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:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006161
Article Type:	Protocol
Date Submitted by the Author:	18-Jul-2014
Complete List of Authors:	Hungerford, Daniel; University of Liverpool, , Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Public Health England, Field Epidemiology Services, Health Protection Vivancos, Roberto; Public Health England, Field Epidemiology Services, Health Protection French, Neil; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Royal Liverpool and Broadgreen University Hospitals NHS Trust, Iturriza-Gomara, Miren; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health Cunliffe, Nigel; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Alder Hey Children's NHS Foundation Trust,
Primary Subject Heading:	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

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

Dan Hungerford[1,4] – d.hungerford@liverpool.ac.uk, 0151 795 9609 (corresponding author)

Dr Roberto Vivancos[4] – roberto.vivancos@phe.gov.uk

Professor Neil French[1,3] – french@liverpool.ac.uk

Dr Miren Iturriza-Gomara[1] – miren@liverpool.ac.uk

Professor Nigel Cunliffe[1,2] – nigelc@liverpool.ac.uk

1. Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health, University of Liverpool, The Ronald Ross Building, 8 West Derby Street, Liverpool, L69 7BE, UK
2. Alder Hey Children's NHS Foundation Trust, Eaton Rd, Liverpool, L12 2AP, UK
3. Royal Liverpool and Broadgreen University Hospitals NHS Trust, Prescot St, Liverpool, L7 8XP, UK
4. Public Health England, Field Epidemiology Services, 5th Floor Rail House, Lord Nelson Street, Liverpool, L1 1JF, UK

Keywords

Rotavirus; Vaccination; Gastroenteritis; Epidemiology; Immunity, Herd

Word Count

3819

ABSTRACT

Introduction

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

Methods and analysis

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

Ethics and dissemination

NHS ethics approval has been granted. The findings will be disseminated through scientific conferences and peer-reviewed journal articles. The findings will enable demonstration of 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 provide a template for ecological methodology vaccine evaluations 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 cover all ages for rotavirus and all cause gastroenteritis incidence three years post-vaccination, minimising cofounding caused by yearly variance in rotavirus numbers.
- Additionally it is powered to measure the 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 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.
- Using syndromic indicators that are non-specific to rotavirus limits the study to measuring large effects rather than small variations.

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 admissions and emergency department (ED) attendances for acute gastroenteritis (AGE), respectively in children under 5 years of age.[3] The economic cost of RVGE to the health service is estimated to be approximately £14 million per year in England and Wales.[3] At Alder Hey Children's NHS Foundation Trust, Liverpool, UK rotavirus is a major cause of community-acquired and healthcare-associated diarrhoea; in a 2-year prospective study among hospitalised children, rotavirus was detected by RT-PCR in 43% of community-

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

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

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

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

METHODS

Study aim

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

- Laboratory detections of rotavirus in faecal samples
- Admissions to hospital for RVGE or AGE
- Attendances to Emergency departments for AGE
- Number of nosocomially acquired cases of RVGE
- General practice (GP) and community consultations for diarrhoea and AGE in children less than 5 and in all ages

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

Study setting and location

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

Study overview and choice of study designs

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

Study data

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

Hospital admission and emergency department attendance data will be obtained from hospital episode statistics (HES), which record all inpatient admissions in NHS hospitals in England and directly from NHS Trusts which cover the population of Merseyside.

The study will obtain GP consultations for diarrhoea or gastroenteritis from Clinical Commissioning Groups covering Merseyside or from government held sentinel surveillance systems. Community consultations for diarrhoea and gastroenteritis at Walk-in Centres will be sourced from NHS Community Health Trusts. Walk-in Centres are primarily nurse led primary care facilities for illness and injuries without the need for an appointment.

The infection control team at Alder Hey Children's NHS Foundation Trust in Liverpool classifies rotavirus cases as community acquired or healthcare associated (nosocomial). Alder Hey NHS Foundation Trust's footprint covers the majority of Merseyside's children, so these data will enable evaluation of the effect of rotavirus vaccination on nosocomial rotavirus infection in children across Merseyside.

Laboratory detections of rotavirus from Public Health England Laboratory surveillance covering Merseyside residents will be included in the analysis. Other causative agents of AGE identified through laboratory testing including, for example, norovirus, adenovirus, astrovirus will also be extracted for analysis.

Each data set will cover at least three-years either side of vaccine introduction. All data will be pseudoanonymised to allow distinction of records but no linking of datasets or identification of individuals will be undertaken. All data will be either geo-coded from postcode to small statistical geographical community units termed Lower Super Output Areas (LSOA) or sourced with this geography. Denominator populations will be derived from the Office of National Statistics (ONS) mid-year population-estimates by LSOA [29]. Indicators of deprivation at LSOA level will be sourced from the Department for Communities and Local Government.[28] Rotavirus vaccination uptake data will be sourced from the Child Health Information System (CHIS) which is held by community NHS health Trusts in Merseyside.

Table 1: Case definitions for the study 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 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

Quality control

Data sources such as HES and laboratory detections will be influenced by testing practices; for instance testing of some organisms is more likely to occur at certain times of the year. In the hospital admission data

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

Ethical considerations

We do not foresee a requirement to obtain ethical approval for this ecological study, as analysis will be conducted using routinely collected aggregated data. However, a data sharing agreement will be obtained between PHE, participating NHS Trusts and the University of Liverpool. Research governance approval will be sought form all participating NHS Trusts. Ethics approval for quality control of data will be sort from NHS Research Ethics Committee if required.

Data analysis

Changes in trends of primary care consultations, community consultations, ED attendances, hospitalisations and rotavirus detections will be explored using interrupted time series analysis. Moving averages will be examined to highlight any long-term trends whilst smoothing out any short-term fluctuations. Standardized rates for a minimum of a three-year period prior to vaccination and year on year after vaccination (for three years) will be compared. For the regression analysis, Poisson regression will be used. We will first compute monthly rates that are ‘‘expected’’ to occur in the absence of a rotavirus vaccination programme by fitting the model to pre-vaccine data. We will then adjust for seasonality. The model will be used to estimate “expected” rates after vaccination and we will then compare with “observed” rates. We will then calculate rate ratios and assess the magnitude of decline in rates. Using a Poisson regression model, and including demographic and vaccine uptake indicators we would be able to predict impact of vaccination on the AGE

and RVGE indicators at various services and vaccine uptake levels. Potential data biases will be controlled for by the access and analysis multiple health data sources over a minimum of six years.

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

Power calculation

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

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

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

Timeline

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

Project governance

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

Dissemination of research findings

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

DISCUSSION

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

Strengths

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

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

At the time of writing there has been limited published evidence on the indirect effect of routine vaccination on un-vaccinated older children and adults (herd protection) and the majority of studies have focused on hospital admissions. As this study will collect data for all ages and cover RVGE and AGE incidence 3 years post-vaccination it will provide sufficient data for measurement of the herd effect on hospital admissions. Additionally, whilst the majority of studies into the indirect effect of vaccination have focused on hospital admissions this study will provide evidence for impact on the indirect effect in emergency departments and

community settings. This is particularly important as it is perhaps more likely that severe RVGE in un-vaccinated older children and adults will be treated at emergency departments and through community consultations.

Another potential strength of the study is the ability to conduct analysis at small community (LSOA) level. This will enable small area socio-demographic information such as deprivation to be included in the analyses as a covariate at the lowest possible unit of analyses other than the individual. Thus, allowing the exploration of the association between deprivation, burden of RVGE / AGE and vaccine uptake whilst limiting the ecological fallacy of analysis.

As many of the data sources included in this study do not include specific RVGE classification, we are using AGE as an outcome measure for most datasets. Laboratory detections data which are organism specific will allow us to adjust these measures based on the seasonal contribution of organisms other than rotavirus such as norovirus. For example RVGE seasonality is fairly constant but that of norovirus tends to vary over the winter and spring months in the UK. These AGE indicators can therefore be adjusted for changes in norovirus seasonality (Figure 3)[35] to give a better proxy of the contribution of rotavirus to overall GI causes and the relative impact of rotavirus vaccination

Limitations

The gold standard for measurement of vaccine efficacy is the randomised controlled trial. However, the intention of this study is to look at the generalisabilty of vaccine effectiveness on population disease burden and impact on a health system therefore an ecological study is appropriate. Conversely it is recognised we cannot show individual level effects of vaccine and we can only infer the impact of the vaccine at the population level without causation. Additionally a key focus of this study is to quantify variation in the outcomes measured according to vaccine uptake levels and deprivation. Confounding may be an issue here with cases living in areas with low vaccine uptake or high deprivation may also have other characteristics that will affect the risk of RVGE or AGE.

