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The impact of rotavirus vaccination on hospital pressures in a large paediatric hospital in the United Kingdom

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Manuscripts

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3 1 **The impact of rotavirus vaccination on hospital pressures in a large paediatric hospital in**
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6 2 **the United Kingdom**

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48
49 20 **Abbreviated title:** Hospital pressures post rotavirus vaccination

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1
2
3 **23 ABSTRACT**
4

5 **24 Objective** Hospitals in the United Kingdom are under increasing clinical and financial
6
7
8 **25 pressures.** Post introduction of childhood rotavirus vaccination in the UK in 2013, rotavirus
9
10 **26 gastroenteritis (RVGE) hospitalisations** reduced significantly. We evaluated the impact of
11
12
13 **27 rotavirus vaccine introduction on ‘hospital pressure’** (demand on healthcare resources and
14
15 **28 staff) in a paediatric setting in the UK.**

16
17
18 **29 Design** Ecological impact study using retrospective hospital database analysis between July
19
20 **30 2007 and June 2015.**

21
22
23 **31 Setting** A large paediatric hospital providing primary, secondary and tertiary care in
24
25 **32 Merseyside, UK.**

26
27
28 **33 Participants** Hospital admissions aged < 15 years. Outcomes were calculated for four
29
30 **34 different patient groups identified through diagnosis coding (ICD-10) and/or laboratory**
31
32 **35 confirmation: all admissions; any infection, acute gastroenteritis; and RVGE.**

33
34
35 **36 Methods** Hospital pressures were compared before and after rotavirus vaccine
36
37 **37 introduction: these included bed occupancy, hospital-acquired infection rate, unplanned**
38
39 **38 readmission rate, and outlier rate (medical patients admitted to surgical wards due to lack**
40
41 **39 of medical beds). Interrupted time-series analysis was used to evaluate changes in bed**
42
43 **40 occupancy.**

44
45
46
47 **41 Results** There were 116,871 admissions during the study period. Lower bed occupancy in
48
49 **42 the rotavirus season in the post-vaccination period was observed for RVGE (-89%, 95%CI**
50
51 **43 73%-95%), acute gastroenteritis (-63%, 95%CI 39%-78%) and any infection (-23%, 95%CI**
52
53 **44 15%-31%). No significant overall reduction in bed occupancy was observed (-4%, 95%CI -1%-**
54
55 **45 9%). No changes were observed for the other outcomes.**
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3 46 **Conclusions** Rotavirus vaccine introduction was not associated with reduced hospital
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6 47 pressures. A reduction in RVGE hospitalisation without change in overall bed occupancy
7
8 48 suggests that beds available were used for a different patient population, possibly reflecting
9
10
11 49 a previously unmet need.

12
13 50 **Clinical trials identifier** ClinicalTrials.gov NCT03271593

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3 52 **'Strengths and limitations of this study'**
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- 5 53 • This study used 8 years of retrospective routinely collected data from a large
6
7
8 54 paediatric hospital in the United Kingdom.
9
10 55 • This is the first study to examine the effects of a vaccine on wider measures of
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12
13 56 hospital pressures in the United Kingdom.
14
15 57 • Our analysis highlights the importance of the presentation of data from the full study
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18 58 period in a time series analysis, rather than restricting the results to a "before-after"
19
20
21 59 comparison.
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23 60 • Our analysis was complicated by inevitable changes in hospital practices over the 8-
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26 61 year study period, in particular changes in patient flow, laboratory procedures,
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28 62 infection control and clinical coding.
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63 INTRODUCTION

64 In the context of increasing patient need and constrained resources, the United Kingdom's
65 (UK) National Health Service (NHS) faces growing clinical and financial pressures. Currently,
66 the NHS is failing to meet targets for urgent, emergency and planned care.[1, 2] Hospital
67 admission rates have been increasing for the past decade; if the increases continue at the
68 current rate an extra 22 hospitals with 800 beds each will be required by 2022.[3] Although
69 highest for the elderly, increases in admission rates are occurring across all age groups.[3] In
70 children aged 0-14 years, the number of finished consultant episodes increased from 1.7 to
71 2.0 million between 2004-05 and 2014-15 [4] and emergency department (ED) attendances
72 have risen by approximately 300,000 between 2011-12 and 2014-15,[5] leaving paediatric
73 services with increased demand but a short fall of medical staffing.[6]

