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Impact of the national rotavirus vaccination programme on acute gastroenteritis in England and associated costs averted

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ABSTRACT

Background: Introduction of infant oral rotavirus vaccination in the UK in July 2013 has resulted in decreased hospitalisations and Emergency Department (ED) visits for acute gastroenteritis (AGE), for both adults and children. We investigated reductions in AGE incidence seen in primary care in the two years after vaccine introduction, and estimated the healthcare costs averted across healthcare settings in the first year of the vaccination programme.

Methods: We used primary care data from the Clinical Practice Research Datalink and age-stratified time-series analyses to derive adjusted incidence rate ratios (IRR_a) for AGE in the first two years of the post-vaccination era (July 2013-April 2015) compared to the pre-vaccination era (July 2008-June 2013). We estimated cases averted among children aged <5 years in the first year of the vaccination programme by comparing observed numbers of AGE cases in 2013–2014 to numbers predicted from the time-series models. We then estimated the healthcare costs averted for general practice consultations, ED visits and hospitalisations.

Results: In general practice, AGE rates in infants (the target group for vaccination) decreased by 15% overall after vaccine introduction (IRR_a = 0.85; 95%CI = 0.76–0.95), and by 41% in the months of historically high rotavirus circulation (IRR_a = 0.59; 95%CI = 0.53–0.66). Rates also decreased in other young children and to a lesser degree in older individuals, indicating herd immunity. Across all three settings (general practice, EDs, and hospitalisations) an estimated 87,376 (95% prediction interval: 62,588–113,561) AGE visits by children aged <5 years were averted in 2013–14, associated with an estimated £12.5 million (9,209–16,198) reduction in healthcare costs.

Conclusions: The marked decreases in the general practice AGE burden after rotavirus vaccine introduction mirror decreases seen in other UK healthcare settings. Overall, these decreases are associated with substantial averted healthcare costs.

1. Introduction

Rotavirus is the commonest cause of diarrhoea in young children, and results in considerable morbidity and healthcare utilisation [1–3]. Introduction of the monovalent live-attenuated oral vaccine Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) into national infant immunisation programmes has led to large decreases in both rotavirus-associated and all-cause acute gastroenteritis (AGE) hospital admissions [4–8]. In the UK, Rotarix was introduced in July 2013 as a 2-dose schedule given at 2 and 3 months of age. By the end of the first year, vaccine coverage reached 93% for one dose and 88% for two doses [9]. We have shown that vaccine introduction was followed by marked reductions in laboratory-confirmed rotavirus infections and AGE hospitalisations in England in the subsequent year [10]. Initial analyses using syndromic surveillance data also showed reductions in general practice consultations for gastroenteritis, diarrhoea and vomiting, and in emergency department (ED) visits for AGE [11].

Here we report in-depth analyses of the trends in incident AGE episodes presenting to general practice in England in the first two years after vaccine introduction (July 2013-April 2015). We also

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present estimates of the health care costs averted across NHS settings (general practice, EDs and hospital) in the first year of the vaccination programme because of reductions in AGE cases in young children.

2. Methods

2.1. Data sources

For the general practice analyses, we used data from the Clinical Practice Research Datalink (CPRD). This database contains anonymised primary care medical records from a representative 7% sample of the UK population [12]. Data available include all diagnoses and symptoms (coded using Read codes), referrals, prescriptions, and feedback from secondary care.

For healthcare cost estimates, we also used data on hospitalisations and ED visits. Hospitalisation data comprised Hospital Episode Statistics (HES), which contain information on all hospital admissions in England. ED attendance data were accessed from the Emergency Department Syndromic Surveillance System (EDSSS), a near real-time sentinel system that provides daily automated data extracts for ED visits [13]. We used EDSSS data from the eighteen participating EDs in England that used International Classification of Diseases version 10 or Snomed-CT diagnosis coding systems, to enable identification of AGE attendances.

Meteorological data, used to adjust for potential confounding by temperature and humidity in the general practice analyses, were downloaded from the UK Meteorological Office website and the MIDAS Land Surface Observation database [14–16].

