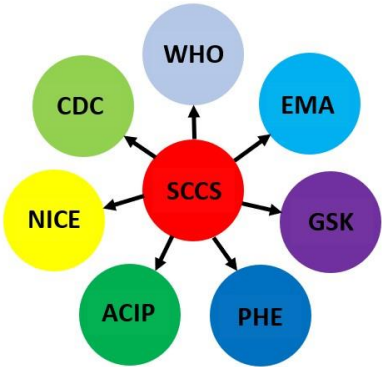


Institution: The Open University		
Unit of Assessment: B10 Mathematical Sciences		
Title of case study: Policy impacts of the Self-Controlled Case Series method in epidemiology		
Period when the underpinning research was undertaken: 1 Jan 2003 - 31 December 2011		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Paddy Farrington Dr Heather Whitaker	Professor of Statistics Senior Lecturer	1998 – 2015 2001 – 2018
Period when the claimed impact occurred: 1 August 2013 - 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact		
 <p>This impact case study documents policy impacts of the self-controlled case series (SCCS) method, a statistical design used in epidemiology. The method has contributed to shaping public health policy and advice to patients and health practitioners on the safety of vaccines and pharmaceutical drugs. Seven impacts are described, involving health organisations with global reach (see diagram). The policies, guidance and plans issued by these bodies are underpinned by epidemiological studies that rely on innovative statistical methods developed at the Open University.</p>		
2. Underpinning research		
<p>The self-controlled case series (SCCS) method is used to study the association between an exposure, such as vaccination or taking a pharmaceutical drug, and an adverse health event. It is a case-only method, so called because it requires data only on cases, that is, individuals who have experienced the adverse event. Control is achieved within individuals, with the result that time-invariant confounders (which may otherwise distort the association between exposure and outcome) are automatically adjusted. These are the two key features of the method that account for its popularity.</p> <p>The method was first developed by Farrington, who maintains an active link with The Open University (OU) as Emeritus Professor. The research undertaken at the OU from 2003 has embedded the method as a standard tool in pharmacoepidemiology.</p> <p>Two themes guided this research. The first was to ground the method in statistical theory. The major advance in this respect is [O1] (a 'Read Paper' to the Royal Statistical Society), which sets out a semiparametric SCCS model and makes explicit the assumptions upon which it is based. An important step was to develop an SCCS model for endogenous exposures; applicable, for example, when the adverse event of interest is a contraindication for vaccination. This new model, described in [O4], is based on the theory of unbiased estimating equations rather than maximum likelihood. Another development was the SCCS model in [O6] that applies when the observation period depends on the event, as is the case when the event increases mortality. This new model uses a 2-step estimation procedure.</p> <p>The second theme of the research was to enhance the accessibility of the methods developed in [O1] by making them available in standard software [O2], describing them in less technical terms [O2, O5], and obtaining simple mathematical expressions for sample sizes [O3]. [O2] has received well over 500 citations according to Google Scholar and, as illustrated below, is the standard reference for applied work using SCCS.</p>		

3. References to the research

- O1. Farrington, C.P., and Whitaker, H.J.** (2006) Semiparametric analysis of case series data (with discussion), *Journal of the Royal Statistical Society, Series C* 55(5): 553–94. <https://doi.org/10.1111/j.1467-9876.2006.00554.x>
- O2. Whitaker, H.J., Farrington, C.P., Spiessens, B., and Musonda, P.** (2006) Tutorial in biostatistics: the self-controlled case series method, *Statistics in Medicine* 25(10): 1768–98. <https://doi.org/10.1002/sim.2302>
- O3. Musonda, P., Farrington C.P., and Whitaker H.J.** (2006) Sample sizes for self-controlled case series studies. *Statistics in Medicine* 25(15): 2618-31. <https://doi.org/10.1002/sim.2477>
- O4. Farrington, C.P., Whitaker, H.J., and Hocine, M.N.** (2009) Case series analysis for censored, perturbed or curtailed post-event exposures, *Biostatistics* 10(1): 3–16. <https://doi.org/10.1093/biostatistics/kxn013>
- O5. Whitaker, H.J., Hocine, M.N., and Farrington, C.P.** (2009) The methodology of self-controlled case series studies, *Statistical Methods in Medical Research* 18(1): 7–26. <https://doi.org/10.1177/0962280208092342>
- O6. 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* 106(494): 417–26. <https://doi.org/10.1198/jasa.2011.ap10108>

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Farrington (PI). *Development of the self-controlled case series method for evaluating vaccine safety.* Wellcome Trust 2003-06; GBP112,000.

