PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Ecological assessment of the direct and indirect effects of routine rotavirus vaccination in Merseyside, UK using data from multiple health systems: a study protocol
AUTHORS	Hungerford, Daniel; Vivancos, Roberto; French, Neil; Iturriza-Gomara, Miren; Cunliffe, Nigel

VERSION 1 - REVIEW

REVIEWER	Evan Anderson Emory University School of Medicine USA
REVIEW RETURNED	23-Sep-2014

GENERAL COMMENTS	Hungerford et al. describe their planned ecological study of the direct and indirect effect of routine rotavirus vaccination upon the burden of rotavirus and viral gastroenteritis in Merseyside UK. This manuscript details the plans to conduct this large multifaceted study. I am personally not in favor of publishing papers that detail a planned study since the final iteration of the study often differs in its actual methods and results. The proposed study, although methodologically sound, does not add much to the current rotavirus literature. The tense of the verbs throughout the manuscript should be consistent. In some places it is stated as "will or will be", in other places it is stated as past tense. The manuscript should be clear in the abstract that this is a paper publishing the methods of a study that will be conducted in the future. This is not clear in the abstract or manuscript itself until well into the manuscript. Deprivation needs to be better defined as to what this means since this is not an intuitive term to those potentially reading this manuscript from outside the UK. Please use consistent terminology of either "indirect effect" or "herd effect" but do not mix and match the use of the terms throughout the manuscript. On page 4, lines 95 - 97, they list the rates of what appears to be all-cause viral gastroenteritis in the UK. Notable, I do not think that these are the rates of rotavirus gastroenteritis (and would be much higher than US rates), but these are the numbers used for power calculations later in the manuscript on page 11. I do not think that these will apply to these power calculations since rotavirus gastroenteritis is just a subset of all viral gastroenteritis. Lopman et al. were unable to demonstrate much impact upon the adult

	population until several years out from vaccine implementation (see Lopman JAMA 2013), and even then they had trouble identifying this definitively in the oldest populations. Page 5, line 114: Additional details of Merseyside should be provided. How stable is this population? This study has aspects of being a population-based study, but how certain are the authors that study participants only receive healthcare in Merseyside? Are there individuals, particularly children, who get transferred out of Merseyside for a higher level of hospital-based care? In the methods, the authors should be more clear about what is defined as AGE and RVGE. Are these clinically defined or ICD10 coding defined (like other outcomes)?How reliable are rotavirus vaccine coverage estimates? Have these been validated? US data had a transitional year in 2007 as vaccine uptake was occurring in which there was perhaps a very mild blunting of the burden of rotavirus disease. In this manuscript the authors just state that they will use 3 years of data, have they planned for this in their data analysis? Page 9, are the "rates" in the data analysis population based rates? Again, this raises the question regarding the extent to which this is a population-based study. The authors should be more explicit in stating that it is RV1 which is being implemented and that the study is being sponsored by GSK.

REVIEWER	Carl Kirkwood Murdoch Childrens Research Institute Australia
REVIEW RETURNED	10-Oct-2014

GENERAL COMMENTS	The manuscript by Hungerfield et al describes a protocol to undertake an ecological study of the impact that the introduction of rotavirus vaccination has had on diarrhoeal disease in one setting of the UK. This manuscript clearly describes a protocol and includes no data. It is well designed and plans to investigate a period of 3 years pre and post vaccine introduction, so infact data colection will not be completed until late 2016 at the earliest. Importantly the protocol proposes to capture a range of diarrhoeal cases, from mild/moderate to severe cases which require hospitalisation. This is an important aspect of the study as most published studies investiagate severe cases. How confident are the authors that capture of mild/moderate cases is possible. Is data readily available and accessable for the walk-in centres? How will sampels be collected and tested for rotavirus? The study assumes that vaccine coverage will reach the predicted 90+% as observed for other vaccines. It is unclear if RV vaccines are part of actual routine administration and what actual uptake will be in first 3 years. How will authors handle data if a lower vaccine uptake occurs? The manuscript is very well written and protocol is clear and well

	defined.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Dear Professor Anderson,

On behalf of all the authors thank you for agreeing to review our study protocol. The comments you have provided are extremely helpful and have identified some important issues. I hope in our response below we have addressed any concerns you may have about the paper.

