

# BMJ Open

**An ecological study, using data from multiple health systems in Merseyside, UK to assess the direct and indirect effect of routine rotavirus vaccination.**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006161
Article Type:	Protocol
Date Submitted by the Author:	18-Jul-2014
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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health, Gastroenterology and hepatology, Immunology (including allergy)
Keywords:	Epidemiology < INFECTIOUS DISEASES, IMMUNOLOGY, Gastrointestinal infections < GASTROENTEROLOGY, Public health < INFECTIOUS DISEASES, STATISTICS & RESEARCH METHODS

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Manuscripts

1 **An ecological study, using data from multiple health systems in Merseyside, UK to assess the**  
2 **direct and indirect effect of routine rotavirus vaccination.**

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## 38 39 40 **Keywords**

41  
42  
43 Rotavirus; Vaccination; Gastroenteritis; Epidemiology; Immunity, Herd

## 44 45 46 **Word Count**

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49 3819

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## 22 ABSTRACT

### 23 Introduction

24 Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide.  
25 Currently 67 countries include rotavirus vaccine in childhood immunisation programmes, but uptake in  
26 Western Europe has been slow. In July 2013 rotavirus vaccine was introduced into the UK's childhood  
27 immunisation programme. Prior to vaccine introduction in the UK rotavirus was estimated to result in  
28 750,000 diarrhoea episodes and 80,000 GP consultations each year, together with 45% and 20% of hospital  
29 admissions and emergency department attendances for acute gastroenteritis, in children under 5 years of  
30 age. It is therefore important to assess vaccine impact in the UK, to support continued vaccination and to  
31 inform rotavirus immunisation policy in other Western European countries.

### 32 Methods and analysis

33 In Merseyside, Northwest England we will conduct an ecological study using a "before and after" approach  
34 to examine changes in gastroenteritis and rotavirus incidence following the introduction of rotavirus  
35 vaccination in the UK. Data will be collected on mortality, hospital admissions, healthcare associated  
36 infection, emergency department attendances, GP consultations and community health consultations to  
37 capture all healthcare providers that people access with symptoms of acute gastroenteritis and rotavirus  
38 gastroenteritis. We will assess both the direct and indirect (herd) effect of the vaccine on the study  
39 population. Comparisons of outcome indicator rates will be made in relation to vaccine uptake and the  
40 association with deprivation examined.

### 41 Ethics and dissemination

42 NHS ethics approval has been granted. The findings will be disseminated through scientific conferences and  
43 peer-reviewed journal articles. The findings will enable demonstration of a complete health system  
44 perspective of the impact of rotavirus vaccination on the burden of disease. It will also identify key areas that  
45 require improved data collection tools to maximise the usefulness of this surveillance approach and provide  
46 a template for ecological methodology vaccine evaluations in the UK.

## 47 STRENGTHS AND LIMITATIONS

- 48 • Strengths include use of data from multiple health systems that will allow examination of the  
49 relative impact of vaccination on the various health providers and communities rather than the  
50 individual. These multiple data sources will provide robustness, enabling easier identification of  
51 outliers from overall trends.
- 52 • The study will cover all ages for rotavirus and all cause gastroenteritis incidence three years post-  
53 vaccination, minimising cofounding caused by yearly variance in rotavirus numbers.
- 54 • Additionally it is powered to measure the herd effect on hospital admissions and whilst the majority  
55 of studies have focused on this, this study will also provide evidence for the indirect effect in  
56 emergency departments and community settings.
- 57 • The study is limited by the ecological before and after design, and the difficulties of ascribing  
58 causality to vaccine, as well as the inherent risks of bias and confounding in observational studies  
59 particularly due to underlying secular trends.
- 60 • Using syndromic indicators that are non-specific to rotavirus limits the study to measuring large  
61 effects rather than small variations.

## 62 INTRODUCTION

63 Rotavirus is the most common cause of severe gastroenteritis in infants and young children, responsible for  
64 an estimated annual 453,000 deaths worldwide among children under age 5 years, with over 90% of deaths  
65 occurring in the developing countries.[1] In the UK, rotavirus gastroenteritis (RVGE) is seasonal and most  
66 cases occur between February and April each year. Rotavirus is estimated to result in 750,000 diarrhoea  
67 episodes and 80,000 GP consultations each year in the UK,[2] together with 45% and 20% of hospital  
68 admissions and emergency department (ED) attendances for acute gastroenteritis (AGE), respectively in  
69 children under 5 years of age.[3] The economic cost of RVGE to the health service is estimated to be  
70 approximately £14 million per year in England and Wales.[3] At Alder Hey Children's NHS Foundation Trust,  
71 Liverpool, UK rotavirus is a major cause of community-acquired and healthcare-associated diarrhoea; in a 2-  
72 year prospective study among hospitalised children, rotavirus was detected by RT-PCR in 43% of community-

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73 acquired and in 31% of healthcare-associated gastroenteritis cases.[4] AGE hospital admissions are known  
74 to have a positive correlation with deprivation [5] and globally the burden of severe RVGE is much higher in  
75 low-income countries. However, no statistical correlation between RVGE in infants and deprivation has been  
76 shown to exist in the UK.

77 In July 2013, the Department of Health introduced rotavirus vaccine into the UK's childhood immunisation  
78 programme.[6,7] The live-attenuated, two-dose oral monovalent vaccine (Rotarix™, GlaxoSmithKline  
79 Biologicals, Belgium) is administered at two and three months of age. Clinical trials in Europe and the  
80 Americas with both currently licensed rotavirus vaccines (Rotarix™ and a pentavalent vaccine RotaTeq™  
81 developed by Merck), led to a WHO recommendation in 2007 to vaccinate children in these regions.[8–10]  
82 Subsequent trials in Africa and Asia led to an extension of the recommendation to include all children  
83 worldwide.[10–12] At present more than 60 countries include a rotavirus vaccine in childhood immunisation  
84 programmes.[13] Uptake in Western Europe has been slow however, with only Austria, Belgium, Finland,  
85 Luxemburg and most recently the UK having rolled out universal rotavirus vaccination programmes to  
86 date.[14] Based on the uptake of other routine childhood vaccinations in UK; vaccine uptake over 90% would  
87 be expected for rotavirus immunisation,[15] and initial uptake figures for England support this with 93% for  
88 first dose and 88% for the second dose.[16]

89 Clinical trials in middle and high income countries demonstrated high (> 85%) efficacy against severe  
90 rotavirus gastroenteritis.[10] The introduction of rotavirus vaccines in the immunisation programmes of  
91 these countries has demonstrated direct benefits on a par with those observed in clinical trials, with  
92 significant reductions in diarrhoea hospitalisations.[17] An unanticipated but beneficial consequence of  
93 rotavirus vaccination is the reduction of rotavirus disease in unvaccinated individuals (herd protection), likely  
94 due to reduced virus transmission. Such “indirect benefits” include reduced disease in non-vaccinated older  
95 children and adults who were not thought to sustain a significant burden of rotavirus disease.[18] In the UK  
96 the burden of RVGE in older children and adults is difficult to estimate but admissions for viral gastroenteritis  
97 are 2 per 1,000 population in 5-14 year olds and 7 per 1,000 in those 15+ years.[19] Hence monitoring  
98 changes in AGE incidence in non-vaccinated older children and adults is critical to assess indirect impact.

1 99 Ecological rotavirus vaccine effectiveness studies have primarily focused on mortality, hospitalisations and  
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4 100 laboratory detections as a measure of burden.[20–27] Severe cases of rotavirus will often end up in hospital  
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6 101 and receive full diagnostics. However, many cases of rotavirus particularly older children and adults will not  
7  
8 102 attend hospital but be seen by primary and community healthcare providers. Therefore in order to better  
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10 103 understand the burden of RVGE and AGE on all ages and the impact of routine immunisation on the health  
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12 104 system; it is crucial to study routine data sources for all health service providers in a defined study area.  
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14 105 Taking advantage of a range of regional healthcare facilities in Merseyside, England, we describe an  
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16 106 ecological study using a “before and after” approach that will allow comprehensive evaluation of the direct  
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18 107 and indirect vaccine impact following its introduction into the UK’s childhood immunisation programme.  
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21 108 Whilst investigating the correlation of deprivation and vaccination uptake with burden. These data will  
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23 109 provide evidence to support future rotavirus vaccination in the UK and will inform rotavirus immunisation  
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25 110 policy in other Western European countries.[6]

## 28 111 **METHODS**

### 32 112 **Study aim**

35 113 Routine data sources will be used to estimate the direct and indirect effects of rotavirus vaccination on  
36  
37 114 gastroenteritis indicators in the population of Merseyside, and the relationship of such effects to vaccine  
38  
39 115 coverage and socio-demographic indicators. We also hope to identify the key areas that require extended  
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41 116 and improved data collection tools to maximise the usefulness of this surveillance approach. The main  
42  
43 117 outcome measures are as follows:

- 47 118 • Laboratory detections of rotavirus in faecal samples
- 49 119 • Admissions to hospital for RVGE or AGE
- 51 120 • Attendances to Emergency departments for AGE
- 53 121 • Number of nosocomially acquired cases of RVGE
- 55 122 • General practice (GP) and community consultations for diarrhoea and AGE in children less than 5 and in  
57 123 all ages

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- 124 • Routine rotavirus vaccine coverage mapping by small area geography
  - 125 • Relative contribution of direct (those vaccinated) and indirect (not vaccinated) effects to overall vaccine  
126 benefit in health system usage for both RVGE and AGE
  - 127 • Relationship between deprivation, vaccine uptake and RVGE / AGE incidence

### 128 **Study setting and location**

129 The study will be conducted in the large metropolitan area of Merseyside in North West England which  
130 contains the city of Liverpool. Merseyside has a population of nearly 1.4 million people, with approximately  
131 80,000 of its population under 5 years of age. Deprivation within Merseyside is variable but over 60% of its  
132 population live in a more deprived area than the England average (Figure 1).[28] Vaccination uptake for most  
133 routine childhood vaccinations is also variable in small areas, but overall Merseyside has uptake above the  
134 average for England.[15]

### 135 **Study overview and choice of study designs**

136 The study is ecological in design utilising routine health surveillance data. The evaluation design incorporates  
137 interrupted time-series analyses of outcome indicators across the study population. Comparisons of  
138 outcome indicator rates will be made between communities with high vaccine uptake and those with lower  
139 vaccine uptake and the relationship with deprivation. The ecological study approach allows rates of  
140 outcomes to be compared in space and time using vaccine uptake and community level deprivation as  
141 covariates.

### 142 **Study data**

143 The National Health Service (NHS) in England and other government service agencies collect a range of  
144 administrative and health care related data which is held at both local service level and centrally. Figure 2  
145 outlines the data sources that will be used for the evaluation and table 1 shows the case definitions.

1 146 Hospital admission and emergency department attendance data will be obtained from hospital episode  
2  
3 147 statistics (HES), which record all inpatient admissions in NHS hospitals in England and directly from NHS  
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5 148 Trusts which cover the population of Merseyside.  
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8 149 The study will obtain GP consultations for diarrhoea or gastroenteritis from Clinical Commissioning Groups  
9  
10 150 covering Merseyside or from government held sentinel surveillance systems. Community consultations for  
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12 151 diarrhoea and gastroenteritis at Walk-in Centres will be sourced from NHS Community Health Trusts. Walk-in  
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14 152 Centres are primarily nurse led primary care facilities for illness and injuries without the need for an  
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16 153 appointment.  
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20 154 The infection control team at Alder Hey Children's NHS Foundation Trust in Liverpool classifies rotavirus  
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22 155 cases as community acquired or healthcare associated (nosocomial). Alder Hey NHS Foundation Trust's  
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24 156 footprint covers the majority of Merseyside's children, so these data will enable evaluation of the effect of  
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26 157 rotavirus vaccination on nosocomial rotavirus infection in children across Merseyside.  
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30 158 Laboratory detections of rotavirus from Public Health England Laboratory surveillance covering Merseyside  
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32 159 residents will be included in the analysis. Other causative agents of AGE identified through laboratory testing  
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34 160 including, for example, norovirus, adenovirus, astrovirus will also be extracted for analysis.  
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37 161 Each data set will cover at least three-years either side of vaccine introduction. All data will be  
38  
39 162 pseudoanonymised to allow distinction of records but no linking of datasets or identification of individuals  
40  
41 163 will be undertaken. All data will be either geo-coded from postcode to small statistical geographical  
42  
43 164 community units termed Lower Super Output Areas (LSOA) or sourced with this geography. Denominator  
44  
45 165 populations will be derived from the Office of National Statistics (ONS) mid-year population-estimates by  
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47 166 LSOA [29]. Indicators of deprivation at LSOA level will be sourced from the Department for Communities and  
48  
49 167 Local Government.[28] Rotavirus vaccination uptake data will be sourced from the Child Health Information  
50  
51 168 System (CHIS) which is held by community NHS health Trusts in Merseyside.  
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55 169 **Table 1: Case definitions for the study by health data set**

Data set	Case definition
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Nosocomial and community acquired	Nosocomial – Laboratory confirmed rotavirus case. Gastroenteritis symptoms beginning more than two days after admission  Community acquired – Laboratory confirmed rotavirus case.  Gastroenteritis symptoms starting within two days of admission
Hospital admissions	Rotavirus case definition - Inpatient finished consultant episodes (FCE) with a primary or subsidiary diagnosis International Classification of Disease version 10 (ICD10) diagnosis code of A08.0  AGE case definition – inpatient FCE with a primary or subsidiary diagnosis ICD10 code of A08 --A09
Emergency attendances	Attendance with a primary or secondary diagnosis code Z:III  Gastrointestinal conditions-Other (those subsequently admitted excluded to prevent duplication in hospital admissions)
GP Consultations	GP consultations (Read codes in parenthesis) vomiting (1992.), diarrhoea (19F2) and viral gastro-enteritis (A07y0). Viral gastro-enteritis will be used as the primary case definition but diarrhoea/vomiting will be used for a secondary indicator of burden.
Community consultations (Walk-in-Centres)	There is no code system for diagnosis in Walk-in-Centre data. Therefore the description of patient symptoms field will be queried using the following key words: diarrhoea, vomiting, GI and gastroenteritis. A Soundex script will be used to allow for spelling inaccuracies.
Laboratory detections	Detection of rotavirus in a faecal specimen by a standard assay.  Detection of other AGE causative organisms