74 While the problems the NHS faces are complex, there are ongoing disease prevention
75 mechanisms which can help alleviate some of the burden. Vaccines for example, are the
76 most effective defence against infectious diseases.[7] For highly efficacious vaccines
77 targeting childhood diseases with a large hospitalisation burden, it is possible that the
78 reduction in beds occupied for infections caused by the vaccine target pathogen reduces
79 hospital pressures, and potentially nosocomial infections.[8, 9]

80 Prior to vaccine introduction in the UK, rotavirus gastroenteritis (RVGE) was a major cause
81 of hospital admission in young children during the winter/spring months. It was estimated
82 that in children less than 5 years of age, 20% of ED attendances and 45% of hospitalisations
83 for acute gastroenteritis (AGE) were due to rotavirus infections.[10] The UK introduced the
84 monovalent two-dose rotavirus vaccination (*Rotarix*, GSK) into the routine childhood
85 immunisation schedule in July 2013. Rotavirus vaccine uptake increased rapidly to over 90%
86 for one dose [11] and early vaccine impact studies suggest a significantly reduced incidence

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3 87 of RVGE hospitalisations in children.[7, 12, 13] The aim of this study was to assess hospital
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6 88 pressures at a large UK NHS paediatric hospital pre- and post- rotavirus vaccine introduction
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8 89 using routinely collected data. As there are no direct measures of hospital clinical pressures
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10
11 90 (on healthcare resources and staff), evidenced proxy indicators were used: bed occupancy,
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14 91 hospital-acquired infection rate, unplanned readmission rate, and rate of outliers (medical
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16 92 patients admitted to surgical wards).
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94 **METHODS**

95 **Setting**

96 Alder Hey Children's NHS foundation Trust (Alder Hey) provides primary, secondary and
97 tertiary care facilities for >200,000 children each year and has approximately 240 inpatient
98 beds; this study utilized data prior to the opening of a new hospital premises in October
99 2016. General medicine, general surgery, and a range of specialist services are provided.
100 There is also a large ED. Patients with a suspected or confirmed RVGE are admitted to a
101 room within the cubicle areas of one of the general medical wards. If no beds are available
102 in the general medical wards, cubicle areas in specialized medical wards or surgical wards
103 are used.

104 **Data sources**

105 Retrospective hospital database analysis (ClinicalTrials.gov NCT03271593) was conducted at
106 Alder Hey. Anonymised bed admission and laboratory data were extracted by the hospital
107 informatics department from routine patient databases. Patient data were extracted for the
108 period July 2000 – June 2015; analysis was restricted to the period July 2007 – June 2015
109 since changes were made to clinical coding in 2006, and bed availability data were only
110 available from February 2006 onwards.

111 **Study population and definitions**

112 We included all inpatients aged 0-14 years admitted between 1st July 2007 and 30th June
113 2015, who attended at least one ward other than the ED. Excluded from analysis were any
114 patients 15 years or older at time of admission, day patients, and those who were admitted
115 and discharged from the ED or observation unit without attending another ward.