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

A further limitation of the study is that investigators are not in control of direct data collection as all data are secondary, and the consequent risk of bias that this brings. There is potential for clinical coding to lead to misclassification of disease, and this misclassification may vary by different data source. We will describe these biases through the quality control audit and subsequently adjust for at the analysis stage. The studies use of multi-data sets for outcome indicators limit these issues by improving robustness.

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

The study currently does not include any economic component which given the cost of rotavirus to the health service is essential. However, previous studies have reported the likely cost-effectiveness of rotavirus vaccination for the population under 5 years of age.[36] This study would provide the results and data necessary for economic evaluation based on the direct and indirect impact of rotavirus vaccination

Contributions

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

study co-ordination and contribute to analyses. NC conceived of the study, participated in its design and will contribute to study co-ordination. All authors were involved in revising the manuscript and read and approved the final manuscript.

Acknowledgements The authors gratefully acknowledge the effort and assistance provided by all the research and development staff, laboratory technicians, data entry staff and support staff at the collaborating sites. This work is support by the GlaxoSmithKline Biologicals. The funding body had no role in the study design, the collection, analysis and interpretation of data, the writing of the manuscript, or the decision to submit the manuscript for publication.

Funding This work is to be partially supported by GlaxoSmithKline Biologicals, Belgium, including salary contributions to the lead author DH and resources for quality control of data sources.

Competing interests

Financial competing interests

The Rotarix™ vaccine used in the UK national immunisation programme evaluated by this study is developed and licensed by GlaxoSmithKline Biologicals. NC is in receipt of research grant support from GSK Biologicals (to University of Liverpool) and has received honoraria for participation in GSK Rotavirus Vaccine Advisory Board Meetings.

Non-financial competing interests

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

Peer review Peer reviewed and reviewed internally prior to sponsor and ethical approval.

Ethics approval The study has received NHS ethics approval.

References

1 Tate JE, Burton AH, Boschi-Pinto C, *et al.* 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:136–41. doi:10.1016/S1473-3099(11)70253-5

2 Tam CC, Rodrigues LC, Viviani L, *et al.* Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. *Gut* 2012;**61**:69–77. doi:10.1136/gut.2011.238386

3 Harris JP, Jit M, Cooper D, *et al.* Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. *Vaccine* 2007;**25**:3962–70. doi:10.1016/j.vaccine.2007.02.072

4 Cunliffe NA, Booth JA, Elliot C, *et al.* Healthcare-associated viral gastroenteritis among children in a large pediatric hospital, United Kingdom. *Emerg Infect Dis* 2010;**16**:55–62. doi:10.3201/eid1601.090401

5 Pockett RD, Adlard N, Carroll S, *et al.* Paediatric hospital admissions for rotavirus gastroenteritis and infectious gastroenteritis of all causes in England: an analysis of correlation with deprivation. *Curr Med Res Opin* 2011;**27**:777–84. doi:10.1185/03007995.2011.555757

6 Iturriza-Gómara M, Cunliffe N. Rotavirus vaccine: a welcome addition to the immunisation schedule in the UK. *BMJ* 2013;**346**:f2347.

7 Nakagomi O, Iturriza-Gomara M, Nakagomi T, *et al.* Incorporation of a rotavirus vaccine into the national immunisation schedule in the United Kingdom: a review. *Expert Opin Biol Ther* 2013;**13**:1613–21. doi:10.1517/14712598.2013.840285

8 Soares-Weiser K, Goldberg E, Tamimi G, *et al.* Rotavirus vaccine for preventing diarrhoea. *Cochrane Database Syst Rev* 2004;:CD002848. doi:10.1002/14651858.CD002848.pub2

9 World Health Organization. Rotavirus vaccines. *Relevé Épidémiologique Hebd Sect Hygiène Secrétariat Société Nations Wkly Epidemiol Rec Health Sect Secr Leag Nations* 2007;**82**:285–95.

10 Soares-Weiser K, Maclehose H, Bergman H, *et al.* Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev* 2012;**11**:CD008521. doi:10.1002/14651858.CD008521.pub3

11 Rotavirus vaccines WHO position paper: January 2013 - Recommendations. *Vaccine* 2013;**31**:6170–1. doi:10.1016/j.vaccine.2013.05.037

12 World Health Organization. Rotavirus vaccines. WHO position paper – January 2013. *Relevé Épidémiologique Hebd Sect Hygiène Secrétariat Société Nations Wkly Epidemiol Rec Health Sect Secr Leag Nations* 2013;**88**:49–64.

13 PATH. Country introductions | Maps and list – Rotavirus Vaccine Access and Delivery - PATH. http://sites.path.org/rotavirusvaccine/rotavirus-advocacy-and-communications-toolkit/country-introduction-maps-and-list/ (accessed 7 Jul2014).

14 Parez N, Giaquinto C, Du Roure C, *et al.* Rotavirus vaccination in Europe: drivers and barriers. *Lancet Infect Dis* 2014;**14**. doi:10.1016/S1473-3099(14)70035-0

15 Health and Social Care Information Centre. NHS Immunisation Statistics, England -2012-13. England: : Health and Social Care Information Centre 2013. http://www.hscic.gov.uk/searchcatalogue?q=title%3A%22NHS+Immunisation+Statistics%22&area=&size=10&sort=RelevanceDesc (accessed 17 Apr2014).

16 Public Health England. Early evidence of the impact of the national rotavirus immunisation programme. *Health Prot Rep Wkly Rep* 2014;**8**.

17 Patel MM, Glass R, Desai R, *et al.* Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis* 2012;**12**:561–70. doi:10.1016/S1473-3099(12)70029-4

18 Lopman BA, Curns AT, Yen C, *et al.* Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. *J Infect Dis* 2011;**204**:980–6. doi:10.1093/infdis/jir492

19 Health and Social Care Information Centre. Hospital Episode Statistics. Admitted Patient Care, England - 2012-13: Diagnosis. Health Soc. Care Inf. Cent. 2014.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

20 Braeckman T, Van Herck K, Meyer N, *et al.* Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. *BMJ* 2012;**345**:e4752.

21 Bayard V, DeAntonio R, Contreras R, *et al.* Impact of rotavirus vaccination on childhood gastroenteritis-related mortality and hospital discharges in Panama. *Int J Infect Dis* 2012;**16**:E94–E98. doi:10.1016/j.ijid.2011.09.003

22 Buttery JP, Lambert SB, Grimwood K, *et al.* Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. *Pediatr Infect Dis J* 2011;**30**:S25–29. doi:10.1097/INF.0b013e3181fefdee

23 Cortese MM, Immergluck LC, Held M, *et al.* Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics* 2013;**132**. doi:10.1542/peds.2012-3804

24 Field EJ, Vally H, Grimwood K, *et al.* Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. *Pediatrics* 2010;**126**:e506–512. doi:10.1542/peds.2010-0443

25 Rissardo L, Karina, Furlan MCR, Marcon S, Silva, *et al.* Hospital morbidity before and after vaccination program against rotavirus in the state of ParanÃ¡-Brazil: descriptive- ecological study [Portuguese]. *Online Braz J Nurs* 2010;**9**:1–1.

26 Pendleton A, Galic M, Clarke C, *et al.* Impact of rotavirus vaccination in Australian children below 5 years of age A database study. *Hum Vaccines Immunother* 2013;**9**:1617–25. doi:10.4161/hv.24831

27 Paulke-Korinek M, Kollaritsch H, Aberle SW, *et al.* Sustained low hospitalization rates after four years of rotavirus mass vaccination in Austria. *Vaccine* 2013;**31**:2686–91. doi:10.1016/j.vaccine.2013.04.001

28 Department for Communities and Local Government. The English Indices of Deprivation 2010. England: : Department for Communities and Local Government 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf (accessed 14 Jan2014).

29 Office for National Statistics. Super Output Area Population Estimates - Mid-2011 (Census Based). Off. Natl. Stat. 2013.http://www.ons.gov.uk/ons/rel/sape/soa-mid-year-pop-est-engl-wales-exp/mid-2011--census-based-/stb---super-output-area---mid-2011.html (accessed 17 Apr2014).