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171 **Quality control**

172 Data sources such as HES and laboratory detections will be influenced by testing practices; for instance

173 testing of some organisms is more likely to occur at certain times of the year. In the hospital admission data

1 174 set it is possible that some cases of RVGE will not be coded as rotaviral enteritis (ICD10: A08.0) and may be  
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3 175 classified as other-unspecified either due to an absence of lab confirmation or misclassification / miscoding.  
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5 176 In order to attempt to quantify this information bias the investigator team will perform quality control on  
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7 177 hospital admissions and lab detections at the lead NHS Trust hospital site. Using a sample of cases from at  
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9 178 least 3 years, those cases with a lab confirmation will be checked against clinical records and clinic coding  
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11 179 and those coded as ICD10 A08.0 rotaviral enteritis will be cross-matched against laboratory detections.  
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13 180 Based on the results audit, it may be applicable to adjust the recorded number of hospital admissions for any  
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15 181 ascertainment bias identified.  
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### 20 182 **Ethical considerations**

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22 183 We do not foresee a requirement to obtain ethical approval for this ecological study, as analysis will be  
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24 184 conducted using routinely collected aggregated data. However, a data sharing agreement will be obtained  
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26 185 between PHE, participating NHS Trusts and the University of Liverpool. Research governance approval will be  
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28 186 sought from all participating NHS Trusts. Ethics approval for quality control of data will be sort from NHS  
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30 187 Research Ethics Committee if required.  
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### 34 188 **Data analysis**

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37 189 Changes in trends of primary care consultations, community consultations, ED attendances, hospitalisations  
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39 190 and rotavirus detections will be explored using interrupted time series analysis. Moving averages will be  
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41 191 examined to highlight any long-term trends whilst smoothing out any short-term fluctuations. Standardized  
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43 192 rates for a minimum of a three-year period prior to vaccination and year on year after vaccination (for three  
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45 193 years) will be compared. For the regression analysis, Poisson regression will be used. We will first compute  
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47 194 monthly rates that are “expected” to occur in the absence of a rotavirus vaccination programme by fitting  
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49 195 the model to pre-vaccine data. We will then adjust for seasonality. The model will be used to estimate  
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51 196 “expected” rates after vaccination and we will then compare with “observed” rates. We will then calculate  
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53 197 rate ratios and assess the magnitude of decline in rates. Using a Poisson regression model, and including  
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55 198 demographic and vaccine uptake indicators we would be able to predict impact of vaccination on the AGE  
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199 and RVGE indicators at various services and vaccine uptake levels. Potential data biases will be controlled for  
 200 by the access and analysis multiple health data sources over a minimum of six years.

201 Environmental factors which may influence rotavirus incidence and seasonality are difficult to identify or  
 202 indeed quantify. To account for any potential environmental confounders, correlation of laboratory  
 203 confirmations of viral gastroenteritis causing organisms (e.g. norovirus, astrovirus) with rotavirus laboratory  
 204 confirmations will be established. If a significant correlation between any other viral gastroenteritis and  
 205 rotavirus can be identified, the resulting correlation coefficients will be used to estimate relative  
 206 contribution of vaccination and undefined environmental factors to any changes in rotavirus incidence.  
 207 Furthermore we will explore a potential rebound effect on an increase in other viral agents (e.g. norovirus)  
 208 due to a decrease in circulating rotavirus, and potential increase in susceptible individuals particularly in  
 209 those under 5 years of age.

#### 210 **Power calculation**

211 Based on hospital admission for RVGE in 2012 obtained from HES data, the estimated rate of hospitalisation  
 212 is approximately 1 per 1,000 children under age 5 years.[19] Assuming reductions in this rate between 25%  
 213 and 75%, and high vaccine uptake rates (i.e. 95%), similar to uptake of other routine childhood vaccines in  
 214 Merseyside, we used a one sample comparison of proportions for a two sided test to calculated the power  
 215 estimates shown in table 2. Studies from other high income countries on the population effects of rotavirus  
 216 vaccination have shown reductions in hospital admissions of over 50% in children under 5 years of age [13].  
 217 Supposing a similar reduction in Merseyside, this study is powered at over 90% to detect a significant change  
 218 in RVGE hospital admissions.

219 **Table 2: Predicted power of study for main outcome (hospitalisation rate) in Merseyside and selected sub-**  
 220 **districts.**

Area	Population (children <5 years)	Assumed reduction in rotavirus hospitalisation rate				
		25%	30%	40%	50%	75%
Liverpool	27000	0.22	0.31	0.56	0.82	1

Liverpool and Sefton	41000	0.34	0.48	0.78	0.96	1
Liverpool, Sefton and Knowsley	50000	0.41	0.58	0.87	0.99	1
Merseyside	80000	0.63	0.8	0.98	1	1

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222 The study is also powered for detecting an indirect effect in adults. Using an AGE hospital admission rate of 7  
 223 per 1000 population aged 15+ years[18] we would expect power to be at least 0.97 for Merseyside at  
 224 assumed hospitalisation rate reductions post vaccination of 5%, 8%, 10%. No formal power calculations have  
 225 been undertaken for other end-points under study.

### 226 **Timeline**

227 The study will be conducted over a three year period beginning in April 2014, which includes time for  
 228 administrative procedures to be undertaken such as data sharing agreements, consultation with data  
 229 providers, database development for storing all sourced data, data analysis and report writing (including  
 230 interim yearly, final and peer review papers).

### 231 **Project governance**

232 A stakeholder group within Merseyside will be established to enable effective achievement of the project  
 233 objectives and ownership by the professional community. The stakeholder group will include representatives  
 234 from: [Liverpool Health Partners](#);<sup>[30]</sup> [Liverpool Community Health NHS Trust](#);<sup>[31]</sup> [NHS England Merseyside](#)  
 235 [Area Team Screening and Immunisation Team](#);<sup>[32]</sup> [Alder Hey Children's NHS Foundation Trust](#)<sup>[33]</sup> and [Public](#)  
 236 [Health England](#)<sup>[34]</sup>-Liverpool.

### 237 **Dissemination of research findings**

238 The findings will be presented at professional and scientific conferences. The results will also be published in  
 239 peer review journal articles. Interim and final reports will be presented to the funders and the stakeholder  
 240 group.

## 241 **DISCUSSION**

1 242 This study will enable demonstration of a complete health system perspective of the impact of rotavirus  
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3 243 vaccination on the burden of disease in Merseyside, UK. It aims to study both direct and indirect effect from  
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5 244 routine rotavirus vaccination. The study will also enable data on vaccine efficacy to infer the relative  
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7 245 contribution of RVGE to AGE primary care, and emergency care consultations. Furthermore as data will be  
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9 246 linked to specific geographical units, for which information on deprivation and vaccine uptake is available,  
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11 247 we will be able to explore the association of these with overall vaccine effectiveness. Quality control audits  
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13 248 contained with the study will provide a means of adjusting analysis for information bias and also enable  
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15 249 identification of the key data collection issues that require improvement to maximise the usefulness of this  
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17 250 surveillance approach. It is also hoped that this study will provide a learning resource and template for  
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19 251 future ecological vaccine effectiveness studies in the UK.

## 22 252 **Strengths**

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26 253 A whole health system approach in a geographically defined area provides a number of strengths. Using data  
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28 254 sets from a range of health care providers within a health economy will allow us to examine the relative  
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30 255 impact of vaccination on the various health providers rather than the individual. The use of multiple data  
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32 256 sources to measure independent indicators of vaccination effect will also provide robustness, enabling easier  
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34 257 identification of outliers from overall trends.

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37 258 There is annual variability in the number of rotavirus cases therefore it is imperative to conduct surveillance  
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39 259 of rotavirus incidence over a number of year's pre and post vaccine introduction. This study will provide a  
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41 260 mechanism to do this as it will be conducted over 3 years covering 3 rotavirus seasons post vaccine  
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43 261 introduction. Thus cofounding caused by yearly variance in rotavirus numbers will be minimised.

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46 262 At the time of writing there has been limited published evidence on the indirect effect of routine vaccination  
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48 263 on un-vaccinated older children and adults (herd protection) and the majority of studies have focused on  
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50 264 hospital admissions. As this study will collect data for all ages and cover RVGE and AGE incidence 3 years  
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52 265 post-vaccination it will provide sufficient data for measurement of the herd effect on hospital admissions.  
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54 266 Additionally, whilst the majority of studies into the indirect effect of vaccination have focused on hospital  
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56 267 admissions this study will provide evidence for impact on the indirect effect in emergency departments and  
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1 268 community settings. This is particularly important as it is perhaps more likely that severe RVGE in un-  
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4 269 vaccinated older children and adults will be treated at emergency departments and through community  
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6 270 consultations.  
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9 271 Another potential strength of the study is the ability to conduct analysis at small community (LSOA) level.  
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11 272 This will enable small area socio-demographic information such as deprivation to be included in the analyses  
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13 273 as a covariate at the lowest possible unit of analyses other than the individual. Thus, allowing the exploration  
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15 274 of the association between deprivation, burden of RVGE / AGE and vaccine uptake whilst limiting the  
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17 275 ecological fallacy of analysis.  
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20 276 As many of the data sources included in this study do not include specific RVGE classification, we are using  
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22 277 AGE as an outcome measure for most datasets. Laboratory detections data which are organism specific will  
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24 278 allow us to adjust these measures based on the seasonal contribution of organisms other than rotavirus such  
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26 279 as norovirus. For example RVGE seasonality is fairly constant but that of norovirus tends to vary over the  
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28 280 winter and spring months in the UK. These AGE indicators can therefore be adjusted for changes in norovirus  
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30 281 seasonality (Figure 3)[35] to give a better proxy of the contribution of rotavirus to overall GI causes and the  
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32 282 relative impact of rotavirus vaccination  
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### 34 283 **Limitations**

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38 284 The gold standard for measurement of vaccine efficacy is the randomised controlled trial. However, the  
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40 285 intention of this study is to look at the generalisability of vaccine effectiveness on population disease burden  
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42 286 and impact on a health system therefore an ecological study is appropriate. Conversely it is recognised we  
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44 287 cannot show individual level effects of vaccine and we can only infer the impact of the vaccine at the  
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46 288 population level without causation. Additionally a key focus of this study is to quantify variation in the  
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48 289 outcomes measured according to vaccine uptake levels and deprivation. Confounding may be an issue here  
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50 290 with cases living in areas with low vaccine uptake or high deprivation may also have other characteristics  
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52 291 that will affect the risk of RVGE or AGE.  
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1 292 For measures of AGE activity in community settings (e.g. GP and Walk-in-Centre), we use syndromic  
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3 293 indicators that are non-specific to rotavirus e.g. diarrhoea, gastroenteritis symptoms. An inherent issue is  
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5 294 that the ability to detect effect on these is likely to be limited to large effects rather than small variations.  
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8 295 A further limitation of the study is that investigators are not in control of direct data collection as all data are  
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10 296 secondary, and the consequent risk of bias that this brings. There is potential for clinical coding to lead to  
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12 297 misclassification of disease, and this misclassification may vary by different data source. We will describe  
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14 298 these biases through the quality control audit and subsequently adjust for at the analysis stage. The studies  
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16 299 use of multi-data sets for outcome indicators limit these issues by improving robustness.  
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20 300 It is likely that there has been changes in data collection methods over the study period for example changes  
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22 301 to the assay used for rotavirus laboratory testing, leading to testing bias. One way to adjust for this in the  
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24 302 analysis is to pool data over a number of years to smooth fluctuations caused by changes in testing methods.  
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26 303 The investigators will identify changes through contact with rotavirus testing laboratories and NHS Trusts, so  
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28 304 that changes may be described and where possible assist appropriate analytical adjustments. It is also  
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30 305 feasible that the introduction of vaccination may also trigger changes in clinician requests for rotavirus and  
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32 306 other AGE diagnostic testing, particularly in the vaccination age group. Any possible testing bias will be  
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34 307 assessed at the lead NHS Trust via comparisons with pre-vaccine testing probabilities.  
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38 308 The study currently does not include any economic component which given the cost of rotavirus to the  
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40 309 health service is essential. However, previous studies have reported the likely cost-effectiveness of rotavirus  
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42 310 vaccination for the population under 5 years of age.[36] This study would provide the results and data  
43  
44 311 necessary for economic evaluation based on the direct and indirect impact of rotavirus vaccination  
45  
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47

## 312 **Contributions**

313 DH participated in the design of the study, will oversee the study co-ordination, data collection and analysis,  
314 and wrote the manuscript. RV conceived of the study and participated in its design; and will contribute to  
315 study co-ordination and analysis. MIG conceived of the study and participated in its design; and will  
316 contribute to study co-ordination. NF conceived of the study and participated in its design; and will oversee

1 317 study co-ordination and contribute to analyses. NC conceived of the study, participated in its design and will  
2  
3 318 contribute to study co-ordination. All authors were involved in revising the manuscript and read and  
4  
5 319 approved the final manuscript.  
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8  
9 320 **Acknowledgements** The authors gratefully acknowledge the effort and assistance provided by all the  
10  
11 321 research and development staff, laboratory technicians, data entry staff and support staff at the  
12  
13 322 collaborating sites. This work is support by the GlaxoSmithKline Biologicals. The funding body had no role in  
14  
15 323 the study design, the collection, analysis and interpretation of data, the writing of the manuscript, or the  
16  
17 324 decision to submit the manuscript for publication.  
18  
19

20 325 **Funding** This work is to be partially supported by GlaxoSmithKline Biologicals, Belgium, including salary  
21  
22 326 contributions to the lead author DH and resources for quality control of data sources.  
23  
24

#### 25 327 **Competing interests**

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28 328 Financial competing interests  
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30  
31 329 The Rotarix™ vaccine used in the UK national immunisation programme evaluated by this study is developed  
32  
33 330 and licensed by GlaxoSmithKline Biologicals. NC is in receipt of research grant support from GSK Biologicals  
34  
35 331 (to University of Liverpool) and has received honoraria for participation in GSK Rotavirus Vaccine Advisory  
36  
37 332 Board Meetings.  
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40  
41 333 Non-financial competing interests  
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43  
44 334 The authors declare that they have no non-financial competing interests.  
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47 335 **Peer review** Peer reviewed and reviewed internally prior to sponsor and ethical approval.  
48  
49

50 336 **Ethics approval** The study has received NHS ethics approval.  
51  
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## 13 426 **Additional figure titles and legends**

### 17 427 **Figure 1. Indices of multiple deprivation in Merseyside**

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20 428 Produced using the English Indices of Deprivation 2010, national quintiles for the index of multiple  
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22 429 deprivation [19].