116 Outcomes were calculated for four different patient groups identified through ICD-10
117 (International Classification of Disease, tenth edition) hospital discharge diagnosis codes:

- 1
2
3 118 • *All admissions*
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6 119 • *Any infection:* Admissions coded as any infection (ICD-10 A00-B99 and J09-J22 in any
7
8 120 diagnostic code) or as non-infectious gastroenteritis (K52.9).[14]
9
10
11 121 • *Acute gastroenteritis (AGE):* Admissions coded as acute gastroenteritis (ICD-10 A00-
12
13 122 A09 in any diagnostic code) or as non-infectious gastroenteritis (K52.9).[14]
14
15
16 123 • *Rotavirus gastroenteritis (RVGE):* Admissions coded as rotavirus gastroenteritis (ICD-
17
18 124 10 A08.0 in any diagnostic code) and/or laboratory-confirmed as rotavirus.[14]
19
20 125 Laboratory confirmation for RVGE was defined as rotavirus antigen detected by
21
22
23 126 either immunochromatographic test or by enzyme immunoassay in a faecal
24
25 127 specimen of a child with AGE. A distinction was made between community-acquired
26
27
28 128 (CA) and hospital-acquired (HA) RVGE: HA RVGE was defined as any patient with a
29
30 129 positive test for rotavirus infection with a sample date more than 2 days after
31
32
33 130 admission and no record of diarrhoea or vomiting on admission.[7] Testing for RVGE
34
35 131 was done on clinicians' request. The testing policy for RVGE did not change over the
36
37
38 132 study period.

39
40 133 Diagnosis coding for non-infectious gastroenteritis (ICD-10 K52.9) was included since
41
42 134 unspecified gastroenteritis was classified under this code until April 2012.[15]
43
44

45 135 The pre-vaccination period was defined as 1st July 2007 - 30th June 2013; the post
46
47 136 vaccination period was defined as 1st July 2013 – 30th June 2015. The rotavirus season was
48
49 137 defined as 1st January – 31st May; the period when laboratory detection rate in the UK is
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51
52 138 highest.[16]
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54 139 **Outcomes**

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57 140 The following outcomes were calculated:
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3 141 • *Bed occupancy*: number of patients allocated a bed on a specific ward divided by
4
5
6 142 number of available beds at that ward at 12.00 noon. Bed occupancy for any
7
8 143 infection, AGE and RVGE were determined using the definitions above. For HA-RVGE,
9
10 144 only bed occupancy on the ward where the patient tested positive for rotavirus was
11
12
13 145 included. For CA-RVGE, total hospital stay was attributed to rotavirus. Sensitivity
14
15 146 analyses were done with bed availability data collected at 9am and 5pm.
- 17
18 147 • *HA bloodstream infection rate*: number of HA bloodstream infections per 1,000
19
20 148 admissions with length of stay >2 days. We used indicator organisms to describe HA
21
22
23 149 infection: a HA bloodstream infection was defined as identification of methicillin-
24
25 150 sensitive *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* or
26
27
28 151 *Escherichia coli* or *Candida* species in a blood sample obtained >2 days after
29
30 152 admission.
- 32
33 153 • *Unplanned readmission*: number of patients with an emergency readmission within 7
34
35 154 days after discharge per 1,000 admissions.[8]
- 37
38 155 • *Outlier rate*: number of medical patients admitted to a surgical ward per 1,000
39
40 156 admissions. A medical patient was defined as any patient classified under
41
42 157 haematology/oncology, general paediatrics, endocrinology, nephrology,
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44
45 158 rheumatology, respiratory medicine, dermatology or accident & emergency.

47 159 Calculations of bed occupancy, HA infection rate, and unplanned readmission rate were
48
49 160 restricted to nine general medical wards. Several wards opened or closed during the study
50
51
52 161 period. Changes in ward structure were taken into account in the outcomes calculated by
53
54
55 162 including data according to the wards' opening periods.

163 **Descriptive analysis**

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3 164 Data analyses were performed using R version 3.2.0 (R Core Team, Vienna). The number of
4
5
6 165 admissions for each patient group, length of stay and age of RVGE patients was described
7
8 166 pre and post-vaccine introduction during the rotavirus season. Differences between
9
10 167 continuous variables were tested using Student's t-test or Wilcoxon rank-sum test if not
11
12
13 168 normally distributed and χ^2 -test or Fisher's exact test for categorical variables.

