Project Details	
Project Code	MRCPHS25Ba McDonald
Title	Causal inference tools to study vaccines using real-world data: how can we make better use of negative control outcomes?
Research Theme	Population Health Sciences
Summary	Vaccination saves lives! Observational vaccine studies are important to assess real-world effectiveness and safety, but people who receive vaccines differ from those who do not, so confounding is a major challenge. Negative control outcomes, which share the same confounding structures as the outcome but are not related to vaccination, have the potential to identify and address confounding. This PhD will develop and test negative control outcomes for vaccine safety or effectiveness studies and demonstrate their use in a study using electronic health records. This will improve research methods to support evidence-based policy-making and public trust in vaccine research.
Description	**Research question**: Can negative control outcomes address bias in vaccine studies, and what should be best practice for their use? **Background** Vaccines have saved an estimated 154 million lives worldwide over the last 50 years – one every six minutes.(1) Rigorous vaccine research is vital for public trust.[2] Before licensing, vaccines are tested in clinical trials. Once in general use, observational studies assess real-world vaccine effectiveness (for example against new strains of disease) and any safety signals, as rolling vaccines out to a large population may uncover rare adverse events.[3] Anonymised electronic health records are a key data source.[3,4] A major challenge for observational vaccine studies is confounding, as people who receive vaccines are different from those who do not. Furthermore, much confounding is unmeasured, such as quality of healthcare access. Modern study designs such as self-controlled case series and test-negative case-control studies can address unmeasured confounding, but only when specific assumptions are met.[4,5] There is a need for other methods to address confounding bias in vaccine studies. Negative control outcomes are a promising way to detect and address bias from unmeasured confounding. For example, if influenza vaccination is estimated to be effective outside the influenza season this suggests bias.[6] Difference-in-difference analysis with a negative control outcome can produce estimates adjusted for unmeasured confounding.[7] Negative control outcomes also require assumptions – they should not be causally affected by the exposure (vaccination), and should share the same confounding structures as the outcome of interest. The suitability of a potential negative control is therefore specific to the research question.[6,8] There is a shortage of research assessing negative control outcomes for vaccine studies, and those used (such as falls and non-infection-related hospitalisations) are controversial.[9,10] Time periods immediately before or after vaccination may be suitable,[11] but may be affected by atypical outcome rates as vaccination is deferred when people are acutely unwell.[12] Methodological developments in electronic health

record research means that the assumptions about relevant confounding structures could now be tested, using proxy markers of characteristics not directly measured, such as health-seeking behaviour and healthcare access.[13] This PhD will address this research gap.

Observational studies of vaccine effectiveness and safety using electronic health records guide national and international vaccine policy. This PhD will develop validated negative control outcomes for vaccine studies using electronic health records, and demonstrate their use. This will improve the robustness of vaccine research, generating better evidence to support policy-making and public trust in vaccines.

Aim and objectives

This research will aim to develop and validate the use of negative control outcomes in observational vaccine studies using electronic health records, and conduct an example study using a negative control outcome to identify and address confounding bias.

Objectives:

1. Conduct a scoping review of negative controls outcomes in observational vaccine studies.
2. Develop and apply criteria for assessing suitability of negative control outcomes in vaccine studies using real-world data.
3. Conduct an observational study using electronic health records to investigate the suitability of negative control outcomes for vaccine studies.
4. Conduct an observational study of vaccine effectiveness or safety using a negative control outcome to detect bias, and difference-in-difference analysis to adjust for confounding bias.

Opportunities to shape the project

The student will be supported to develop their area of interest within vaccine epidemiology throughout the PhD. The student's Prep period, training plan, conference attendance, and Broadening Horizons placement will be developed together with the student to reflect their training needs and career interests.

In the Prep period, the student will have the opportunity to meet researchers across a range of vaccine-related research areas, at both Universities and across the supervisors' research and policy networks. The supervisors will support the student to select a policy-relevant research question of vaccine safety or effectiveness as a focus for objectives 2 and 3, shaped by the student's interests. These could range from current policy questions such as the safety of existing vaccines such as COVID-19, or the effectiveness of recombinant shingles vaccine for people with immunosuppression to support recommendations on booster doses; through to preparing research methods to support upcoming changes in the UK vaccination schedule such as the introduction of chickenpox and respiratory syncytial virus (RSV) vaccines.

References

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