### 25 430 **Figure 2. Schematic of study data sources and outcome measures**

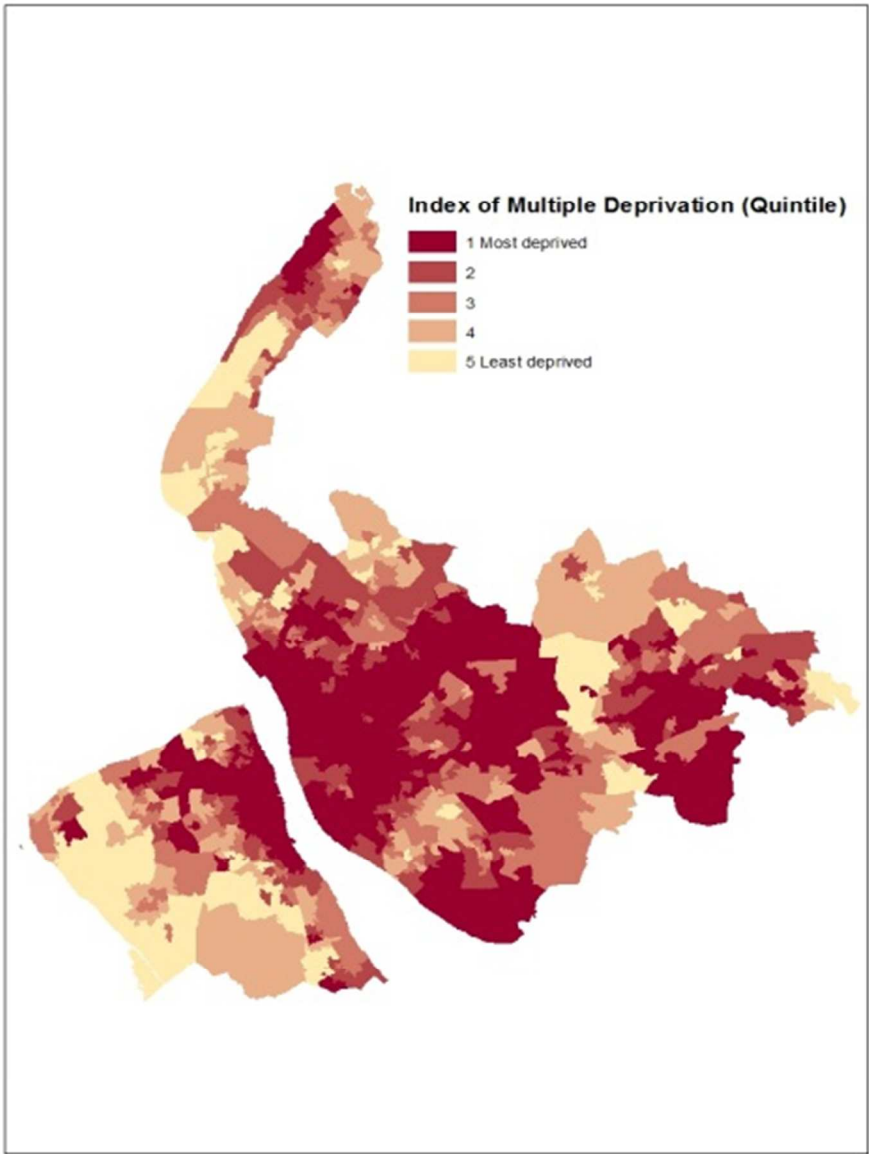
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28 431 Data sources cover a variety of health care providers at different levels of the health system. This shows  
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30 432 from which data sources outcome measures will be obtained.

### 33 433 **Figure 3. Laboratory detections of rotavirus and norovirus in the North West, England, 2009/10-2013-14**

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36 434 Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the  
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38 435 norovirus season as compared to the rotavirus season.

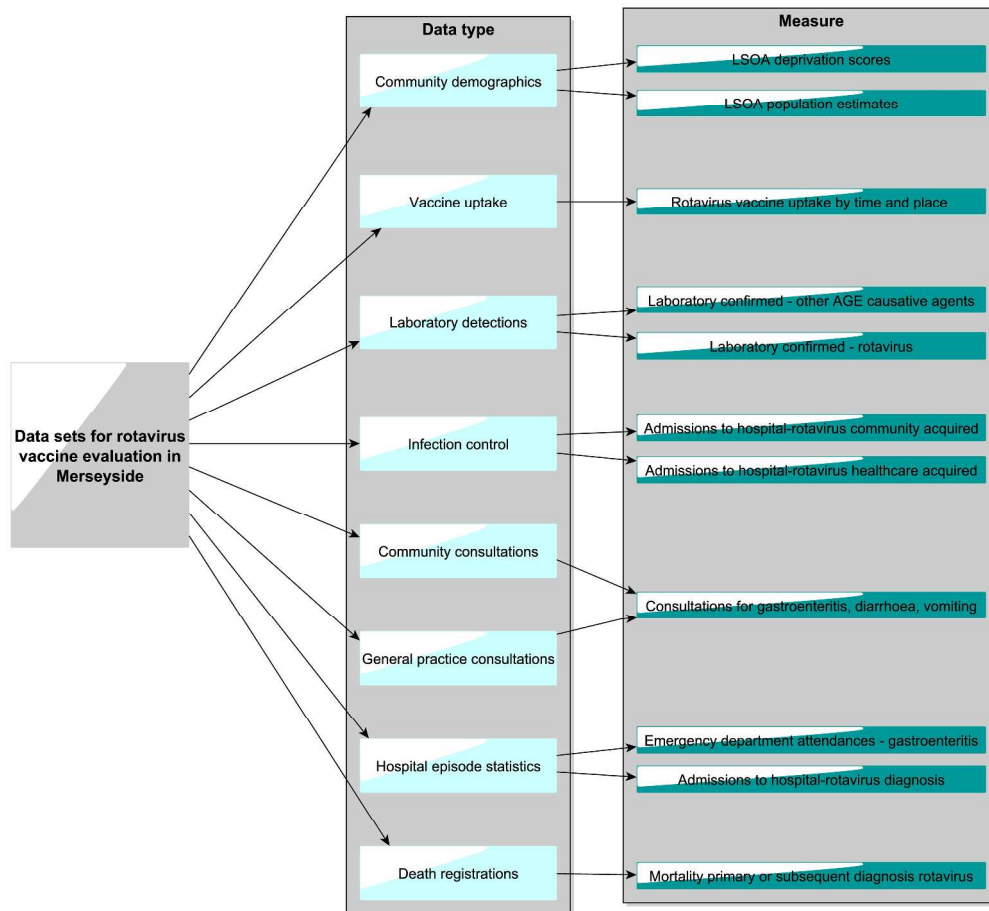
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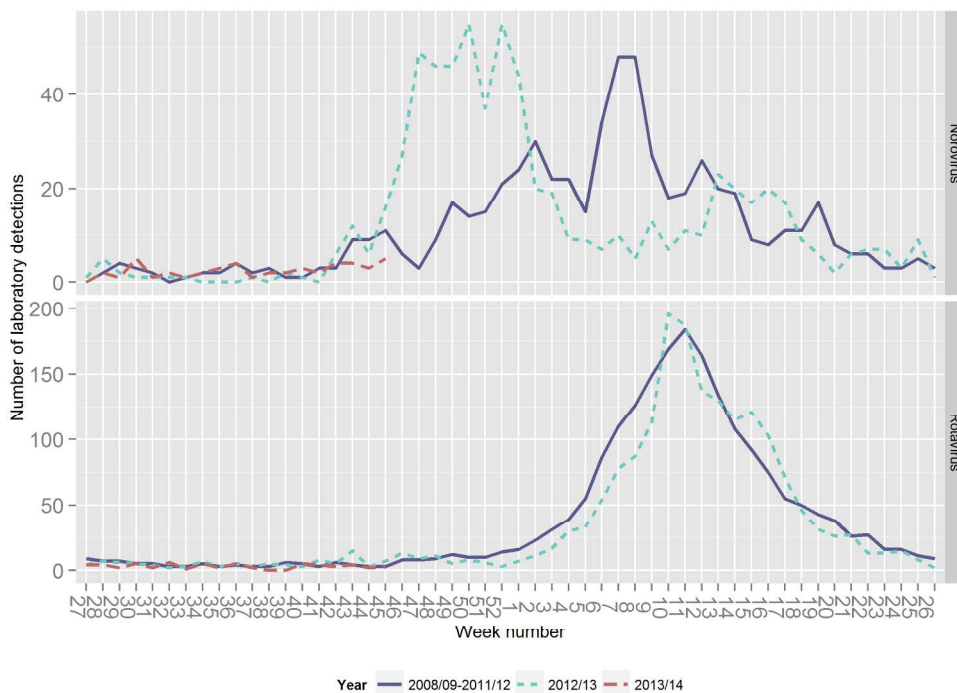


Data sources cover a variety of health care providers at different levels of the health system. This shows from which data sources outcome measures will be obtained.

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Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the norovirus season as compared to the rotavirus season.  
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# BMJ Open

## Ecological assessment of the direct and indirect effects of routine rotavirus vaccination in Merseyside, UK using data from multiple health systems: a study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006161.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Nov-2014
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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health, Gastroenterology and hepatology, Immunology (including allergy)
Keywords:	Epidemiology < INFECTIOUS DISEASES, IMMUNOLOGY, Gastrointestinal infections < GASTROENTEROLOGY, Public health < INFECTIOUS DISEASES, STATISTICS & RESEARCH METHODS

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1 **Ecological assessment of the direct and indirect effects of routine rotavirus vaccination in**  
2 **Merseyside, UK using data from multiple health systems: a study protocol**

3

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16 **Keywords**

17 Rotavirus; Vaccination; Gastroenteritis; Epidemiology; Immunity, Herd

18 **Word Count**

19 3,624 (excluding footnotes)

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21



## 22 ABSTRACT

### 23 Introduction

24 Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide.  
25 Currently 67 countries include rotavirus vaccine in childhood immunisation programmes, but uptake in  
26 Western Europe has been slow. In July 2013 rotavirus vaccine was introduced into the UK's routine  
27 childhood immunisation programme. Prior to vaccine introduction in the UK rotavirus was estimated to  
28 result in 750,000 diarrhoea episodes and 80,000 GP consultations each year, together with 45% and 20% of  
29 hospital admissions and emergency department attendances for acute gastroenteritis, in children under five-  
30 years of age. This paper describes a protocol for an ecological study that will assess rotavirus vaccine impact  
31 in the UK, to inform rotavirus immunisation policy in the UK and in other Western European countries.

### 32 Methods and analysis

33 In Merseyside, UK we will conduct an ecological study using a "before and after" approach to examine  
34 changes in gastroenteritis and rotavirus incidence following the introduction of rotavirus vaccination. Data  
35 will be collected on mortality, hospital admissions, nosocomial infection, emergency department  
36 attendances, GP consultations and community health consultations to capture all healthcare providers in the  
37 region. We will assess both the direct and indirect effects of the vaccine on the study population.  
38 Comparisons of outcome indicator rates will be made in relation to vaccine uptake and socioeconomic  
39 status.

### 40 Ethics and dissemination

41 The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference:  
42 14/SC/1140. Study outputs will be disseminated through scientific conferences and peer-reviewed  
43 publications. The study will demonstrate the impact of rotavirus vaccination on the burden of disease from a  
44 complete health system perspective. It will identify key areas that require improved data collection tools to  
45 maximise the usefulness of this surveillance approach and will provide a template for vaccine evaluations  
46 using ecological methods in the UK.

## 47 STRENGTHS AND LIMITATIONS

- 48 • Strengths include use of data from multiple health systems that will allow examination of the  
49 relative impact of vaccination on the various health providers and communities rather than the  
50 individual. These multiple data sources will provide robustness, enabling easier identification of  
51 outliers from overall trends.
- 52 • The study will include all ages for rotavirus and all cause gastroenteritis incidence for three years  
53 post-vaccination, thereby minimising cofounding caused by yearly variance in rotavirus numbers.
- 54 • Additionally the study is powered to measure the indirect (herd) effect on hospital admissions and  
55 whilst the majority of studies have focused on this, this study will also provide evidence for the  
56 indirect effect in emergency departments and community settings.
- 57 • The study will be limited by the ecological before and after design, and the difficulties of ascribing  
58 causality to vaccine, as well as the inherent risks of bias and confounding in observational studies  
59 particularly due to underlying secular trends.
- 60 • Use of syndromic indicators that are non-specific to rotavirus will limit the study to measuring large  
61 effects rather than small variations for emergency departments and community health outcome  
62 measures.