15 169 **Statistical analysis**

17
18 170 To assess the impact of rotavirus vaccine introduction on bed occupancy, interrupted time-
19
20 171 series analysis was used as previously described.[7] Monthly expected bed occupancy was
21
22
23 172 estimated by fitting a negative binomial regression model to pre-vaccine monthly bed
24
25 173 occupancy data, adjusted for seasonality and secular trends using calendar month and
26
27 174 rotavirus year (July to June), respectively. A negative binomial model was chosen to account
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29
30 175 for overdispersion in the data. This model was used to predict the expected bed occupancy
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32
33 176 rate in the absence of vaccination, where the impact of vaccination is expressed by the
34
35 177 difference between the expected and observed bed occupancy. To quantify change in
36
37 178 average bed occupancy in the rotavirus season as a result of introduction of the vaccine, a
38
39
40 179 second model included a binary indicator variable for the vaccine period, enabling the
41
42 180 computation of risk ratios (RR) and associated 95% confidence intervals (CI). This second
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44
45 181 model was restricted to the rotavirus season and adjusted for calendar month and rotavirus
46
47 182 year. Percentage change in average bed occupancy was calculated as $100(1 - RR)$.

49 183 **Ethics**

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51
52 184 Ethics approval was provided by the NHS Research Ethics Committee, North East –
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54 185 Newcastle & North Tyneside 2 and by the Alder Hey Children's NHS Foundation Trust
55
56
57 186 Research and Development Department.

187 **RESULTS**

188 In total, there were 116,871 admissions among 68,838 unique patients at any time in the
189 year during the study period from 1st July 2007 – 30th June 2015. Of those admissions,
190 48,852 occurred during the rotavirus season.

191 Testing for rotavirus remained stable throughout the pre-vaccination study period, with a
192 mean of 513 (standard deviation 36) admissions tested each rotavirus season, of which 138
193 (26.9%) were positive (Figure 1). In the rotavirus seasons following rotavirus vaccine
194 introduction, the proportion of rotavirus-positive test results amongst admissions tested
195 dropped to 3.8% (13/338) and 5.9% (16/272) in 2014 and 2015 respectively.

196 The median age of patients with RVGE was 11 months in the pre-vaccination period, and 22
197 months in the post-vaccination period ($p=0.06$). Median length of hospital stay for patients
198 with CA RVGE did not differ between the pre- and post-vaccination period (2.2 vs. 2.4 days,
199 $p=0.89$). Median length of stay from RVGE diagnosis to discharge for patients with HA RVGE
200 was not significantly different between the pre- and post-vaccination period (8.5 days pre
201 vs. 5.0 days post, $p=0.88$) (Figure 2).

202 Length of stay for all admissions was highest during the respiratory virus season in
203 November/December and slightly increased from 2007 to 2012 ($p<0.001$) (Supplementary
204 Figure 1). No significant change in length of stay for all admissions was observed for the
205 period 2012 to 2015 ($p=0.21$).

206 **Bed occupancy**

207 Figure 3 shows the average monthly bed occupancy for general medical wards for all
208 admissions, admissions with a diagnosis of any infection, and admissions with a diagnosis of
209 RVGE. Bed occupancy for AGE is shown in Supplementary Figure 2. Clear seasonal patterns
210 were observed for total bed occupancy, with highest overall bed occupancy for the

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3 211 respiratory virus season in November/December, and lowest overall bed occupancy in the
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6 212 summer months. A year-on-year increase was observed for overall bed occupancy over the
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8 213 study period ($p<0.001$), from 79% bed occupancy in December 2007 to 90% in December
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10 214 2014.

