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Cost-impact study of Rotavirus Vaccination Programme in Scotland

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Full Title:	Cost-impact study of Rotavirus Vaccination Programme in Scotland
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Abstract:	In July 2013, the Scottish Government introduced a rotavirus vaccination programme into the childhood immunisation schedule. The aim of this research was to estimate the cost impact of this programme. Methods: Data for rotavirus-related resource use were identified including laboratory reports, hospitalisations, attendances at Accident and Emergency Departments, GP consultations, calls to the National Health Service telephone helpline and prescriptions for common rehydration treatments. We used an interrupted time series analysis approach to assess the impact on resource utilisation in all categories. Appropriate costs were added to the models and predicted pre and post vaccination mean annual costs were estimated. The cost of the vaccination programme was estimated using costs from the literature. Results: The vaccination programme was associated with a reduction in utilisation in all measured healthcare resource categories. These reductions were all statistically significant (at the 95% level) with p-values less than 0.001. Reductions ranged from 18% in calls to NHS24 to 73% in positive laboratory reports. The vaccination programme was associated with a reduction in annual healthcare resource costs of 38% (£595,000 per 100,000 infants under five years old) in our measured categories (including £495,000 from a reduction in hospital stays). The annual overall cost-impact of the rotavirus vaccination programme (Cost of delivering the programme minus the reduction in resource costs) was estimated at approximately £435,000 per 100,000 infants under 5 years old. Conclusion: The rotavirus vaccination programme was associated with a reduction in all measured categories of rotavirus-related resource use by infants under 5 years old.
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Cost-impact study of Rotavirus Vaccination Programme in Scotland

Heggie, R* [a]. Murdoch, H [b]. McIntosh, E [a], Cameron, C [b]. Smith-Palmer, A [b]. Bouttell, J [a]

[a] Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing, University of Glasgow, United Kingdom

[b] Health Protection Scotland, Glasgow, United Kingdom

Highlights

- The Rotavirus vaccination programme for infants <5 years old in Scotland was associated with a reduction in healthcare resource utilisation.
- The Rotavirus vaccination programme was associated with a reduction in healthcare resource costs of 38% (approximately £595,000 per 100,000 infants under five years old) before accounting for the cost of the programme.
- 83% of the reduction in costs associated with rotavirus-related resources use came from reduced hospitalisations.
- Based on our assumed costing of vaccine at £23.91 per single dose the cost of the vaccination programme is estimated at approximately £1,031,000 per 100,000 infants under five years old, resulting in an overall annual cost of the programme of approximately £435,000 per 100,000 infants under five years old.

**corresponding author at: Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing, 1 Lilybank Gardens, University of Glasgow, United Kingdom, G12 8RZ. Email: robert.heggie@glasgow.ac.uk, Tel: +44 (0)141 330 3047*

Abstract

Aim*:* In July 2013, the Scottish Government introduced a rotavirus vaccination programme into the childhood immunisation schedule. The aim of this research was to estimate the cost impact of this programme. **Methods***:* Data for rotavirus-related resource use were identified including laboratory reports, hospitalisations, attendances at Accident and Emergency Departments, general practice consultations, calls to the National Health Service telephone helpline and prescriptions for common rehydration treatments. We used an interrupted time series analysis approach to assess the impact on resource utilisation in all categories. Appropriate costs were added to the models and predicted and post vaccination mean annual costs were estimated. The cost of the vaccination programme was estimated using costs from the literature. **Results***:* The vaccination programme was associated with a reduction in utilisation in all measured healthcare resource categories. These reductions were all statistically significant (at the 95% level) with p-values less than 0.001. Reductions ranged from 18% in calls to NHS24 to 73% in positive laboratory reports. The vaccination programme was associated with a reduction in annual healthcare resource costs of 38% (£595,000 per 100,000 infants under five years old) in our measured categories (including £495,000 from a reduction in hospital stays). The annual overall cost-impact of the rotavirus vaccination programme (the cost of delivering the programme minus the reduction in resource costs) was estimated at approximately £435,000 per 100,000 infants under 5 years old. **Conclusion:** The rotavirus vaccination programme was associated with a reduction in all measured categories of rotavirus-related resource use by infants under 5 years old.

1. Introduction

Rotavirus is the leading cause of severe gastroenteritis in infants worldwide and results in approximately 500,000 deaths annually in infants under the age of 5 years [1]. Unlike in the developing world, rotavirus rarely causes mortality in the UK, however infection results in a high number of hospital admissions for severe dehydration in infants [1] and impacts on health related quality of life (HRQOL) [2]. It has been estimated that rotavirus causes around 45% of hospitalisations for acute gastroenteritis in infants under the age of 5 years [2]. In addition, infections resulting in hospitalisation represent only a fraction of cases that occur in the community which cause substantial morbidity with consequent impact on healthcare providers such as general practitioners (GPs) and out-of-hours services.

In July 2013, the Scottish Government, along with the rest of the UK, introduced the GlaxoSmithKline (GSK) vaccine Rotarix® [3]. The vaccine was made available to all infants born in Scotland on or after May 1st 2013 and delivered as part of the routine childhood immunisation programme. Over the first evaluation quarter 1st July – 30th September 2014, uptake of the rotavirus vaccine was 93% [4]. The vaccine was made available to all infants at age 8 weeks (1st dose) and again at 12 weeks (2nd dose).

Routine surveillance carried out by Health Protection Scotland (HPS) found evidence of substantial reductions in rotavirus-related burden of disease in infants [5] similar to that reported elsewhere [6-10]. The aim of this research was to estimate the cost-impact of the rotavirus vaccination programme in Scotland, based on a retrospective analysis of routinely collected data on actual healthcare utilisation.

2. Results

2.1 Overall cost-impact

Table 1 shows the overall cost-impact of the rotavirus vaccination programme. Results are reported in terms of the cost of the programme, the monetary value of the reduction in resource use pre-and

post-vaccination period, and the difference between the cost of the programme and the value of the reduction in resource use is estimated as the overall cost-impact of the programme.

[INSERT TABLE 1]

2.2 Cost of vaccination programme

Based on the actual number of infants who received the vaccine over the evaluation period 1st July-30th September 2013, it was calculated that 18,575 infants received the vaccination in 2013, per 100,000 infants <5 years old living in Scotland (note: the vaccine uptake rate was 92.7% however rates per 100,000 are calculated over the entire relevant population of infants <5 years old) [4]. This figure is multiplied by the vaccine cost per 2 doses. On the assumption of a vaccine price of £23.91 per dose [11], we estimated a total vaccine cost of £888,278 per 100,000 infants <5 years old in Scotland in 2013/14. The additional administrative payment made to GPs of £7.67 per infant (per two doses) [4] equates to £142,474 per 100,000 infants <5 years old in Scotland. Taken together, this indicates that the cost of the vaccination programme was £1,030,751 per 100,000 infants <5 years old in Scotland.

2.3 Sensitivity analysis

We undertook sensitivity analysis to estimate the impact of alternative vaccine prices on the overall cost of the vaccination programme. Table 2 presents the results based on a 50% increase or reduction from the price given in the base case. The results suggest that the overall cost of the programme is highly sensitive to the price of the vaccine.

[INSERT TABLE 2]

2.3 Reduction in rotavirus-related resource use

Table 3 shows the reduction in rotavirus-related resource use associated with infants <5 years old for the mean year pre- and post-vaccination programme. Data is presented as incident rate ratios

(IRRs) which can be interpreted as representing a percentage reduction in resource use. For example, the IRR associated with vaccination for laboratory reports is 0.273 which equates to a reduction of 72.7% (1-0.273 expressed as a percentage). Also presented are the model predicted pre and post vaccination annual number of events, the 95% confidence intervals (CIs) and the p-value associated with the vaccination variable in the model. For each resource use appropriate cost data were attached and the resulting annual costs per 100,000 infants <5 are presented.

Table 3: Adjust incidence rate ratios (IRRs) for the association between vaccination and rotavirus-related annual events and costs, for infants <5 years old in Scotland

[INSERT TABLE 3]

Notes: CI – confidence intervals. IRR–Incidence Rate Ratio. An IRR below 1 indicates a reduction in events and costs associated with the vaccination programme. P-value is a measure of statistical significance and a result under 0.05 is considered statistically significant for the purposes of this study. All models were adjusted for seasonality and underlying trend. The mean costs are estimated by applying a unit cost to the event rates predicted by the model.

All measured resource categories showed statistically significant reductions associated with the introduction of the rotavirus vaccination programme. These varied in magnitude according to the resource category with laboratory reports showing the highest reduction of 73% (IRR 0.273, p<0.001) and the smallest reduction of 17% in calls to NHS24 (IRR 0.826, p<0.001). Table 3 also presents the cost difference estimated from the predicted pre and post vaccination mean costs. The reduction in hospital stays forms the largest part of the cost difference. Figures 1 and 2 present the actual and predicted counts for laboratory reports and hospital stays respectively. Equivalent figures for the other resource categories are presented in the Appendix. These figures were selected for presentation in the main body of the article as they illustrate the model fit achieved in the most specific measure of rotavirus (positive laboratory reports) and the largest cost category (hospital stays).

Figure 1: Positive laboratory reports for rotavirus (weekly rates per 100,000), for infants <5 years old in Scotland – 2009 to 2015.

[INSERT FIGURE 1]

Notes: R^2=0.86. Dashed line represents introduction of vaccination programme

Figure 2: Hospital length of stay for rotavirus (weekly rates per 100,000), for infants <5 years old in Scotland – 2010 to 2015.

[INSERT FIGURE 2]

Notes: R^2=0.83. Dashed line represents introduction of vaccination programme

3. Discussion

Our study found statistically significant reductions in all rotavirus-related health-care resource categories examined following the introduction of the vaccination programme. However, the range of the reductions varied from 17% to 73%. The size of the reduction is driven by the ability of the data source to accurately capture cases of rotavirus. The highest reduction was found in the most specific data source, positive laboratory reports and the lowest in the least specific areas of NHS24 calls and prescriptions for rehydration treatments. We found a 40% reduction in hospital stays, which are the main cost driver among health-care resource categories.

Our findings are in line with the extensive literature across diverse geographies finding that the introduction of a rotavirus vaccination programme leads to reductions in a broad range of health-care resource categories [16, 17]. Prior to the introduction of the rotavirus vaccination programme, the Scottish Government predicted that such a programme could reduce the number of rotavirus-related hospital stays by approximately 70% [12]. Forrest et al (2017) found a reduction of 85% and 91% in rotavirus related admissions and bed-days, respectively, in a paediatric hospital setting in Lothian, Scotland [13]. This study used a highly specific definition of rotavirus-based admissions based on positive laboratory reports so is comparable with the 73% reduction suggested by our study. In undertaking this study, we gave much consideration to the issue of how best to capture the impact of rotavirus on hospital resources. When we considered the changes in solely those hospital admissions and bed-days which were coded for rotavirus specific (ICD10 code “A080” in

either 1st and 2nd diagnostic position), we observed higher reductions in hospital admissions for rotavirus and rotavirus-related hospital stays similar to the reductions found by Forrest et al [12]. However, many hospital admissions relating to rotavirus are coded as generic viral enteritis, particularly when specific organism testing is not required for clinical management. As the aim of this study is to estimate the cost impact we chose to increase the sensitivity of our measure by including viral enteritis unspecified (possible rotavirus) "A083", "A084" and "A085" as well as the specific rotavirus code "A080". This would have the effect of increasing the volume of cases in both the pre and post vaccination periods as well as reducing the percentage differences between the periods. It is likely that using these codes will miss a proportion of rotavirus cases as they are likely to be coded under general acute gastroenteritis codes [13]. Our finding of a 40% reduction in hospital admissions is in line with a the 44% reduction found in a study of five local authority areas in Merseyside, England over the period 2013-2016 (consisting of five hospitals with emergency and secondary care facilities and a paediatric hospital)[14]. .

We found that the impact of the vaccine in primary care was lower than that predicted by Jit et al (2007), with a substantial proportion of overall reduction in healthcare cost due to a decrease in GP consultations [11]. Data were available on consultations for diarrhoea, vomiting and all gastrointestinal illness, however due to possible double counting and for consistency with other data analysed for this study, we decided only to include the impact from consultations for diarrhoea. This may therefore represent an underestimate, which may explain the 32% reduction in prescriptions during the rotavirus season, despite only a 16% reduction in consultations. Lack of adherence to the use of appropriate Read codes may also help to explain this underestimate.