Farrington (PI). *Validation and extension of the self-controlled case series method.* EPSRC CASE Studentship with GSK 2003-06; GBP45,000 (EPSRC) plus GBP24,000 (GSK).

Farrington (PI). *Prospective surveillance of vaccine safety by case series analysis.* MRC 2006-07; GBP70,000.

Farrington (PI). *New statistics for the self-controlled case series method.* EPSRC 2007-10; GBP236,000.

Farrington. *Statistical methods for pharmacoepidemiology and infectious disease epidemiology.* Royal Society Wolfson Research Merit Award 2011-15; GBP10,000 per annum salary uplift.

Farrington (PI 2014-15) and Whitaker (PI 2015-17). *Software tools and online resources for the self-controlled case series method and its extensions.* MRC 2014-17; GBP330,000.

In 2013 this body of work contributed to the award to **Farrington** of the Bradford Hill Medal by the Royal Statistical Society. The Medal is awarded for “*outstanding or influential contributions to the development, application or exposition of medical statistics*”.

4. Details of the impact

Seven impacts of this research are described, all in the field of pharmacoepidemiology. Impacts 1 to 3 relate to public health policy development; impacts 4 to 6 relate to health information to patients and medical practitioners; impact 7 relates to COVID-19 vaccines. As with all statistical methodology, impact pathways are indirect: SCCS methodology is used in epidemiological studies, which then influence health policy.

Impact 1. WHO policy update on rotavirus vaccination worldwide, 2018

The World Health Organisation (WHO) issues regular updates on vaccination policy, which influence public health policy and practice worldwide, particularly in countries with limited public health infrastructure. This impact relates to WHO policy on rotavirus vaccine. The first rotavirus vaccine was withdrawn in 2000 because it caused intussusception (telescoping of the bowel). This was a major setback because acute gastroenteritis (AGE) from rotavirus infection caused some 440,000 deaths each year in children aged under 5 years, mainly in low-income countries [C1, p.2]. New vaccines were developed and were recommended by WHO’s Global Advisory Committee on Vaccine Safety. Deaths from AGE have since dropped by 36% in the 100+ countries using these vaccines [C1, p.10].

The safety of these new vaccines was investigated in post-licensure epidemiological studies. Following a thorough review of this evidence, the WHO's Global Advisory Committee on Vaccine Safety published the following advice in 2018: "*Overall, the Committee continues to be reassured that the benefit of rotavirus vaccination in preventing severe diarrhoea is greater than the small potential risk of intussusception identified in most, but not all post-licensure studies*" [C2 p.21].

The evidence underpinning this policy statement was, in large part, obtained from SCCS studies based on the underpinning research. Evidence from low-income countries was obtained from a large multi-centre SCCS study in 7 African countries [C3]; provisional data from an ongoing SCCS study in South Africa were also considered. Evidence from medium to high income countries was obtained from a systematic review that included 8 SCCS studies [C4]. All these SCCS studies were based on (and in 6 cases directly reference) the underpinning research, notably [O2-O5]. The methodological advance in [O4] is particularly relevant, as occurrence of intussusception can preclude subsequent rotavirus vaccination in some settings.

Thus, OU research on the SCCS method contributed significantly to the epidemiological studies upon which this important WHO policy update is based.

Impact 2. CDC guidelines on influenza vaccination, 2016

The US Centers for Disease Control and Prevention (CDC) issue guidelines on vaccination policy, based on recommendations drawn up by the Advisory Committee on Immunization Practice (ACIP). These guidelines determine vaccination practice in the USA. The 2016 guidelines on influenza vaccine policy are based on evidence that includes a substantial contribution from SCCS studies. The evidence review states: "*A self-controlled case series study conducted through medical record review of over 17,000 persons aged ≥ 18 years who had experienced a stroke found a reduction of 55% in the risk for stroke in the first 1-3 days after vaccination; subsequent reductions were 36% at 4-7 days, 30% at 8-14 days, 24% at 15-28 days and 17% at 29-56 days*" [C5 p.13]. The review also refers to 7 further SCCS studies undertaken to investigate the association between influenza vaccination and Guillain-Barré Syndrome (GBS), a form of paralysis that is of major concern with some influenza vaccines. It is concluded that "*As a precaution, persons who are not at high risk for severe influenza complications...and who are known to have experienced GBS within 6 weeks of influenza vaccination generally should not be vaccinated*" [C5 p.22].