2.2. AGE incidence in general practice

The study period comprised July 2008-June 2013 (the pre-vaccination period) and July 2013-April 2015 (the post-vaccination period). Individuals' start of follow up was the latest of their registration date with the practice (if ⩽3 months old at registration), six months after their registration date (if >3 months old, to avoid including historical AGE episodes recorded retrospectively after registration), the date the practice reached established quality standards and 1st July 2008 [17]. Follow up ended when the patient died or left the practice, when the practice stopped providing data or 30th April 2015.

Most infectious gastroenteritis presentations to general practice are diagnosed clinically without laboratory confirmation of the causative pathogen. Furthermore, general practitioners (GPs) often record gastroenteritis diagnoses using symptom codes such as "diarrhoea and vomiting". We therefore used a comprehensive list of Read codes to define AGE, categorising each code into one of four AGE subgroups: (AGE1) infectious gastroenteritis; (AGE2) non-infectious gastroenteritis of specified cause (e.g. "allergic gastroenteritis"); (AGE3) non-infectious gastroenteritis of unspecified cause; and (AGE4) gastroenteritis of unspecified type (e.g. "Diarrhoea and vomiting"; codelists available on request).

To accommodate multiple consultations for an ongoing illness, AGE diagnostic codes recorded ⩽28 days after a previous consultation were considered part of the same AGE episode. The first consultation within the episode was the incident date of that episode. Episodes of AGE first seen and diagnosed in hospital or in EDs (identified from the consultation type in the CPRD data) were excluded, to restrict analyses to AGE diagnosed in primary care. We then excluded episodes unlikely to be rotavirus AGE, namely episodes of non-infectious AGE of specified type (AGE2), and episodes of possible chronic diarrhoea, identified as AGE of unspecified type (AGE4) in individuals with pre-existing conditions that cause chronic diarrhoea (large bowel cancer, inflammatory bowel disease, irritable bowel syndrome, coeliac disease, cystic fibrosis, chronic pancreatitis, post-gastrectomy syndromes, post-bariatric surgery conditions or radiation colitis). In line with previous studies, non-infectious AGE of unspecified cause (AGE3) was retained in the primary analysis because previous investigations indicate that this is often a miscoding for infectious AGE [3,10].

Covariates of interest included age, subdivided into year of age for the first 5 years, then 5–14, 15–44, 45–64 and 65+ years; rotavirus epidemiological year (July-June); rotavirus season, classified based on historical rotavirus laboratory reports into high (February-April), medium (October-January, May) and low season (July-September, June). In each rotavirus year, temperature and rainfall were based on the median values of the daily mean central England temperature and rainfall for the two winter months (January, February) that captured the weather in the period spanning the start of rotavirus high season each year.

We performed age-stratified time series analyses of monthly counts of incident AGE cases, using negative binomial regression with an offset for the denominator (age-specific person-time). We included a variable in the model for the post-vaccination period to obtain adjusted incidence rate ratios (IRR_a) compared with the pre-vaccination period. Year was added to the model as a linear term to account for underlying secular trends. We initially considered using a longer pre-vaccination period (starting July 2003), but AGE counts in the earliest years were unusually low, which resulted in

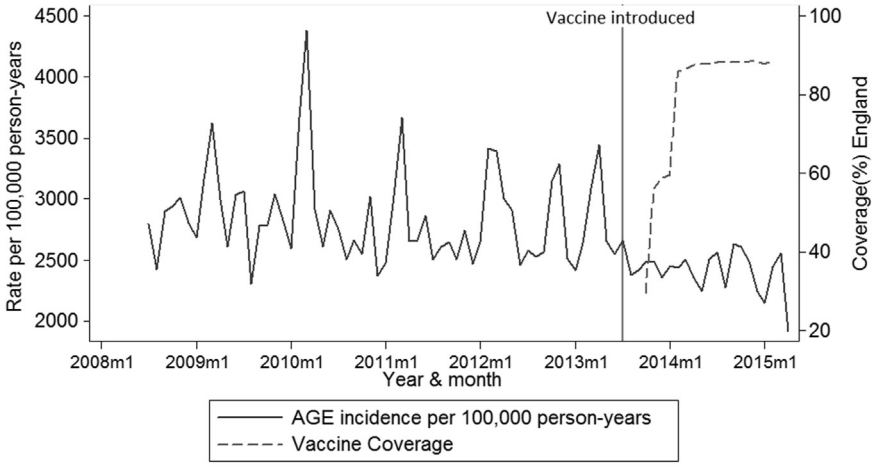

Fig. 1. Rates of new episodes of acute gastroenteritis (AGE) seen in UK primary care (per 100,000 person years), July 2008-April 2015.