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12
13 215 Bed occupancy for RVGE showed clear seasonal peaks before introduction of the vaccine,
14
15 216 with highest occupancy shown for February/March. After introduction of the rotavirus
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17
18 217 vaccine, bed occupancy for RVGE in the rotavirus season was reduced by 89% (95%CI 73% –
19
20 218 95%) (Table 1). Bed occupancy for any infectious disease increased year on year in the pre-
21
22
23 219 vaccination period, both within and outside the rotavirus season ($p<0.001$ and $p<0.001$
24
25 220 respectively), as did bed occupancy for AGE ($p<0.001$ within, $p=0.04$ outside rotavirus
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27
28 221 season). Post introduction of the vaccine, observed bed occupancy for AGE in the rotavirus
29
30 222 season was reduced by 63% (95%CI 39% - 78%) after adjustment for the positive trend in
31
32
33 223 the pre-vaccination period. Observed bed occupancy for any infection in the rotavirus
34
35 224 season was reduced by 23% (95%CI 15% - 31%). No significant reduction was observed
36
37
38 225 when considering observed vs. expected bed occupancy for any cause of admission (decline
39
40 226 4%, 95%CI -1% - 9%). Sensitivity analyses with bed availability data taken at 9am and 5pm
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42 227 provided the similar results.
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228 **Table 1:** Average monthly bed occupancy and decline in bed occupancy comparing the pre-
 229 and post-rotavirus vaccination period for any admission, any infection, acute gastroenteritis
 230 and rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust,
 231 July 2007 – June 2015.

Variable	Average bed occupancy		Crude Risk ratio (95% CI)	Adjusted Risk ratio (95% CI) ¹	Decline in bed occupancy (95% CI)	P-value
	in rotavirus season (range)	(range)				
	Pre-vaccination n	Post-vaccination n				
All	77% (70% - 85%)	79% (67% - 87%)	1.03 (0.99 - 1.08)	0.96 (0.91 - 1.01)	4% (-1% - 9%)	0.15
Any infection ²	39% (25% - 56%)	42% (33% - 51%)	1.09 (0.95 - 1.25)	0.77 (0.69 - 0.85)	23% (15% - 31%)	<0.001
AGE ²	5% (1% - 16%)	3% (1% - 8%)	0.72 (0.45 - 1.13)	0.37 (0.22 - 0.61)	63% (39% - 78%)	<0.001
RVGE ³	5% (0% - 17%)	1% (0% - 4%)	0.18 (0.09 - 0.35)	0.11 (0.05 - 0.27)	89% (73% - 95%)	<0.001

232 AGE: acute gastroenteritis; CI: confidence interval; NHS: National Health Service; RVGE:
 233 rotavirus gastroenteritis.

234 ¹ Adjusted for seasonality and secular trend. ² Diagnosis of any infection and AGE by clinical

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3 235 coding only.³ Diagnosis of RVGE by clinical coding and laboratory results.
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8 237 **Hospital-acquired (HA) bloodstream infection rate**
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10 238 A decrease in HA bloodstream infection was observed in the post-vaccination period,
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12
13 239 although this did not appear different from secular trends in the pre-vaccination period
14
15 240 (Figure 4).
16

17
18 241 **Unplanned readmission rate**
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20 242 No difference was observed between the unplanned readmission rate in the pre-vaccination
21
22
23 243 period and the post-vaccination period (Figure 5).
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25 244 **Outlier rate**
26

27 245 Clear seasonal patterns were observed for the outlier rate, with the highest peak during the
28
29
30 246 respiratory virus season in November/December, and a secondary peak during the rotavirus
31
32 247 season in January-May (Figure 6). The outlier rate increased in 2012, and remained high
33
34
35 248 throughout 2013-2015, both within and outside the rotavirus season. The increase in outlier
36
37 249 rate is synchronous with the closure of one specific ward, a large general medical ward in
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39
40 250 November 2011, and the opening of a new medical admission unit (short-stay department
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42 251 prior to discharge or admission to other wards).
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DISCUSSION

This is the first study to examine the effects of national vaccine introduction on wider measures of hospital pressures in the UK. The introduction of rotavirus vaccine has led to a large reduction in RVGE hospitalisation,[7] reflected in the reduction in proportion of admissions tested rotavirus-positive and the reduction in bed occupancy due to RVGE and AGE as described here. Lower bed occupancy for RVGE and AGE in the rotavirus season post-vaccine introduction was concordant with lower bed occupancy for any infection in the rotavirus season in the post-vaccination period. Despite the reduction in RVGE hospitalisation, overall bed occupancy was not reduced. This suggests that a large, busy NHS Trust, such as Alder Hey, operates at full capacity and that the beds that became available by the reduction of RVGE hospitalisations were occupied by a different patient population, probably reflecting a previously unmet need and/or physicians having greater freedom to admit patients if beds have become available. The absence of a reduction in overall bed occupancy could explain why reductions in the other proxy measures (HA-infection rate, unplanned readmission rate, outlier rate) were not observed.