The 8 SCCS studies referred to in this report are based on (and in 5 cases directly reference) the underpinning research, notably [O2] and [O3]. Thus, OU research on the SCCS method contributed significantly to some of the key epidemiological studies underpinning these CDC guidelines, notably those on GBS.

Impact 3. Methodological guidance from ENCePP, 2020

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) is a public-private partnership to strengthen the monitoring of pharmaceutical products in Europe. It is coordinated by the European Medicines Agency; in 2019 it comprised 183 centres and 26 networks across 20 European countries.

The ENCePP Methodological Guide (revision 8, July 2020) aims to improve the quality of the epidemiological evidence on the benefits and risks of pharmaceuticals. The introduction states that the Guide "*does not describe traditional study designs [...] but it discusses important aspects of more recent designs such as the self-controlled case series (SCCS) design*" [C6 p.7]. Detailed advice on the SCCS method, explicitly and extensively mentioning the underpinning research, notably [O2] and [O4], is provided in the sections on case-only designs [C6 p.34].

Thus, ENCePP recommends the underpinning research on the SCCS method to its network.

Impact 4. Package insert for GSK's Menveo™ vaccine, 2020

Menveo™ is a vaccine against meningitis for use in persons aged over 2 years. It is manufactured by GlaxoSmithKline, the market leader for meningitis vaccines; global turnover for Menveo™ in 2019 was GBP267,000,000 [C7, p.25 and p.262]. The package insert for the

vaccine, approved by the US Federal Drugs Agency, was altered in 2017 to include the results of a SCCS study using OU research which revealed an association with Bell's Palsy (a type of facial paralysis), thus providing vaccine users and vaccinators with a fuller picture of the safety profile of the vaccine.

The latest (2020) version of the FDA-approved package insert reads: "*Using a **self-controlled case series method**, Bell's palsy showed a statistically significant increased risk in the period 1 to 84 days post vaccination compared with the control period, with an overall adjusted relative incidence of 2.9 (95% CI: 1.1 – 7.5)*" [C8 pp.17-18]. Thus, OU research on the SCCS method contributed explicitly to this update to the Menveo™ package insert.

The lead author of the SCCS study referred to in [C8] has indicated that [O2] was "*the most helpful*" statistics reference used to conduct the study. This correspondence is listed as [C9]. The research collaboration between the OU and GSK is also pertinent. The 3rd author on reference [O2] worked for GSK; the collaboration was further enhanced by a CASE studentship.

Impact 5. CDC parent information sheet on Gardasil™ vaccine, 2016

Gardasil™ protects against human papillomavirus, which causes cervical cancer. Manufactured by Merck, this vaccine is the market leader; sales in 2019 were USD3,700,000,000 [C7, p.321].

The impact relates to a parent information leaflet published by the US Centers for Disease Control and Prevention (CDC) regarding this vaccine [C10]. The leaflet reviews the safety evidence, and states: "*A 2014 study that included over 1 million women found Gardasil was not associated with venous thromboembolism, also called VTE or blood clots*" and "*A 2015 study found women and girls who received Gardasil were not more likely than those who were unvaccinated to develop multiple sclerosis (MS) or other similar diseases*" [C10, p.2].

Both these studies are SCCS studies that reference [O2] for the statistical methods used and are thus based on the underpinning research from the OU, which thus contributed significantly to the evidence upon which this CDC information sheet was based.

Impact 6. NICE Medicines Evidence Commentary on antipsychotic drugs, 2016

The UK National Institute for Health and Care Excellence (NICE) provides evidence-based guidance to contextualise important new information. The present Commentary [C11] relates to the risk of myocardial infarction with antipsychotic drugs. The new information is a systematic review and meta-analysis of 9 studies, which includes two SCCS studies based on the underpinning research. The Commentary concludes that the new evidence "*highlights the importance of continuing to follow current advice that antipsychotic medicines should be used with caution in people with cardiovascular disease*" [C11, p.2].