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an apparent quadratic trend that we were cautious about extrapolating beyond the pre-vaccination era. We therefore modelled the data in the five years before vaccine introduction, during which time AGE incidence decreased linearly. We also tested the addition of various combinations of the two weather variables to our model, including temperature and rainfall added separately, or added together with and without interaction terms (including interaction with each other and with rotavirus season). The association of each combination of temperature/rainfall with AGE incidence was assessed using likelihood ratio tests, and the effect on each IRR_a of adjusting for the weather variables was examined.

As in our previous hospitalisation analyses, we assessed autocorrelation by examining the residuals from the models, but found that the estimates and standard errors for the vaccine indicator

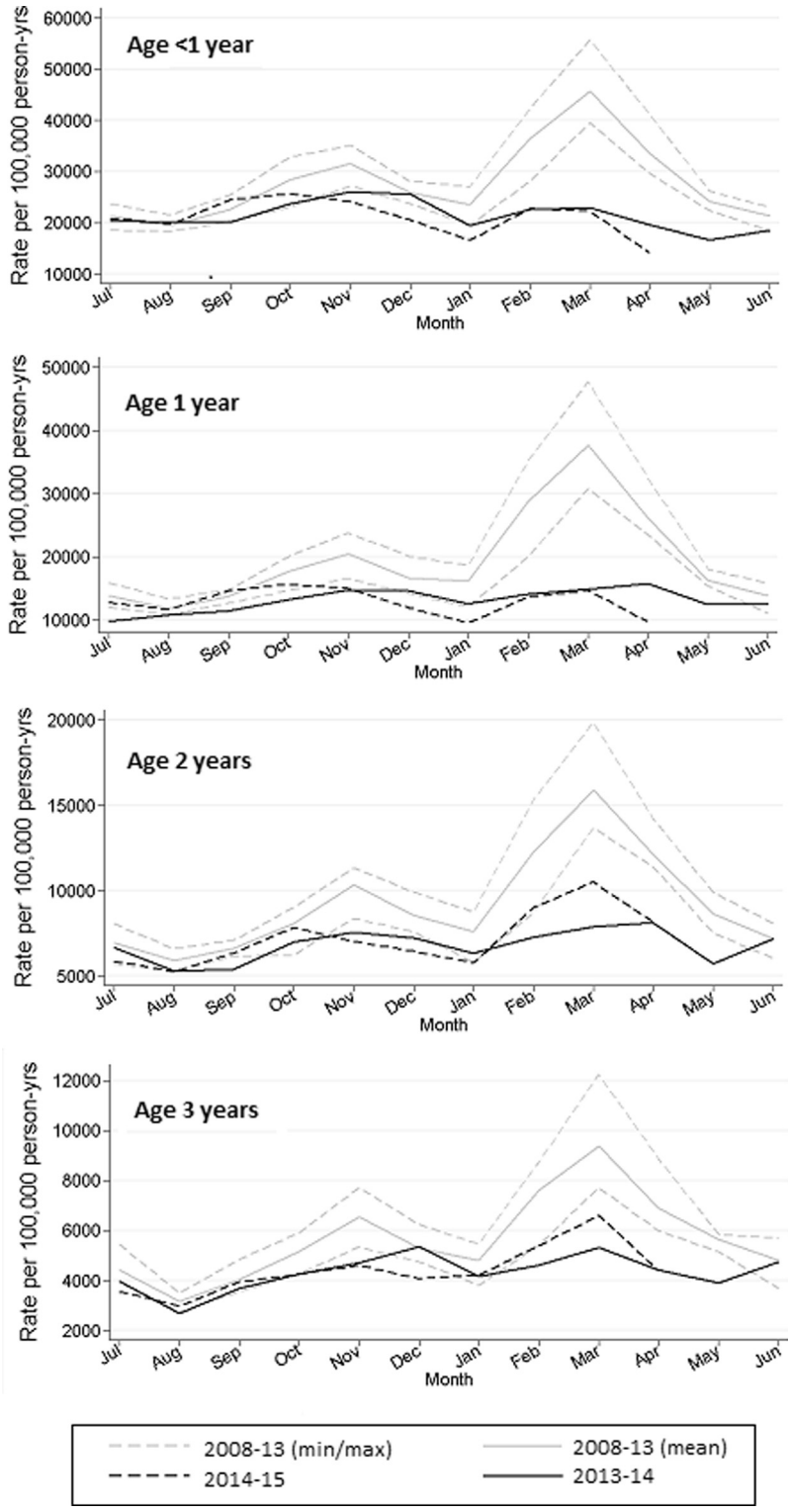

Fig. 2. Comparison of post-vaccination incidence of AGE seen in primary care (episodes per 100,000 person years) in young children, stratified by year of age, July 2008-April 2015.

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variable were very similar with and without lag terms and thus these terms were not included in the final models [10].

In sensitivity analyses, we restricted the data to episodes of infectious and unspecified AGE only (AGE1 and AGE4). We also generated IRR_a estimates for each post-vaccination year separately (2013–14 and 2014–15).

2.3. Cases and healthcare costs averted

We calculated the number of healthcare contacts for AGE that were averted among children aged <5 years in the first year after vaccine introduction, including general practice consultations, hospital admissions and ED attendances.

For general practice, the number of incident AGE cases averted in England were derived from the time-series models, using the expected number of AGE episodes in 2013–14 predicted by the model and the age-stratified IRR, and extrapolating the numbers to the England child population. The total number of general practice consultations averted in each age group were then calculated by multiplying the number of incident cases averted in that age group by the average number of GP consultations per AGE episode. The numbers of hospitalisations averted were derived similarly, from our previous time series analyses of England-wide hospitalisation data (July 2007-June 2014) [10]. For AGE ED visits averted, we used EDSSS data collected between July 2012 and June 2014; each