Two other studies have examined hospital pressures since rotavirus vaccination introduction. A study conducted in two Finnish hospitals concluded that bed occupancy for RVGE and AGE decreased since introduction of the vaccine.[17] There is no discussion of the impact of vaccine introduction on the total bed occupancy, or on other proxy measures for hospital pressures. A study conducted in a general hospital in Belgium (36 paediatric beds) concluded that bed-day occupancy, bed-day turnover and unplanned readmissions for AGE were lower in the post-vaccination compared with the pre-vaccination periods, and that this resulted in improved quality of care for overall admissions.[8] In our study, the reduction of bed occupancy for RVGE did not result in a change in overall bed occupancy or other

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2
3 276 measures of hospital pressure. No change in hospital length of stay for RVGE patients was
4
5
6 277 observed. Median hospital stay for CA RVGE was shorter in Alder Hey NHS Foundation Trust
7
8 278 than reported in the Belgian study (2.2 vs. 4.1 days), suggesting a difference in management
9
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11 279 of RVGE cases, and could be an indicator of higher hospital pressure and more rapid patient
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13 280 turnover in Alder Hey.

14
15 281 Several caveats need to be considered when using routinely collected data. Our analysis was
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17
18 282 complicated by changes in hospital practises, in particular changes in patient flow,
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20
21 283 laboratory procedures, infection control and clinical coding. Firstly, several wards relevant
22
23 284 to this study opened or closed during the study period. Although ward closures were
24
25 285 accounted for in the bed occupancy analysis, more subtle changes in patient dynamics still
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27
28 286 influenced our results. A steep increase was observed for the outlier rate in 2012, with the
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30
31 287 higher level sustained throughout 2013-2015. The increase in outlier rate is synchronous
32
33 288 with the closure of a large general medical ward in November 2011, and the opening of a
34
35 289 new medical admission. It is possible that the change in ward structure led to an increased
36
37
38 290 bed usage in surgical and specialised medical wards.

39
40 291 Secondly, several changes in laboratory procedures were observed during the study period,
41
42
43 292 most notably the introduction of polymerase chain reaction for the rapid testing of
44
45 293 respiratory pathogens in 2013. Faster diagnosis of respiratory infection could have had
46
47
48 294 implications for patient treatment, isolation practices and patient flow, and could have
49
50 295 influenced the measured hospital pressure outcomes. The number of admissions tested for
51
52 296 rotavirus did not change significantly over the study period, which provides confidence that
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54
55 297 the drop in RVGE in the post-vaccine era is a real effect, and not caused by a change in
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57 298 testing policy.
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3 299 Thirdly, there were changes in infection prevention and control (IPC) practices in later years
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6 300 of the study, including an increase in IPC staff; the introduction of isolation and hand
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8 301 hygiene posters, bed space dividers screens and infection control enclosure isolation pods;
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10 302 and changes in environmental cleaning. Changes in IPC practices will most likely have
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13 303 resulted in changes in HA infection rates – it is difficult to disentangle their effect on HA
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15 304 infection from any effect due to a reduction in hospital pressures post-rotavirus vaccination
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17
18 305 introduction.

19
20 306 We observed that bed occupancy for any infectious disease increased in the pre-vaccination
21
22
23 307 period, both within and outside the rotavirus season. An increase in bed occupancy for any
24
25 308 respiratory infection (supplementary Figure 3) and any gastroenteritis was observed, but
26
27
28 309 neither increase can fully account for the overall increase in any infection. It is possible that
29
30 310 the increase in infection observed is due to an artefact of the recording of the data.