The impact of childhood rotavirus infection and the vaccine on nonmedical costs was not included in this study, however it is likely that there are significant costs associated with productivity loss (or "time-off" work) of the parent(s). Different studies give different estimates of the number of work days lost – typically ranging from around two to five days [15]. The typical UK worker earns a median

daily wage of £103.6 [16]. Hence, 2 days (5 days) forgone work on behalf of the caregiver results in £207.2 (£518) in lost earnings per childhood rotavirus case. Some estimates suggest that the loss in productivity to the economy is the difference between a rotavirus vaccination programme being, not only cost-effective, but cost saving in the UK [17].

This study only considers costs and does not value the improved quality of life which a reduction in rotavirus incidence would deliver. Jit and Edmunds (2007) report a quality of life (QALY) loss due to rotavirus of 0.0022 for a child and 0.00184 for an adult per case of rotavirus [11]. In our study, there was a mean of 472 laboratory confirmed cases of rotavirus pre-vaccination programme, compared with 110 cases post- vaccination programme, per 100,000 infants <5 in Scotland. If we use this as a proxy for the mean number of rotavirus cases pre- and post-vaccination, then we estimate the QALY loss averted per family (2 adults, 1 infant) as 2.13 QALYs per 100,000 infants <5 years old in Scotland between the mean year pre-and post-vaccination period.

Since completion of our analysis, the first full year of data became available for calendar year 2015 (infants born Jan-Dec 2014). These indicate 53,013 infants (18,141 infants per 100,000) received rotavirus vaccine in 2015. This is comparable with the estimate used in our analysis (18,575 infants, per 100,000).

Strengths and limitations

At time of publication, this is the only study the authors are aware of which attempts to estimate the cost-impact of the rotavirus vaccination programme for the whole of Scotland, based on observational data.

The challenge with using indicators of gastrointestinal illness such as reporting of symptoms of diarrhoea as a proxy for rotavirus is that it also captures changes in the prevalence of other gastrointestinal illnesses unrelated to rotavirus. As a result, there are uncertainties in the estimates of resource use both pre and post vaccination and these differ depending upon the type of resource-

use considered. In comparing our results with other studies it is, therefore, important to note the precise definitions included in the analysis.

We obtained data on the number of prescriptions made per day per patient population, however, we did not have a further breakdown of composition of these prescriptions (i.e. which hydration drugs were given). Hence, it was not possible to calculate the change in mean prescriptions and then attach unit costs. Rather, we calculated the change in the mean gross cost of prescriptions pre-and post-vaccination programme. A detailed breakdown of the prescriptions given would have provided a more accurate estimate of the cost-impact, however it is not clear whether an absence of this breakdown suggests an over-or underestimate of the overall cost-impact. The data we obtained was based on prescriptions for rotavirus in primary care. However, there is the possibility that these prescriptions, which are mainly rehydration drugs, could have been prescribed for alternative conditions requiring rehydration.

Due to duplication concerns, it was not possible to use calls relating to vomiting and diarrhoea, combined, from NHS24 data. Hence, data on calls citing diarrhoea in infants <1 year old and <5 years old were used as a proxy for rotavirus. It is acknowledged that this is likely to be an underestimate of the true total cost associated with NHS24. Similarly, for duplication concerns, only GP consultations for diarrhoea were included. This is also likely to represent a considerable underestimate of the cost.

The overall cost-impact of the vaccination programme was highly sensitive to the cost of the vaccine, which we were not able to confirm. Our analysis relies on an estimate from the literature which we varied in sensitivity analysis.

4. Conclusion

In this study we have estimated the mean change in rotavirus-related resource use before-and-after the introduction of the Scottish Government's rotavirus vaccination programme in 2013. In doing so, we have observed reductions in the burden placed on rotavirus-related; laboratory reports;

hospitalisations; GP consultations; A&E attendances; and NHS24 calls. Our analysis showed a reduction in the mean number of rotavirus-related hospital bed-days of 40%. This reduction accounted for 83% of the overall cost reduction associated with the implementation of the rotavirus vaccination programme. This study found that the overall cost impact of the rotavirus vaccination programme (that is, the cost of delivering the programme minus the reduction in resource costs) was £435,000 increase (2013 prices) per annum per 100,000 infants <5 years.

5. Methods

5.1 Statistical analysis

In line with previous research [18] and European Centre for Disease Prevention and Control (ECDC) [19] guidance, this study adopted a "before and after" approach with the pre-vaccination period serving as a reference point from which to compare the post-vaccination period.

This study defined the net cost-impact of the programme as being the cost of the vaccination programme minus cost reductions in resource use. As such, the net cost-impact was defined as follows:

Net cost impact = (cost of vaccine + administration payment) – (cost reductions from lab reports, hospitalisations, A&E attendances, GP consultations, prescriptions and NHS24 calls).

To compare the impact of the rotavirus vaccination programme, in terms of the change in resource use and cost-impact, we used an interrupted time series analysis [20].

To estimate the overall cost-impact of the rotavirus vaccination programme, we first estimated the rotavirus-related resource utilisation for each resource pre- and post-vaccination programme, in units determined by how the data were collected (i.e. resource use per week or per month). We attached unit costs to resource use to estimate the cost of this resource over each time period for which the data were collected. Mean resource use in the pre-and post-vaccination periods were

estimated using a range of modelling approaches. We selected a Generalised Linear Model (GLM) with a Poisson family and log link as this reduced autocorrelation and provided the best model fit. We assessed goodness of fit of alternative models using the Akaike and Bayesian Information Criteria [21] Underlying trend was accounted for within the regression framework and seasonality were modelled by including Fourier terms (sine and cosine terms) [20] and a dummy variable representing the peak rotavirus season (January-May). We also included an interaction term between the seasonality variables and the relevant period variable (week or month) to allow seasonality to vary in different time periods. We hypothesised that the rotavirus vaccination programme would result in a permanent level change in resource use [20]. We therefore included a single binary variable to represent the intervention which was coded '0' in the period prior to the vaccination programme and '1' in the period following the introduction of the programme.

Population data for all infants <5 years old living in Scotland over the study period were obtained from the National Records of Scotland and used as an offset variable [22]. Incidence rates per 100,000 were calculated as the number of incidents (i.e. days in hospital or GP consultations) divided by the study population (number of infants <5 years old living in Scotland) per year multiplied by 100,000. The same approach was used to estimate the cost of the programme, hence cost per 100,000 represents the cost of providing the vaccination to eligible infants (age 8 weeks and again at 12 weeks) to realise the benefits over the population of all infants <5 years.

One-way sensitivity analysis was undertaken to estimate the impact on the cost of the vaccination programme of alternative vaccine prices. Vaccine price was varied +/-50% of the base case price.. The results are presented in the appendix.

5.2 Perspective

This study takes the perspective of the UK National Health Service (NHS) and includes resource use associated with laboratory reports, hospitalisations, A&E attendances, GP consultations,

prescriptions and NHS24 calls. This is the only study at present to take such a wide perspective in estimation of the economic benefits from a national rotavirus vaccination programme in Scotland.

5.3 Measurement of resource use

Data available for each resource were; 2009-2014 for laboratory reports; 2010-2014 for hospitalisations; 2010-2014 for NHS24 calls; 2010-2014 for prescriptions; 2011-2014 for A&E; and 2011-2014 for GP consultations.

5.3.1 Laboratory confirmed reports

All laboratory confirmed cases of rotavirus infection in Scotland are reported to HPS via the Electronic Communications of Surveillance in Scotland (ECOSS) system [23]. A positive laboratory sample was detected using a real-time PCR and were only counted for the first sample from any patient episode and repeated laboratory tests for the same episode were not included. Laboratory reports for infants <5 years old in the pre-and post-vaccination years were used.

5.3.2 Hospitalisation data

All hospitalisations for infants <5 years were extracted using Scottish Morbidity Records (SMR01) database using predefined International Classification of Diseases 10 (ICD10) codes Rotavirus enteritis “A080” and Viral enteritis unspecified (possible rotavirus) “A083”, “A084” and “A085” [24]. This aimed to capture admissions for rotavirus, which are not laboratory confirmed due to the relatively short length of stay and which are coded under the more general term of viral enteritis. Due to concerns of possible double counting of patients only data with the relevant ICD10 code as main diagnosis were included.

When a patient is discharged from hospital or transferred between hospitals, specialties or to the care of a different consultant, an episode is generated. Episode data were grouped together to

identify continuous inpatient stays (CIS) and it is this level of analysis that was used to monitor hospital admissions and length of stay in this study.

5.3.3 Accident and Emergency (A&E) data

Age specific monthly data on attendances at A&E data for symptoms associated with gastrointestinal illness was available from Information Services Division (ISD). These data are based on a combination of ICD10 codes and, where coding was not used, free text analysis. Data were analysed for infants aged <5 years.

5.3.4 GP consultation data

Data on GP consultations, who provide all primary care for infants in Scotland, recorded for all infants <5 years old for diarrhoea were obtained as the best proxy for rotavirus-related GP attendances. Weekly aggregate data are received by HPS from approximately 50% of General Practices (GP) across Scotland on the number of consultations based on defined Read codes, which are currently the standard clinical classification terminology system used in GPs in the United Kingdom [25]. Data were obtained from a broad geographical spread of Scotland and were considered representative of Scotland as a whole. Data were scaled to account for 100% of GP practices.

5.3.5 NHS24 syndromic surveillance data

HPS monitor trends in calls made to the NHS24 telephone helpline in Scotland. NHS24 is also the route to out-of-hours general practice care. Data gathered on the number of calls relating to vomiting and diarrhoea give an indication into the incidence of gastroenteritis in the community. Due to duplication concerns, it was not possible to use data relating to vomiting and diarrhoea combined. Hence, data on calls citing diarrhoea in infants <5 years old were used as a proxy for rotavirus.

5.3.6 Prescription data

Data on rotavirus-related drug prescriptions were collected by the Prescribing Information System (PIS) provided by ISD Scotland and based on prescriptions administered in the primary care setting. Treatment for rotavirus typically involves the prescription of oral rehydration drugs. Data on prescription of the following drugs, listed in local formularies, were used as a proxy for rotavirus and viral enteritis: Dioralyte; Dioralyte Relief; Electrolade; O.R.S Oral, Peach. Data were provided in terms of the gross ingredient cost (£) per month for infants <5 years old over the period 2010-2015. Hence, change in gross cost pre-and post-vaccination were reported, rather than change in resource use (i.e. unit costs were not necessary).

5.3.7 Vaccine price

The Joint Committee on Vaccination and Immunisation (JCVI) carried out a review of the published literature on the cost-effectiveness of rotavirus vaccines on behalf of the Scottish Government [26]. The JCVI statement on rotavirus vaccine assumes a vaccine unit price of £35 per dose (2006 prices), based on the work of Jit & Edmunds [11]. At the price of £35 per dose, the incremental cost per QALY gained would be £61,000 and hence unlikely to be considered cost-effective. Further modelling by the authors suggested that the vaccine would have to be priced at £19 per dose for the cost of the programme to be less that £30,000 per QALY gained and hence deemed cost effective, given the current UK threshold. For this reason, we chose to assume a vaccine price of £19 per dose [11]. Inflating this to 2014 prices equates to £23.91 per dose and this was used as our base case price. Due to commercial sensitivities, there is no published price for the vaccine other than the JCVI statement.

The local health board pay each relevant GP an administrative payment of £7.67 per child receiving the rotavirus vaccination (one payment for two doses)[27]. This payment was therefore included as a direct cost of providing the service.

5.3.8 Valuation of resource use

All prices are expressed in 2013/14 prices and have been inflated (where necessary) using the Hospital and Community Health Services (HCHS) Index which uses an inflation rate specific to the UK health service (PSSRU, 2014).

Any stool sample taken from an infant suffering from diarrhoea and vomiting would undergo a full screening for a range of gastrointestinal pathogens, rather than for one specific causative agent. Hence, the unit cost of a routine enteritis laboratory report was given by Lorgelly et al as £15.08 per report (in 2001/02 prices, £20.99 in 2013/14 prices) [28].

The unit cost estimate for hospitalisations in 2013/14 was obtained from ISD. Using their new patient-level costing data, they were able to estimate the cost per day of hospital treatment for rotavirus (based on ICD10 code A080). The unit cost per day for rotavirus was estimated at £920 (2013/14). This unit cost is applied to both incidents of rotavirus coded as “rotavirus” and “viral enteritis” in SMR01 hospitalisation data.

A standard unit cost of £107 per attendance at A&E was obtained from ISD’s annual Scottish Health Service Costs [29].

The unit cost of a GP consultation was obtained from the Personal Social Services Research Unit 2014 publication [30]. The unit cost was £37.50, per GP visit lasting 11.7 minutes (excluding qualification costs).