## 63 INTRODUCTION

64 Rotavirus is the most common cause of severe gastroenteritis in infants and young children, responsible for  
65 an estimated annual 453,000 deaths worldwide among children under age 5 years, with over 90% of deaths  
66 occurring in the developing countries.[1] In the UK, rotavirus gastroenteritis (RVGE) is seasonal and most  
67 cases occur between February and April each year. Rotavirus is estimated to result in 750,000 diarrhoea  
68 episodes and 80,000 GP consultations each year in the UK,[2] together with 45% and 20% of hospital  
69 admissions and emergency department (ED) attendances for acute gastroenteritis (AGE), respectively in  
70 children under 5 years of age.[3] The economic cost of RVGE to the health service is estimated to be  
71 approximately £14 million per year in England and Wales.[3] At Alder Hey Children's NHS Foundation Trust,  
72 Liverpool, UK rotavirus is a major cause of community-acquired and healthcare-associated diarrhoea; in a 2-

1 73 year prospective study among hospitalised children, rotavirus was detected by RT-PCR in 43% of community-  
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3 74 acquired and in 31% of healthcare-associated gastroenteritis cases.[4] AGE hospital admissions are known to  
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5 75 have a positive correlation with socioeconomic deprivation [5] and globally the burden of severe RVGE is  
6  
7 76 much higher in low-income countries. However, RVGE has not yet been correlated with socioeconomic  
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9 77 deprivation in the UK.

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13 78 In July 2013, the Department of Health introduced a rotavirus vaccine into the UK's routine childhood  
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15 79 immunisation programme.[6,7] The live-attenuated, two-dose oral monovalent vaccine (Rotarix™,  
16  
17 80 GlaxoSmithKline Biologicals, Belgium) is administered at two and three months of age. Clinical trials in  
18  
19 81 Europe and the Americas with both currently licensed rotavirus vaccines (Rotarix™ and a pentavalent vaccine  
20  
21 82 RotaTeq™ developed by Merck), led to a WHO recommendation in 2007 to vaccinate children in these  
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23 83 regions.[8–10] Subsequent trials in Africa and Asia led to an extension of the recommendation to include all  
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25 84 children worldwide.[10–12] At present more than 60 countries include a rotavirus vaccine in childhood  
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27 85 immunisation programmes.[13] Introduction of rotavirus vaccination in Western Europe has been slow  
28  
29 86 however, with only Austria, Belgium, Finland, Luxemburg and most recently the UK having rolled out  
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31 87 universal rotavirus vaccination programmes to date.[14] Based on the uptake of other routine childhood  
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33 88 vaccinations in UK, coverage of over 90% would be expected for rotavirus vaccine;[15] initial figures for  
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35 89 England indicate 93% uptake for first dose and 88% for the second dose of rotavirus vaccine.[16]

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40 90 Clinical trials in middle and high income countries demonstrated high (> 85%) efficacy against severe  
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42 91 rotavirus gastroenteritis.[10] The introduction of rotavirus vaccines in the immunisation programmes of  
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44 92 these countries has demonstrated direct benefits on a par with those observed in clinical trials, with  
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46 93 significant reductions in diarrhoea hospitalisations.[17] An unanticipated but beneficial consequence of  
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48 94 rotavirus vaccination has been the reduction of rotavirus disease in unvaccinated individuals (herd  
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50 95 protection), likely due to reduced virus transmission. Such “indirect benefits” include reduced disease in  
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52 96 non-vaccinated older children and adults who were not thought to sustain a significant burden of rotavirus  
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54 97 disease.[18] In the UK the burden of RVGE in older children and adults is difficult to estimate but admissions  
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56 98 for AGE are 2 per 1,000 population in 5-14 year olds and 7 per 1,000 in those 15+ years.[19] Hence  
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1 99 monitoring changes in AGE incidence in non-vaccinated older children and adults is critical to assess indirect  
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4 100 impact.  
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7 101 Ecological rotavirus vaccine effectiveness studies have primarily focused on mortality, hospitalisations and  
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9 102 laboratory detections as a measure of burden.[20–27] Severe cases of rotavirus infection will often end up in  
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11 103 hospital and receive full diagnostic evaluation. However, many cases of rotavirus infection particularly in  
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13 104 older children and adults will not attend hospital but will be seen by primary and community healthcare  
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15 105 providers. Therefore in order to better understand the burden of RVGE and AGE on all ages and the impact  
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17 106 of routine immunisation on the health system, it is crucial to examine routine data sources for all health  
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19 107 service providers in a defined study area. Taking advantage of a range of regional healthcare facilities in  
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21 108 Merseyside, UK, we describe a protocol for an ecological study which will use a “before and after” approach  
22  
23 109 allowing comprehensive evaluation of the direct and indirect vaccine impact following the introduction of  
24  
25 110 the monovalent rotavirus vaccine into the UK’s routine childhood immunisation programme. We will  
26  
27 111 investigate the relationship between socioeconomic deprivation, and vaccine uptake and disease burden.  
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29 112 These data will provide evidence to support future rotavirus vaccination in the UK and will inform rotavirus  
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31 113 immunisation policy in other Western European countries.[6]  
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## 35 114 **METHODS**

### 36 115 **Study aim**

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39 116 Routine data sources will be used to estimate the direct and indirect effects of monovalent rotavirus  
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41 117 vaccination on gastroenteritis indicators in the population of Merseyside, UK, and their relationship to  
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43 118 vaccine coverage and socio-demographic indicators. We also hope to identify the key areas that require  
44  
45 119 extended and improved data collection tools to maximise the usefulness of this surveillance approach. The  
46  
47 120 main outcome measures are:

- 48 121 • Laboratory detections of rotavirus in faecal samples
  - 49 122 • Admissions to hospital for RVGE or AGE
  - 50 123 • Attendances to EDs for AGE
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- 124 • Number of nosocomially-acquired cases of RVGE
  - 125 • General practice (GP) and community consultations for diarrhoea and AGE in children less than 5 and in  
126 all ages
  - 127 • Routine rotavirus vaccine coverage mapping by small area geography
  - 128 • Relative contribution of direct (those vaccinated) and indirect (not vaccinated) effects to overall vaccine  
129 benefit in health system usage for both RVGE and AGE
  - 130 • Relationship between socioeconomic deprivation, vaccine uptake and RVGE / AGE incidence

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### 131 **Study setting and location**

132 The study will be conducted in the large metropolitan area of Merseyside in North West England which  
133 contains the city of Liverpool. Merseyside has a population of nearly 1.4 million people, with approximately  
134 80,000 of its population under 5 years of age. Socioeconomic deprivation within Merseyside is variable but  
135 over 60% of its population live in a more socioeconomically deprived area than the England average (Figure  
136 1).[28]. Vaccination uptake for most routine childhood vaccinations is also variable in small areas, but overall  
137 Merseyside has uptake above the average for England.[15] Healthcare for the population is self-contained  
138 with the region and including a specialist paediatric hospital. Further detail of healthcare provision is  
139 provided below.

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### 140 **Study overview and choice of study designs**

141 The study will employ an ecological design, utilising routine health surveillance data before and after  
142 rotavirus vaccine introduction. The evaluation incorporates interrupted time-series analyses of outcome  
143 indicators across the study population. Comparisons of outcome indicator rates will be made between  
144 communities with high vaccine uptake and those with lower vaccine uptake and the relationship with  
145 socioeconomic deprivation. The ecological study approach allows population based rates of outcomes to be  
146 compared in space and time using vaccine uptake and community level socioeconomic deprivation as  
147 covariates.

### 148 **Study data**

1 149 The National Health Service (NHS) in England and other government service agencies collect a range of  
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3 150 administrative and health care data which is held at both local service level and centrally. Figure 2 outlines  
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5 151 the data sources that will be used for the evaluation and table 1 shows the case definitions.  
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9 152 Hospital admission and ED attendance data will be obtained from hospital episode statistics (HES),[19] which  
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11 153 record all inpatient admissions in NHS hospitals in England. The study will therefore measure hospitalisations  
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13 154 and ED attendances for residents of Merseyside receiving care in hospitals throughout England.  
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15  
16 155 The study will obtain GP consultation data for diarrhoea or gastroenteritis from Clinical Commissioning  
17  
18 156 Groups covering Merseyside or from government held sentinel surveillance systems. Community  
19  
20 157 consultations for diarrhoea and gastroenteritis at “Walk-in Centres” will be sourced from NHS Community  
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22 158 Health Trusts. Walk-in Centres are primarily nurse-led primary care facilities for illness and injuries without  
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24 159 need for prior appointment.  
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27  
28 160 Rotavirus gastroenteritis at Alder Hey Children’s NHS Foundation Trust (Alder Hey) in Liverpool is classified  
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30 161 as community acquired or nosocomial. Alder Hey’s footprint covers the majority of Merseyside’s children, so  
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32 162 these data will enable evaluation of the effect of rotavirus vaccination on nosocomial rotavirus infection in  
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34 163 children across Merseyside.  
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37 164 Laboratory detections of rotavirus from Public Health England Laboratory surveillance covering Merseyside  
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39 165 residents will be included in the analysis. Other causative agents of AGE identified through laboratory testing  
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41 166 including, for example, norovirus, adenovirus, and astrovirus will also be extracted for analysis.  
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44 167 Each data set will cover at least three-years either side of vaccine introduction. All data will be pseudo-  
45  
46 168 anonymised to allow distinction of records but no linking of data sets or identification of individuals will be  
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48 169 undertaken. All data will be either geo-coded from postcode to small statistical geographical community  
49  
50 170 units termed Lower Super Output Areas (LSOA) or sourced with this geography. LSOAs consist of  
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52 171 approximately 1,500 persons and denominator populations will be derived from the Office of National  
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54 172 Statistics (ONS) mid-year population-estimates by LSOA.[29] Indicators of socioeconomic deprivation at LSOA  
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56 173 level will be measured using the English Indices of Deprivation. The UK Department for Communities and  
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174 Local Government produce the English indices of Deprivation using census and other local administrative  
 175 data.[28] Rotavirus vaccination uptake data will be sourced from the Child Health Information System (CHIS)  
 176 which is held by community NHS health Trusts in Merseyside. Records of doses of vaccinations given as part  
 177 of the UK childhood vaccine schedule are recorded in CHIS for each child.

178 **Table 1: Case definitions by health data set**

Data set	Case definition
Nosocomial and community acquired	Nosocomial – Laboratory confirmed rotavirus case. Gastroenteritis symptoms beginning more than two days after admission  Community acquired – Laboratory confirmed rotavirus case. Gastroenteritis symptoms starting within two days of admission
Hospital admissions	Rotavirus case definition - Inpatient finished consultant episodes (FCE) with a primary or subsidiary diagnosis International Classification of Disease version 10 (ICD10) diagnosis code of A08.0  AGE case definition – inpatient FCE with a primary or subsidiary diagnosis ICD10 code of A08 --A09
Emergency department attendances	Attendance with a primary or secondary diagnosis code Z:III  Gastrointestinal conditions-Other (those subsequently admitted excluded to prevent duplication in hospital admissions)
GP Consultations	GP consultations (Read codes in parenthesis): Diarrhoea and vomiting (19G); Diarrhoea symptom NOS (19F6), Viral Gastroenteritis (A07y0), Diarrhoea (19F2); Gastroenteritis - presumed infectious origin (A0812), Diarrhoea of presumed infectious origin (A083); Infantile viral gastroenteritis (A07y1); Infectious gastroenteritis (A0803); Enteritis due to rotavirus (A0762); and, Infectious diarrhoea (A082). Viral gastroenteritis will be used as the primary case definition but diarrhoea/vomiting will be used for a secondary indicator of burden.

<p>1 2 3 4 5 6 7 8 9 10 11 12</p> <p>Community consultations (Walk-in-Centres)</p>	<p>There is no coding system for diagnosis in Walk-in-Centre data.</p> <p>Therefore the description of patient symptoms field will be queried using the following key words: diarrhoea, vomiting, GI and gastroenteritis. A Soundex script will be used to allow for spelling inaccuracies.</p>
<p>13 14 15 16</p> <p>Laboratory detections</p>	<p>Detection of rotavirus in a faecal specimen by a standard assay.</p> <p>Detection of other AGE causative organisms</p>

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20 **180 Quality control**

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23 **181** Data sources such as HES and laboratory detections will be influenced by testing practices; for instance  
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25 **182** testing of some organisms is more likely to occur at certain times of the year. In the hospital admission data  
26  
27 **183** set it is possible that some cases of RVGE will not be coded as rotaviral enteritis (ICD10: A08.0) and may be  
28  
29 **184** classified as other-unspecified either due to an absence of laboratory confirmation or misclassification /  
30  
31 **185** miscoding. In order to attempt to quantify this information bias the investigator team will perform quality  
32  
33 **186** control on hospital admissions and laboratory detections at the lead NHS Trust hospital site (Alder Hey).  
34  
35 **187** Using a sample of cases from at least 3 years, those cases with a laboratory confirmation will be checked  
36  
37 **188** against clinical records and clinic coding and those coded as ICD10 A08.0 rotaviral enteritis will be cross-  
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39 **189** matched against laboratory detections. Based on the results of this assessment, it may be necessary to  
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41 **190** adjust the recorded number of hospital admissions for any ascertainment bias identified.

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45 **191 Ethical considerations**

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48 **192** The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference:  
49  
50 **193** 14/SC/1140. Data sharing agreement will be obtained between PHE, participating NHS Trusts and the  
51  
52 **194** University of Liverpool. Research governance approval will be sought form all participating NHS Trusts.