31
32
33 311 Supplementary Figure 4 shows that all clinical diagnostic coding increased over the study
34
35 312 period. Clinical diagnostic coding increased for both cases with and without any infection
36
37
38 313 recorded. We observed that bed occupancy for any infection in the rotavirus season was
39
40 314 lower than the expected bed occupancy for any infection based on pre-vaccination
41
42 315 estimates. The increase in any clinical diagnostic coding was sustained in 2014 and 2015,
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44
45 316 providing confidence that our observation of lower than expected bed occupancy for any
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47 317 infection in the post-vaccination period is a true finding.

48
49 318 Our analysis highlights the importance of the presentation of data from the full study period
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52 319 in a time-series analysis, rather than restricting the results to a “before-after” comparison,
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54
55 320 when there is non-homogeneity in disease management, hospital management and data
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57 321 collection over time. A long-term increase in bed occupancy for any infection could be
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59 322 observed (possibly due to an increase in clinical coding) that predated the introduction of
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3 323 vaccination: taking this ongoing increase in admissions coded as infection into account, a
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6 324 reduction in bed occupancy for any infection can be observed.
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8 325 Routinely collected hospital data can be used for the evaluation of a (vaccination) policy, but
9
10 326 our study highlights the difficulty of evaluating a (vaccination) policy in a period with
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12
13 327 concurrent changes in patient flow, laboratory procedures and IPC practices.
14

15 328 The introduction of rotavirus vaccination has led to a dramatic reduction in hospitalisation
16
17 329 for RVGE and thus a reduction in bed occupancy for RVGE. However, overall bed occupancy
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19
20 330 was not reduced further highlighting the severe strain the NHS is under and that demand is
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22
23 331 outstripping capacity. Bed occupancy continues to rise and even a highly effective routine
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25 332 vaccine only freed-up beds which were then filled by admissions, making no overall
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28 333 headway into reducing the overall pressures the NHS is facing.
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5
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7

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9
10 338 stages of study conduct. GlaxoSmithKline Biologicals SA also took in charge all costs
11
12
13 339 associated with the development and publication of this manuscript.
14

15 340 **Conflicts of interest**
16

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18
19 341 Rotarix is a trademark of the GSK group of companies.
20
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22
23 342 NC, NF, and DH are in receipt of research grant support from the GSK group of companies
24

25 343 for the conduct of the present study. NC has received honoraria for participation in GSK
26

27 344 Rotavirus Vaccine Advisory Board Meetings from the GSK group of companies and from
28

29
30 345 Watermark Research Partners for participation in independent data monitoring committee
31

32 346 of GSK-sponsored clinical trials of Rotavirus vaccine. NC and NF's institution received grant
33

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35

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37

38 349 Merck & Co., Inc. (Kenilworth, NJ USA) outside the submitted work. NBZ reports grants from
39

40 350 the GSK group of companies and from Takeda Pharmaceuticals outside the submitted work.
41

42 351 BS and ET are employees of the GSK group of companies. EH, RC, MC and JC have nothing to
43

44
45 352 disclose.
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50 353 **Authorship and manuscript preparation**
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52
53
54 354 DH, RPDC, MC, NC, NF designed the study and wrote the protocol. EH performed the
55

56 355 analyses and wrote the manuscript. JSC and MC provided data for the study. NBZ provided
57

58 356 statistical support. DH, RPDC, MC, JSC, NBZ, NF, NAC provided advice on the understanding
59
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3 357 of the findings. ET and BS provided external advice. All authors approved the final version of
4
5
6 358 the paper for submission.

7
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11
12
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17
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19
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21 22 23 365 **Data sharing**

24
25 366 The results summary for this study (GSK study identifier: 205369 - ClinicalTrials.gov
26
27 367 identifier: NCT03271593) is available on the GSK Clinical Study Register and can be accessed
28
29
30 368 at www.gsk-clinicalstudyregister.com.

