high-quality studies of rare conditions, using computerised databases of clinical records

- better control of time-invariant confounders than is normally possible in other study designs such as cohort and case-control studies

- to extend the range of study designs that can be carried out on the same data set, which, owing to the contrasting assumptions they make, can help throw new light on causal mechanisms.

This has led to several positive comparative reviews and recommendations involving non-academic practitioners [5.4].

The methodological advance represented by the SCCS method has helped to improve the quality and versatility of statistical methods in pharmacoepidemiology, resulting in better studies and well-informed medical decisions. Two specific examples of how SCCS methodology has had an impact on major public health issues are as follows.

- Between 2008 and 2013, the SCCS method was used by GlaxoSmithKline and the CDC to study the safety of the new Rotarix vaccine against rotavirus infection, following the withdrawal of the Wyeth RotaShield vaccine (confirmed by evidence from a 2001 study involving the SCCS method). The importance of this impact derives from the fact that, worldwide, it is estimated that more than 500,000 children under 5 years old die annually from rotavirus diarrhoea [5.5].

- In 2008–2013, several SCCS studies were undertaken to investigate the safety of influenza vaccination, notably in relation to Guillain-Barré syndrome. The issue shot to prominence in 2009 with the advent of H1N1 influenza A ('swine flu'), and the SCCS method was used by several agencies to investigate the safety of influenza vaccines against various influenza strains [5.6].

5. Sources to corroborate the impact

The pervasive use of the SCCS method has resulted in a large number of relevant sources, and a selection of these is given here.

5.1 Use of SCCS by international health agencies

World Health Organisation: Zuber, P.L.F. et al. (2009) 'Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS', *Expert Review of Vaccines*, vol. 8, pp. 705–16. See p. 708, column 2, paragraph 2.

European Centre for Disease Prevention and Control: Lopalco, P.L. et al. (2010) 'Monitoring and assessing vaccine safety: a European perspective', *Expert Review of Vaccines*, vol. 9, pp. 371–80. See p. 373, column 1, paragraphs 6–7.

5.2 Use of SCCS by public health institutes and private sector companies

For examples of use by public health bodies in the USA (Centers for Disease Control and Prevention), UK (Public Health England), Quebec (Ministry of Health), and by Kaiser Permanente (private healthcare provider) and GSK (pharmaceutical company), see Sections 5.5 and 5.6 below. Recommendations by several other public and private sector users are listed in Section 5.4 below. Other public health bodies using the SCCS method include the Robert Koch Institute, Berlin (Uphoff et al. (2011) *PLoS One*, vol. 6, e19932) and Public Health Ontario (Hawken et al. (2012) *American Journal of Epidemiology*, vol. 176, pp. 1035–42).

5.3 List of studies undertaken using SCCS

See the citations of paper [3.4] given in Section 2, from which all these examples are drawn.

5.4 Recommendations from non-academic practitioners

Authors from Johnson & Johnson, Kaiser Permanente, and BC Ministry of Health Services: Gagne et al. (2012) *Pharmacoepidemiology and Drug Safety*, vol. 21 (supplement 1), pp. 32–40.

Authors from Roche Products, Amgen and Novartis: Quartey et al. (2011) *Pharmaceutical Statistics*, vol. 10, pp. 539–47.

Author from PHE (UK): Andrews (2012) *Biologicals*, vol. 40, pp. 389–92.

Author from Institut National de la Santé et de la Recherche Médicale (Paris): Hocine, M.N. and Chavance, M. (2010) *Revue d'Epidémiologie et de Santé Publique*, vol. 58, pp. 435–40.

Authors from the US Food and Drug Administration and Kaiser Permanente (USA): Maclure et al. (2012) *Pharmacoepidemiology and Drug Safety*, vol. 21 (supplement 1), pp. 50–61.

Authors from Denver Health and Kaiser Permanente: McClure et al. (2008) *Vaccine*, vol. 26, pp.3341–5.

5.5 SCCS and new rotavirus vaccines, 2008–2013: studies by practitioners

Study by GlaxoSmithKline: Velasquez et al. (2012) *Pediatric Infectious Disease Journal*, vol. 31, pp. 736–44.

Study by the CDC: Patel et al. (2011) *New England Journal of Medicine*, vol. 364, pp. 2283–92.

5.6 SCCS and influenza vaccine safety, 2008–2013: studies by practitioners

Studies by the UK PHE: Stowe et al. (2008) *American Journal of Epidemiology*, vol. 169, pp. 382–8; Andrews et al. (2011) *Vaccine*, vol. 29, pp. 7878–82.

Study by Quebec Ministry of Health: De Wals et al. (2012) *Journal of the American Medical Association*, vol. 308, pp. 175–86.

Study by the CDC: Tokars et al. (2012) *Pharmacoepidemiology and Drug Safety*, vol. 21, pp. 546–52.

Study involving Kaiser Permanente: Greene et al. (2012) *American Journal of Epidemiology*, vol. 175, pp. 1100–1109.