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55 **195 Data analysis**

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1 196 Changes in trends of primary care consultations, community consultations, ED attendances, hospitalisations  
2  
3 197 and rotavirus detections will be explored using interrupted time series analysis. Moving averages will be  
4  
5 198 examined to highlight any long-term trends whilst smoothing out any short-term fluctuations. Standardized  
6  
7 199 population based rates for a minimum of a three-year period prior to vaccination and year on year after  
8  
9 200 vaccination (for three years) will be compared. For the regression analysis, Poisson regression will be used.  
10  
11 201 We will first compute monthly population based rates that are “expected” to occur in the absence of a  
12  
13 202 rotavirus vaccination programme by fitting the model to pre-vaccine data. We will then adjust for  
14  
15 203 seasonality. The model will be used to estimate “expected” population based rates after vaccination and we  
16  
17 204 will then compare with “observed” population based rates. We will then calculate rate ratios and assess the  
18  
19 205 magnitude of decline in rates. Using a Poisson regression model, and including demographic and vaccine  
20  
21 206 uptake indicators we would be able to predict impact of vaccination on the AGE and RVGE indicators at  
22  
23 207 various services and vaccine uptake levels. Potential data biases will be controlled for by the access and  
24  
25 208 analysis multiple health data sources over a minimum of six years.  
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30 209 Environmental factors which may influence rotavirus incidence and seasonality are difficult to identify or  
31  
32 210 indeed quantify. To account for any potential environmental confounders, correlation of laboratory  
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34 211 confirmations of viral gastroenteritis causing organisms (e.g. norovirus, astrovirus) with rotavirus laboratory  
35  
36 212 confirmations will be established. If a significant correlation between any other viral gastroenteritis and  
37  
38 213 rotavirus can be identified, the resulting correlation coefficients will be used to estimate relative  
39  
40 214 contribution of vaccination and undefined environmental factors to any changes in rotavirus incidence.  
41  
42 215 Furthermore we will explore a potential reciprocal increase in other viral agents (e.g. norovirus) due to a  
43  
44 216 decrease in circulating rotavirus, and potential increase in susceptible individuals particularly in those under  
45  
46 217 5 years of age.

#### 218 **Power calculation**

219 Based on hospital admissions for RVGE in 2012 obtained from HES data, the estimated rate of RVGE  
220 hospitalisation is approximately 1 per 1,000 children under age 5 years in England.[19] Assuming high  
221 vaccine uptake rates (i.e. 95%), similar to uptake of other routine childhood vaccines in Merseyside, we used

222 a one sample comparison of proportions for a two sided test to calculate the power estimates (Table 2).  
 223 Studies from other high income countries on the population effects of rotavirus vaccination have shown  
 224 reductions in hospital admissions of over 50% in children under 5 years of age [14]. Assuming a similar  
 225 reduction in Merseyside, this study has over 90% power to detect a significant change in RVGE hospital  
 226 admissions.

227 **Table 2: Predicted power of study for main outcome (hospitalisation rate) in Merseyside and selected sub-**  
 228 **districts.**

Area	Population (children <5 years)	Assumed reduction in rotavirus hospitalisation rate				
		25%	30%	40%	50%	75%
Liverpool	27000	0.22	0.31	0.56	0.82	1
Liverpool and Sefton	41000	0.34	0.48	0.78	0.96	1
Liverpool, Sefton and Knowsley	50000	0.41	0.58	0.87	0.99	1
Merseyside	80000	0.63	0.8	0.98	1	1

229  
 230 The study is also powered for detecting an indirect effect in adults. Using an AGE hospital admission rate of 7  
 231 per 1,000 population aged 15+ years [19] we would expect power to be at least 0.97 for Merseyside at  
 232 assumed hospitalisation rate reductions post vaccination of 5%, 8%, and 10%. Additionally, for GP  
 233 consultations in the children under five, using case definitions defined above a power of 0.89 and 1 can be  
 234 achieved, for detecting a significant change in GP consultations. For assumed consultation rate reductions  
 235 post vaccination of 5% and 10% respectively. No formal power calculations have been undertaken for other  
 236 end-points under study.

### 237 **Timeline**

238 The study will be conducted over a three year period beginning in April 2014. Prior to study commencement,  
 239 r administrative procedures will be undertaken including data sharing agreements, consultation with data  
 240 providers, database development for storing all sourced data, data analysis and report writing (including  
 241 interim yearly, final and peer review papers).

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242 **Project governance**

243 A stakeholder group within Merseyside will be established to enable effective achievement of the project  
244 objectives and ownership by the professional community. The stakeholder group will include representatives  
245 from: [Liverpool Health Partners](#);<sup>[30]</sup> [Liverpool Community Health NHS Trust](#);<sup>[31]</sup> [NHS England Merseyside](#)  
246 [Area Team Screening and Immunisation Team](#);<sup>[32]</sup> [Alder Hey Children's NHS Foundation Trust](#)<sup>[33]</sup> and [Public](#)  
247 [Health England](#)<sup>[34]</sup>-Liverpool.

248 **Dissemination of research findings**

249 The findings will be presented at professional and scientific conferences. The results will also be published in  
250 peer review publications. Interim and final reports will be submitted to the funders and the stakeholder  
251 group.

252 **DISCUSSION**

253 This study will enable demonstration of a complete health system perspective of the impact of rotavirus  
254 vaccination on the burden of disease in Merseyside, UK. It aims to study both direct and indirect effects of  
255 routine rotavirus vaccination. The study will also enable data on vaccine efficacy to infer the relative  
256 contribution of RVGE to AGE primary care, and emergency care consultations. Furthermore as data will be  
257 linked to specific geographical units, for which information on socioeconomic deprivation and vaccine  
258 uptake is available, we will be able to explore the association of these with disease burden. Quality control  
259 procedures contained within the study will provide a means of adjusting analysis for information bias and  
260 also enable identification of the key data collection issues that require improvement to maximise the  
261 usefulness of this surveillance approach. It is also hoped that this study will provide a learning resource and  
262 template for similar ecological approaches to examine effectiveness of other vaccines in the UK in the future.

263 **Strengths**

264 A whole health system approach in a geographically defined area provides a number of strengths. Using data  
265 sets from a range of health care providers within a health economy will allow us to examine the relative  
266 impact of vaccination on the various health providers rather than the individual. The use of multiple data

1 267 sources to measure independent indicators of vaccination effect will also provide robustness, enabling easier  
2  
3 268 identification of outliers from overall trends.  
4

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6 269 Since there is annual variability in the number of rotavirus cases, it is imperative to conduct surveillance of  
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8 270 rotavirus incidence over a number of years pre- and post- vaccine introduction. This study will provide a  
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10 271 mechanism to do this as it will cover three rotavirus seasons post vaccine introduction. Thus cofounding  
11  
12 272 caused by yearly variance in rotavirus numbers will be minimised.  
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14  
15 273 There are limited published data describing the indirect effect of routine vaccination on un-vaccinated older  
16  
17 274 children and adults and the majority of studies have focused on hospital admissions. As this study will collect  
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19 275 data for all ages and cover RVGE and AGE incidence 3 years post-vaccination it will provide sufficient data for  
20  
21 276 measurement of the indirect effect on hospital admissions. Additionally, whilst the majority of studies into  
22  
23 277 the indirect effect of vaccination have focused on hospital admissions, this study will examine indirect effects  
24  
25 278 in EDs and community settings. This is particularly important as it is perhaps more likely that  
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27 279 moderate/severe RVGE in un-vaccinated older children and adults will be treated at EDs and through  
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29 280 community consultations.  
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33 281 Another potential strength of the study is the ability to conduct analysis at small community (LSOA) level.  
34  
35 282 This will enable small area socio-demographic information such as socioeconomic deprivation to be included  
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37 283 in the analyses as a covariate at the lowest possible unit of analyses other than the individual. Thus, allowing  
38  
39 284 the exploration of the association between socioeconomic deprivation, burden of RVGE / AGE and vaccine  
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41 285 uptake whilst limiting the ecological fallacy of analysis.  
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44 286 As many of the data sources included in this study do not include specific RVGE classification, we will be  
45  
46 287 using AGE as an outcome measure for most data sets. Laboratory detection data which are organism specific  
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48 288 will allow us to adjust these measures based on the seasonal contribution of organisms other than rotavirus  
49  
50 289 such as norovirus. For example RVGE seasonality is fairly constant but that of norovirus tends to vary over  
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52 290 the winter and spring months in the UK. These AGE indicators can therefore be adjusted for changes in  
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54 291 norovirus seasonality (Figure 3)[35] to give a better proxy of the contribution of rotavirus to overall GI causes  
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56 292 and the relative impact of rotavirus vaccination  
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293 **Limitations**

294 The gold standard for measurement of vaccine efficacy is the randomised controlled trial. However, this  
295 ecological study will investigate the impact of vaccination on population disease burden within a health  
296 system; therefore an ecological study is appropriate. Conversely it is recognised an ecological approach  
297 cannot show individual level effects of vaccine and can only infer the impact of the vaccine at the population  
298 level without causation. Additionally, a key focus of this study will be to quantify variation in the outcomes  
299 measured according to vaccine uptake levels and socioeconomic deprivation. Confounding may be an issue  
300 since cases living in areas with low vaccine uptake or high socioeconomic deprivation may also have other  
301 characteristics that will affect the risk of RVGE or AGE.

302 For measures of AGE activity in community settings (e.g. GP and Walk-in-Centre), we will use syndromic  
303 indicators that are non-specific to rotavirus e.g. diarrhoea, vomiting. An inherent issue is that the ability to  
304 detect effect on these is likely to be limited to large effects rather than small variations.

305 A further limitation of the study is that investigators will not collect data directly as all data are secondary,  
306 with consequent risk of bias.. There is potential for clinical coding to lead to misclassification of disease, and  
307 this misclassification may vary by different data sources. We will describe these biases through quality  
308 control and subsequently adjust for them at the analysis stage. The use of multiple data sets for outcome  
309 indicators limits these issues by improving robustness.

310 It is likely that there have been changes in data collection methods over the study period, for example  
311 changes to the assay used for rotavirus laboratory testing, leading to testing bias. One way to adjust for this  
312 in the analysis is to pool data over a number of years to smooth fluctuations caused by changes in testing  
313 methods. The investigators will identify changes through contact with rotavirus testing laboratories and NHS  
314 Trusts, so that changes may be described and where possible assist appropriate analytical adjustments. It is  
315 also feasible that the introduction of vaccination may also trigger changes in clinician requests for rotavirus  
316 and other AGE diagnostic testing, particularly in the vaccination age group. Any possible testing bias will be  
317 assessed at the lead NHS Trust via comparisons with pre-vaccine testing probabilities.

1 318 The study currently will not include any economic component. However, previous studies have reported the  
2  
3 319 likely cost-effectiveness of rotavirus vaccination for the population under 5 years of age.[36] This study will  
4  
5 320 provide the results and data necessary for economic evaluation based on the direct and indirect impact of  
6  
7 321 rotavirus vaccination.  
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## 10 322 **FOOTNOTES**

### 11 323 **Contributions**

12  
13  
14  
15  
16  
17 324 DH participated in the design of the study, will oversee the study co-ordination, data collection and analysis,  
18  
19 325 and wrote the manuscript. RV conceived of the study and participated in its design; and will contribute to  
20  
21 326 study co-ordination and analysis. MIG conceived of the study and participated in its design; and will  
22  
23 327 contribute to study co-ordination. NF conceived of the study and participated in its design; and will oversee  
24  
25 328 study co-ordination and contribute to analyses. NC conceived of the study, participated in its design and will  
26  
27 329 contribute to study co-ordination. All authors were involved in revising the manuscript and read and  
28  
29 330 approved the final manuscript.  
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32  
33 331 **Acknowledgements** The authors gratefully acknowledge the effort and assistance provided by all the  
34  
35 332 research and development staff, laboratory technicians, data entry staff and support staff at the  
36  
37 333 collaborating sites.  
38  
39

### 40 334 **Funding**

41  
42  
43 335 This study is in part supported (approximately 35% of total cost) by GlaxoSmithKline Biologicals SA.  
44  
45 336 GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this  
46  
47 337 manuscript for factual accuracy but the authors are solely responsible for final content and interpretation.  
48  
49 338 The authors received no financial support or other form of compensation related to the development of the  
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51 339 manuscript..  
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### 54 340 **Competing interests**

55  
56  
57 341 Financial competing interests  
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1 342 The Rotarix™ vaccine used in the UK national immunisation programme evaluated by this study is developed  
2  
3 343 and licensed by GlaxoSmithKline Biologicals. NC is in receipt of research grant support from GSK Biologicals  
4  
5 344 (to University of Liverpool) and has received honoraria for participation in GSK Rotavirus Vaccine Advisory  
6  
7  
8 345 Board Meetings.

9  
10 346 Non-financial competing interests

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14 347 The authors declare that they have no non-financial competing interests.

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16  
17 348 **Peer review** The protocol was peer reviewed externally and internally prior to sponsor and ethical approval.

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20 349 **Ethics approval** The study has been approved by NHS Research Ethics Committee, South Central-Berkshire

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22 350 REC Reference: 14/SC/1140

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## 39 438

### 40 439 **Additional figure titles and legends**

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#### 42 440 **Figure 1. Socioeconomic deprivation in Merseyside**

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44 441 Produced using the English Indices of Deprivation 2010, national quintiles for the Index of Multiple

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46 442 Deprivation [19].

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#### 48 443 **Figure 2. Schematic of study data sources and outcome measures**

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50 444 Data sources cover a variety of health care providers at different levels of the health system. This shows

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52 445 from which data sources outcome measures will be obtained.

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446 **Figure 3. Laboratory detections of rotavirus and norovirus in the North West, England, 2009/10-2013-14**

447 Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the  
448 norovirus season as compared to the rotavirus season.