30 Liverpool Health Partners. http://www.liverpoolhealthpartners.org.uk/index.html

31 Liverpool Community Health NHS Trust. http://www.liverpoolcommunityhealth.nhs.uk/

32 NHS England Merseyside Area Team. http://www.england.nhs.uk/north/mers-at/

33 Alder Hey Children's NHS Foundation Trust. http://www.alderhey.nhs.uk/

34 Public Health England. https://www.gov.uk/government/organisations/public-health-england

35 Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. *Vaccine* 2007;**25**:3971–9. doi:10.1016/j.vaccine.2007.02.070

36 Public Health England, Field Epidemiology Service North West. North West Infectious Intestinal Disease Activity Winter 2013/14 Bulletin: Week 44. Public Health England 2013. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317140237031

Additional figure titles and legends

Figure 1. Indices of multiple deprivation in Merseyside

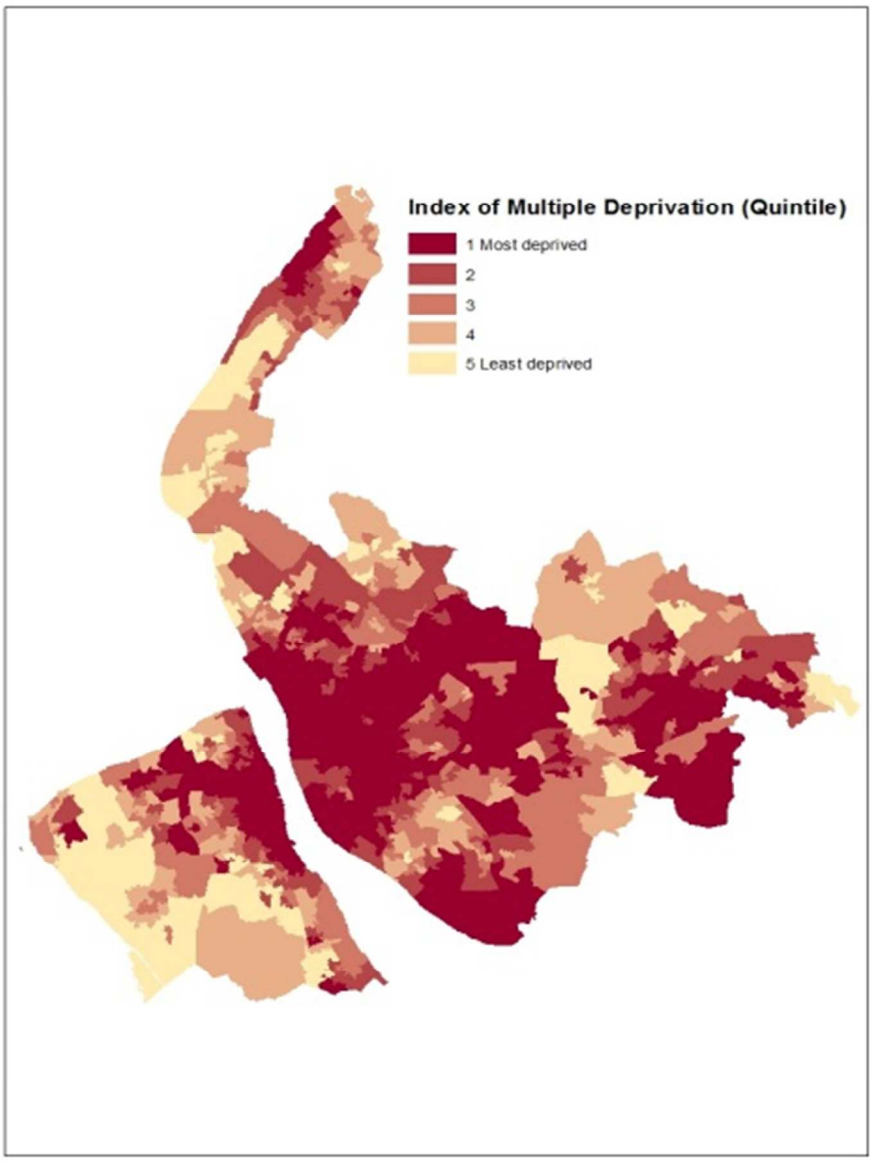
Produced using the English Indices of Deprivation 2010, national quintiles for the index of multiple deprivation [19].

Figure 2. Schematic of study data sources and outcome measures

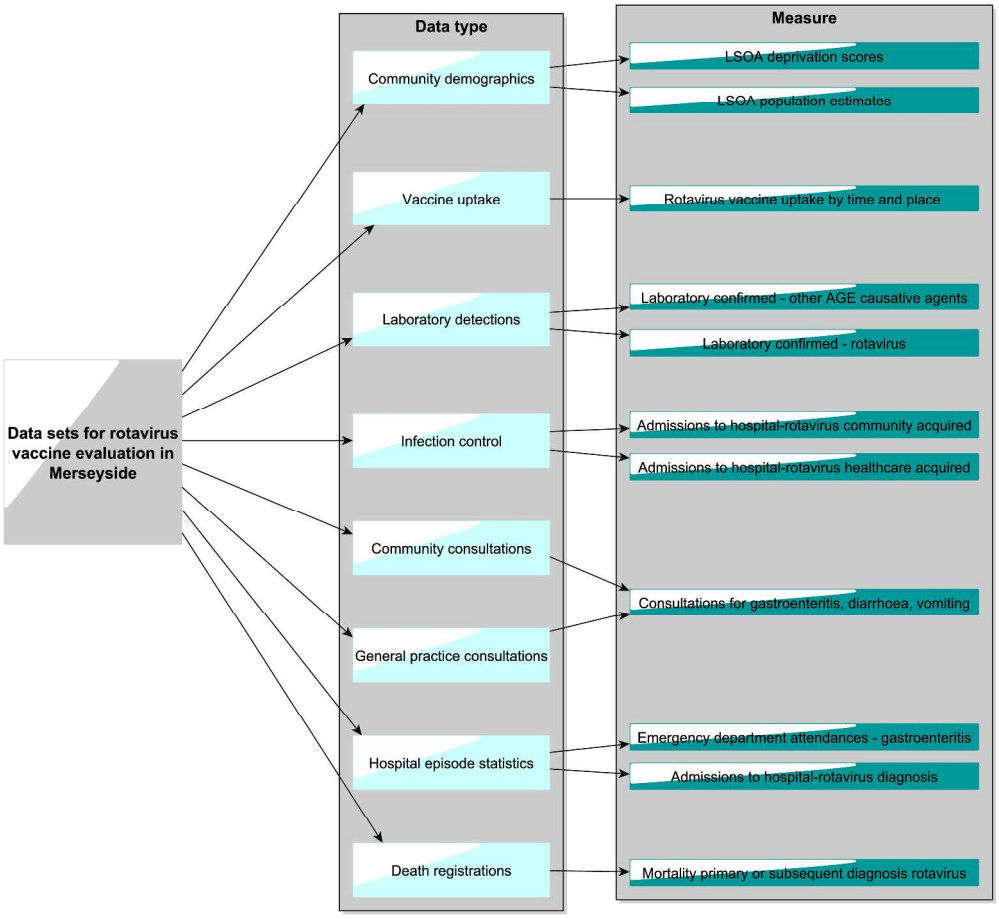
Data sources cover a variety of health care providers at different levels of the health system. This shows from which data sources outcome measures will be obtained.