The proposed study, although methodologically sound, does not add much to the current rotavirus literature.

We believe the benefits of this study are three fold. Firstly no study has yet been conducted in the UK, and it is essential that the real world impact of a new vaccine be assessed in a new setting. Secondly, we are able to access health data from wide range of sources covering the full spectrum of secondary and primary care services. This will provide a valuable insight into the burden of rotavirus GEI pre and post vaccine and how this relates to different aspects of the health service, i.e. does RVV affect total disease burden or is the burden of disease shifted to milder presentations and therefore appearing in other health service delivery settings. Thirdly, we intend that this protocol would be used as a template for future vaccine evaluation studies in the UK, providing much needed guidance on what can be achieved with routine secondary data and where to access it.

The tense of the verbs throughout the manuscript should be consistent. In some places it is stated as “will or will be”, in other places it is stated as past tense.

We agree that this is an issue and have now used future tense throughout.

The manuscript should be clear in the abstract that this is a paper publishing the methods of a study that will be conducted in the future. This is not clear in the abstract or manuscript itself until well into the manuscript.

We have added a sentence to the abstract (lines 30-31) and the title now identifies that this is a study protocol. The above mentioned changes to future tense should also assist.

Deprivation needs to be better defined as to what this means since this is not an intuitive term to those potentially reading this manuscript from outside the UK.

We have added more detailed information on the measure of deprivation (lines 181-183). We have also been more specific in our terminology using the term socioeconomic deprivation and have changed this throughout the manuscript.

Please use consistent terminology of either “indirect effect” or “herd effect” but do not mix and match the use of the terms throughout the manuscript.

We have changed the terminology to indirect effect with herd in parentheses for the first occurrence.

On page 4, lines 95 - 97, they list the rates of what appears to be all-cause viral gastroenteritis in the UK. Notable, I do not think that these are the rates of rotavirus gastroenteritis (and would be much higher than US rates), but these are the numbers used for power calculations later in the manuscript

on page 11. I do not think that these will apply to these power calculations since rotavirus gastroenteritis is just a subset of all viral gastroenteritis. Lopman et al. were unable to demonstrate much impact upon the adult population until several years out from vaccine implementation (see Lopman JAMA 2013), and even then they had trouble identifying this definitively in the oldest populations.

Our mistake in line 95-97 (now line 103) these are figures for AGE, this has been edited in the text. We understand that the low numbers of RVGE admissions in older age groups precludes us from using RVGE in older children and adults as an outcome measure. We are therefore measuring viral gastroenteritis and using this for our power calculations. As can be seen from the power calculations we have assumed a very small change in hospitalisations in adults and intend to measure this over three years, it is indeed possible that we will be unable to detect a change over three years but measuring this is critical regardless of detecting a significant change. Like Lopman's paper it will be interesting to determine if an indirect effect develops over time. Additionally we have added a power calculation for GP consultations for the identified syndromic indicators (lines 245-248).

Page 5, line 114: Additional details of Merseyside should be provided. How stable is this population? This study has aspects of being a population-based study, but how certain are the authors that study participants only receive healthcare in Merseyside? Are there individuals, particularly children, who get transferred out of Merseyside for a higher level of hospital-based care?

Merseyside is a UK metropolitan borough of 1.4 million population. Health care for the population is self contained within the region, including a specialist paediatric hospital. We have added more detail to lines 144-146. For the population of Merseyside we are able to access A&E and hospital records regardless of where their care is given. So we will have care records for all Merseyside residents who have been hospitalisation and/or attended ED. We have added this detail to lines 160-161. For GPs, we will only have access to Merseyside residents who are registered with a GP in Merseyside, so it is possible that Merseyside residents use GPs outside of Merseyside for their care. For Walk-in-Centres we will only have access to data on residents of Merseyside that have attended walk-in-centres in Merseyside.