week, data were restricted to the EDs that reported fully for every day of that week. As not all EDs were included weekly, we estimated total AGE visits each week by calculating the proportion of all ED visits each week that were AGE (from those that did report), and multiplying this by the estimated average weekly number of all ED visits in England during the study period. To estimate this average we multiplied the weekly average number of visits per ED in those reporting in our study period by the number of ED departments in England [18]. The number of AGE cases averted in EDs was obtained by subtracting the calculated number of AGE visits during the rotavirus season (weeks 5–17 inclusive) in 2013/14 from the numbers in the same period in 2012/13.

Costs were calculated using a number of data sources; details of calculations are in Supplementary Appendix [19]. The healthcare costs averted were calculated by multiplying the number of healthcare visits averted by the cost of the visit for each age group, then summed across the type of healthcare visit (hospital, GP or ED). To generate a distribution of annual costs averted, we sampled 100,000 times from each of the listed distributions (for costs), from the respective lognormal distributions (for predicted number of GP visits and hospital visits), and from the normal distribution (for predicted number of ED visits). We report the mean costs averted with their 95% prediction intervals, overall and stratified by healthcare setting and age.

We analysed data using STATA MP v.13.1 (StatCorp, College Station, TX) and MATLAB R2014b version 8.4.0 (Natick, Massachusetts:The MathWorks Inc., 2014)

3. Ethics approval

Approval was received from the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (ISAC number: 15_066R) and the Ethics Committee of the London School of Hygiene & Tropical Medicine (Reference number: 11843).

4. Results

Between 1st July 2008 and 30th April 2015, after excluding 845 episodes of non-infectious AGE of specified type and 160,550 episodes of chronic diarrhoea, there were 804,141 incident episodes of AGE seen in general practice during 29,228,316 person-years of follow-up. In children aged <5 years, most (81.6%) of the 201,921 AGE episodes were categorised as non-specific gastroenteritis, with 18.3% categorised as infectious and 0.1% as non-infectious of unspecified cause. For older children/adults, the relative percentages were 76.8%, 23% and 0.2% respectively. Only 0.2% of episodes (1634 episodes in children <5 yrs, 453 episodes in older children/adults) were labelled specifically as rotavirus AGE.