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

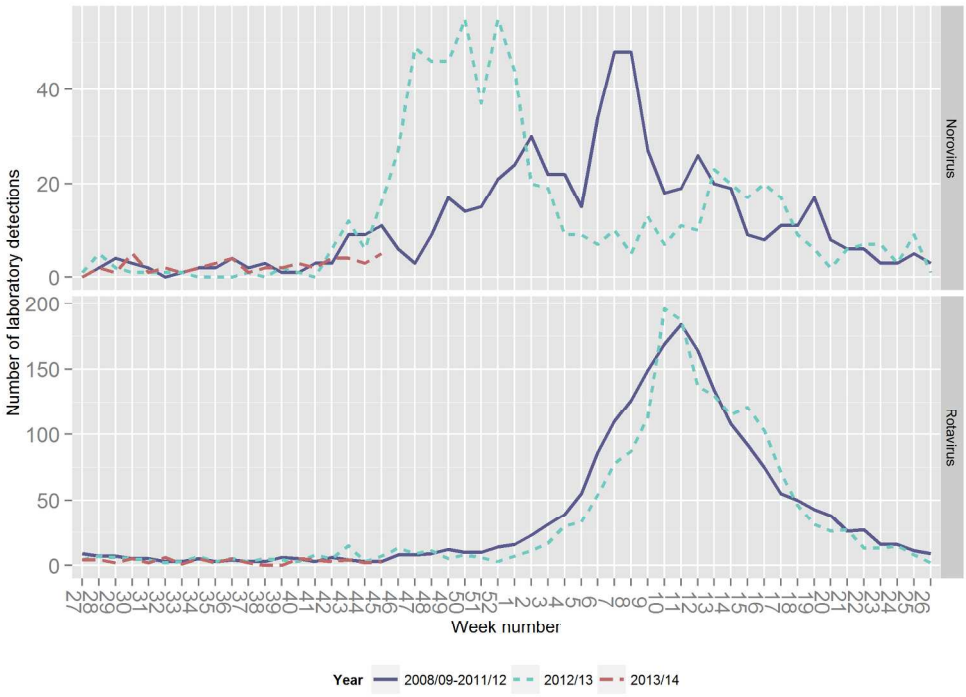
Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the norovirus season as compared to the rotavirus season.



Produced using the English Indices of Deprivation 2010, national quintiles for the index of multiple deprivation [19].
57x74mm (220 x 220 DPI)



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.
361x332mm (300 x 300 DPI)



Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the norovirus season as compared to the rotavirus season.
203x152mm (300 x 300 DPI)

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:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006161.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Nov-2014
Complete List of Authors:	Hungerford, Daniel; University of Liverpool, , Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Public Health England, Field Epidemiology Services, Health Protection Vivancos, Roberto; Public Health England, Field Epidemiology Services, Health Protection French, Neil; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Royal Liverpool and Broadgreen University Hospitals NHS Trust, Iturriza-Gomara, Miren; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health Cunliffe, Nigel; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Alder Hey Children's NHS Foundation Trust,
Primary Subject Heading:	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

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

Dan Hungerford[1,4] – d.hungerford@liverpool.ac.uk, 0151 795 9609 (corresponding author)

Dr Roberto Vivancos[4] – roberto.vivancos@phe.gov.uk

Professor Neil French[1,3] – french@liverpool.ac.uk

Dr Miren Iturriza-Gomara[1] – miren@liverpool.ac.uk

Professor Nigel Cunliffe[1,2] – nigelc@liverpool.ac.uk

1. Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health, University of Liverpool, The Ronald Ross Building, 8 West Derby Street, Liverpool, L69 7BE, UK
2. Alder Hey Children's NHS Foundation Trust, Eaton Rd, Liverpool, L12 2AP, UK
3. Royal Liverpool and Broadgreen University Hospitals NHS Trust, Prescot St, Liverpool, L7 8XP, UK
4. Public Health England, Field Epidemiology Services, 5th Floor Rail House, Lord Nelson Street, Liverpool, L1 1JF, UK

Keywords

Rotavirus; Vaccination; Gastroenteritis; Epidemiology; Immunity, Herd

Word Count

3,624 (excluding footnotes)

ABSTRACT

Introduction

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

Methods and analysis

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

Ethics and dissemination

The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference: 14/SC/1140. Study outputs will be disseminated through scientific conferences and peer-reviewed publications. The study will demonstrate the impact of rotavirus vaccination on the burden of disease from a complete health system perspective. It will identify key areas that require improved data collection tools to maximise the usefulness of this surveillance approach and will provide a template for 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 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 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 syndromic indicators that are non-specific to rotavirus will limit 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 admissions and emergency department (ED) attendances for acute gastroenteritis (AGE), respectively in children under 5 years of age.[3] The economic cost of RVGE to the health service is estimated to be approximately £14 million per year in England and Wales.[3] At Alder Hey Children's NHS Foundation Trust, Liverpool, UK rotavirus is a major cause of community-acquired and healthcare-associated diarrhoea; in a 2-

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

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

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

monitoring changes in AGE incidence in non-vaccinated older children and adults is critical to assess indirect impact.

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

METHODS

Study aim

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

- Laboratory detections of rotavirus in faecal samples
- Admissions to hospital for RVGE or AGE
- Attendances to EDs for AGE

- Number of nosocomially-acquired cases of RVGE
- General practice (GP) and community consultations for diarrhoea and AGE in children less than 5 and in all ages
- Routine rotavirus vaccine coverage mapping by small area geography
- Relative contribution of direct (those vaccinated) and indirect (not vaccinated) effects to overall vaccine benefit in health system usage for both RVGE and AGE
- Relationship between socioeconomic deprivation, vaccine uptake and RVGE / AGE incidence

Study setting and location

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

Study overview and choice of study designs

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

Study data

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

Hospital admission and ED attendance data will be obtained from hospital episode statistics (HES),[19] which record all inpatient admissions in NHS hospitals in England. The study will therefore measure hospitalisations and ED attendances for residents of Merseyside receiving care in hospitals throughout England.

The study will obtain GP consultation data for diarrhoea or gastroenteritis from Clinical Commissioning Groups covering Merseyside or from government held sentinel surveillance systems. Community consultations for diarrhoea and gastroenteritis at "Walk-in Centres" will be sourced from NHS Community Health Trusts. Walk-in Centres are primarily nurse-led primary care facilities for illness and injuries without need for prior appointment.

Rotavirus gastroenteritis at Alder Hey Children's NHS Foundation Trust (Alder Hey) in Liverpool is classified as community acquired or nosocomial. Alder Hey's footprint covers the majority of Merseyside's children, so these data will enable evaluation of the effect of rotavirus vaccination on nosocomial rotavirus infection in children across Merseyside.

Laboratory detections of rotavirus from Public Health England Laboratory surveillance covering Merseyside residents will be included in the analysis. Other causative agents of AGE identified through laboratory testing including, for example, norovirus, adenovirus, and astrovirus will also be extracted for analysis.

Each data set will cover at least three-years either side of vaccine introduction. All data will be pseudo-anonymised to allow distinction of records but no linking of data sets or identification of individuals will be undertaken. All data will be either geo-coded from postcode to small statistical geographical community units termed Lower Super Output Areas (LSOA) or sourced with this geography. LSOAs consist of approximately 1,500 persons and denominator populations will be derived from the Office of National Statistics (ONS) mid-year population-estimates by LSOA.[29] Indicators of socioeconomic deprivation at LSOA level will be measured using the English Indices of Deprivation. The UK Department for Communities and

Local Government produce the English indices of Deprivation using census and other local administrative data.[28] Rotavirus vaccination uptake data will be sourced from the Child Health Information System (CHIS) which is held by community NHS health Trusts in Merseyside. Records of doses of vaccinations given as part of the UK childhood vaccine schedule are recorded in CHIS for each child.

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 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

Quality control

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

Ethical considerations

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

Data analysis

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

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

Power calculation

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

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

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

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

Timeline

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

Project governance

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

Dissemination of research findings

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

DISCUSSION

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

Strengths

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

sources to measure independent indicators of vaccination effect will also provide robustness, enabling easier identification of outliers from overall trends.

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

There are limited published data describing the indirect effect of routine vaccination on un-vaccinated older children and adults and the majority of studies have focused on hospital admissions. As this study will collect data for all ages and cover RVGE and AGE incidence 3 years post-vaccination it will provide sufficient data for measurement of the indirect effect on hospital admissions. Additionally, whilst the majority of studies into the indirect effect of vaccination have focused on hospital admissions, this study will examine indirect effects in EDs and community settings. This is particularly important as it is perhaps more likely that moderate/severe RVGE in un-vaccinated older children and adults will be treated at EDs and through community consultations.

Another potential strength of the study is the ability to conduct analysis at small community (LSOA) level. This will enable small area socio-demographic information such as socioeconomic deprivation to be included in the analyses as a covariate at the lowest possible unit of analyses other than the individual. Thus, allowing the exploration of the association between socioeconomic deprivation, burden of RVGE / AGE and vaccine uptake whilst limiting the ecological fallacy of analysis.