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1 **Ecological assessment of the direct and indirect effects of routine rotavirus vaccination in**  
2 **Merseyside, UK using data from multiple health systems: a study protocol**

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15  
16 **Keywords**

17 Rotavirus; Vaccination; Gastroenteritis; Epidemiology; Immunity, Herd

18 **Word Count**

19 3,577-624 (excluding footnotes)

## 22 ABSTRACT

### 23 Introduction

24 Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide.  
25 Currently 67 countries include rotavirus vaccine in childhood immunisation programmes, but uptake in  
26 Western Europe has been slow. In July 2013 rotavirus vaccine was introduced into the UK's [routine](#)  
27 childhood immunisation programme. Prior to vaccine introduction in the UK rotavirus was estimated to  
28 result in 750,000 diarrhoea episodes and 80,000 GP consultations each year, together with 45% and 20% of  
29 hospital admissions and emergency department attendances for acute gastroenteritis, in children under five-  
30 years of age. ~~It is therefore important to assess vaccine impact in the UK.~~ This paper describes a protocol for  
31 an ecological study ~~to that will assess rotavirus vaccine impact in the UK, to support continued vaccination~~  
32 ~~and~~ inform rotavirus immunisation policy [in the UK and](#) in other Western European countries.

### 33 Methods and analysis

34 In Merseyside, UK we will conduct an ecological study using a “before and after” approach to examine  
35 changes in gastroenteritis and rotavirus incidence following the introduction of rotavirus vaccination. Data  
36 will be collected on mortality, hospital admissions, nosocomial infection, emergency department  
37 attendances, GP consultations and community health consultations to capture all healthcare providers [in the](#)  
38 ~~region that people access with symptoms of rotavirus and acute gastroenteritis and rotavirus gastroenteritis.~~  
39 We will assess both the direct and indirect (~~herd~~) effects of the vaccine on the study population.  
40 Comparisons of outcome indicator rates will be made in relation to vaccine uptake and ~~the association with~~  
41 ~~socioeconomic status, deprivation examined.~~

### 42 Ethics and dissemination

43 ~~The study has been approved by~~ NHS [Research Ethics Committee, South Central-Berkshire REC Reference:](#)  
44 ~~14/SC/1140 approval has been granted. The Study outputs findings~~ will be disseminated through scientific  
45 conferences and peer-reviewed publications. The ~~study findings will enable~~ [demonstration of the impact of](#)  
46 ~~rotavirus vaccination on the burden of disease from~~ a complete health system perspective. ~~of the impact of~~

~~rotavirus vaccination on the burden of disease.~~ It will ~~also~~ identify key areas that require improved data collection tools to maximise the usefulness of this surveillance approach and will provide a template for ~~ecological methodology~~ vaccine evaluations using ecological methods in the UK.

## STRENGTHS AND LIMITATIONS

- Strengths include use of data from multiple health systems that will allow examination of the relative impact of vaccination on the various health providers and communities rather than the individual. These multiple data sources will provide robustness, enabling easier identification of outliers from overall trends.
- The study will ~~include~~ cover all ages for rotavirus and all cause gastroenteritis incidence for three years post-vaccination, thereby minimising cofounding caused by yearly variance in rotavirus numbers.
- Additionally ~~the study~~ is powered to measure the indirect (herd) effect on hospital admissions and whilst the majority of studies have focused on this, this study will also provide evidence for the indirect effect in emergency departments and community settings.
- The study ~~is~~ will be limited by the ecological before and after design, and the difficulties of ascribing causality to vaccine, as well as the inherent risks of bias and confounding in observational studies particularly due to underlying secular trends.
- ~~Use of~~ ing syndromic indicators that are non-specific to rotavirus will ~~limits~~ the study to measuring large effects rather than small variations for emergency departments and community health outcome measures.

## INTRODUCTION

Rotavirus is the most common cause of severe gastroenteritis in infants and young children, responsible for an estimated annual 453,000 deaths worldwide among children under age 5 years, with over 90% of deaths occurring in the developing countries.[1] In the UK, rotavirus gastroenteritis (RVGE) is seasonal and most cases occur between February and April each year. Rotavirus is estimated to result in 750,000 diarrhoea episodes and 80,000 GP consultations each year in the UK,[2] together with 45% and 20% of hospital

1 73 admissions and emergency department (ED) attendances for acute gastroenteritis (AGE), respectively in  
2  
3 74 children under 5 years of age.[3] The economic cost of RVGE to the health service is estimated to be  
4  
5 75 approximately £14 million per year in England and Wales.[3] At Alder Hey Children's NHS Foundation Trust,  
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7 76 Liverpool, UK rotavirus is a major cause of community-acquired and healthcare-associated diarrhoea; in a 2-  
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9 77 year prospective study among hospitalised children, rotavirus was detected by RT-PCR in 43% of community-  
10  
11 78 acquired and in 31% of healthcare-associated gastroenteritis cases.[4] AGE hospital admissions are known to  
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13 79 have a positive correlation with [socioeconomic](#) deprivation [5] and globally the burden of severe RVGE is  
14  
15 80 much higher in low-income countries. However, ~~no statistical correlation between RVGE in infants has not~~  
16  
17 81 ~~yet been correlated with and socioeconomic~~ deprivation ~~has been shown to exist~~ in the UK.  
18  
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20  
21 82 In July 2013, the Department of Health introduced a rotavirus vaccine into the UK's [routine](#) childhood  
22  
23 83 immunisation programme.[6,7] The live-attenuated, two-dose oral monovalent vaccine (Rotarix™,  
24  
25 84 GlaxoSmithKline Biologicals, Belgium) is administered at two and three months of age. Clinical trials in  
26  
27 85 Europe and the Americas with both currently licensed rotavirus vaccines (Rotarix™ and a pentavalent vaccine  
28  
29 86 RotaTeq™ developed by Merck), led to a WHO recommendation in 2007 to vaccinate children in these  
30  
31 87 regions.[8–10] Subsequent trials in Africa and Asia led to an extension of the recommendation to include all  
32  
33 88 children worldwide.[10–12] At present more than 60 countries include a rotavirus vaccine in childhood  
34  
35 89 immunisation programmes.[13] ~~Uptake Introduction of rotavirus vaccination~~ in Western Europe has been  
36  
37 90 slow however, with only Austria, Belgium, Finland, Luxemburg and most recently the UK having rolled out  
38  
39 91 universal rotavirus vaccination programmes to date.[14] Based on the uptake of other routine childhood  
40  
41 92 vaccinations in UK, ~~vaccine coverage uptake of~~ over 90% would be expected for rotavirus  
42  
43 93 ~~vaccine immunisation;~~[15] and initial ~~uptake~~ figures for England ~~indicate support this with~~ 93% ~~uptake~~ for  
44  
45 94 first dose and 88% for the second dose ~~of rotavirus vaccine~~. [16]  
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51 95 Clinical trials in middle and high income countries demonstrated high (> 85%) efficacy against severe  
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53 96 rotavirus gastroenteritis.[10] The introduction of rotavirus vaccines in the immunisation programmes of  
54  
55 97 these countries has demonstrated direct benefits on a par with those observed in clinical trials, with  
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57 98 significant reductions in diarrhoea hospitalisations.[17] An unanticipated but beneficial consequence of  
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59 99 rotavirus vaccination ~~has been~~ the reduction of rotavirus disease in unvaccinated individuals (herd  
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100 protection), likely due to reduced virus transmission. Such “indirect benefits” include reduced disease in  
101 non-vaccinated older children and adults who were not thought to sustain a significant burden of rotavirus  
102 disease.[18] In the UK the burden of RVGE in older children and adults is difficult to estimate but admissions  
103 for [viral gastroenteritis AGE](#) are 2 per 1,000 population in 5-14 year olds and 7 per 1,000 in those 15+  
104 years.[19] Hence monitoring changes in AGE incidence in non-vaccinated older children and adults is critical  
105 to assess indirect impact.

106 Ecological rotavirus vaccine effectiveness studies have primarily focused on mortality, hospitalisations and  
107 laboratory detections as a measure of burden.[20–27] Severe cases of rotavirus [infection](#) will often end up in  
108 hospital and receive full diagnostic [evaluations](#). However, many cases of rotavirus [infection](#) particularly [in](#)  
109 older children and adults will not attend hospital but [will](#) be seen by primary and community healthcare  
110 providers. Therefore in order to better understand the burden of RVGE and AGE on all ages and the impact  
111 of routine immunisation on the health system, it is crucial to [examine](#) routine data sources for all  
112 health service providers in a defined study area. Taking advantage of a range of regional healthcare facilities  
113 in Merseyside, [England UK](#), we describe [a protocol for](#) an ecological study [which will use](#) a “before and  
114 after” approach [that will allow](#) comprehensive evaluation of the direct and indirect vaccine impact  
115 following [its introduction](#) [the introduction of the monovalent rotavirus vaccine](#) into the UK’s [routine](#)  
116 childhood immunisation programme. [We will](#) ~~Whilst~~ [investigate](#) the [relationship](#) ~~correlation~~ [between](#)  
117 [socioeconomic](#) deprivation, and vaccination uptake [and disease](#) ~~with~~ burden. These data will provide  
118 evidence to support future rotavirus vaccination in the UK and will inform rotavirus immunisation policy in  
119 other Western European countries.[6]

## 120 METHODS

### 121 Study aim

122 Routine data sources will be used to estimate the direct and indirect effects of [monovalent](#) rotavirus  
123 vaccination on gastroenteritis indicators in the population of Merseyside, [UK](#), and their [relationship](#) ~~of such~~  
124 [effects](#) to vaccine coverage and socio-demographic indicators. We also hope to identify the key areas that

- 1 125 require extended and improved data collection tools to maximise the usefulness of this surveillance  
2  
3  
4 126 approach. The main outcome measures are:  
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7 127 • Laboratory detections of rotavirus in faecal samples  
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9 128 • Admissions to hospital for RVGE or AGE  
10  
11 129 • Attendances to EDs for AGE  
12  
13 130 • Number of nosocomially-acquired cases of RVGE  
14  
15 131 • General practice (GP) and community consultations for diarrhoea and AGE in children less than 5 and in  
16  
17 132 all ages  
18  
19  
20 133 • Routine rotavirus vaccine coverage mapping by small area geography  
21  
22 134 • Relative contribution of direct (those vaccinated) and indirect (not vaccinated) effects to overall vaccine  
23  
24 135 benefit in health system usage for both RVGE and AGE  
25  
26 136 • Relationship between [socioeconomic](#) deprivation, vaccine uptake and RVGE / AGE incidence  
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29

### 137 **Study setting and location**

138 The study will be conducted in the large metropolitan area of Merseyside in North West England which  
139 contains the city of Liverpool. Merseyside has a population of nearly 1.4 million people, with approximately  
140 80,000 of its population under 5 years of age. [Socioeconomic](#) deprivation within Merseyside is variable but  
141 over 60% of its population live in a more [socioeconomically](#) deprived area than the England average (Figure  
142 1).<sup>[28]</sup> Vaccination uptake for most routine childhood vaccinations is also variable in small areas, but  
143 overall Merseyside has uptake above the average for England.<sup>[15]</sup> [Healthcare for the population is self-  
144 contained with the region and including a specialist paediatric hospital. Further detail of healthcare provision  
145 is provided below.](#)

### 146 **Study overview and choice of study designs**

147 The study ~~is~~ [will employ an ecological in](#) design, utilising routine health surveillance data [before and after](#)  
148 [rotavirus vaccine introduction](#). The evaluation ~~design~~ incorporates interrupted time-series analyses of  
149 outcome indicators across the study population. Comparisons of outcome indicator rates will be made



1 150 between communities with high vaccine uptake and those with lower vaccine uptake and the relationship  
2  
3  
4 151 with [socioeconomic](#) deprivation. The ecological study approach allows [population based](#) rates of outcomes  
5  
6 152 to be compared in space and time using vaccine uptake and community level [socioeconomic](#) deprivation as  
7  
8 153 covariates.

#### 10 154 **Study data**

14 155 The National Health Service (NHS) in England and other government service agencies collect a range of  
15  
16 156 administrative and health care ~~related~~ data which is held at both local service level and centrally. Figure 2  
17  
18 157 outlines the data sources that will be used for the evaluation and table 1 shows the case definitions.  
19  
20  
21 158 Hospital admission and ED attendance data will be obtained from hospital episode statistics (HES),<sup>[19]</sup> which  
22  
23 159 record all inpatient admissions in NHS hospitals in England, ~~and directly from NHS Trusts which cover the~~  
24  
25 160 ~~population of Merseyside~~ [The study will therefore measure hospitalisations and ED attendances for residents](#)  
26  
27 161 [of Merseyside receiving care in hospitals throughout England.](#)

30 162 The study will obtain GP consultation ~~datas~~ for diarrhoea or gastroenteritis from Clinical Commissioning  
31  
32 163 Groups covering Merseyside or from government held sentinel surveillance systems. Community  
33  
34 164 consultations for diarrhoea and gastroenteritis at “Walk-in Centres” will be sourced from NHS Community  
35  
36 165 Health Trusts. Walk-in Centres are primarily nurse-led primary care facilities for illness and injuries without  
37  
38 166 need for prior appointment.

41  
42 167 ~~The infection control team Rotavirus gastroenteritis~~ at Alder Hey Children’s NHS Foundation Trust ([Alder](#)  
43  
44 168 [Hey](#)) in Liverpool ~~is classifieds rotavirus cases~~ as community acquired or ~~healthcare associated~~ (nosocomial).  
45  
46 169 Alder Hey’s ~~NHS Foundation Trust’s~~ footprint covers the majority of Merseyside’s children, so these data will  
47  
48 170 enable evaluation of the effect of rotavirus vaccination on nosocomial rotavirus infection in children across  
49  
50 171 Merseyside.

