Author’s response to reviews

Title: Rotavirus vaccine impact and socioeconomic deprivation: an interrupted time-series analysis of gastrointestinal disease outcomes across primary and secondary care in the UK.

Authors:

Daniel Hungerford (d.hungerford@liverpool.ac.uk)
Roberto Vivancos (roberto.vivancos@phe.gov.uk)
Jonathan Read (jonathan.Read@lancaster.ac.uk)
Miren Iturriza-Gómara (miren@liverpool.ac.uk)
Neil French (french@liverpool.ac.uk)
Nigel Cunliffe (niglec@liverpool.ac.uk)

Version: 1 Date: 14 Nov 2017

Author’s response to reviews:

Response to Reviewer’s Comments

On behalf of all the authors thank you for agreeing to review our paper. Hopefully our response below and edits to the manuscript will satisfy your queries.

Reviewer #1:

This is a well-designed analysis looking at the impact of rotavirus vaccine introduction on healthcare utilization for acute gastroenteritis in the UK. An important and novel part of the study assesses vaccine coverage, and impact by socioeconomic status and estimates the expected benefit from increasing vaccine utilization in the most deprived population.

Below are several comments and suggestions:

L.149-150: Would be informative to further explain (quantitatively) how different is the study population (Merseyside) from the general population in the UK and why this led the researchers to combine Categories 4/5.

We have the added the following to line 158 (Methods pg 8),
“(45% of the population are in the most deprived quintile and 8% in the least deprived)”

L198-217: Because rotavirus vaccine coverage rates tend to be unstable during early post-introduction period, most vaccine impact evaluations describe annual declines in post-introduction years. In the present study it seems like vaccine uptake was rapid and high coverage was rapidly obtained among vaccine eligible children (figure 1). The authors used the interrupted time-series design and report proportional reductions for the entire post-introduction period. It might be beneficial to report annual pre- and post- introduction rates and rate reductions as well (perhaps add an appendix). Providing the reader with these data would make it easier to compare these data to other studies assessing rotavirus vaccine impact in similar settings.

We have added a table with annual rates, by age-group and outcome measure, as an appendix.

L285: This is indeed a pioneer study in several aspects but not the first to look at rotavirus vaccine impact in a defined geographic area or across all levels of healthcare settings.

Edited on line 293 (Discussion, pg 14) to read:

“In this, one of the few studies to simultaneously evaluate the impact of rotavirus vaccine introduction across all levels of the healthcare system in a defined geographic area,…”

Table 1: Hospital episode statistics - admitted patient care. Did the authors attempt to extract rotavirus-coded hospitalizations by ICD10 code? Seems like rota confirmed hospitalizations were extracted based on lab data (Alder Hey Children's NHS Foundation Trust). If these lab data capture all lab confirmed rota hospitalizations I may have missed this part in the methods section.

We had access to rotavirus coded (ICD10) hospitalisations for Merseyside. However numbers were very low as most rotavirus is coded under other ICD-10 codes used for AGE. We therefore used laboratory confirmed rotavirus hospitalisations from laboratory data at Alder Hey linked to the patient hospital episode. We have clarified this in the limitations and discussion section (354-360) and in table 1.
Discussion, pg 17, Line 358 “Therefore, in this study, for the RVGE hospitalisation outcome measure, we used hospitalisations that were laboratory confirmed rotavirus from Alder Hey rather than ICD-10 codes.”

Reviewer #2:
This well-designed study provides important and timely information regarding the impact of rotavirus immunization in the UK. The authors assessed vaccine impact in relation to socioeconomic status.

Specific comments

Abstract
Since the manuscript assessed the impact of rotavirus immunization in relation to socioeconomic deprivation, it is important to add some details in the abstract, on the cost of the vaccine to parents (or whether it is free of charge). Also, please add information on the type of the vaccine (monovalent) and recommended ages for immunization.

This has been added to the abstract in line 24 (Abstract, pg 2):

“The UK introduced the monovalent rotavirus vaccine (Rotarix®) in July 2013. Vaccination is free of charge to parents, with two doses delivered at 8 and 12 weeks of age”

Background
Paragraph 1, lines 63-66, please note that currently various estimates exist on the number of global deaths attributed to rotavirus.


We have changed line 65 (Background, pg 4) and added appropriate references:

“(recently estimated at between ~120 000 and ~215 000)”.

Paragraph 2. Please add information on the health care system in the UK with emphasis on administration of early childhood vaccines (e.g., cost to parents, access to care).
To clarify we have added the following to line 71 (Background, pg 4):

“The national health service (NHS) in the England is free at the point of use for all UK residents, with vaccinations included in the routine immunisation schedule also free of charge.”

Methods

Page 6, lines 106-111. Since socioeconomic deprivation is a main variable in this study, please elaborate on how socioeconomic index was calculated, and which components were included in the calculation.

We have added a detailed description of the IMD to line 115 (Methods, pg 6):

“The English indices of deprivation are produced and quality controlled using national census and other administrative data.[13] They are constructed from 37 robust indicators in seven domains: Education Skills and Training, Employment, Income, Living Environment, Crime and Barriers to Housing and Other Services.[13] These domains are combined and weighted to calculate one of the most robust and commonly used measures of deprivation in England, the IMD.[13,16]”

The detection of rotavirus among hospitalized children at the Alder Hey Children's NHS Foundation Trust was performed using immunochromatography test or enzyme immunoassay. Please add information on the validity of the two methods, the period in which each method was employed, and whether this might have affected the results.

The time period for each method has been added to the Table 1. From the literature the immunochromatographic technique used (VIKIA® Rota-Adeno) is concordant with the ELISA in 93.6% of tests. Diagnostic accuracy is slightly lower for the immunochromatographic method therefore between 2005 and 2008 there is likely to have been a slightly higher rate false positives and false negatives, than when EIA was used. However, because the time-series spans 11 years pre-vaccine introduction we would not expect results to alter effect estimates.

To line 361 (Strengths and Limitations, pg 17) we have added:

“In the context of this outcome measure it is important to acknowledge the change in rotavirus diagnostic testing methods that occurred at Alder Hey during the study period (Table 1). Enzyme immunoassay (EIA) was used for 10/14 study years, whilst immuno-chromatography was utilised between 2005 and 2008. The immuno-chromatographic method used (VIKIA® Rota-Adeno) has a slightly lower diagnostic accuracy compared to EIA methods.[52,53] However, the pre-vaccine introduction time-series spanned 11 years and since the change in testing practices
was not accompanied by clear non-secular variation in RVGE hospitalisation rates, we would not expect this change to have impacted significantly on effect estimates.”

Discussion

Please see the following citation on the impact of rotavirus immunization on clinic visits:


We have referenced the above paper in line 324 (Discussion, pg 15)

“…..and all-cause AGE community clinic visits in Israel (19% reduction in infants; 16% for 12-23 month olds) [46].