The unit cost per call to NHS24 was reported by Munro et al as £15 (2001 prices). Inflating this to 2014, provides a unit cost of £20.88 [31].

Declaration of conflict of interest

None of the authors reported any conflicts of interest.

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Cost-impact study of Rotavirus Vaccination Programme in Scotland

Heggie, R* [a]. Murdoch, H [b]. McIntosh, E [a], Cameron, C [b]. Smith-Palmer, A [b]~~, McIntosh, E~~. Bouttell, J [a]

[a] Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing, University of Glasgow, United Kingdom

[b] Health Protection Scotland, Glasgow, United Kingdom

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Highlights

- The Rotavirus vaccination programme for infants <5 years old in Scotland was associated with a ~~reduced incidence of rotavirus~~reduction in ~~infants <5 years old~~healthcare resource utilisation.
- The Rotavirus vaccination programme was ~~also was~~ associated with a reduction in healthcare resource ~~use~~costs of 38% (approximately £595,000 per 100,000 infants under five years old) before accounting for the cost of the programme.
- ~~Almost all (95%)~~83% of the reduction in ~~healthcare resource use~~costs associated with ~~this vaccination programme was observed between January and April~~rotavirus-related resources use came from reduced hospitalisations.

- Based on our assumed costing of vaccine at £23.91 per single dose the cost of the vaccination programme is estimated at approximately £1,031,000 per 100,000 infants under five years old, resulting in an overall annual cost of the programme of approximately £435,000 per 100,000 infants under five years old.

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*corresponding author at: Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing, 1 Lilybank Gardens, University of Glasgow, United Kingdom, G12 8RZ. Email: robert.heggie@glasgow.ac.uk, Tel: +44 (0)141 330 3047

Abstract

Aim: In July 2013, the Scottish Government introduced a rotavirus vaccination programme into the ~~routine childhood immunisation schedule. The aim of this research was to identify and measure the cost impact of the rotavirus vaccination programme~~childhood immunisation schedule. The aim of this research was to estimate the cost impact of this programme. **Methods**: Data for rotavirus-related resource use were identified including laboratory reports, hospitalisations, attendances at Accident and Emergency Departments, general practice consultations, calls to the National Health Service telephone helpline and prescriptions for common rehydration treatments. We used an interrupted time series analysis approach to assess the impact on resource utilisation in all categories. Appropriate costs were added to the models and predicted pre and post vaccination mean annual costs were estimated. The cost of the vaccination programme was estimated using costs from the literature. **Results**: The vaccination programme was associated with a reduction in utilisation in all measured healthcare resource categories. These reductions were all statistically significant (at the 95% level) with p-values less than 0.001. Reductions ranged from 18% in calls to NHS24 to 73% in positive laboratory reports. The vaccination programme was associated with a reduction in annual

healthcare resource costs of 38% (£595,000 per 100,000 infants under five years old) in our measured categories (including £495,000 from a reduction in hospital stays). The annual overall cost-impact of the rotavirus vaccination programme (the cost of delivering the programme minus the reduction in resource costs) was estimated at approximately £435,000 per 100,000 infants under 5 years old. **Conclusion:** The rotavirus vaccination programme was associated with a reduction in all measured categories of rotavirus-related resource use by infants under 5 years old.

~~**Methods**: Data from a range of sources representing healthcare utilisation across the patient pathway were identified, measured and valued. These included data on laboratory confirmed reports of rotavirus, hospitalisations for rotavirus and viral enteritis and attendances at A&E. Additionally surrogate markers of rotavirus infection were used to identify and measure vaccine impact in the community, specifically general practice consultations and calls to the National Health Service telephone helpline in Scotland, NHS24 and prescribing data for common rehydration treatments. In line with previous research and European Centre for Disease Prevention and Control (ECDC) guidance, this study adopted a "before and after" methodology. Based on multiple years of resources use, we estimated resource use in a "mean year" before and after the vaccination programme for all infants <5 years old living in Scotland. We investigated these changes annually and over the "rotavirus season".~~

~~**Results**: The overall cost-impact of the rotavirus vaccination programme (that is, the cost of delivering the programme minus the reduction in resource costs) was £633,499 (2013/14 prices) per mean year, per 100,000 infants <5 years old living in Scotland. Considering only the rotavirus season, we find that the total cost impact of the vaccination programme was £653,354 per mean year.~~

~~**Conclusion:** The rotavirus vaccination programme in Scotland cost approximately £1,030,751 and was associated with a significant reduction in rotavirus-related resource use and health service costs of approximately £397,458, per 100,000 infants <5 years old living in Scotland.~~

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~~2.1 Background~~

1. Introduction

Rotavirus is the leading cause of severe gastroenteritis in infants worldwide and results in approximately 500,000 deaths annually in ~~children <5 yrs old [1]. Unlike in the developing world, rotavirus rarely causes mortality in the UK, however infection results in a significant~~infants under the age of 5 years [1]. Unlike in the developing world, rotavirus rarely causes mortality in the UK, however infection results in a high number of hospital admissions for severe dehydration in infants [1] and ~~significantly~~ impacts on health related quality of life (HRQOL) ~~[2].~~[2]. It has been estimated that rotavirus causes around 45% of hospitalisations for acute gastroenteritis in ~~children~~infants under the age of 5 years [2]. In addition, infections resulting in hospitalisation represent only a fraction of cases that occur in the community~~ and~~ which cause substantial morbidity with consequent impact on healthcare providers such as general practitioners (GPs) and out-of-hours services.

In July 2013, the Scottish Government, along with the rest of the UK, introduced the GlaxoSmithKline (GSK) vaccine Rotarix® [3]. The vaccine was made available to all infants born in Scotland on or after May 1st 2013 and delivered as part of the routine childhood immunisation programme. ~~Childhood vaccine uptake is generally high in Scotland with quarterly uptake figures for children aged 12 months routinely greater than 92% [4]. The vaccine was made available to all babies~~Over the first evaluation quarter 1st July – 30th September 2014, uptake of the rotavirus vaccine was 93% [4]. The vaccine was made available to all infants at age 8 weeks (1st dose) and again at 12 weeks (2nd dose).

~~Following this, routine~~Routine surveillance carried out by Health Protection Scotland (HPS) found evidence of ~~significant~~substantial reductions in rotavirus-related burden of disease in ~~children~~infants ~~[5]~~[5] similar to that reported elsewhere ~~[6-10]~~[6-10]. ~~Against this background, this~~The aim of this research was to estimate the cost-impact of the rotavirus vaccination programme ~~on~~in Scotland, based on a retrospective analysis of routinely collected data on actual healthcare utilisation.

2. Results

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2.1 Overall cost-impact

Table 1 shows the overall cost-impact of the rotavirus vaccination programme. Results are reported in terms of the cost of the programme, the monetary value of the reduction in resource use ~~in Scotland~~pre-and post-vaccination period, and the difference between the cost of the programme and the value of the reduction in resource use is estimated as the overall cost-impact of the programme.

[INSERT TABLE 1]

2.2 Cost of vaccination programme

Based on the actual number of infants who received the vaccine over the evaluation period 1st July-30th September 2013, it was calculated that 18,575 infants received the vaccination in 2013, per 100,000 infants <5 years old living in Scotland (note: the vaccine uptake rate was 92.7% however rates per 100,000 are calculated over the entire relevant population of infants <5 years old) [4]. This figure is multiplied by the vaccine cost per 2 doses. On the assumption of a vaccine price of £23.91 per dose [11], we estimated a total vaccine cost of £888,278 per 100,000 infants <5 years old in Scotland in 2013/14. The additional administrative payment made to GPs of £7.67 per infant (per two doses) [4] equates to £142,474 per 100,000 infants <5 years old in Scotland. Taken together, this indicates that the cost of the vaccination programme was £1,030,751 per 100,000 infants <5 years old in Scotland.

2.3 Sensitivity analysis

We undertook sensitivity analysis to estimate the impact of alternative vaccine prices on the overall cost of the vaccination programme. Table 2 presents the results based on a 50% increase or reduction from the price given in the base case. The results suggest that the overall cost of the programme is highly sensitive to the price of the vaccine.

[INSERT TABLE 2]

2.3 Reduction in rotavirus-related resource use

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Table 3 shows the reduction in rotavirus-related resource use associated with infants <5 years old for the mean year pre- and post-vaccination programme. Data is presented as incident rate ratios (IRRs) which can be interpreted as representing a percentage reduction in resource use. For example, the IRR associated with vaccination for laboratory reports is 0.273 which equates to a reduction of 72.7% (1-0.273 expressed as a percentage). Also presented are the model predicted pre and post vaccination annual number of events, the 95% confidence intervals (CIs) and the p-value associated with the vaccination variable in the model. For each resource use appropriate cost data were attached and the resulting annual costs per 100,000 infants <5 are presented.

Table 3: Adjust incidence rate ratios (IRRs) for the association between vaccination and rotavirus-related annual events and costs, for infants <5 years old in Scotland

[INSERT TABLE 3]

Notes: CI – confidence intervals. IRR–Incidence Rate Ratio. An IRR below 1 indicates a reduction in events and costs associated with the vaccination programme. P-value is a measure of statistical significance and a result under 0.05 is considered statistically significant for the purposes of this study. All models were adjusted for seasonality and underlying trend. The mean costs are estimated by applying a unit cost to the event rates predicted by the model.

All measured resource categories showed statistically significant reductions associated with the introduction of the rotavirus vaccination programme. These varied in magnitude according to the resource category with laboratory reports showing the highest reduction of 73% (IRR 0.273, p<0.001) and the smallest reduction of 17% in calls to NHS24 (IRR 0.826, p<0.001). Table 3 also presents the cost difference estimated from the predicted pre and post vaccination mean costs. The reduction in hospital stays forms the largest part of the cost difference. Figures 1 and 2 present the actual and predicted counts for laboratory reports and hospital stays respectively. Equivalent figures for the other resource categories are presented in the Appendix. These figures were selected for presentation in the main body of the article as they illustrate the model fit achieved in the most specific measure of rotavirus (positive laboratory reports) and the largest cost category (hospital stays).

Figure 1: Positive laboratory reports for rotavirus (weekly rates per 100,000), for infants <5 years old in Scotland – 2009 to 2015.

[INSERT FIGURE 1]

Notes: R^2=0.86. Dashed line represents introduction of vaccination programme

Figure 2: Hospital length of stay for rotavirus (weekly rates per 100,000), for infants <5 years old in Scotland – 2010 to 2015.

[INSERT FIGURE 2]

Notes: R^2=0.83. Dashed line represents introduction of vaccination programme

3. Discussion

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Our study found statistically significant reductions in all rotavirus-related health-care resource categories examined following the introduction of the vaccination programme. However, the range of the reductions varied from 17% to 73%. The size of the reduction is driven by the ability of the data source to accurately capture cases of rotavirus. The highest reduction was found in the most specific data source, positive laboratory reports and the lowest in the least specific areas of NHS24 calls and prescriptions for rehydration treatments. We found a 40% reduction in hospital stays, which are the main cost driver among health-care resource categories.

Our findings are in line with the extensive literature across diverse geographies finding that the introduction of a rotavirus vaccination programme leads to reductions in a broad range of health-care resource categories [16, 17]. Prior to the introduction of the rotavirus vaccination programme, the Scottish Government predicted that such a programme could reduce the number of rotavirus-related hospital stays by approximately 70% [12]. Forrest et al (2017) found a reduction of 85% and 91% in rotavirus related admissions and bed-days, respectively, in a paediatric hospital setting in Lothian, Scotland [13]. This study used a highly specific definition of rotavirus-based admissions based on

positive laboratory reports so is comparable with the 73% reduction suggested by our study. In undertaking this study, we gave much consideration to the issue of how best to capture the impact of rotavirus on hospital resources. When we considered the changes in solely those hospital admissions and bed-days which were coded for rotavirus specific (ICD10 code "A080" in either 1st and 2nd diagnostic position), we observed higher reductions in hospital admissions for rotavirus and rotavirus-related hospital stays similar to the reductions found by Forrest et al [12]. However, many hospital admissions relating to rotavirus are coded as generic viral enteritis, particularly when specific organism testing is not required for clinical management. As the aim of this study is to estimate the cost impact we chose to increase the sensitivity of our measure by including viral enteritis unspecified (possible rotavirus) "A083", "A084" and "A085" as well as the specific rotavirus code "A080". This would have the effect of increasing the volume of cases in both the pre and post vaccination periods as well as reducing the percentage differences between the periods. It is likely that using these codes will miss a proportion of rotavirus cases as they are likely to be coded under general acute gastroenteritis codes [13]. Our finding of a 40% reduction in hospital admissions is in line with a the 44% reduction found in a study of five local authority areas in Merseyside, England over the period 2013-2016 (consisting of five hospitals with emergency and secondary care facilities and a paediatric hospital)[14]. .