52  
53  
54 172 Laboratory detections of rotavirus from Public Health England Laboratory surveillance covering Merseyside  
55  
56 173 residents will be included in the analysis. Other causative agents of AGE identified through laboratory testing  
57  
58 174 including, for example, norovirus, adenovirus, ~~astrovirusand astrovirus~~ will also be extracted for analysis.  
59  
60

175 Each data set will cover at least three-years either side of vaccine introduction. All data will be pseudo-

176 anonymised to allow distinction of records but no linking of data sets or identification of individuals will be

177 undertaken. All data will be either geo-coded from postcode to small statistical geographical community

178 units termed Lower Super Output Areas (LSOA) or sourced with this geography. [LSOAs consist of](#)

179 [approximately 1,500 persons and d](#)Denominator populations will be derived from the Office of National

180 Statistics (ONS) mid-year population-estimates by LSOA.<sup>[29]</sup> Indicators of [socioeconomic](#) deprivation at LSOA

181 level will [be measured using the English Indices of Deprivation. The UK Department for Communities and](#)

182 [Local Government produce the English indices of Deprivation using census and other local administrative](#)

183 [database sourced from the Department for Communities and Local Government.](#)<sup>[28]</sup> Rotavirus vaccination

184 uptake data will be sourced from the Child Health Information System (CHIS) which is held by community

185 NHS health Trusts in Merseyside. [Records of doses of vaccinations given as part of the UK childhood vaccine](#)

186 [schedule are recorded in CHIS for each child.](#)

187 **Table 1: Case definitions by health data set**

Data set	Case definition
Nosocomial and community acquired	Nosocomial – Laboratory confirmed rotavirus case. Gastroenteritis symptoms beginning more than two days after admission  Community acquired – Laboratory confirmed rotavirus case.  Gastroenteritis symptoms starting within two days of admission
Hospital admissions	Rotavirus case definition - Inpatient finished consultant episodes (FCE) with a primary or subsidiary diagnosis International Classification of Disease version 10 (ICD10) diagnosis code of A08.0  AGE case definition – inpatient FCE with a primary or subsidiary diagnosis ICD10 code of A08 --A09
Emergency department attendances	Attendance with a primary or secondary diagnosis code Z:III  Gastrointestinal conditions-Other (those subsequently admitted excluded to prevent duplication in hospital admissions)

GP Consultations	GP consultations (Read codes in parenthesis): <a href="#">Diarrhoea and vomiting (19G)</a> ; <a href="#">Diarrhoea symptom NOS (19F6)</a> , <a href="#">Viral Gastroenteritis (A07y0)</a> , <a href="#">Diarrhoea (19F2)</a> ; <a href="#">Gastroenteritis - presumed infectious origin (A0812)</a> , <a href="#">Diarrhoea of presumed infectious origin (A083)</a> ; <a href="#">Infantile viral gastroenteritis (A07y1)</a> ; <a href="#">Infectious gastroenteritis (A0803)</a> ; <a href="#">Enteritis due to rotavirus (A0762)</a> ; and, <a href="#">Infectious diarrhoea (A082)</a> <del>vomiting (1992-), diarrhoea (19F2) and viral gastro-enteritis (A07y0)</del> . Viral gastro-enteritis will be used as the primary case definition but diarrhoea/vomiting will be used for a secondary indicator of burden.
Community consultations (Walk-in-Centres)	There is no coding system for diagnosis in Walk-in-Centre data. Therefore the description of patient symptoms field will be queried using the following key words: diarrhoea, vomiting, GI and gastroenteritis. A Soundex script will be used to allow for spelling inaccuracies.
Laboratory detections	Detection of rotavirus in a faecal specimen by a standard assay.  Detection of other AGE causative organisms

188

189 **Quality control**

190 Data sources such as HES and laboratory detections will be influenced by testing practices; for instance  
 191 testing of some organisms is more likely to occur at certain times of the year. In the hospital admission data  
 192 set it is possible that some cases of RVGE will not be coded as rotaviral enteritis (ICD10: A08.0) and may be  
 193 classified as other-unspecified either due to an absence of laboratory confirmation or misclassification /  
 194 miscoding. In order to attempt to quantify this information bias the investigator team will perform quality  
 195 control on hospital admissions and laboratory detections at the lead NHS Trust hospital site ([Alder Hey](#)).  
 196 Using a sample of cases from at least 3 years, those cases with a laboratory confirmation will be checked  
 197 against clinical records and clinic coding and those coded as ICD10 A08.0 rotaviral enteritis will be cross-

1 198 | matched against laboratory detections. Based on the results of [this assessment audit](#), it may be  
2  
3 199 | [necessary applicable](#) to adjust the recorded number of hospital admissions for any ascertainment bias  
4  
5 200 | identified.

## 201 Ethical considerations

202 | [The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference:](#)  
203 | [14/SC/1140](#) ~~We do not foresee a requirement to obtain ethical approval for this ecological study, as analysis~~  
204 | ~~will be conducted using routinely collected aggregated data.~~ ~~However, a~~ data sharing agreement will be  
205 | obtained between PHE, participating NHS Trusts and the University of Liverpool. Research governance  
206 | approval will be sought from all participating NHS Trusts. ~~Ethics approval for quality control of data will be~~  
207 | ~~sort from NHS Research Ethics Committee if required.~~

## 208 Data analysis

209 | Changes in trends of primary care consultations, community consultations, ED attendances, hospitalisations  
210 | and rotavirus detections will be explored using interrupted time series analysis. Moving averages will be  
211 | examined to highlight any long-term trends whilst smoothing out any short-term fluctuations. Standardized  
212 | [population based](#) rates for a minimum of a three-year period prior to vaccination and year on year after  
213 | vaccination (for three years) will be compared. For the regression analysis, Poisson regression will be used.  
214 | We will first compute monthly [population based](#) rates that are “expected” to occur in the absence of a  
215 | rotavirus vaccination programme by fitting the model to pre-vaccine data. We will then adjust for  
216 | seasonality. The model will be used to estimate “expected” [population based](#) rates after vaccination and we  
217 | will then compare with “observed” [population based](#) rates. We will then calculate rate ratios and assess the  
218 | magnitude of decline in rates. Using a Poisson regression model, and including demographic and vaccine  
219 | uptake indicators we would be able to predict impact of vaccination on the AGE and RVGE indicators at  
220 | various services and vaccine uptake levels. Potential data biases will be controlled for by the access and  
221 | analysis multiple health data sources over a minimum of six years.

222 Environmental factors which may influence rotavirus incidence and seasonality are difficult to identify or  
 223 indeed quantify. To account for any potential environmental confounders, correlation of laboratory  
 224 confirmations of viral gastroenteritis causing organisms (e.g. norovirus, astrovirus) with rotavirus laboratory  
 225 confirmations will be established. If a significant correlation between any other viral gastroenteritis and  
 226 rotavirus can be identified, the resulting correlation coefficients will be used to estimate relative  
 227 contribution of vaccination and undefined environmental factors to any changes in rotavirus incidence.  
 228 Furthermore we will explore a potential ~~“rebound” effect on an~~reciprocal increase in other viral agents (e.g.  
 229 norovirus) due to a decrease in circulating rotavirus, and potential increase in susceptible individuals  
 230 particularly in those under 5 years of age.

### 231 Power calculation

232 Based on hospital admissions for RVGE in 2012 obtained from HES data, the estimated rate of RVGE  
 233 hospitalisation is approximately 1 per 1,000 children under age 5 years in England. [19] Assuming reductions  
 234 ~~in this rate between 25% and 75%, with and~~ high vaccine uptake rates (i.e. 95%), similar to uptake of other  
 235 routine childhood vaccines in Merseyside, we used a one sample comparison of proportions for a two sided  
 236 test to calculate the power estimates ~~shown in (T~~table 2). Studies from other high income countries on the  
 237 population effects of rotavirus vaccination have shown reductions in hospital admissions of over 50% in  
 238 children under 5 years of age [14]. ~~Assuming~~ Supposing a similar reduction in Merseyside, this study ~~has is~~  
 239 ~~powered at~~ over 90% power to detect a significant change in RVGE hospital admissions.

240 **Table 2: Predicted power of study for main outcome (hospitalisation rate) in Merseyside and selected sub-**  
 241 **districts.**

Area	Population (children <5 years)	Assumed reduction in rotavirus hospitalisation rate				
		25%	30%	40%	50%	75%
Liverpool	27000	0.22	0.31	0.56	0.82	1
Liverpool and Sefton	41000	0.34	0.48	0.78	0.96	1
Liverpool, Sefton and Knowsley	50000	0.41	0.58	0.87	0.99	1
Merseyside	80000	0.63	0.8	0.98	1	1

1 242  
2  
3  
4 243 The study is also powered for detecting an indirect effect in adults. Using an AGE hospital admission rate of 7  
5  
6 244 per 1,000 population aged 15+ years [19] we would expect power to be at least 0.97 for Merseyside at  
7  
8 245 assumed hospitalisation rate reductions post vaccination of 5%, 8%, and 10%. [Additionally, for GP](#)  
9  
10 246 [consultations in the children under five, using case definitions defined above a power of 0.89 and 1 can be](#)  
11  
12 247 [achieved, for detecting a significant change in GP consultations. For assumed consultation rate reductions](#)  
13  
14 248 [post vaccination of 5% and 10% respectively.](#) No formal power calculations have been undertaken for other  
15  
16  
17 249 end-points under study.

## 20 250 **Timeline**

21  
22  
23 251 The study will be conducted over a three year period beginning in April 2014. [Prior to study commencement,](#)  
24  
25 252 [which includes time for](#) administrative procedures [will to](#) be undertaken [including such as](#) data sharing  
26  
27 253 agreements, consultation with data providers, database development for storing all sourced data, data  
28  
29 254 analysis and report writing (including interim yearly, final and peer review papers).

## 30 255 **Project governance**

31  
32  
33 256 A stakeholder group within Merseyside will be established to enable effective achievement of the project  
34  
35 257 objectives and ownership by the professional community. The stakeholder group will include representatives  
36  
37 258 from: [Liverpool Health Partners](#);[30] [Liverpool Community Health NHS Trust](#);[31] [NHS England Merseyside](#)  
38  
39 259 [Area Team Screening and Immunisation Team](#);[32] [Alder Hey Children's NHS Foundation Trust](#)[33] and [Public](#)  
40  
41 260 [Health England](#)[34]-Liverpool.

## 42 261 **Dissemination of research findings**

43  
44  
45 262 The findings will be presented at professional and scientific conferences. The results will also be published in  
46  
47 263 peer review publications. Interim and final reports will be submitted to the funders and the stakeholder  
48  
49 264 group.

## 50 265 **DISCUSSION**

1  
2 266 This study will enable demonstration of a complete health system perspective of the impact of rotavirus  
3  
4 267 vaccination on the burden of disease in Merseyside, UK. It aims to study both direct and indirect effects of  
5  
6 268 routine rotavirus vaccination. The study will also enable data on vaccine efficacy to infer the relative  
7  
8 269 contribution of RVGE to AGE primary care, and emergency care consultations. Furthermore as data will be  
9  
10 270 linked to specific geographical units, for which information on [socioeconomic](#) deprivation and vaccine  
11  
12 271 uptake is available, we will be able to explore the association of these with ~~overall vaccine~~  
13  
14 272 ~~effectiveness~~[disease burden](#). Quality control ~~procedures~~[audits](#) contained within the study will provide a  
15  
16 273 means of adjusting analysis for information bias and also enable identification of the key data collection  
17  
18 274 issues that require improvement to maximise the usefulness of this surveillance approach. It is also hoped  
19  
20 275 that this study will provide a learning resource and template for ~~similar future~~ ecological [approaches to](#)  
21  
22 276 ~~examine vaccine~~ effectiveness [of other vaccines studies](#) in the UK [in the future](#).

## 277 **Strengths**

278 A whole health system approach in a geographically defined area provides a number of strengths. Using data  
279 sets from a range of health care providers within a health economy will allow us to examine the relative  
280 impact of vaccination on the various health providers rather than the individual. The use of multiple data  
281 sources to measure independent indicators of vaccination effect will also provide robustness, enabling easier  
282 identification of outliers from overall trends.

283 Since there is annual variability in the number of rotavirus cases, it is imperative to conduct surveillance of  
284 rotavirus incidence over a number of years pre- and post- vaccine introduction. This study will provide a  
285 mechanism to do this as it will cover three rotavirus seasons post vaccine introduction. Thus confounding  
286 caused by yearly variance in rotavirus numbers will be minimised.

287 There are limited published data describing the indirect effect of routine vaccination on un-vaccinated older  
288 children and adults (~~herd protection~~) and the majority of studies have focused on hospital admissions. As  
289 this study will collect data for all ages and cover RVGE and AGE incidence 3 years post-vaccination it will  
290 provide sufficient data for measurement of the [herd indirect](#) effect on hospital admissions. Additionally,  
291 whilst the majority of studies into the indirect effect of vaccination have focused on hospital admissions, this

1 292 study will ~~examine~~ ~~provide evidence for impact on the~~ indirect effects in [emergency departmentsEDs](#) and  
2  
3 293 community settings. This is particularly important as it is perhaps more likely that [moderate/severe](#) RVGE in  
4  
5 294 un-vaccinated older children and adults will be treated at [emergency departmentsEDs](#) and through  
6  
7  
8 295 community consultations.

9  
10 296 Another potential strength of the study is the ability to conduct analysis at small community (LSOA) level.

11 297 This will enable small area socio-demographic information such as [socioeconomic](#) deprivation to be included  
12  
13 298 in the analyses as a covariate at the lowest possible unit of analyses other than the individual. Thus, allowing  
14  
15 299 the exploration of the association between [socioeconomic](#) deprivation, burden of RVGE / AGE and vaccine  
16  
17 300 uptake whilst limiting the ecological fallacy of analysis.