Before vaccine introduction, incident AGE consultations followed the expected seasonal pattern with annual peaks in February-March. Incidence decreased markedly after vaccine introduction, with a complete loss of the seasonal peak for both 2013–14 and 2014–15 (Fig. 1). The decrease was most marked in young children targeted for vaccination (aged <2 years between July 2013 and April 2015, Fig. 2), but was also seen to a lesser extent in older children and in adults (Supplementary Figure), suggesting herd immunity. For younger children, the monthly AGE rates in rotavirus season (February-April) remained lower in

Table 1
Incident AGE episodes seen in general practice before and after rotavirus vaccine introduction in England.

Age (years)	Number of incident AGE episodes							
	Pre-introduction Mean (minimum)	2013–14 Observed	2014–15 Observed	2013–14 IRR[a] (95% CI)	p value	2014–15 IRR[a] (95% CI)	p value	Overall IRR[a] (95% CI)
<1	13,029 (12,337)	8709	6068	0.85 (0.76,0.95)	0.0050	0.85 (0.74,0.97)	0.0145	0.85 (0.76,0.95)
1	10,096 (9367)	6090	4101	0.79 (0.69,0.90)	0.0005	0.79 (0.67,0.93)	0.0051	0.79 (0.69,0.90)
2	4808 (4347)	3223	2340	0.87 (0.79,0.96)	0.0062	0.93 (0.83,1.05)	0.2411	0.89 (0.81,0.98)
3	2952 (2705)	2068	1457	0.88 (0.79,0.98)	0.0192	0.92 (0.81,1.05)	0.2008	0.89 (0.81,0.99)
4	2145 (2017)	1597	1118	0.86 (0.78,0.96)	0.0061	0.87 (0.77,0.99)	0.0378	0.87 (0.79,0.96)
5–14	9573 (9023)	7399	5103	0.92 (0.86,0.99)	0.0284	0.92 (0.84,1.00)	0.0484	0.92 (0.86,0.99)
15–44	33,736 (30,880)	26,044	17,473	0.95 (0.90,1.00)	0.0592	0.94 (0.88,1.00)	0.0658	0.95 (0.90,1.00)
45–64	23,064 (21,707)	18,144	12,130	0.92 (0.87,0.97)	0.0042	0.89 (0.83,0.95)	0.0006	0.91 (0.86,0.96)
65+	28,664 (27,600)	23,917	16,822	0.94 (0.89,1.00)	0.0403	0.95 (0.89,1.01)	0.1128	0.94 (0.90,1.00)

[a] Incidence rate ratio (compared to the pre-introduction period), adjusted for month and rotavirus epidemiological year.

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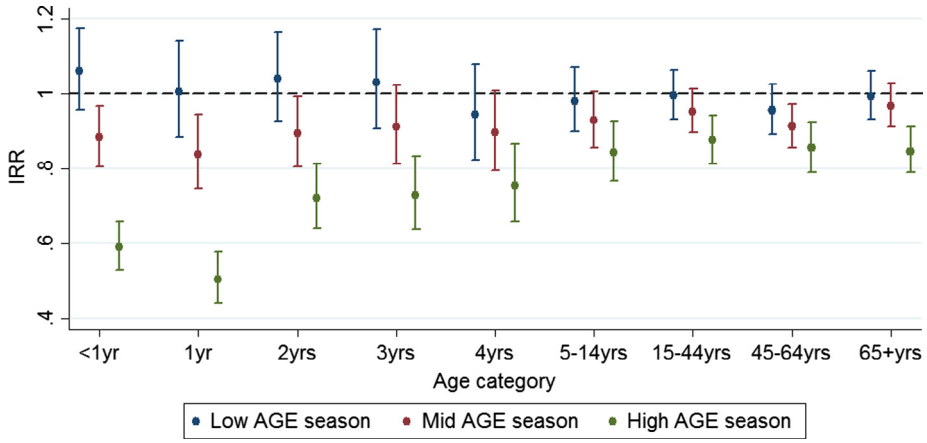

Fig. 3. Adjusted incidence rate ratios (IRR) for the incidence of AGE in the post-vaccination period (July 2013-April 2015) compared with the pre-vaccination period, stratified by age and rotavirus season.

Table 2
Estimated AGE cases and costs averted in general practice, hospital and Emergency Departments in 2013/14 among children aged <5 years in England.