We found that the impact of the vaccine in primary care was lower than that predicted by Jit et al (2007), with a substantial proportion of overall reduction in healthcare cost due to a decrease in GP consultations [11]. Data were available on consultations for diarrhoea, vomiting and all gastrointestinal illness, however due to possible double counting and for consistency with other data analysed for this study, we decided only to include the impact from consultations for diarrhoea. This may therefore represent an underestimate, which may explain the 32% reduction in prescriptions during the rotavirus season, despite only a 16% reduction in consultations. Lack of adherence to the use of appropriate Read codes may also help to explain this underestimate.

The impact of childhood rotavirus infection and the vaccine on nonmedical costs was not included in this study, however it is likely that there are significant costs associated with productivity loss (or "time-off" work) of the parent(s). Different studies give different estimates of the number of work days lost – typically ranging from around two to five days [15]. The typical UK worker earns a median daily wage of £103.6 [16]. Hence, 2 days (5 days) forgone work on behalf of the caregiver results in £207.2 (£518) in lost earnings per childhood rotavirus case. Some estimates suggest that the loss in productivity to the economy is the difference between a rotavirus vaccination programme being, not only cost-effective, but cost saving in the UK [17].

This study only considers costs and does not value the improved quality of life which a reduction in rotavirus incidence would deliver. Jit and Edmunds (2007) report a quality of life (QALY) loss due to rotavirus of 0.0022 for a child and 0.00184 for an adult per case of rotavirus [11]. In our study, there was a mean of 472 laboratory confirmed cases of rotavirus pre-vaccination programme, compared with 110 cases post- vaccination programme, per 100,000 infants <5 in Scotland. If we use this as a proxy for the mean number of rotavirus cases pre- and post-vaccination, then we estimate the QALY loss averted per family (2 adults, 1 infant) as 2.13 QALYs per 100,000 infants <5 years old in Scotland between the mean year pre-and post-vaccination period.

Since completion of our analysis, the first full year of data became available for calendar year 2015 (infants born Jan-Dec 2014). These indicate 53,013 infants (18,141 infants per 100,000) received rotavirus vaccine in 2015. This is comparable with the estimate used in our analysis (18,575 infants, per 100,000).

Strengths and limitations

At time of publication, this is the only study the authors are aware of which attempts to estimate the cost-impact of the rotavirus vaccination programme for the whole of Scotland, based on observational data.

The challenge with using indicators of gastrointestinal illness such as reporting of symptoms of diarrhoea as a proxy for rotavirus is that it also captures changes in the prevalence of other gastrointestinal illnesses unrelated to rotavirus. As a result, there are uncertainties in the estimates of resource use both pre and post vaccination and these differ depending upon the type of resource-use considered. In comparing our results with other studies it is, therefore, important to note the precise definitions included in the analysis.

We obtained data on the number of prescriptions made per day per patient population, however, we did not have a further breakdown of composition of these prescriptions (i.e. which hydration drugs were given). Hence, it was not possible to calculate the change in mean prescriptions and then attach unit costs. Rather, we calculated the change in the mean gross cost of prescriptions pre-and post-vaccination programme. A detailed breakdown of the prescriptions given would have provided a more accurate estimate of the cost-impact, however it is not clear whether an absence of this breakdown suggests an over-or underestimate of the overall cost-impact. The data we obtained was based on prescriptions for rotavirus in primary care. However, there is the possibility that these prescriptions, which are mainly rehydration drugs, could have been prescribed for alternative conditions requiring rehydration.

Due to duplication concerns, it was not possible to use calls relating to vomiting and diarrhoea, combined, from NHS24 data. Hence, data on calls citing diarrhoea in infants <1 year old and <5 years old were used as a proxy for rotavirus. It is acknowledged that this is likely to be an underestimate of the true total cost associated with NHS24. Similarly, for duplication concerns, only GP consultations for diarrhoea were included. This is also likely to represent a considerable underestimate of the cost.

The overall cost-impact of the vaccination programme was highly sensitive to the cost of the vaccine, which we were not able to confirm. Our analysis relies on an estimate from the literature which we varied in sensitivity analysis.

4. Conclusion

In this study we have estimated the mean change in rotavirus-related resource use before-and-after the introduction of the Scottish Government's rotavirus vaccination programme in 2013. In doing so, we have observed reductions in the burden placed on rotavirus-related; laboratory reports; hospitalisations; GP consultations; A&E attendances; and NHS24 calls. Our analysis showed a reduction in the mean number of rotavirus-related hospital bed-days of 40%. This reduction accounted for 83% of the overall cost reduction associated with the implementation of the rotavirus vaccination programme. This study found that the overall cost impact of the rotavirus vaccination programme (that is, the cost of delivering the programme minus the reduction in resource costs) was £435,000 increase (2013 prices) per annum per 100,000 infants <5 years.

5. Methods

~~In line with previous research [11] and European Centre for Disease Prevention and Control (ECDC) [12] guidance, this study adopted a "before and after" approach with the pre-vaccination period serving as a reference point from which to compare the post-vaccination period.~~

5.1 Statistical analysis

In line with previous research [18] and European Centre for Disease Prevention and Control (ECDC) [19] guidance, this study adopted a "before and after" approach with the pre-vaccination period serving as a reference point from which to compare the post-vaccination period.

This study defined the net cost-impact of the programme as being the cost of the vaccination programme minus cost ~~savings~~reductions in resource use. As such, the net cost-impact was defined as follows:

Net cost impact = (cost of vaccine + administration payment) – (cost ~~saving~~reductions from lab reports, hospitalisations, A&E attendances, GP consultations, prescriptions and NHS24 calls).

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~~*2.1 Sample*~~

To compare the impact of the rotavirus vaccination programme, in terms of the change in resource use and cost-impact, we used an interrupted time series analysis [20].

To estimate the overall cost-impact of the rotavirus vaccination programme, we first estimated the rotavirus-related resource utilisation for each resource pre- and post-vaccination programme, in units determined by how the data were collected (i.e. resource use per week or per month). We attached unit costs to resource use to estimate the cost of this resource over each time period for which the data were collected. Mean resource use in the pre-and post-vaccination periods were estimated using a range of modelling approaches. We selected a Generalised Linear Model (GLM) with a Poisson family and log link as this reduced autocorrelation and provided the best model fit. We assessed goodness of fit of alternative models using the Akaike and Bayesian Information Criteria [21] Underlying trend was accounted for within the regression framework and seasonality were modelled by including Fourier terms (sine and cosine terms) [20] and a dummy variable representing the peak rotavirus season (January-May). We also included an interaction term between the seasonality variables and the relevant period variable (week or month) to allow seasonality to vary in different time periods. We hypothesised that the rotavirus vaccination programme would result in a permanent level change in resource use [20]. We therefore included a single binary variable to represent the intervention which was coded '0' in the period prior to the vaccination programme and '1' in the period following the introduction of the programme.

Population data for all infants <5 years old living in Scotland over the study period were obtained from ~~appropriate sources~~the National Records of Scotland and used as ~~the denominator in all calculations.~~an offset variable [22]. Incidence rates per 100,000 were calculated as the number of ~~incidence~~incidents (i.e. days in hospital or GP consultations) divided by the study population (number of ~~children~~infants <5 years old living in Scotland) per year multiplied by 100,000. The same approach was used to estimate the cost of the programme, hence cost per 100,000 represents the cost of

providing the vaccination to eligible ~~babies~~infants (age 8 weeks and again at 12 weeks) to realise the benefits over the population of all infants <5 years. ~~Mid-year population estimates obtained from the National Records of Scotland database were used to calculate incidence rates for all resource use [13].~~

One-way sensitivity analysis was undertaken to estimate the impact on the cost of the vaccination programme of alternative vaccine prices. Vaccine price was varied +/-50% of the base case price.. The results are presented in the appendix.

~~2.2~~5.2 *Perspective*

This study takes the perspective of the UK National Health Service (NHS) and includes resource use associated with laboratory reports, hospitalisations, A&E attendances, GP consultations, prescriptions and NHS24 calls. This is the only study at present to take such a wide perspective in estimation of the economic benefits from a national rotavirus vaccination programme in Scotland.

~~*2.3 Time horizon for evaluation*~~

~~To estimate the overall cost impact of the rotavirus vaccination programme, we calculated the difference in rotavirus-related resource utilisation between a "mean year" prior to and following the vaccination programme. However, as rotavirus infection is highly seasonal, calculating the change in healthcare utilisations over the rotavirus season provides a more accurate estimation of the change occurring primarily from rotavirus vaccine. This approach helps distinguish the impact of rotavirus from other gastrointestinal infections such as norovirus, which will feature in the surrogate data sources such as calls to NHS24 citing diarrhoea and vomiting. The precise occurrence and duration of the rotavirus season varies between countries [12]. For the purposes of this study, we defined the rotavirus season as January to April (week 1-18). The years used for each resource were: 2009-2014 for laboratory reports; 2010-2014 for hospitalisations; 2011-2014 for A&E; 2011-2014 for GP consultations; 2010-2014 for NHS24 calls; and 2010-2014 for prescriptions. For each resource, the pre-vaccination years were used to construct a pre-vaccination mean year to compare with post-~~

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~~vaccination. Two years of post-vaccination data were used for each resource to calculate the post-vaccination mean year.~~

~~In addition to examining annual cost, we also looked at the impact of the programme over the rotavirus season only. However, the cost of the programme remains the cost per *full* year. This is because, to obtain the benefits we observe over the rotavirus period only, the programme would still have to be delivered year round.~~

~~*2.4 Measurement of resource use*~~

5.3 Measurement of resource use

Data available for each resource were; 2009-2014 for laboratory reports; 2010-2014 for hospitalisations; 2010-2014 for NHS24 calls; 2010-2014 for prescriptions; 2011-2014 for A&E; and 2011-2014 for GP consultations.

~~*2.4.1*~~ *5.3.1 Laboratory confirmed reports*

All laboratory confirmed cases of rotavirus infection in Scotland are reported to HPS via the Electronic Communications of Surveillance in Scotland (ECOSS) system ~~[14]. A positive laboratory sample was~~[23]. A positive laboratory sample was detected using a real-time PCR and were only counted for the first sample from any patient episode and repeated laboratory tests for the same episode were not included~~ in this cost exercise.~~. Laboratory reports for ~~children~~infants <5 years old in the pre-and post-vaccination years were used.

~~*2.4.2*~~ *5.3.2 Hospitalisation data*

All hospitalisations for ~~children~~infants <5 years were extracted using Scottish Morbidity Records (SMR01) database using predefined International Classification of Diseases 10 (ICD10) codes Rotavirus enteritis "A080" and Viral enteritis unspecified (possible rotavirus) "A083", "A084" and "A085" ~~[15].~~[24]. This aimed to capture admissions for rotavirus, which are not laboratory confirmed due to

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the relatively short length of stay and which are coded under the more general term of viral enteritis. Due to concerns of possible double counting of patients only data with the relevant ICD10 code as main diagnosis were included.

~~The unit of analysis is an "episode".~~ When a patient is discharged from hospital or transferred between hospitals, specialties or to the care of a different consultant, an episode is generated. Episode data ~~was~~were grouped together to identify continuous inpatient stays (CIS) and it is this level of analysis that was used to monitor hospital admissions and length of stay in this study.

~~2.4.3~~ 5.3.3 *Accident and Emergency (A&E) data*

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Age specific monthly data on attendances at A&E data for symptoms associated with gastrointestinal illness was available from Information Services Division (ISD). ~~The~~These data ~~is~~are based on a combination of ICD10 codes and, where coding was not used, free text analysis~~ and data~~. Data were analysed for ~~children~~infants aged <5 years.

~~2.4.4~~ 5.3.4 *GP consultation data*

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Data on GP consultations, who provide all primary care for infants in Scotland, recorded for all infants <5 years old for diarrhoea were obtained as the best proxy for rotavirus-related GP attendances. Weekly aggregate data are received by HPS from approximately 50% of General Practices (GP) across Scotland on the number of consultations based on defined Read codes, which are currently the standard clinical classification terminology system used in GPs in the United Kingdom~~. Data on GP consultations recorded for all children <5 years old for diarrhoea were obtained as the best proxy for rotavirus-related GP attendances.~~ [25]. Data were obtained from a broad geographical spread of Scotland and were considered representative of Scotland as a whole. Data were scaled to account for 100% of GP practices.