As many of the data sources included in this study do not include specific RVGE classification, we will be using AGE as an outcome measure for most data sets. Laboratory detection data which are organism specific will allow us to adjust these measures based on the seasonal contribution of organisms other than rotavirus such as norovirus. For example RVGE seasonality is fairly constant but that of norovirus tends to vary over the winter and spring months in the UK. These AGE indicators can therefore be adjusted for changes in norovirus seasonality (Figure 3)[35] to give a better proxy of the contribution of rotavirus to overall GI causes and the relative impact of rotavirus vaccination

Limitations

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

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

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

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

The study currently will not include any economic component. However, previous studies have reported the likely cost-effectiveness of rotavirus vaccination for the population under 5 years of age.[36] This study will provide the results and data necessary for economic evaluation based on the direct and indirect impact of rotavirus vaccination.

FOOTNOTES

Contributions

DH participated in the design of the study, will oversee the study co-ordination, data collection and analysis, and wrote the manuscript. RV conceived of the study and participated in its design; and will contribute to study co-ordination and analysis. MIG conceived of the study and participated in its design; and will contribute to study co-ordination. NF conceived of the study and participated in its design; and will oversee study co-ordination and contribute to analyses. NC conceived of the study, participated in its design and will contribute to study co-ordination. All authors were involved in revising the manuscript and read and approved the final manuscript.

Acknowledgements The authors gratefully acknowledge the effort and assistance provided by all the research and development staff, laboratory technicians, data entry staff and support staff at the collaborating sites.

Funding

This study is in part supported (approximately 35% of total cost) by GlaxoSmithKline Biologicals SA. GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this manuscript for factual accuracy but the authors are solely responsible for final content and interpretation. The authors received no financial support or other form of compensation related to the development of the manuscript..

Competing interests

Financial competing interests

The Rotarix™ vaccine used in the UK national immunisation programme evaluated by this study is developed and licensed by GlaxoSmithKline Biologicals. NC is in receipt of research grant support from GSK Biologicals (to University of Liverpool) and has received honoraria for participation in GSK Rotavirus Vaccine Advisory Board Meetings.

Non-financial competing interests

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

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

Ethics approval The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference: 14/SC/1140

References

1 Tate JE, Burton AH, Boschi-Pinto C, *et al.* 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:136–41. doi:10.1016/S1473-3099(11)70253-5

2 Tam CC, Rodrigues LC, Viviani L, *et al.* Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. *Gut* 2012;**61**:69–77. doi:10.1136/gut.2011.238386

3 Harris JP, Jit M, Cooper D, *et al.* Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. *Vaccine* 2007;**25**:3962–70. doi:10.1016/j.vaccine.2007.02.072

4 Cunliffe NA, Booth JA, Elliot C, *et al.* Healthcare-associated viral gastroenteritis among children in a large pediatric hospital, United Kingdom. *Emerg Infect Dis* 2010;**16**:55–62. doi:10.3201/eid1601.090401

5 Pockett RD, Adlard N, Carroll S, *et al.* Paediatric hospital admissions for rotavirus gastroenteritis and infectious gastroenteritis of all causes in England: an analysis of correlation with deprivation. *Curr Med Res Opin* 2011;**27**:777–84. doi:10.1185/03007995.2011.555757

6 Iturriza-Gómara M, Cunliffe N. Rotavirus vaccine: a welcome addition to the immunisation schedule in the UK. *BMJ* 2013;**346**:f2347.

7 Nakagomi O, Iturriza-Gomara M, Nakagomi T, *et al.* Incorporation of a rotavirus vaccine into the national immunisation schedule in the United Kingdom: a review. *Expert Opin Biol Ther* 2013;**13**:1613–21. doi:10.1517/14712598.2013.840285

8 Soares-Weiser K, Goldberg E, Tamimi G, *et al.* Rotavirus vaccine for preventing diarrhoea. *Cochrane Database Syst Rev* 2004;:CD002848. doi:10.1002/14651858.CD002848.pub2

9 World Health Organization. Rotavirus vaccines. *Relevé Épidémiologique Hebd Sect Hygiène Secrétariat Société Nations Wkly Epidemiol Rec Health Sect Secr Leag Nations* 2007;**82**:285–95.

10 Soares-Weiser K, Maclehose H, Bergman H, *et al.* Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev* 2012;**11**:CD008521. doi:10.1002/14651858.CD008521.pub3

11 Rotavirus vaccines WHO position paper: January 2013 - Recommendations. *Vaccine* 2013;**31**:6170–1. doi:10.1016/j.vaccine.2013.05.037

12 World Health Organization. Rotavirus vaccines. WHO position paper – January 2013. *Relevé Épidémiologique Hebd Sect Hygiène Secrétariat Société Nations Wkly Epidemiol Rec Health Sect Secr Leag Nations* 2013;**88**:49–64.

13 PATH. Country introductions | Maps and list – Rotavirus Vaccine Access and Delivery - PATH. http://sites.path.org/rotavirusvaccine/rotavirus-advocacy-and-communications-toolkit/country-introduction-maps-and-list/ (accessed 7 Jul2014).

14 Parez N, Giaquinto C, Du Roure C, *et al.* Rotavirus vaccination in Europe: drivers and barriers. *Lancet Infect Dis* 2014;**14**. doi:10.1016/S1473-3099(14)70035-0

15 Health and Social Care Information Centre. NHS Immunisation Statistics, England -2012-13. England: : Health and Social Care Information Centre 2013. http://www.hscic.gov.uk/searchcatalogue?q=title%3A%22NHS+Immunisation+Statistics%22&area=&size=10&sort=RelevanceDesc (accessed 17 Apr2014).

16 Public Health England. Early evidence of the impact of the national rotavirus immunisation programme. *Health Prot Rep Wkly Rep* 2014;**8**.

17 Patel MM, Glass R, Desai R, *et al.* Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis* 2012;**12**:561–70. doi:10.1016/S1473-3099(12)70029-4

18 Lopman BA, Curns AT, Yen C, *et al.* Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. *J Infect Dis* 2011;**204**:980–6. doi:10.1093/infdis/jir492

19 Health and Social Care Information Centre. Hospital Episode Statistics. Admitted Patient Care, England - 2012-13: Diagnosis. Health Soc. Care Inf. Cent. 2014.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

20 Braeckman T, Van Herck K, Meyer N, *et al.* Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. *BMJ* 2012;**345**:e4752.

21 Bayard V, DeAntonio R, Contreras R, *et al.* Impact of rotavirus vaccination on childhood gastroenteritis-related mortality and hospital discharges in Panama. *Int J Infect Dis* 2012;**16**:E94–E98. doi:10.1016/j.ijid.2011.09.003

22 Buttery JP, Lambert SB, Grimwood K, *et al.* Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. *Pediatr Infect Dis J* 2011;**30**:S25–29. doi:10.1097/INF.0b013e3181fefdee

23 Cortese MM, Immergluck LC, Held M, *et al.* Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics* 2013;**132**. doi:10.1542/peds.2012-3804

24 Field EJ, Vally H, Grimwood K, *et al.* Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. *Pediatrics* 2010;**126**:e506–512. doi:10.1542/peds.2010-0443

25 Rissardo L, Karina, Furlan MCR, Marcon S, Silva, *et al.* Hospital morbidity before and after vaccination program against rotavirus in the state of ParanÃ¡-Brazil: descriptive- ecological study [Portuguese]. *Online Braz J Nurs* 2010;**9**:1–1.

26 Pendleton A, Galic M, Clarke C, *et al.* Impact of rotavirus vaccination in Australian children below 5 years of age A database study. *Hum Vaccines Immunother* 2013;**9**:1617–25. doi:10.4161/hv.24831

27 Paulke-Korinek M, Kollaritsch H, Aberle SW, *et al.* Sustained low hospitalization rates after four years of rotavirus mass vaccination in Austria. *Vaccine* 2013;**31**:2686–91. doi:10.1016/j.vaccine.2013.04.001

28 Department for Communities and Local Government. The English Indices of Deprivation 2010. England: : Department for Communities and Local Government 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf (accessed 14 Jan2014).

29 Office for National Statistics. Super Output Area Population Estimates - Mid-2011 (Census Based). Off. Natl. Stat. 2013.http://www.ons.gov.uk/ons/rel/sape/soa-mid-year-pop-est-engl-wales-exp/mid-2011--census-based-/stb---super-output-area---mid-2011.html (accessed 17 Apr2014).