Age (years)	Annual visits averted 2013/14 (95% prediction interval)			Annual costs averted (2014 £million) (95% prediction interval)		
	GP	Hospital	EDs	GP	Hospital	EDs
<1	22,977 (6466,40,892)	5300 (2807,8043)	4579 (3284,5873)	1.001 (0.266,1.935)	3.556 (1.841,5.532)	0.557 (0.377,0.760)
1	26,147 (10,458,43,499)	4731 (1872,8068)	5658[a] (2917,8399)	1.112 (0.412,2.023)	3.175 (1.237,5.521)	0.688[a] (0.344,1.069)
2	7336 (1964,13,118)	1591 (545,2788)		0.304 (0.077,0.591)	1.068 (0.361,1.907)	
3	4243 (650,8131)	722 (181,1329)		0.176 (0.026,0.364)	0.484 (0.120,0.908)	
4	3755 (1010,6725)	339 (-2, 715)		0.156 (0.040,0.303)	0.228 (-0.1,0.487)	
All ages	64,457 (40,246,90,135)	12,683 (8600,17,123)	10,236 (7206,13,265)	2.749 (1.496,4.343)	8.511 (5.570,1.1873)	1.245 (0.830,1.715)
Total	87,376 (62,588,113,561)			12.505 (9.209,16.198)		

[a] Ages 1–4 years combined.

the two years after vaccine introduction than the lowest monthly rate for the same period pre-2013 (Fig. 2).

In multivariable analyses, general practice AGE rates in infants dropped by 15% in the post-vaccination period overall (IRR_a = 0.85; 95%CI = 0.76–0.95, Table 1). A graded decrease was seen across the year, with a 41% reduction in high rotavirus season (IRR_a = 0.59; 95%CI = 0.53–0.66) and a 19% reduction in the medium season, but no evidence of a decrease in low season (Fig. 3). Similar decreases were seen for children aged 1 year, with 2013–15 rates dropping by 21% overall and by 50% in high season (Table 1, Fig. 3). Decreases of 11–13% (25–28% in high season) were seen in children aged 3–5 years. For older children and adults there was less strong evidence of a decrease overall, but rates dropped by 12–16% in high season. The reductions were similar in both post-vaccination years (Table 1). Temperature and rainfall (added to the models in any of the planned combinations) had a negligible effect on the adjusted rate ratios (data not shown).

The estimated number of cases averted in young children seeking healthcare services in England in 2013–14 are summarised in Table 2. An estimated 64,457 AGE cases were averted in general practice, 10,236 cases in EDs, and 12,683 in hospitalisations. This translated into averted healthcare costs of £12.5 million (95% prediction interval: 9.21–16.20; Table 2).

5. Discussion

Our analyses can be considered the equivalent of a vaccine probe study, in that the reduction in the AGE burden seen after rotavirus vaccine introduction can be attributed to prevention of AGE cases caused by the vaccine-specific pathogen (rotavirus). The vaccine had high uptake among infants (the target vaccination group), and our analyses show marked decreases in incident AGE episodes among children aged <2 years seen in general practice in the two years after vaccine introduction. Notably, there was complete loss of the seasonal peak in the months of historically high rotavirus circulation. Similar reductions in AGE were also seen in other young children who were ineligible for rotavirus vaccination, and to a certain extent in older individuals, suggesting herd immunity. Across healthcare settings in England, we estimated a large number of AGE cases averted among children aged <5 years in the first year of vaccine introduction, with appreciable health care costs averted.

The marked reductions in AGE cases in general practice echo earlier findings of decreased numbers of laboratory-confirmed rotavirus infections and AGE hospitalisations in England following implementation of rotavirus vaccination [10]. Assessment of the impact of rotavirus vaccination has focused in most countries on reductions in rotavirus- or all-cause AGE hospitalisations, but the impact on primary care has been less studied. Initial analyses of UK general practice data in the first post-vaccination year using rapid syndromic surveillance methods showed reductions of 26–30% in gastroenteritis consultations (GP in-hours and out-of-hours respectively) among infants during high rotavirus season [11]. A later window for rotavirus activity was used (weeks 14–22 for GP in-hours), which may explain the slightly lower reductions compared to our study. Also, the pre-vaccination era data used were restricted to the year before vaccine introduction. Our study combined different modes of AGE (incorporating diarrhoea and vomiting consultations) to provide a composite estimate of incidence. We also modelled pre-vaccination incidence over a longer period and extended analyses to the second year after vaccine introduction (to the end of high rotavirus season) to show

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continued reduction. Our estimate of an overall 15% reduction in general practice AGE burden in infants is similar to that in Finland for infant outpatient AGE visits after vaccine introduction [20]. Our estimated 41% reduction in peak season is also broadly consistent with findings from 33 ambulatory paediatric practices in the USA, which reported a 33% reduction in peak AGE rates in children aged ⩽2 years by the end of the second year of vaccine introduction, in a population with lower vaccine coverage than in the UK [6].