The two SCCS studies reference [O2, O4, O5, O6] for the statistical methods used. Thus, OU research on the SCCS method contributed to the epidemiological evidence upon which this NICE Evidence Commentary is based. The methodological innovation in [O6] is particularly important as myocardial infarction may censor the observation periods.

Impact 7. PHE strategy for COVID-19 vaccine safety evaluation

Public health bodies worldwide are developing plans for the evaluation of the safety of COVID-19 vaccines, using the SCCS method, once these vaccines are in widespread use. Specifically, Public Health England (PHE) has prepared a detailed strategy for evaluating the safety of these vaccines. This document lists self-controlled case series studies among the methods to be used for verifying safety signals: "*There are a range of data sources which PHE will utilise to evaluate and test a signal. These include GP data [...]. Analyses will include cohort, case-control and **self-controlled case series** designs... For hospitalised conditions [other datasets] can be used... Methods employed here typically include the **self-controlled case-series** and case-coverage methods*" [C12, p.8].

This reflects the prominence achieved by the SCCS method as a result of research in [O1-O6].

5. Sources to corroborate the impact**C1.** Rotavirus death rates and efficacy of vaccine:

- A Rotavirus death rates: Parashar U.D. et al, (2003). Global Illness and Deaths Caused by Rotavirus Disease in Children. *Emerging Infectious Diseases* 9(5): 565-72. [pp. 2-8]. <https://doi.org/10.3201/eid0905.020562>
- Efficacy of Rotavirus vaccine: Burnett E. et al, (2020). Global Impact of Rotavirus Vaccination on Diarrhea Hospitalizations and Deaths Among Children <5 Years Old: 2006–2019, *Journal of Infectious Diseases* 222:1731–39. [pp. 9-18]. <https://doi.org/10.1093/infdis/jiaa081>

C2. World Health Organisation 2018. Rotavirus vaccine safety update. *Weekly Epidemiological Record* January 19th 93(3), 19-21. Available from <https://apps.who.int/iris/handle/10665/259874>

C3. Tate J.R., Mwenda J.M., Armah G. et al (2018). Evaluation of intussusception after monovalent rotavirus vaccination in Africa. *New England Journal of Medicine* 378: 1521-1528. <https://doi.org/10.1056/NEJMoa1713909>

C4. Soares-Weiser K. et al (2017). Update of a systematic review and meta-analysis of the safety, effectiveness and efficacy of childhood schedules using Rotavirus vaccines. *Cochrane Response*. Downloaded on 27/10/20 from www.who.int/vaccine_safety/publications/WHO_Rotavirus_vaccines_systematic_review_Cochrane.pdf

C5. Grohskopf LA, Sokolow LZ, Broder KR et al (2016). Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices – United States, 2016-17 influenza season. *MMWR Recommendations and Reports* 65(5). <http://dx.doi.org/10.15585/mmwr.rr6505a1>

C6. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). *Guide on Methodological Standards in Pharmacoepidemiology* (Revision 8). EMA (2020). Downloaded on 27/10/20 from www.encepp.eu/standards_and_guidances

C7. Vaccine sales figures:

- Menveo sales figures: GSK Annual Report 2019 p. 262. [pp. 2-318].
- Gardasil sales figures: Merck Annual Report 2019 p. 2. [pp. 319-454].

C8. FDA-approved Menveo™ package insert (July 2020 revision). Downloaded on 27/10/20 from www.fda.gov/media/78514/download

C9. Testimonial from lead author of postmarketing observational safety study referred to in [C8], dated 15 May 2019.

C10. Information leaflet: HPV Vaccine is Safe – (Gardasil). Published by CDC, 2016. Downloaded from www.cdc.gov/vaccinesafety/pdf/data-summary-hpv-gardasil-vaccine-is-safe.pdf 27/10/20.

C11. National Institute for Health and Care Excellence (2016). Medicines Evidence Commentary: The risk of myocardial infarction with antipsychotics. Downloaded from arms.evidence.nhs.uk/resources/hub/1057872/attachment on 27/10/20.

C12. PHE COVID-19 vaccine surveillance strategy (Version 1). Downloaded from <https://www.gov.uk/government/publications/covid-19-vaccine-surveillance-strategy>