30 Liverpool Health Partners. http://www.liverpoolhealthpartners.org.uk/index.html

31 Liverpool Community Health NHS Trust. http://www.liverpoolcommunityhealth.nhs.uk/

32 NHS England Merseyside Area Team. http://www.england.nhs.uk/north/mers-at/

33 Alder Hey Children's NHS Foundation Trust. http://www.alderhey.nhs.uk/

34 Public Health England. https://www.gov.uk/government/organisations/public-health-england

35 Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. *Vaccine* 2007;**25**:3971–9. doi:10.1016/j.vaccine.2007.02.070

36 Public Health England, Field Epidemiology Service North West. North West Infectious Intestinal Disease Activity Winter 2013/14 Bulletin: Week 44. Public Health England 2013. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317140237031

Additional figure titles and legends

Figure 1. Socioeconomic deprivation in Merseyside

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

Figure 2. Schematic of study data sources and outcome measures

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.

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

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

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

Dan Hungerford[1,4] – d.hungerford@liverpool.ac.uk, 0151 795 9609 (corresponding author)

Dr Roberto Vivancos[4] – roberto.vivancos@phe.gov.uk

Professor Neil French[1,3] – french@liverpool.ac.uk

Dr Miren Iturriza-Gomara[1] – miren@liverpool.ac.uk

Professor Nigel Cunliffe[1,2] – nigelc@liverpool.ac.uk

1. Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health, University of Liverpool, The Ronald Ross Building, 8 West Derby Street, Liverpool, L69 7BE, UK
2. Alder Hey Children's NHS Foundation Trust, Eaton Rd, Liverpool, L12 2AP, UK
3. Royal Liverpool and Broadgreen University Hospitals NHS Trust, Prescot St, Liverpool, L7 8XP, UK
4. Public Health England, Field Epidemiology Services, 5th Floor Rail House, Lord Nelson Street, Liverpool, L1 1JF, UK

Keywords

Rotavirus; Vaccination; Gastroenteritis; Epidemiology; Immunity, Herd

Word Count

3,~~577~~ 624 (excluding footnotes)

ABSTRACT

Introduction

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

Methods and analysis

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

Ethics and dissemination

The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference: 14/SC/1140 ~~approval has been granted~~. ~~The~~ Study outputs~~findings~~ will be disseminated through scientific conferences and peer-reviewed publications. The study ~~findings~~ will ~~enable~~ demonstrat~~eion of~~ the impact of 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 usingin 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 includecover 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 studyit 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 ofing 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

admissions and emergency department (ED) attendances for acute gastroenteritis (AGE), respectively in children under 5 years of age.[3] The economic cost of RVGE to the health service is estimated to be approximately £14 million per year in England and Wales.[3] At Alder Hey Children's NHS Foundation Trust, Liverpool, UK rotavirus is a major cause of community-acquired and healthcare-associated diarrhoea; in a 2-year prospective study among hospitalised children, rotavirus was detected by RT-PCR in 43% of community-acquired and in 31% of healthcare-associated gastroenteritis cases.[4] AGE hospital admissions are known to have a positive correlation with socioeconomic deprivation [5] and globally the burden of severe RVGE is much higher in low-income countries. However, ~~no statistical correlation between~~ RVGE ~~in infants~~ has not yet been correlated with ~~and~~ socioeconomic deprivation ~~has been shown to exist~~ in the UK.

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

Clinical trials in middle and high income countries demonstrated high (> 85%) efficacy against severe rotavirus gastroenteritis.[10] The introduction of rotavirus vaccines in the immunisation programmes of these countries has demonstrated direct benefits on a par with those observed in clinical trials, with significant reductions in diarrhoea hospitalisations.[17] An unanticipated but beneficial consequence of rotavirus vaccination has been~~is~~ the reduction of rotavirus disease in unvaccinated individuals (herd

protection), likely due to reduced virus transmission. Such "indirect benefits" include reduced disease in non-vaccinated older children and adults who were not thought to sustain a significant burden of rotavirus disease.[18] In the UK the burden of RVGE in older children and adults is difficult to estimate but admissions for ~~viral gastroenteritis~~AGE are 2 per 1,000 population in 5-14 year olds and 7 per 1,000 in those 15+ years.[19] Hence monitoring changes in AGE incidence in non-vaccinated older children and adults is critical to assess indirect impact.

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

METHODS

Study aim

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

require extended and improved data collection tools to maximise the usefulness of this surveillance approach. The main outcome measures are:

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

Study setting and location

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

Study overview and choice of study designs

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

between communities with high vaccine uptake and those with lower vaccine uptake and the relationship with socioeconomic deprivation. The ecological study approach allows population based rates of outcomes to be compared in space and time using vaccine uptake and community level socioeconomic deprivation as covariates.

Study data

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

Hospital admission and ED attendance data will be obtained from hospital episode statistics (HES),[19] which record all inpatient admissions in NHS hospitals in England. ~~and directly from NHS Trusts which cover the population of Merseyside~~The study will therefore measure hospitalisations and ED attendances for residents of Merseyside receiving care in hospitals throughout England.

The study will obtain GP consultation data~~s~~ for diarrhoea or gastroenteritis from Clinical Commissioning Groups covering Merseyside or from government held sentinel surveillance systems. Community consultations for diarrhoea and gastroenteritis at "Walk-in Centres" will be sourced from NHS Community Health Trusts. Walk-in Centres are primarily nurse-led primary care facilities for illness and injuries without need for prior appointment.

~~The infection control team~~ Rotavirus gastroenteritis at Alder Hey Children's NHS Foundation Trust (Alder Hey) in Liverpool is classifie~~d~~s ~~rotavirus cases~~ as community acquired or ~~healthcare associated (~~nosocomial~~)~~. Alder Hey's ~~NHS Foundation Trust's~~ footprint covers the majority of Merseyside's children, so these data will enable evaluation of the effect of rotavirus vaccination on nosocomial rotavirus infection in children across Merseyside.

Laboratory detections of rotavirus from Public Health England Laboratory surveillance covering Merseyside residents will be included in the analysis. Other causative agents of AGE identified through laboratory testing including, for example, norovirus, adenovirus, ~~astrovirus~~and astrovirus will also be extracted for analysis.

Each data set will cover at least three-years either side of vaccine introduction. All data will be pseudo-anonymised to allow distinction of records but no linking of data sets or identification of individuals will be undertaken. All data will be either geo-coded from postcode to small statistical geographical community units termed Lower Super Output Areas (LSOA) or sourced with this geography. LSOAs consist of approximately 1,500 persons and dDenominator populations will be derived from the Office of National Statistics (ONS) mid-year population-estimates by LSOA.[29] Indicators of socioeconomic deprivation at LSOA level will be measured using the English Indices of Deprivation. The UK Department for Communities and Local Government produce the English indices of Deprivation using census and other local administrative databe sourced from the Department for Communities and Local Government.[28] Rotavirus vaccination uptake data will be sourced from the Child Health Information System (CHIS) which is held by community NHS health Trusts in Merseyside. Records of doses of vaccinations given as part of the UK childhood vaccine schedule are recorded in CHIS for each child.

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)~~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 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

Quality control

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

matched against laboratory detections. Based on the results of thise assessmentaudit, it may be necessaryapplicable to adjust the recorded number of hospital admissions for any ascertainment bias identified.

Ethical considerations

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

Data analysis

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

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

Power calculation

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

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

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

Timeline

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

Project governance

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

Dissemination of research findings

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

DISCUSSION

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

Strengths

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

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

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

study will examine ~~provide evidence for impact on the~~ indirect effects in ~~emergency departments~~EDs and community settings. This is particularly important as it is perhaps more likely that moderate/severe RVGE in un-vaccinated older children and adults will be treated at ~~emergency departments~~EDs and through community consultations.

Another potential strength of the study is the ability to conduct analysis at small community (LSOA) level. This will enable small area socio-demographic information such as socioeconomic deprivation to be included in the analyses as a covariate at the lowest possible unit of analyses other than the individual. Thus, allowing the exploration of the association between socioeconomic deprivation, burden of RVGE / AGE and vaccine uptake whilst limiting the ecological fallacy of analysis.

As many of the data sources included in this study do not include specific RVGE classification, we ~~are~~ will be using AGE as an outcome measure for most data sets. Laboratory detection~~s~~ data which are organism specific will allow us to adjust these measures based on the seasonal contribution of organisms other than rotavirus such as norovirus. For example RVGE seasonality is fairly constant but that of norovirus tends to vary over the winter and spring months in the UK. These AGE indicators can therefore be adjusted for changes in norovirus seasonality (Figure 3)[35] to give a better proxy of the contribution of rotavirus to overall GI causes and the relative impact of rotavirus vaccination

Limitations

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

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

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

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

The study currently ~~does~~ will not include any economic component~~ which given the cost of rotavirus to the health service is essential.~~ However, previous studies have reported the likely cost-effectiveness of rotavirus vaccination for the population under 5 years of age.[36] This study ~~would~~ will provide the results and data necessary for economic evaluation based on the direct and indirect impact of rotavirus vaccination.