~~2.4.5~~ 5.3.5 *NHS24 syndromic surveillance data*

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HPS monitor trends in calls made to the NHS24 telephone helpline in Scotland. NHS24 is also the route to out-of-hours general practice care. Data gathered on the number of calls relating to vomiting and diarrhoea give an indication into the incidence of gastroenteritis in the community. Due to duplication concerns, it was not possible to use data relating to vomiting and diarrhoea combined. Hence, data on calls citing diarrhoea in ~~children~~infants <5 years old were used as a proxy for rotavirus.

~~2.4.6~~ 5.3.6 *Prescription data*

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Data on rotavirus-related drug prescriptions were collected by the Prescribing Information System (PIS) provided by ISD Scotland~~.~~ and based on prescriptions administered in the primary care setting. Treatment for rotavirus typically involves the prescription of oral rehydration drugs. ~~As such, data~~Data on prescription of the following drugs, listed in local formularies, were ~~obtained;~~used as a proxy for rotavirus and viral enteritis: Dioralyte; Dioralyte Relief; Electrolade; O.R.S Oral, Peach. Data were provided in terms of the gross ingredient cost (£) per month for infants <5 years old over the period 2010-2015. Hence, change in gross cost pre-and post-vaccination were reported, rather than change in resource use (i.e. unit costs were not necessary).

~~2.4.7 Cost of vaccination programme~~

5.3.7 *Vaccine price*

The Joint Committee on Vaccination and Immunisation (JCVI) carried out a review of the published literature on the cost-effectiveness of rotavirus vaccines ~~[16].~~on behalf of the Scottish Government [26]. The JCVI statement on rotavirus vaccine assumes a vaccine unit price of £35 per dose (2006 prices~~). This price is based on the work of Jit & Edmunds [17]. The authors state that the catalogue price of Rotarix® in the UK is £41.38 (2006 prices). Based on this price, they assume that a single dose of Rotarix® would be available to the NHS at £35. At the price of £35 per dose, the cost per QALY gained would be £61,000 and hence unlikely to be considered cost-effective.~~), based on the work of Jit & Edmunds [11]. At the price of £35 per dose, the incremental cost per QALY gained would be

£61,000 and hence unlikely to be considered cost-effective. Further modelling by the authors suggested that the vaccine would have to be priced at £19 per dose for the cost of the programme to be less that £30,000 per QALY gained and hence deemed cost effective~~.~~, given the current UK threshold. For this reason, we chose to assume a vaccine price of £19 per dose ~~[17]. Inflating this to 2014 prices equates to £23.91 per dose.~~[11]. Inflating this to 2014 prices equates to £23.91 per dose and this was used as our base case price. Due to commercial sensitivities, there is no published price for the vaccine other than the JCVI statement.

The local health board pay each relevant GP an administrative payment of £7.67 per child receiving the rotavirus vaccination (one payment for two doses)~~[18].~~[27]. This payment was therefore included as a direct cost of providing the service.

~~*2.4.8*~~ *5.3.8 Valuation of resource use*

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All prices are expressed in 2013/14 prices and have been inflated (where necessary) using the Hospital and Community Health Services (HCHS) Index which uses an inflation rate specific to the UK health service (PSSRU, 2014).

Any stool sample taken from an infant suffering from diarrhoea and vomiting would undergo a full screening for a range of gastrointestinal pathogens, rather than for one specific causative agent. Hence, the unit cost of a routine enteritis laboratory report was given by Lorgelly et al as £15.08 per report (in 2001/02 prices, £20.99 in 2013/14 prices) ~~[19].~~[28].

The unit cost estimate for hospitalisations in 2013/14 was obtained from ISD. Using their new patient-level costing data, they were able to estimate the cost per day of hospital treatment for rotavirus (based on ICD10 code A080). The unit cost per day for rotavirus was estimated at £920 (2013/14). This unit cost is applied to both incidents of rotavirus coded as “rotavirus” and “viral enteritis” in SMR01 hospitalisation data.

~~A standard unit cost of £107 per attendance at A&E was obtained from ISD's annual Scottish Health Service Costs [20].~~

A standard unit cost of £107 per attendance at A&E was obtained from ISD's annual Scottish Health Service Costs [29].

The unit cost of a GP consultation was obtained from the Personal Social Services Research Unit 2014 publication ~~[21].~~[30]. The unit cost was £37.50, per GP visit lasting 11.7 minutes (excluding qualification costs).

The unit cost per call to NHS24 was reported by Munro et al as £15 (2001 prices). Inflating this to 2014, provides a unit cost of £20.88 ~~[22]~~[31].

Declaration~~Results~~

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~~*3.1 Cost*~~ of ~~*vaccination programme*~~

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~~Based on the actual number of infants who received the vaccine over the evaluation period 1st July-30th September 2013, it was calculated that 18,575 infants received the vaccination in 2013, per 100,000 infants <5 years old living in Scotland (note: the vaccine uptake rate was 92.7% however rates per 100,000 are calculated over the entire relevant population of infants <5 years old). This figure is multiplied by the vaccine cost per 2 doses. This equates to a vaccine cost of £888,278 per 100,000 children <5 years old in Scotland in 2013/14. The additional administrative payment made to GPs of £7.67 per infant (per two doses) equates to £142,474 per 100,000 children <5 years old in Scotland.~~

~~Taken together, this indicates that the cost of the vaccination programme was £1,030,751 per 100,000 children <5 years old in Scotland.~~

~~Scaling up the rates per 100,000 infants to the total number of infants we estimate to have received the vaccination over 2013 (54,664), we estimate a total annual vaccine cost of £2,614,032 per year. The total annual estimated cost of GP administration payments for this period, for these uptake~~

~~figures, was £419,273 per year. Taken together, this suggests a total vaccination cost of £3,033,305 for the entire population of eligible infants in Scotland in 2013. This represents the absolute cost outlay for the vaccination programme, rather than the cost per 100,000 infants.~~

~~Table 1 shows the reduction in rotavirus-related resource use associated with children less than 5 years old for the mean year pre- and post-vaccination programme.~~

~~[TABLE 1]~~

~~Table 2 shows the reduction in rotavirus-related resource use associated with children less than 5 years old for the mean rotavirus season pre- and post-vaccination programme.~~

~~[TABLE 2]~~

~~Table 3 shows the overall cost-impact of the rotavirus vaccination programme. Three separate results are given: the change in absolute (total) annual cost between the pre- and post-vaccination period, the change in the annual pre-and post-vaccination period cost per 100,000 infants, the change in cost pre-and post-vaccination period per 100,000 infants over the rotavirus season only.~~

~~[TABLE 3]~~

~~Figure 1 shows that 85% of the cost savings associated with reduced incidence of rotavirus over the mean rotavirus season (Jan-Apr) between 2009-2015 was due to the reduction in hospital bed-days.~~

~~[FIGURE 1]~~

~~Figure 2 gives the estimate of the cost reduction for rotavirus-related resource use for the mean year on an annual and rotavirus season basis. Figure 2 shows that almost all (95%) of the cost reduction for the mean year was accrued over the rotavirus season (Jan-Apr) alone.~~

~~[FIGURE 2]~~

~~2 Discussion~~

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~~Prior to the introduction of the rotavirus vaccination programme, the Scottish Government predicted that such a programme could reduce the number of rotavirus-related hospital stays by approximately 70% [23]. Indeed Forrest (2017) found a reduction of 85% and 91% in rotavirus related admissions and bed days, respectively, in a paediatric hospital setting in Lothian, Scotland [24]. Our analysis showed a reduction in the mean number of rotavirus-related hospital admissions and bed days of 51% and 59%, respectively, over the rotavirus season. In undertaking this study, we gave much consideration to the issue of how best to capture the impact of rotavirus on hospital resources. When we considered the changes in solely those hospital admissions and bed days which were coded for rotavirus specific (1st and 2nd diagnostic position), we observed a reduction in hospital admissions for rotavirus and rotavirus-related hospital stays of 68% and 73%, respectively. However, it became clear that there are many hospital admissions relating to rotavirus which are simply coded as generic viral enteritis. Hence, we decided that to not include viral enteritis in our analysis would mean underestimating the true burden of rotavirus. As a result, we chose to include rotavirus specific and viral enteritis specific (both 1st diagnostic position) as our best estimate of the burden of rotavirus in the hospital setting. However, as the total number of conditions included in our analysis has increased, the percentage change between the pre-and post-vaccination group will not be as large.~~

~~Additionally a paper by Hsu (2005) suggests that there is low sensitivity with the use of ICD codes to capture the burden of rotavirus on hospitalisations [25]. Their findings suggest that current estimates of rotavirus-related hospitalisations based on ICD codes may substantially underestimate the true burden of rotavirus on hospitalisation admissions.~~

~~We found that the impact of the vaccine in primary care was lower than that predicted by Jit et al with a substantial proportion of overall reduction in healthcare cost due to a decrease in GP consultations [17]. Data were available on consultations for diarrhoea, vomiting and all gastrointestinal illness, however due to possible double counting and for consistency with other data analysed for this study, we decided only to include the impact from. consultations for diarrhoea. This may therefore represent~~

~~an underestimate, which may explain the 32% reduction in prescriptions during the rotavirus season, despite only a 16% reduction in consultations. Lack of adherence to the use of appropriate Read codes may also help to explain this underestimate.~~

~~The impact of childhood rotavirus infection and the vaccine on nonmedical costs was not included in this study, however it is likely that there are significant costs associated with productivity loss (or "time off" work) of the parent(s). Different studies give different estimates of the number of work days lost – typically ranging from around two to five days [26]. The typical UK worker earns a median daily wage of £103.6 [27]. Hence, 2 days (5 days) forgone work on behalf of the caregiver results in £207.2 (£518) in lost earnings per childhood rotavirus case. Some estimates suggest that the loss in productivity to the economy is the difference between a rotavirus vaccination programme being, not only cost-effective, but cost saving in the UK [28].~~

~~This cost-impact analysis did not quantify the health-related quality of life (HRQoL) gains associated with the vaccination programme, and as such represents an underestimation of the overall benefits of this programme [2].~~

~~*Strengths and limitations*~~

~~At time of publication, this is the only study the authors are aware of which attempts to estimate the cost-impact of the rotavirus vaccination programme for the whole of Scotland, based on observational data.~~

~~This study examined the cost impact of the introduction of the vaccine over two years post-vaccination, which is important since a common finding of other related studies is that there are further significant reductions in resource use in the second year after rotavirus vaccination [1, 29]. A seasonal trend was evident in all data sources examined prior to the introduction of the vaccine and absent in the two years' post-vaccine.~~

~~The challenge with using indicators of gastrointestinal illness such as reporting of symptoms of diarrhoea as a proxy for rotavirus is that it also captures changes in the prevalence of other gastrointestinal illnesses unrelated to rotavirus. As a result, a reduction in rotavirus one year may be cancelled out by an unrelated increase in norovirus the same year, leaving the all-cause gastrointestinal illness data unchanged. This would result in the change in rotavirus not being adequately captured by the data. While this can be accounted to an extent for by examining the "rotavirus season" it cannot completely rule this out as there could be an overlap in circulation of gastrointestinal pathogens. There are also several limitations with the A&E data such as: differences in recording between health boards, the use of ICD10 codes; free text; and a combination of both. This can also change over time as boards are being encouraged to move towards using ICD10 codes to help standardise data recording. Despite these limitations, it was decided that the inclusion of this data would be more informative than its exclusion.~~

~~We obtained data on the number of prescriptions made per day per patient population, however, we did not have a further breakdown of composition of these prescriptions (i.e. which hydration drugs were given). Hence, it was not possible to calculate the change in mean prescriptions and then attach unit costs. Rather, we calculated the change in the mean gross cost of prescriptions pre and post vaccination programme. A detailed breakdown of the prescriptions given would have provided a more accurate estimate of the cost impact, however it is not clear whether an absence of this breakdown suggests an over or underestimate of the overall cost impact.~~

~~Due to duplication concerns, it was not possible to use calls relating to vomiting and diarrhoea, combined, from NHS24 data. Hence, data on calls citing diarrhoea in children <1 year old and <5 years old were used as a proxy for rotavirus. It is acknowledged that this is likely to be an underestimate of the true total cost associated with NHS24. Similarly, for duplication concerns, only GP consultations for diarrhoea were included. This is also likely to represent a considerable underestimate of the cost.~~

~~3 Conclusion~~

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~~In this study we have estimated the mean change in rotavirus-related resource use before and after the introduction of the Scottish Government's rotavirus vaccination programme in 2013. In doing so, we have observed reductions in the burden placed on rotavirus related; laboratory reports; hospitalisations; GP consultations; A&E attendances; and NHS24 calls. Our analysis showed a reduction in the mean number of rotavirus-related hospital admissions and bed-days of 51% and 59%, respectively, over the rotavirus season. This reduction accounted for 90% of the overall cost reduction associated with the implementation of the rotavirus vaccination programme. This study found that the overall cost impact of the rotavirus vaccination programme (that is, the cost of delivering the programme minus the reduction in resource costs) was £633,499 (2013 prices) per mean year. Considering only the rotavirus season, we find the total cost impact of the vaccination programme to be £653,354 per mean year.~~

~~Conflict~~conflict of interest

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None of the authors reported any conflicts of interest.