Our estimates of the number of AGE cases averted among young children and their associated healthcare costs update earlier estimates from the pre-vaccination era (1995–2003) [3]. The earlier study estimated the AGE healthcare burden attributable to rotavirus infection in children aged <5 years in England and Wales (using regression modelling of seasonal laboratory data against AGE cases), with estimated healthcare costs of £14.2 million. There are several likely explanations for our somewhat lower estimate. Our analyses were for England only, and vaccine effectiveness and vaccine coverage are not 100%; thus not all rotavirus AGE cases will have been averted. Consultations for AGE in general practice have been falling over time; our estimates from a later era reflect this declining AGE burden, accentuated by our removal of AGE cases diagnosed in EDs or in hospital to avoid double-counting of AGE events [3]. The estimated proportions of AGE cases attributable to rotavirus in seasonal regression modelling depend on the incidence of other causes of AGE in young children, and these may have changed over time. The earlier estimate of AGE burden in EDs was based on only five hospitals in the Greater London area, which may have been less generalisable than our ED sample [3]. Finally, the earlier investigation included an estimated £0.56 million due to NHS Direct calls; we did not have updated data to add these costs to our analyses.

We deliberately restricted estimates of healthcare costs averted to young children, to compare with previous analyses and to focus on the age group in which rotavirus is the commonest cause of AGE. Our estimates are thus conservative, as they exclude probable AGE cases averted in older children and adults due to herd immunity and cases averted in additional healthcare settings (such as NHS Direct and NHS 111), and made conservative estimates of other healthcare costs.

Our study has many strengths. Our use of a large general practice data source, an episode structure for AGE and a wide range of AGE diagnostic codes allowed us to capture episodes recorded using symptom codes, and identify AGE subgroups. The choice of AGE as an outcome rather than laboratory-confirmed cases avoided major underestimation of the impact of vaccine introduction due to the rarity of microbiological testing of AGE specimens, especially in general practice. Multivariable analyses using pre-vaccination data over several years allowed adjustment for underlying trends in AGE incidence and health-seeking behaviour, and the potential effects of weather. CPRD patients have been shown repeatedly to be representative of those in the United Kingdom as a whole, and thus our results should be generalizable to the UK population [12].

Some limitations need consideration. These are ecological analyses, and the decrease in AGE we found in the post-vaccination era could be due to factors other than introduction of vaccination. The UK experienced an exceptionally mild and wet winter in 2013/14, which may have decreased rotavirus activity. Low AGE incidence was also seen in 2013/14 in the Netherlands, a country that has not introduced rotavirus vaccination; suggested reasons for this lower incidence included the mild winter, high rotavirus incidence the previous year, and rotavirus vaccination in neighbouring countries [21]. Our detailed investigation of the effects of temperature and rainfall on AGE trends indicated that these were not major contributors. We also found very similar reductions in AGE in the second post-vaccination year, whereas in the Netherlands AGE incidence returned to previous levels (Susan Hahne, personal communication). Thus it is likely that the reduction in AGE we found is mainly due to the rotavirus vaccination programme. Another possible limitation relates to the relatively small number of available ED units, with only a single pre-vaccination year for comparison as the EDSSS was set up to provide enhanced surveillance for the London 2012 Olympic and Paralympic Games. Thus, the ED estimates may be less robust than those obtained for general practice and hospitalisations.

In conclusion, we have demonstrated substantial decreases in AGE in general practice in the first two years of the vaccination programme, with new estimates showing appreciable healthcare costs averted. Continued monitoring of AGE incidence in all healthcare settings in England is important. Analyses of individual-level data are now underway to estimate vaccine effectiveness in different settings.

Conflict of interest

None.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.11.057.

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