FOOTNOTES

Contributions

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

study co-ordination and analysis. MIG conceived of the study and participated in its design; and will contribute to study co-ordination. NF conceived of the study and participated in its design; and will oversee study co-ordination and contribute to analyses. NC conceived of the study, participated in its design and will contribute to study co-ordination. All authors were involved in revising the manuscript and read and approved the final manuscript.

Acknowledgements The authors gratefully acknowledge the effort and assistance provided by all the research and development staff, laboratory technicians, data entry staff and support staff at the collaborating sites. ~~This work is support by the GlaxoSmithKline Biologicals. The funding body had no role in the study design, the collection, analysis and interpretation of data, the writing of the manuscript, or the decision to submit the manuscript for publication.~~

Funding

This study ~~will be~~is in part supported (approximately 35% of total cost) by GlaxoSmithKline Biologicals SA. GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this manuscript for factual accuracy but the authors are solely responsible for final content and interpretation. The authors received no financial support or other form of compensation related to the development of the manuscript.~~This work is to be partially supported by GlaxoSmithKline Biologicals, Belgium, including salary contributions to the lead author DH and resources for quality control of data sources~~.

Competing interests

Financial competing interests

The Rotarix™ vaccine used in the UK national immunisation programme evaluated by this study is developed and licensed by GlaxoSmithKline Biologicals. NC is in receipt of research grant support from GSK Biologicals (to University of Liverpool) and has received honoraria for participation in GSK Rotavirus Vaccine Advisory Board Meetings.

Non-financial competing interests

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

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

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

REC Reference: 14/SC/1140~~The study has received NHS ethics approval.~~

References

1 Tate JE, Burton AH, Boschi-Pinto C, *et al.* 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:136–41. doi:10.1016/S1473-3099(11)70253-5

2 Tam CC, Rodrigues LC, Viviani L, *et al.* Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. *Gut* 2012;**61**:69–77. doi:10.1136/gut.2011.238386

3 Harris JP, Jit M, Cooper D, *et al.* Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. *Vaccine* 2007;**25**:3962–70. doi:10.1016/j.vaccine.2007.02.072

4 Cunliffe NA, Booth JA, Elliot C, *et al.* Healthcare-associated viral gastroenteritis among children in a large pediatric hospital, United Kingdom. *Emerg Infect Dis* 2010;**16**:55–62. doi:10.3201/eid1601.090401

5 Pockett RD, Adlard N, Carroll S, *et al.* Paediatric hospital admissions for rotavirus gastroenteritis and infectious gastroenteritis of all causes in England: an analysis of correlation with deprivation. *Curr Med Res Opin* 2011;**27**:777–84. doi:10.1185/03007995.2011.555757

6 Iturriza-Gómara M, Cunliffe N. Rotavirus vaccine: a welcome addition to the immunisation schedule in the UK. *BMJ* 2013;**346**:f2347.

7 Nakagomi O, Iturriza-Gomara M, Nakagomi T, *et al.* Incorporation of a rotavirus vaccine into the national immunisation schedule in the United Kingdom: a review. *Expert Opin Biol Ther* 2013;**13**:1613–21. doi:10.1517/14712598.2013.840285

8 Soares-Weiser K, Goldberg E, Tamimi G, *et al.* Rotavirus vaccine for preventing diarrhoea. *Cochrane Database Syst Rev* 2004;:CD002848. doi:10.1002/14651858.CD002848.pub2

9 World Health Organization. Rotavirus vaccines. *Relevé Épidémiologique Hebd Sect Hygiène Secrétariat Société Nations Wkly Epidemiol Rec Health Sect Secr Leag Nations* 2007;**82**:285–95.

10 Soares-Weiser K, Maclehose H, Bergman H, *et al.* Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev* 2012;**11**:CD008521. doi:10.1002/14651858.CD008521.pub3

11 Rotavirus vaccines WHO position paper: January 2013 - Recommendations. *Vaccine* 2013;**31**:6170–1. doi:10.1016/j.vaccine.2013.05.037

12 World Health Organization. Rotavirus vaccines. WHO position paper – January 2013. *Relevé Épidémiologique Hebd Sect Hygiène Secrétariat Société Nations Wkly Epidemiol Rec Health Sect Secr Leag Nations* 2013;**88**:49–64.

13 PATH. Country introductions | Maps and list – Rotavirus Vaccine Access and Delivery - PATH. http://sites.path.org/rotavirusvaccine/rotavirus-advocacy-and-communications-toolkit/country-introduction-maps-and-list/ (accessed 7 Jul2014).

14 Parez N, Giaquinto C, Du Roure C, *et al.* Rotavirus vaccination in Europe: drivers and barriers. *Lancet Infect Dis* 2014;**14**. doi:10.1016/S1473-3099(14)70035-0

15 Health and Social Care Information Centre. NHS Immunisation Statistics, England -2012-13. England: : Health and Social Care Information Centre 2013. http://www.hscic.gov.uk/searchcatalogue?q=title%3A%22NHS+Immunisation+Statistics%22&area=&size=10&sort=RelevanceDesc (accessed 17 Apr2014).

16 Public Health England. Early evidence of the impact of the national rotavirus immunisation programme. *Health Prot Rep Wkly Rep* 2014;**8**.

17 Patel MM, Glass R, Desai R, *et al.* Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis* 2012;**12**:561–70. doi:10.1016/S1473-3099(12)70029-4

18 Lopman BA, Curns AT, Yen C, *et al.* Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. *J Infect Dis* 2011;**204**:980–6. doi:10.1093/infdis/jir492

19 Health and Social Care Information Centre. Hospital Episode Statistics. Admitted Patient Care, England - 2012-13: Diagnosis. Health Soc. Care Inf. Cent. 2014.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

20 Braeckman T, Van Herck K, Meyer N, *et al.* Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. *BMJ* 2012;**345**:e4752.

21 Bayard V, DeAntonio R, Contreras R, *et al.* Impact of rotavirus vaccination on childhood gastroenteritis-related mortality and hospital discharges in Panama. *Int J Infect Dis* 2012;**16**:E94–E98. doi:10.1016/j.ijid.2011.09.003

22 Buttery JP, Lambert SB, Grimwood K, *et al.* Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. *Pediatr Infect Dis J* 2011;**30**:S25–29. doi:10.1097/INF.0b013e3181fefdee

23 Cortese MM, Immergluck LC, Held M, *et al.* Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics* 2013;**132**. doi:10.1542/peds.2012-3804

24 Field EJ, Vally H, Grimwood K, *et al.* Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. *Pediatrics* 2010;**126**:e506–512. doi:10.1542/peds.2010-0443

25 Rissardo L, Karina, Furlan MCR, Marcon S, Silva, *et al.* Hospital morbidity before and after vaccination program against rotavirus in the state of ParanÃ¡-Brazil: descriptive- ecological study [Portuguese]. *Online Braz J Nurs* 2010;**9**:1–1.

26 Pendleton A, Galic M, Clarke C, *et al.* Impact of rotavirus vaccination in Australian children below 5 years of age A database study. *Hum Vaccines Immunother* 2013;**9**:1617–25. doi:10.4161/hv.24831

27 Paulke-Korinek M, Kollaritsch H, Aberle SW, *et al.* Sustained low hospitalization rates after four years of rotavirus mass vaccination in Austria. *Vaccine* 2013;**31**:2686–91. doi:10.1016/j.vaccine.2013.04.001

28 Department for Communities and Local Government. The English Indices of Deprivation 2010. England: : Department for Communities and Local Government 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf (accessed 14 Jan2014).

29 Office for National Statistics. Super Output Area Population Estimates - Mid-2011 (Census Based). Off. Natl. Stat. 2013.http://www.ons.gov.uk/ons/rel/sape/soa-mid-year-pop-est-engl-wales-exp/mid-2011--census-based-/stb---super-output-area---mid-2011.html (accessed 17 Apr2014).