Funder

Health Protection Scotland (HPS)

~~Appendix~~

~~[TABLE 4]~~

6. References

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Supplementary material

1. Unit costs used in the study

[INSERT TABLE 4]

2. Graphs for changes in additional resource use categories

Figure 3: Accident and emergency attendances (weekly rates per 100,000), for infants <5 years old in Scotland – 2011 to 2014.

[INSERT FIGURE 3]

Notes: R^2=0.72. Dashed line represents introduction of vaccination programme

Figure 4: GP visits (weekly rates per 100,000), for infants <5 years old in Scotland – 2011 to 2014.

[INSERT FIGURE 4]

Notes: R^2=0.65. Dashed line represents introduction of vaccination programme

Figure 5: NHS 24 calls (weekly rates per 100,000), for infants <5 years old in Scotland – 2010 to 2015.

[INSERT FIGURE 5]

Notes: R^2=0.59. Dashed line represents introduction of vaccination programme

Figure 6: Prescriptions costs (monthly rates per 100,000), for infants <5 years old in Scotland – 2010 to 2015.

[INSERT FIGURE 6]

Notes: R^2=0.71. Dashed line represents introduction of vaccination programme

Response to reviewers' comments

By Robert Heggie 2/10/18

Thank you to the editor and reviewers for their comments. We have undertaken substantial revisions to our paper, including a complete revision of the statistical analysis (which is now modelled as an interrupted time series analysis). We hope very much that you will be pleased with our revised paper.

Editor's comments

1. Move the Methods section after the Discussion in conformity to the style of this journal.

Reply: Text has been amended.

2. Add Figure legends to the manuscript DOC after the References.

Reply: Text has been amended.

Reviewers' Comments

1. To further enrich the discussion section , add a paragraph that compares this cost analysis with a recent published paper on a cost-analysis conducted in an Italian Region (Sicily):
Costantino C, Restivo V, Tramuto F, Casuccio A, Vitale F. Universal rotavirus vaccination program in Sicily: Reduction in health burden and cost despite low vaccination coverage. Hum Vaccin Immunother. 2018 May 14:1-6.
https://www.tandfonline.com/doi/full/10.1080/21645515.2018.1471306

Reply: I have added this reference to the discussion.

2. Line 108 This descriptive study aims to describe difference of resource utilization between pre- and post-vaccine period. Contrary to what the authors answered to the previous comment, there was a hypothesis of non-equality that was to be shown. This hypothesis was different to show a causality "causality between the vaccination program and resource use reduction". According to this, the study needs a statistical test to show a non-equality between pre and post vaccination period due to several interventions as shown in the study mentioned by the same authors of Rosemary et al (2014) in which the statistical section stated "Rather, we are presenting a descriptive analysis of the estimated mean resource use before and after the vaccination programme. Means and medians were compared for continuous data and proportions for categorical data. P <0.05 was considered as statistically significant."
The authors need to conduct a more appropriate statistical analysis.

Reply: We have redone the statistical analysis as an interrupted time series analysis and look forward to receiving your views on this approach.

3. Lines 122-8. To the question on the reference about use of only 1st diagnostic position code to estimate the burden of RV in hospital setting, the authors answered that "Unfortunately, there are no references or guidance for what is most appropriate in this situation. We made this choice as our best attempt to trade-off the risk of double counting (i.e. if we had included rotavirus or viral enteritis in 2nd diagnostic position) against the risk of not capturing the true burden." Contrary to the authors' opinion, several references implement estimation using all diagnostic position to

increase sensibility of the estimation as reported by Restivo et al (2017)
https://www.tandfonline.com/doi/full/10.1080/21645515.2017.1264784
Address this point in the manuscript.

Reply: Thank you for directing us towards the Restivo (2017) study which we were not aware of. We have compared the approach taken in their study with our own and we chose to adopt a more restricted definition of rotavirus.

We selected Rotavirus specific (ICD-10 code: A080) and Viral enteritis unspecified (possible rotavirus) (ICD-10 code: A084), appearing in either first or second diagnostic position and based on hospital discharge codes, reported in Scottish Morbidity Records (SMR01). This was based on advice from our clinical colleagues as these are the only two which either explicitly state that rotavirus was present or that it was possibly present. The inclusion of additional ICD-10 codes would likely increase the sensitivity of our analysis at the cost of reducing the specificity, i.e. we would increase the number of rotavirus cases detected at the cost of increasing the number of non-rotavirus cases included. We make it clear which ICD-10 codes are included and excluded to assist the reader and trust that this approach will be acceptable.

4. Lines 134-7. Are there data on attendance at A&E without ICD-10 codes.? Its it not a standardized procedure? What is the methodology of free text analysis? Which words were included? Can the authors quantify the amount of records without ICD.10 codes?
Address these issues in the text.

RH: These data are routinely captured by Information Service Division (ISD) Scotland and accessed by Health Protection Scotland (both part of NHS Scotland) for monitoring purposes. As A&E data on Scotland were not yet collected in a standard form during the study period this was the most reliable data available to us. This has been clearly stated in the text and included in the limitations in our discussion section.

5. Lines 139-43 did not address the following question: How many (number not percentage) children <5 years old were in charge of pediatrician recruited in the study compared to all Scottish children <5 years old? Have they the same demographics characteristics (sex and age) to evaluate generalizability of data to all Scottish children?

Reply: In Scotland, the health system is a unified national service, free at point of care, with no private paediatrician provision. Care of children who are ill is within primary care by a general practitioner, and then by a paediatrician within secondary and tertiary care for more acute/severe illness. As ours is a retrospective study which covers the whole population of infants in Scotland <5 years old, there are no issues relating to generalisability in relation to demographic characteristics across Scotland.

6. Lines 155-60. The authors are contradicting themselves because of the answer to the lack of data on prescription used as a proxy for rotavirus and viral enteritis: "However, we would argue that since are as estimating the change in resource use before and after the vaccination programme, is it likely the difference is prescribing trends is a results of rotavirus (which was reduced by vaccine) rather than other conditions which would not have been expected to change over this period." but in the following comment the authors write that "The purpose of our study was not to determine causality between the vaccination programme and resource use reduction". The authors had to delete prescription analysis not supported by references.

RH: Thank you for pointing out the inconsistency here, this has been addressed in the text. We have retained our analysis on prescription costs as we have data for this period covering drugs prescribed specifically for rotavirus.

7. Lines 207-12
a. The authors need to rewrite the period of results in a more neutral way, reporting value of percentages with respective P value of difference and 95% confidence interval.
b. Avoid words such as "the greatest reduction" that can be used more appropriately in the Discussion section.

RH: This has been addressed in the text.

8. Lines 124-5
a. The authors should not include viral enteritis unspecified codes from the analysis because as they answered, there are no references on this methodology "This is simply the result of conversations with those stakeholders involved in the treatment of rotavirus."
b. To avoid double counting, use an identification code.

Reply: Further to our comment above (comment 3), we included i) Rotavirus specific and iii) Viral enteritis unspecified (possible rotavirus) in our analysis on the advice of clinical colleagues and coding specialists.

9. Lines 222-225
a. Avoid placing in the Results section the footnotes of Table 2 (Results are reported in terms of the cost of the program, the monetary value or reduction in resource use pre-and post-vaccination period, and the difference between the cost of the program and the value of the reduction in resource use is estimated as the overall cost-impact of the program).
b. Rewrite the heading of Table 2 in a more understandable way.

Reply: Tables have been completed amended.

10. Lines 226-9
a. Rewrite the period of result reporting value of percentages with respective P value of difference and 95% confidence interval.
b. Move the sentence "This is because, even though the reduction in resource use is observed over the rotavirus season, year-round vaccination is required to achieve these reductions" to the Discussion section.

Reply: Results section has been completely redrafted. "Rotavirus season" is no longer included as a separate analysis but is instead modelled as part of the interrupted time series analysis.

11. Lines 346-49
a. Avoid to place here footnotes of Table 3 (which presents the results based on a 50% increase or reduction from the price given in the base case)/
b. Rewrite the period in a more neutral way, reporting the value of percentages with respective P value of difference and 95% confidence interval.
c. Place this period in the Results section instead of the Appendix.

Reply: Results section has been completely redrafted.

12. Line 350. Use vaccine cost available on technical schedule.

Reply: In the UK, there is not a technical schedule. The vaccine is procured nationally, and the costs are not shared, even with national public health organisations, such as health protection Scotland. Only a few people in government working in procurement are privy to this information.

13. Table 1
a. Implement the Table with a column reporting p-value of "% Change in resource use" with 95% Confidence interval.
b. able 1 also should have an exhaustive caption instead of "Result" and footnotes with clarification of the season period.
c. The authors try to explain the use of length of hospital stay instead of more appropriate HRG due to a lack of update HRG price since 2011/12. But if the cost-analysis has to be coherent with real life of Scotland, report HRG price of 2011/12 to show the urgency of update these HRG cost.
d. Add a reference to clarify methods used by Information Service Division Scotland to built up the cost per day spent in hospital due to Rotavirus? Which variables did they include in this parameter?

Reply: Tables have been completed amended (comment a, b). We obtained an up-to-date cost of the cost per day spent in hospital due to rotavirus. This cost has been developed by the Information Division Scotland (ISD) who are responsible for capturing health resource data for Scotland. Details on the methodology of the cost per day for rotavirus estimate will be included within the appendix as supplementary material. This cost is likely to be more appropriate to the Scottish setting than HRG costs based on England and Wales (comment c, d).

14. RH: HRGs (rather than DRGs) are used in the UK. However, Scotland does not have the level of HRG costing that exists in England. Furthermore, Scottish HRG costs were last updated in 2011/12. We obtained the cost per day spent in hospital due to rotavirus directly from the Information Service Division Scotland (part of NHS Scotland). They described this as their best estimate of the cost of a day spent in hospital in Scotland due to rotavirus in 2013/14.
Revise accordingly.

Reply: Please see response to comment 13c and d.

15. Tables 2 and 3
a. Implement the table reporting p-value of the analysis with 95% Confidence interval.
b. This Table should have an exhaustive caption and headings.

Reply: Tables have been amended in line with new analysis.

16. Place Table 5 in the Methods section.

Reply: Tables have been amended in line with new analysis.

Additional comment from RH: In the previous version we had considered a pre-vaccination mean in which the starting year for all resources were equal (i.e. 2011). We have removed this scenario as we

want to ensure we use all data available. This is particular important to maintain statistical power in time series analysis..