In the methods, the authors should be more clear about what is defined as AGE and RVGE. Are these clinically defined or ICD10 coding defined (like other outcomes)?How reliable are rotavirus vaccine coverage estimates? Have these been validated?

The definition of AGE and RVGE is dependent on the data source, for hospital admissions ICD10 coding is used to define both AGE and RVGE.
Rotavirus vaccine coverage estimates come from the Child Health Information System (CHIS). CHIS has been used for a number of years as a means of recording and reporting on uptake of routine childhood vaccine uptake both locally and for national reporting (https://www.gov.uk/government/statistics/cover-of-vaccination-evaluated-rapidly-cover-programme-2013-to-2014-quarterly-figures). Records of doses of vaccinations given as part of the UK childhood vaccine schedule are recorded in CHIS for each child. Routinely scheduled (rotavirus included) immunisations are checked weekly by a dedicated team to keep CHIS up to date (lines 185-186). Data validation for MMR locally has indicated that CHIS is likely to slightly underestimate vaccine uptake (1%-1.5% lower) but this vaccine is subject to catch-up campaigns and immunisations during a recent outbreak. Therefore, rotavirus vaccine uptake data should not be subject to these issues.

US data had a transitional year in 2007 as vaccine uptake was occurring in which there was perhaps a very mild blunting of the burden of rotavirus disease. In this manuscript the authors just state that they will use 3 years of data, have they planned for this in their data analysis?

We have already identified in the UK that vaccine uptake reached high levels of uptake >90% (for 1 dose) for the first rotavirus season post vaccine introduction (lines 93-94). We include vaccine uptake by month for any analysis and will also adjust for proportion susceptible (unvaccinated) under 5 years of age, based on the cohorts of children in CHIS.

Page 9, are the "rates" in the data analysis population based rates? Again, this raises the question regarding the extent to which this is a population-based study.

Yes they are population based rates, we have made this explicit in the text.

The authors should be more explicit in stating that it is RV1 which is being implemented and that the study is being sponsored by GSK.

We have added to the background (line 115)and start of the methods(line 122) that the RV1 vaccine was implemented in the UK. This is also specified in lines 83-84. We have also added more detail of GSK funding to the footnotes (349-358).

Reviewer 2

Dear Dr Kirkwood,

On behalf of all the authors thank you for agreeing to review our study protocol. We appreciate the positive remarks you made about the current manuscript and your comments to help us improve this manuscript. Hopefully our response below and edits to the manuscript will satisfy your queries.

How confident are the authors that capture of mild/moderate cases is possible. Is data readily available and accessible for the walk-in centres? How will samples be collected and tested for rotavirus?

Routine testing of stool samples for rotavirus is not undertaken/recommended in primary care and in walk in centres. For these settings we will therefore be relying on syndromic indicators to identify AGE cases. Data for A&E and GP are accessible and we have identified the coding required to identify AGE cases and are currently pursuing a similar process for Walk-in-Centre data. We will not be actively encouraging change to the process of clinical management/investigation of AGE at present.

The study assumes that vaccine coverage will reach the predicted 90+% as observed for other vaccines. It is unclear if RV vaccines are part of actual routine administration and what actual uptake will be in first 3 years. How will authors handle data if a lower vaccine uptake occurs?

Rotavirus vaccination is part of the routine childhood vaccination schedule across the UK. We have made it more explicit in the background (line 82), abstract (line 26) and methods.
Initial reports of vaccine uptake of rotavirus vaccine in the UK show 93% for 1st dose and 88% for the 2nd dose (lines 93-94). We therefore anticipate that vaccine uptake will at a minimum maintain this level. However, we expect it to increase over the three years to a similar level (~94% for 2 doses) to other routine childhood immunisation given at the same time point. We intend to uses monthly uptake figures in any analysis to take into account changes in vaccine coverage.