30 Liverpool Health Partners. http://www.liverpoolhealthpartners.org.uk/index.html

31 Liverpool Community Health NHS Trust. http://www.liverpoolcommunityhealth.nhs.uk/

32 NHS England Merseyside Area Team. http://www.england.nhs.uk/north/mers-at/

33 Alder Hey Children's NHS Foundation Trust. http://www.alderhey.nhs.uk/

34 Public Health England. https://www.gov.uk/government/organisations/public-health-england

35 Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. *Vaccine* 2007;**25**:3971–9. doi:10.1016/j.vaccine.2007.02.070

36 Public Health England, Field Epidemiology Service North West. North West Infectious Intestinal Disease Activity Winter 2013/14 Bulletin: Week 44. Public Health England 2013. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317140237031

Additional figure titles and legends

Figure 1. Socioeconomic deprivation ~~Indices of multiple deprivation~~ in Merseyside

Produced using the English Indices of Deprivation 2010, national quintiles for the ~~I~~index of M~~m~~ultiple D~~d~~eprivation [19].

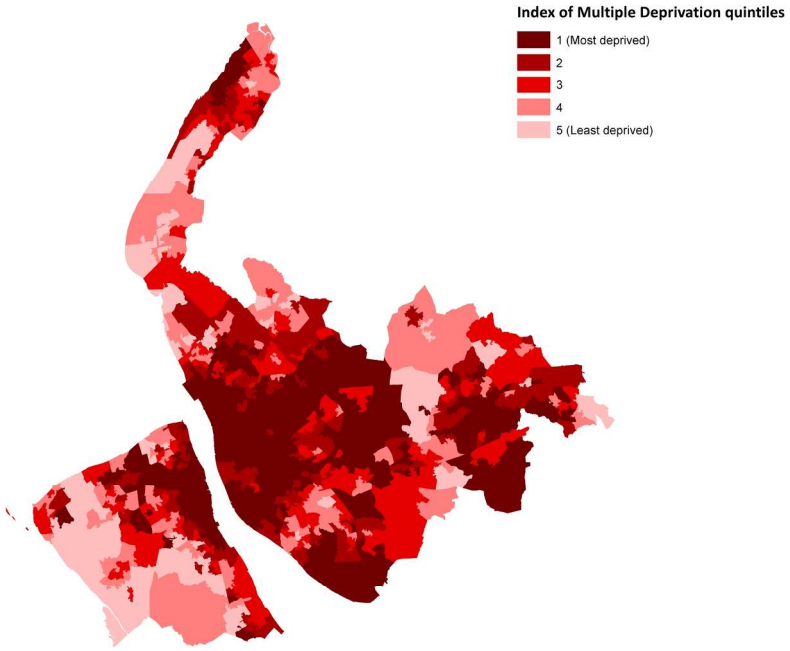
Figure 2. Schematic of study data sources and outcome measures

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.

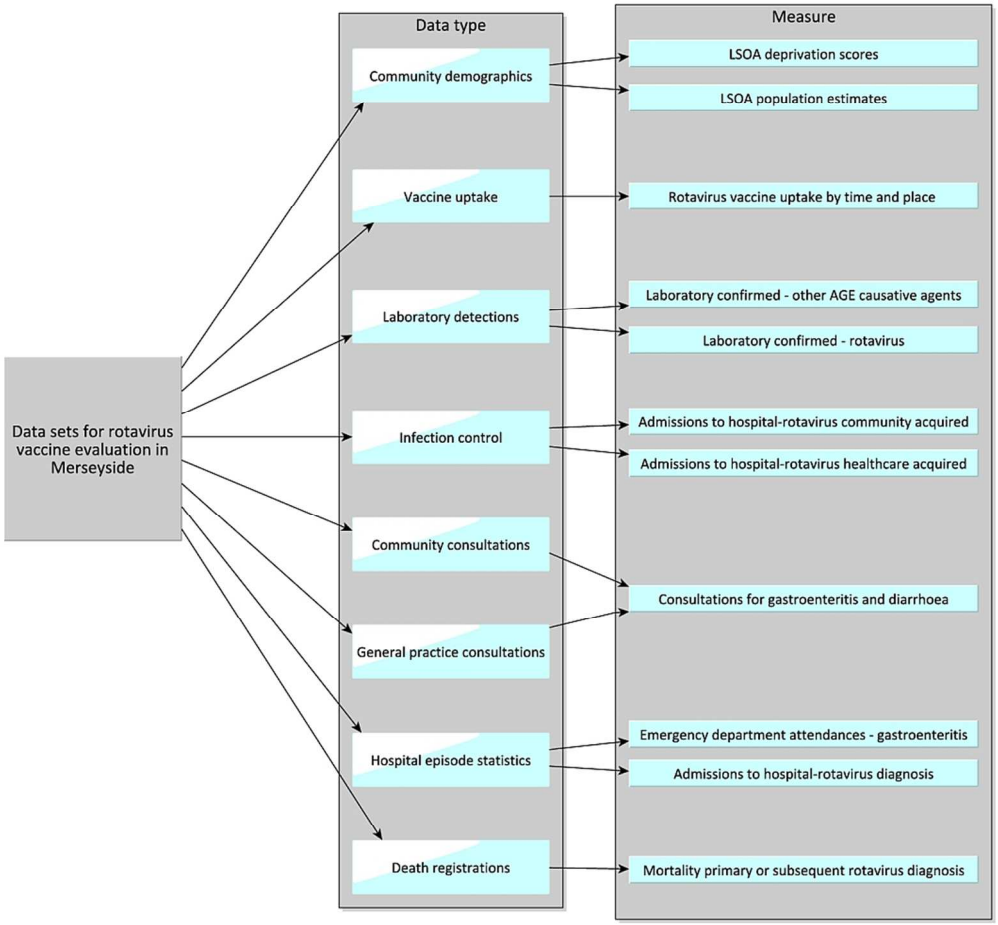
Figure 3. Laboratory detections of rotavirus and norovirus in the North West, England, 2009/10-2013-14

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

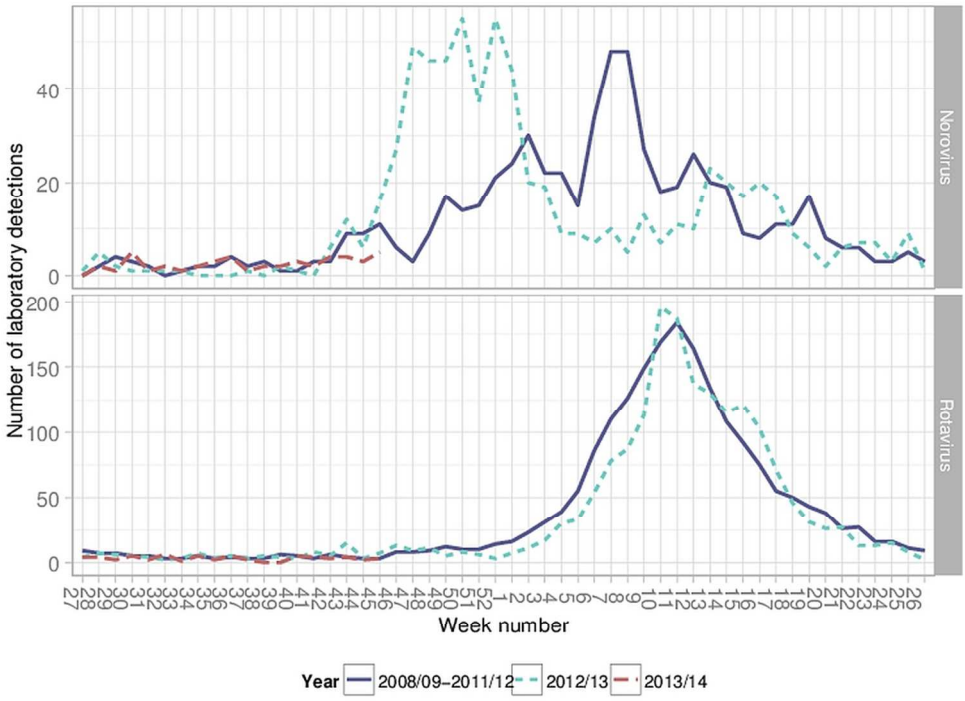
469



Produced using the English Indices of Deprivation 2010, national quintiles for the index of multiple deprivation [19].
210x148mm (300 x 300 DPI)



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.
90x83mm (300 x 300 DPI)



Laboratory reports are from LabBase2 system at Public Health England [35], showing variation in the norovirus season as compared to the rotavirus season.
90x67mm (300 x 300 DPI)