Table 1: Estimated annual cost-impact of the Rotavirus vaccination programme introduced in Scotland in July 2013 (per 100,000 infants under 5 years)

	Cost of vaccination programme	Cost reduction from vaccination programme	Overall cost-impact
Overall cost-impact (annual)	£1,030,751	£595,470	£435,281

Table2

Table 2: Sensitivity analysis of alternative vaccine price on overall cost-impact results

Test cost (dose)	**£11.96**	**£23.91 (base case)**	**£35.87**
Overall cost-impact (annual)	£586,798	£1,030,751	£1,475,076

Table3

Table 3: Adjust incidence rate ratios (IRRs) for the association between vaccination and rotavirus-related annual events and costs, for infants <5 years old in Scotland

Effects	**Pre-vaccination mean events**	**Post-vaccination mean events**	**Incident rate ratio for association (IRR) between introduction of vaccination and resource use (IRR 95% CIs) (p-value)**
Laboratory reports	515	105	0.273 (0.266, 0.279), p<0.001
Hospitalisation days (length of stay)	1,169	631	0.599 (0.589, 0.601), p<0.001
A&E visits	2,177	1,791	0.655 (0.652, 0.658), p<0.001
GP consultation	3,301	2,672	0.736 (0.729, 0.743), p<0.001
NHS24 calls	2,725	2,208	0.826 (0.820, 0.833), p<0.001
Prescriptions	N/A	N/A	0.798 (0.788, 0.808), p<0.001
Costs	**Pre-vaccination mean cost**	**Post-vaccination mean cost**	**Cost difference**
Laboratory reports	£10,825	£2,211	£8,615
Hospitalisation days (length of stay)	£1,075,510	£580,624	£494,886
A&E visits	£232,973	£191,662	£41,311
GP consultation	£119,653	£96,871	£22,782
NHS24 calls	£56,913	£46,113	£10,800
Prescriptions	£71,117	£54,041	£17,076
Total costs	1,566,992	£971,522	£595,470

Table4

Table 4: Unit costs attached to resource use in the study

Resource	Unit cost 2013/14 prices	Unit cost at source year	Source year	Source
Cost of vaccine (per dose)	£23.91	£19	2004	Jit & Edmunds (2007) and JCVI Statement
Incentive payment to GP	£7.67	£7.67	2013/14	GMS Statement of financial entitlements
Laboratory costs (per test)	£20.99	£15.08	2001/02	Lorgelly (2007)
GP consultation (per visit)	£36.25	£28.81	2004	Unit Costs of Health and Social Care 2004 (PSSRU)
NHS 24 Syndromic Surveillance (per call)	£20.88	£15	2001	Munro et al (2001)
Hospitalisations (per day)	£920	£920	2014	ISD
Attendances at A&E (per attendance)	£107	£107	2014	ISD Scotland Cost Book 2014

Figure

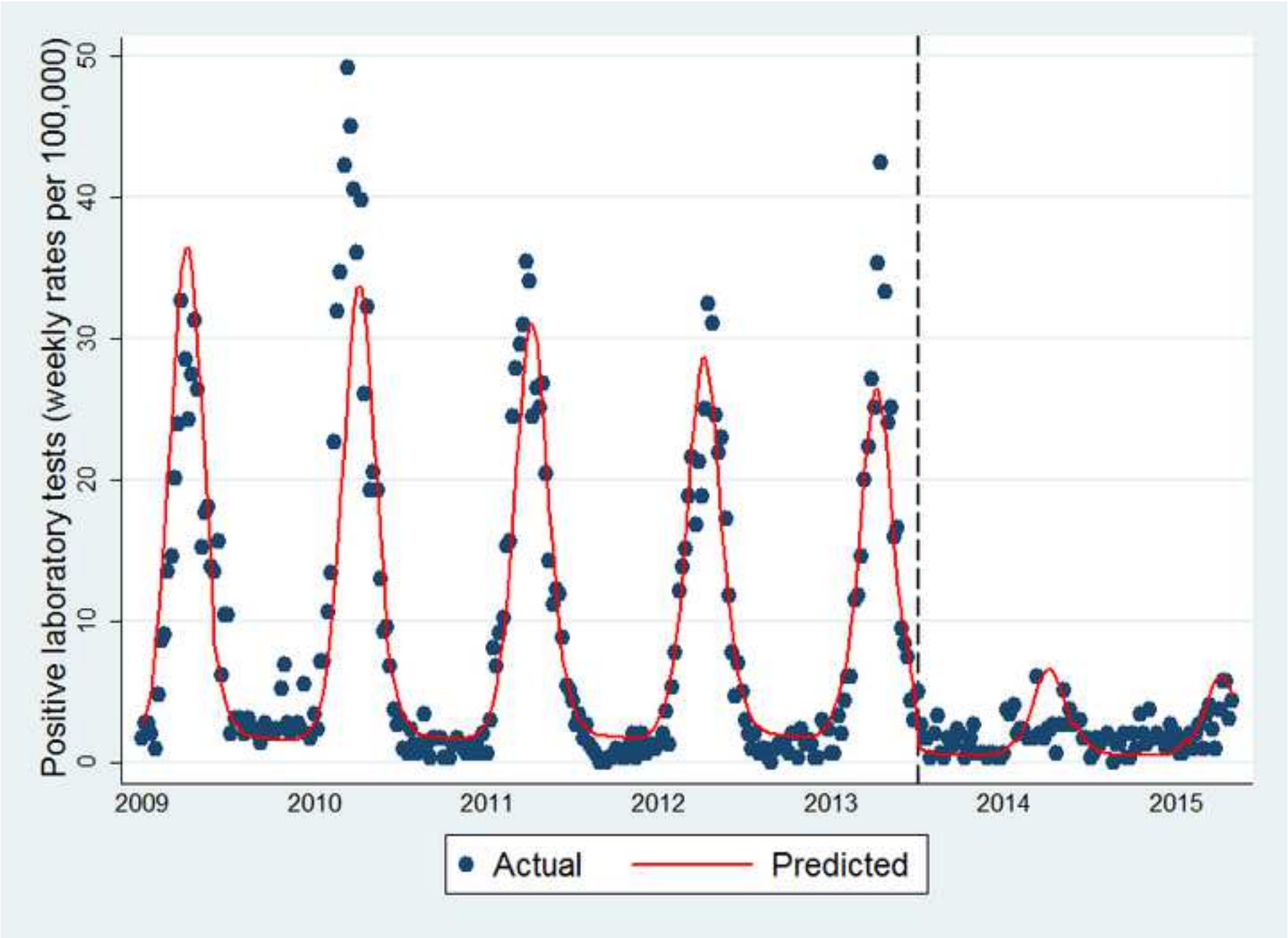

Positive laboratory tests (weekly rates per 100,000)
0
10
20
30
40
50
2009
2010
2011
2012
2013
2014
2015
Actual
Predicted

Figure2

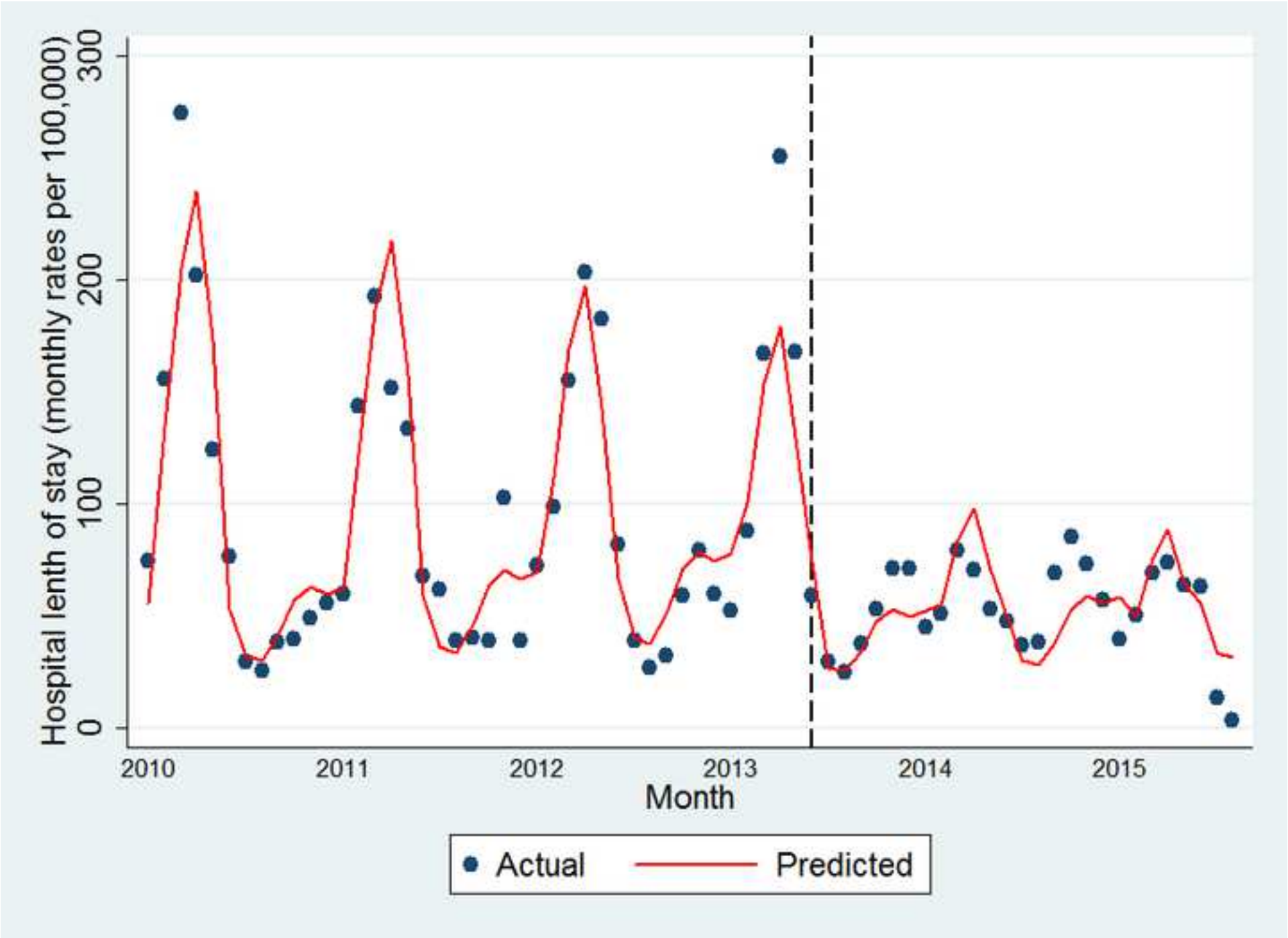

Hospital lenth of stay (monthly rates per 100,000)
0
100
200
300
2010
2011
2012
2013
2014
2015
Month
Actual
Predicted

Figure3

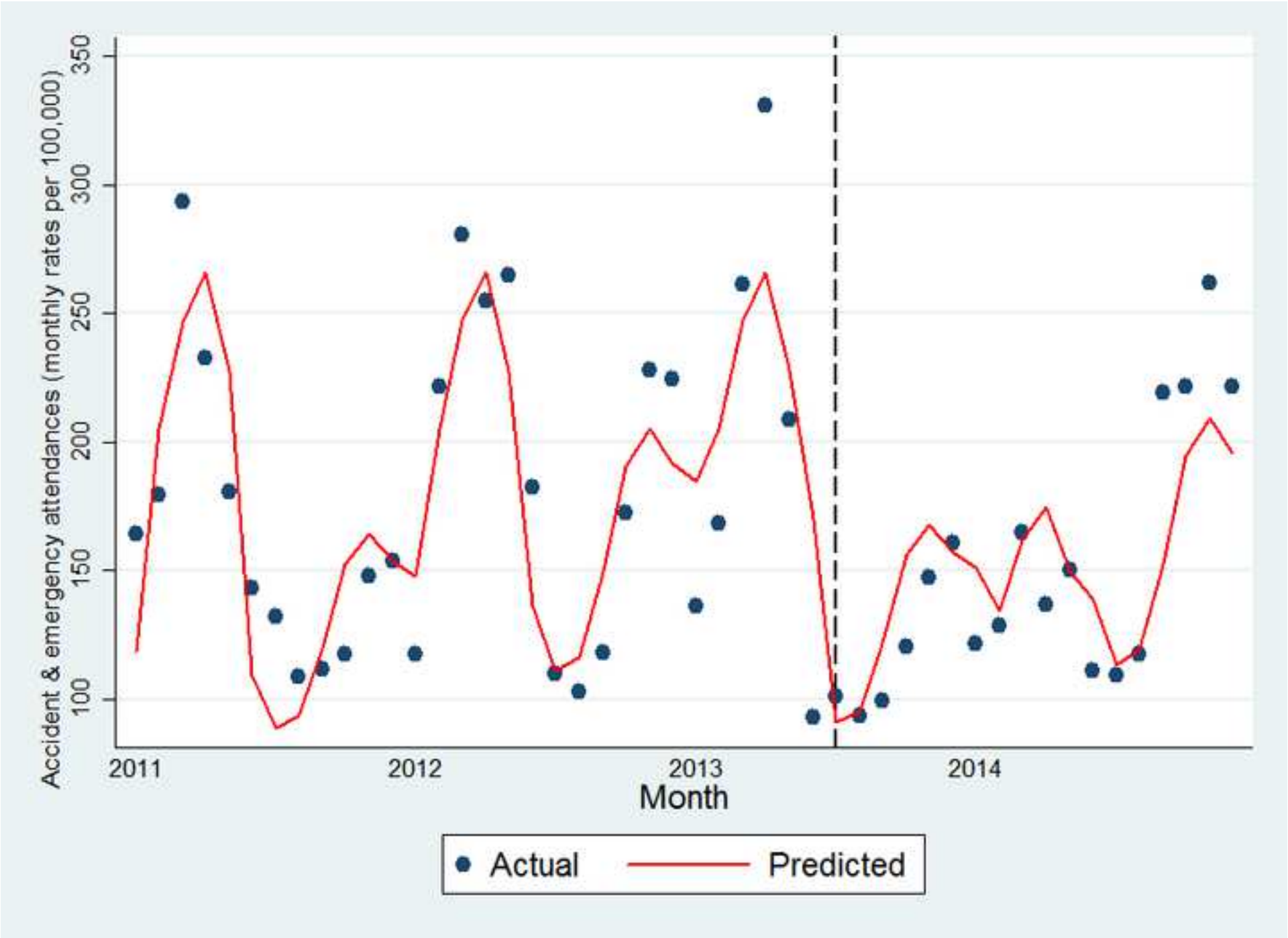

Accident & emergency attendances (monthly rates per 100,000)
350
300
250
200
150
100
2011
2012
2013
2014
Month
Actual
Predicted