18  
19 301 As many of the data sources included in this study do not include specific RVGE classification, we ~~are~~ will be  
20  
21 302 using AGE as an outcome measure for most data sets. Laboratory detections data which are organism  
22  
23 303 specific will allow us to adjust these measures based on the seasonal contribution of organisms other than  
24  
25 304 rotavirus such as norovirus. For example RVGE seasonality is fairly constant but that of norovirus tends to  
26  
27 305 vary over the winter and spring months in the UK. These AGE indicators can therefore be adjusted for  
28  
29 306 changes in norovirus seasonality (Figure 3)[35] to give a better proxy of the contribution of rotavirus to  
30  
31 307 overall GI causes and the relative impact of rotavirus vaccination

### 32 308 **Limitations**

33  
34 309 The gold standard for measurement of vaccine efficacy is the randomised controlled trial. However, this  
35  
36 310 ecological study will investigate the impact of vaccination on population disease burden within a health  
37  
38 311 system; therefore an ecological study is appropriate. Conversely it is recognised [an ecological approach](#)  
39  
40 312 cannot show individual level effects of vaccine and can only infer the impact of the vaccine at the population  
41  
42 313 level without causation. Additionally, a key focus of this study ~~is~~ will be to quantify variation in the outcomes  
43  
44 314 measured according to vaccine uptake levels and [socioeconomic](#) deprivation. Confounding may be an issue  
45  
46 315 since cases living in areas with low vaccine uptake or high [socioeconomic](#) deprivation may also have other  
47  
48 316 characteristics that will affect the risk of RVGE or AGE.



1  
2 317 | For measures of AGE activity in community settings (e.g. GP and Walk-in-Centre), we will use syndromic  
3  
4 318 | indicators that are non-specific to rotavirus e.g. diarrhoea, vomiting. An inherent issue is that the ability to  
5  
6 319 | detect effect on these is likely to be limited to large effects rather than small variations.

7  
8  
9 320 | A further limitation of the study is that investigators will not collect data ~~be in control of~~ directly data  
10  
11 321 | collection as all data are secondary, with and the consequent risk of bias, ~~that this brings~~. There is potential  
12  
13 322 | for clinical coding to lead to misclassification of disease, and this misclassification may vary by different data  
14  
15 323 | sources. We will describe these biases through quality control and subsequently adjust for them at the  
16  
17 324 | analysis stage. The use of multiple data sets for outcome indicators limits these issues by improving  
18  
19 325 | robustness.

20  
21  
22 326 | It is likely that there have been changes in data collection methods over the study period, for example  
23  
24 327 | changes to the assay used for rotavirus laboratory testing, leading to testing bias. One way to adjust for this  
25  
26 328 | in the analysis is to pool data over a number of years to smooth fluctuations caused by changes in testing  
27  
28 329 | methods. The investigators will identify changes through contact with rotavirus testing laboratories and NHS  
29  
30 330 | Trusts, so that changes may be described and where possible assist appropriate analytical adjustments. It is  
31  
32 331 | also feasible that the introduction of vaccination may also trigger changes in clinician requests for rotavirus  
33  
34 332 | and other AGE diagnostic testing, particularly in the vaccination age group. Any possible testing bias will be  
35  
36 333 | assessed at the lead NHS Trust via comparisons with pre-vaccine testing probabilities.

37  
38  
39  
40 334 | The study currently does will not include any economic component, ~~which given the cost of rotavirus to the~~  
41  
42 335 | ~~health service is essential~~. However, previous studies have reported the likely cost-effectiveness of rotavirus  
43  
44 336 | vaccination for the population under 5 years of age.[36] This study would will provide the results and data  
45  
46 337 | necessary for economic evaluation based on the direct and indirect impact of rotavirus vaccination.

## 338 FOOTNOTES

### 339 Contributions

340 DH participated in the design of the study, will oversee the study co-ordination, data collection and analysis,  
341 and wrote the manuscript. RV conceived of the study and participated in its design; and will contribute to

1 342 study co-ordination and analysis. MIG conceived of the study and participated in its design; and will  
2  
3 343 contribute to study co-ordination. NF conceived of the study and participated in its design; and will oversee  
4  
5 344 study co-ordination and contribute to analyses. NC conceived of the study, participated in its design and will  
6  
7  
8 345 contribute to study co-ordination. All authors were involved in revising the manuscript and read and  
9  
10 346 approved the final manuscript.

11  
12  
13 347 **Acknowledgements** The authors gratefully acknowledge the effort and assistance provided by all the  
14  
15 348 research and development staff, laboratory technicians, data entry staff and support staff at the  
16  
17 349 collaborating sites. ~~This work is support by the GlaxoSmithKline Biologicals. The funding body had no role in  
18  
19 350 the study design, the collection, analysis and interpretation of data, the writing of the manuscript, or the  
20  
21 351 decision to submit the manuscript for publication.~~

#### 22 23 24 25 352 **Funding**

26  
27  
28 353 This study will be in part supported (approximately 35% of total cost) by GlaxoSmithKline Biologicals SA.  
29  
30 354 GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this  
31  
32 355 manuscript for factual accuracy but the authors are solely responsible for final content and interpretation.  
33  
34 356 The authors received no financial support or other form of compensation related to the development of the  
35  
36 357 manuscript. This work is to be partially supported by GlaxoSmithKline Biologicals, Belgium, including salary  
37  
38 358 contributions to the lead author DH and resources for quality control of data sources.

#### 39 40 41 359 **Competing interests**

42  
43  
44 360 Financial competing interests

45  
46  
47 361 The Rotarix™ vaccine used in the UK national immunisation programme evaluated by this study is developed  
48  
49 362 and licensed by GlaxoSmithKline Biologicals. NC is in receipt of research grant support from GSK Biologicals  
50  
51 363 (to University of Liverpool) and has received honoraria for participation in GSK Rotavirus Vaccine Advisory  
52  
53 364 Board Meetings.

54  
55  
56  
57 365 Non-financial competing interests  
58  
59  
60

1 366 The authors declare that they have no non-financial competing interests.

2  
3  
4 367 **Peer review** The protocol was peer reviewed externally and internally prior to sponsor and ethical approval.

5  
6  
7 368 **Ethics approval** [The study has been approved by NHS Research Ethics Committee, South Central-Berkshire](#)

8  
9 369 [REC Reference: 14/SC/1140](#)The study has received NHS ethics approval.

10  
11  
12 370

13  
14  
15  
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31 420 [tistics%2c+Admitted+patient+care++England%22&sort=Relevance&size=10&page=1#top](http://www.hscic.gov.uk/searchcatalogue?productid=13264&q=title%3a%22Hospital+Episode+Statistics%2c+Admitted+patient+care++England%22&sort=Relevance&size=10&page=1#top)
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### 459 Additional figure titles and legends

460 **Figure 1. Socioeconomic deprivation Indices of multiple deprivation in Merseyside**

461 Produced using the English Indices of Deprivation 2010, national quintiles for the Index of Multiple  
462 Deprivation [19].

463 **Figure 2. Schematic of study data sources and outcome measures**

464 Data sources cover a variety of health care providers at different levels of the health system. This shows  
465 from which data sources outcome measures will be obtained.

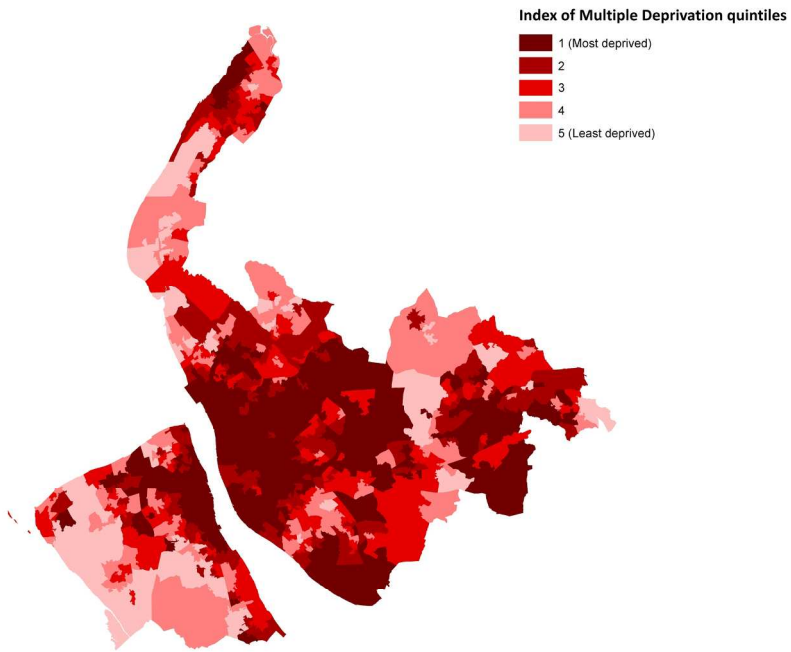
466 **Figure 3. Laboratory detections of rotavirus and norovirus in the North West, England, 2009/10-2013-14**

467 Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the  
468 norovirus season as compared to the rotavirus season.

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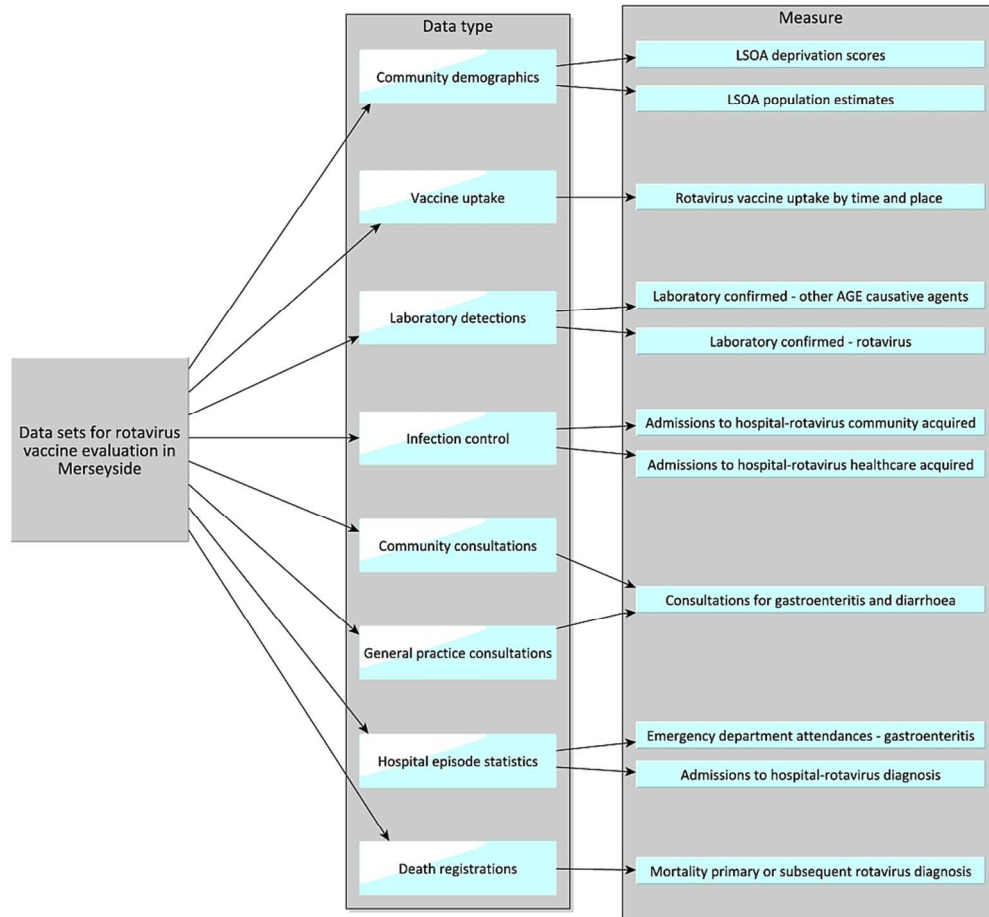
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Produced using the English Indices of Deprivation 2010, national quintiles for the index of multiple deprivation [19].  
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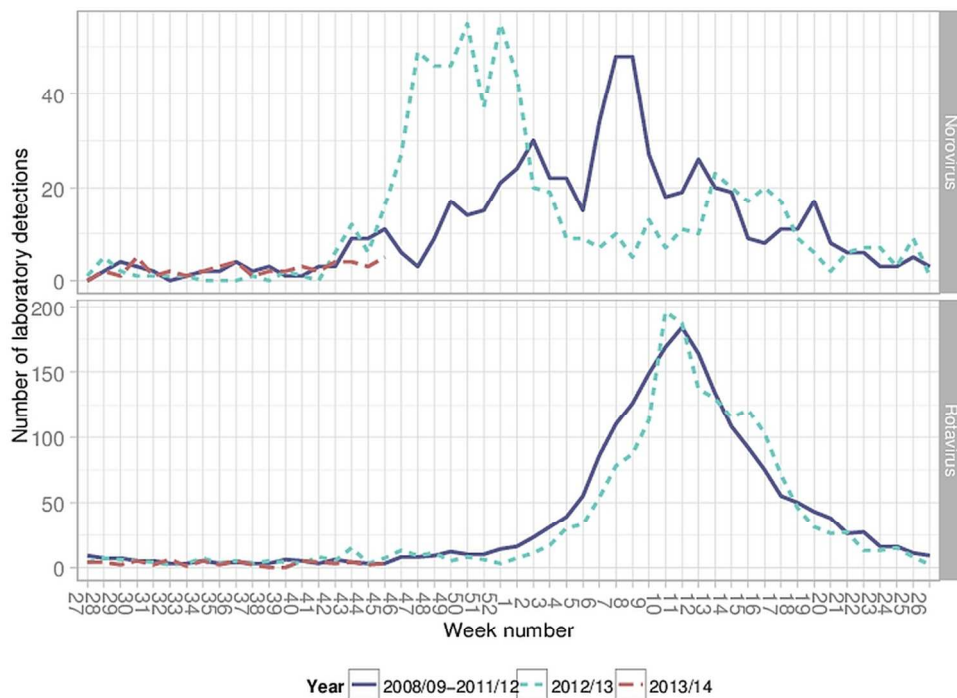


Data sources cover a variety of health care providers at different levels of the health system. This shows from which data sources outcome measures will be obtained.  
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Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the norovirus season as compared to the rotavirus season.  
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