Figure4

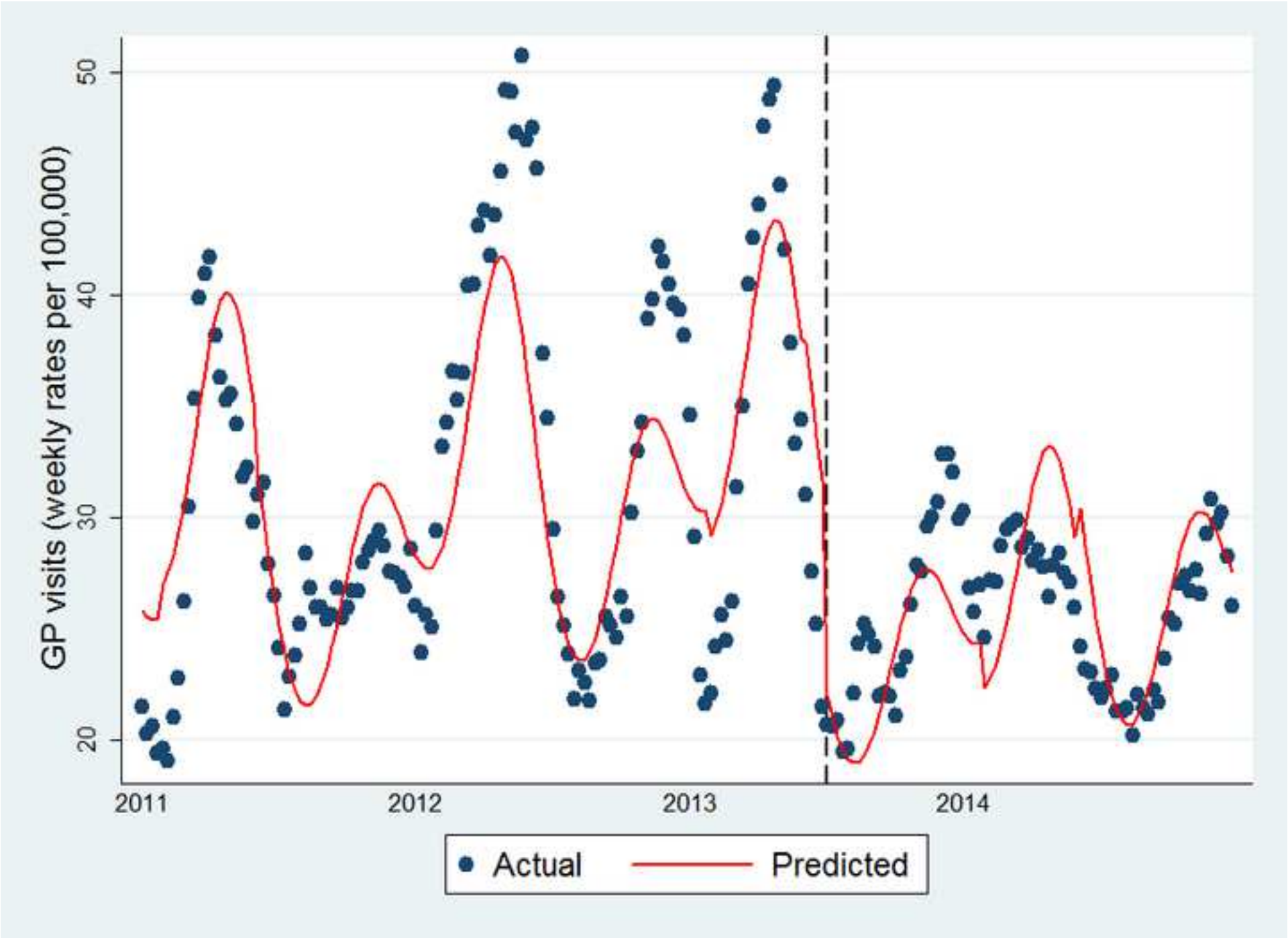

GP visits (weekly rates per 100,000)
50
40
30
20
2011
2012
2013
2014
Actual
Predicted

Figure5

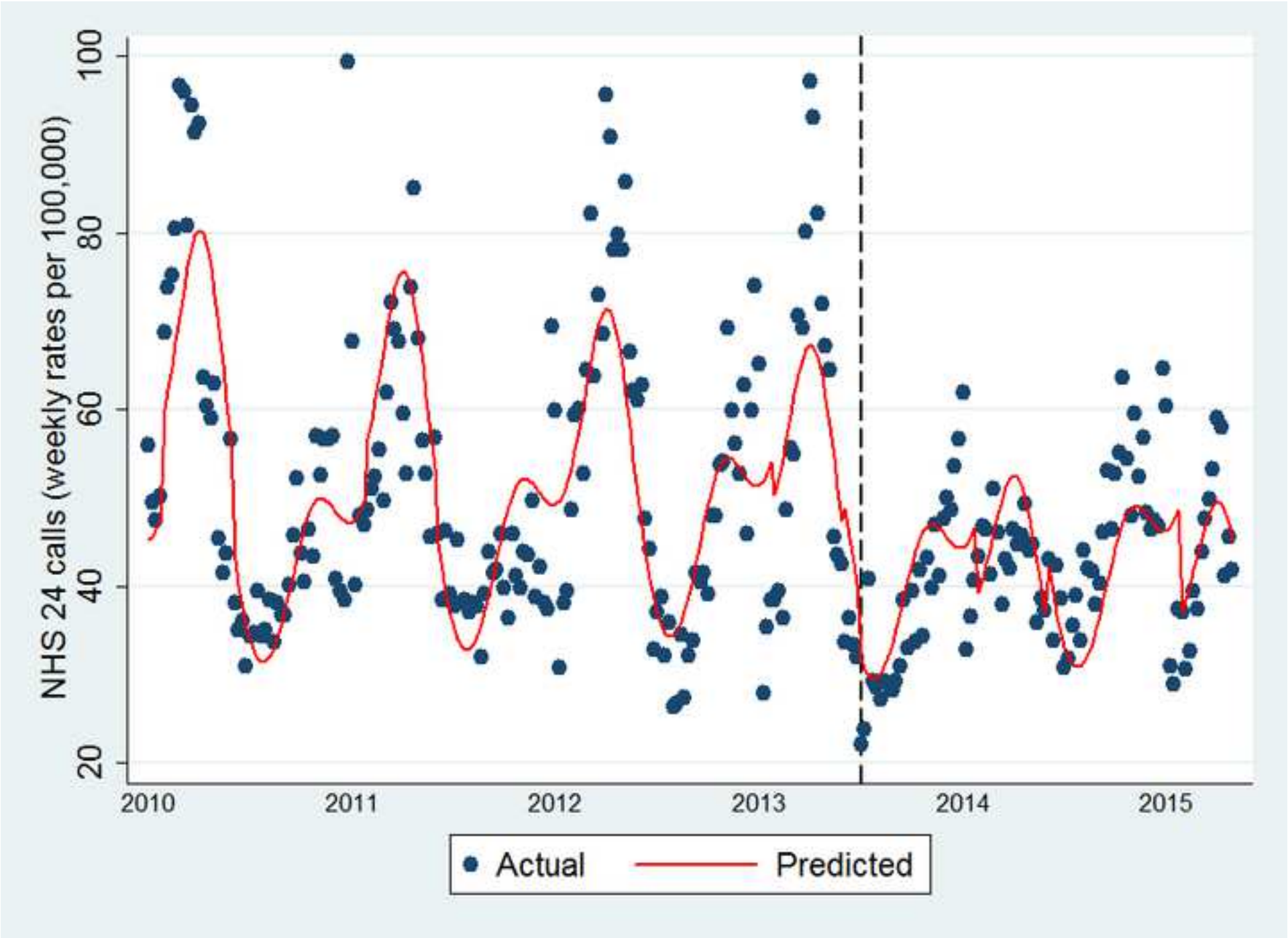
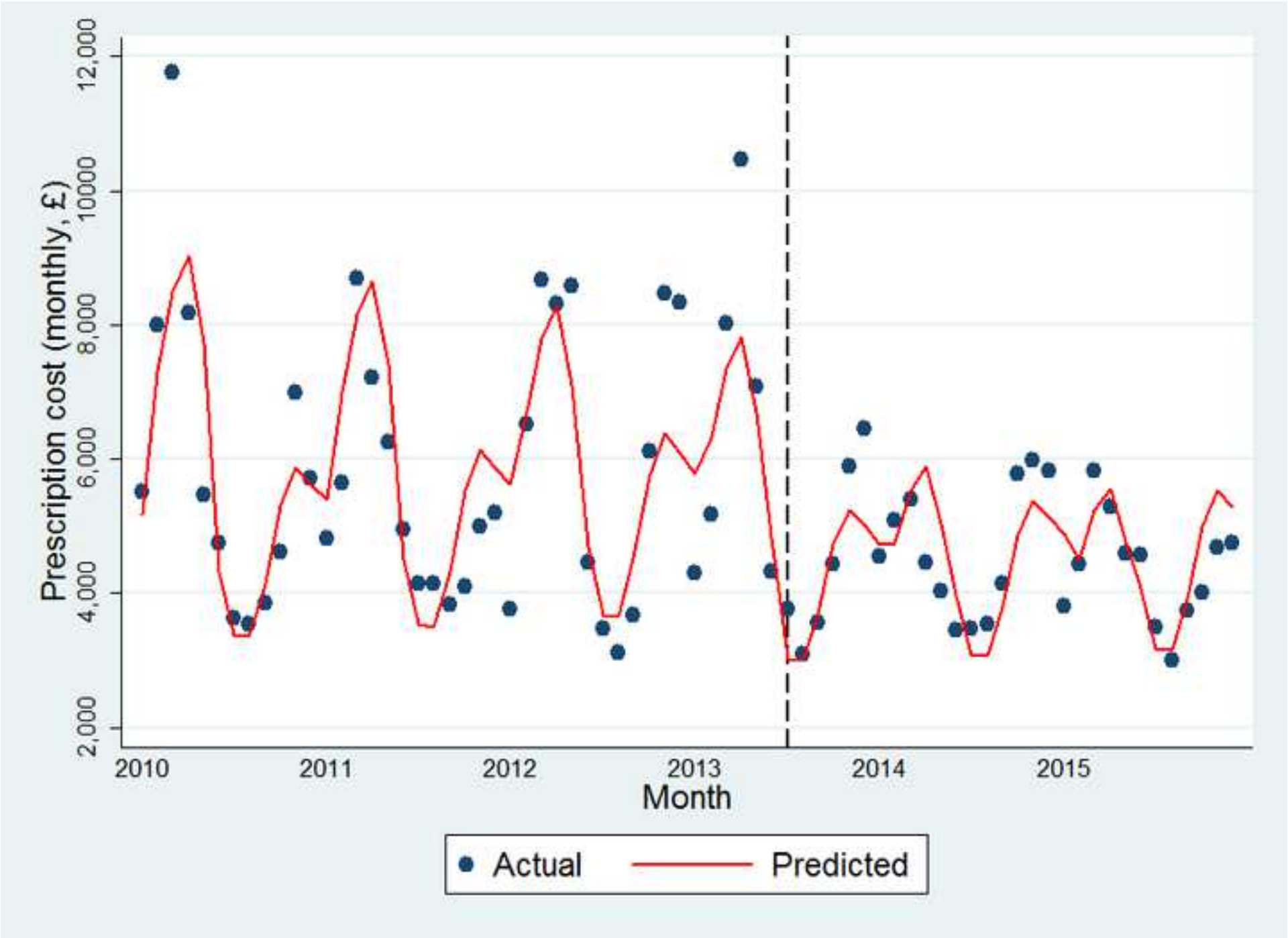

NHS 24 calls (weekly rates per 100,000)
100
80
60
40
20
2010
2011
2012
2013
2014
2015
Actual
Predicted

Figure6


Prescription cost (monthly, £)
12,000
10000
8,000
6,000
4,000
2,000
2010
2011
2012
2013
2014
2015
Month
Actual
Predicted