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46 410 the national rotavirus vaccination program with RotaTeq(R). *BMC Health Serv Res*
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3 414 **Figures Captions**
4

5 415 **Figure 1. Number of admissions tested for rotavirus in the rotavirus season in Alder Hey**
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8 416 **NHS Foundation Trust, July 2007 – June 2015.**

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10 417 *NHS: National Health Service.*
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12
13 418 **Figure 2. Total length of stay for CA and HA RVGE.**

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15 419 For HA RVGE, length of stay was calculated from date of first positive test.

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17 420 *CA: community-acquired; HA: hospital-acquired.*
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20 421 **Figure 3. Observed and expected bed occupancy for any admission, any infection and**
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22
23 422 **rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust,**
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25 423 **July 2007 – June 2015.**

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27 424 The coloured shading represents the 95% confidence intervals for the expected incidence.

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29 425 Grey shading represents the rotavirus season (January-May). The vertical hashed line

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31 426 represents the introduction of rotavirus vaccine in the UK in July 2013.

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33 427 *NHS: National Health Service.*
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37 428 **Figure 4. Hospital acquired bloodstream infection rate on general medical wards in Alder**
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39 429 **Hey NHS Foundation Trust, July 2007 – June 2015.**

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41 430 Black line shows raw data, red line shows smoothed data. Grey shading represents the

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43 431 rotavirus season (January-May). The vertical hashed line represents the introduction of

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45 432 rotavirus vaccine in the UK in July 2013.

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47 433 *HA: hospital-acquired; NHS: National Health Service.*
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50 434 **Figure 5. Unplanned readmission rate for any admission on general medical wards in Alder**
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53 435 **Hey NHS Foundation Trust, July 2007 – June 2015.**

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55 436 Raw data in black, smoothed data in red. Grey shading represents the rotavirus season

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57 437 (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in
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3 438 the UK in July 2013.
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6 439 *NHS: National Health Service.*
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8 440 **Figure 6. Outlier rate for any admission in Alder Hey NHS Foundation Trust, July 2007 –**
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10 441 **June 2015.**
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13 442 Raw data in black, smoothed data in red. Grey shading represents the rotavirus season
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15 443 (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in
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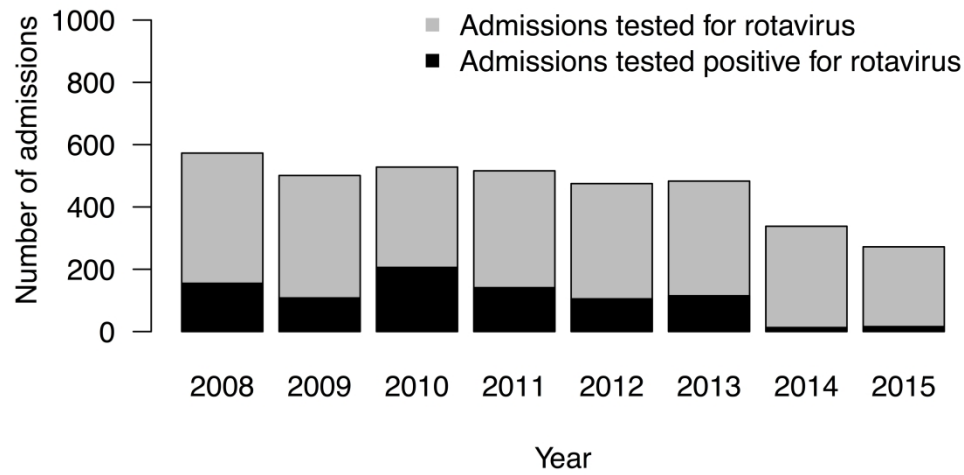


Figure 1. Number of admissions tested for rotavirus in the rotavirus season in Alder Hey NHS Foundation Trust, July 2007 – June 2015. NHS: National Health Service.

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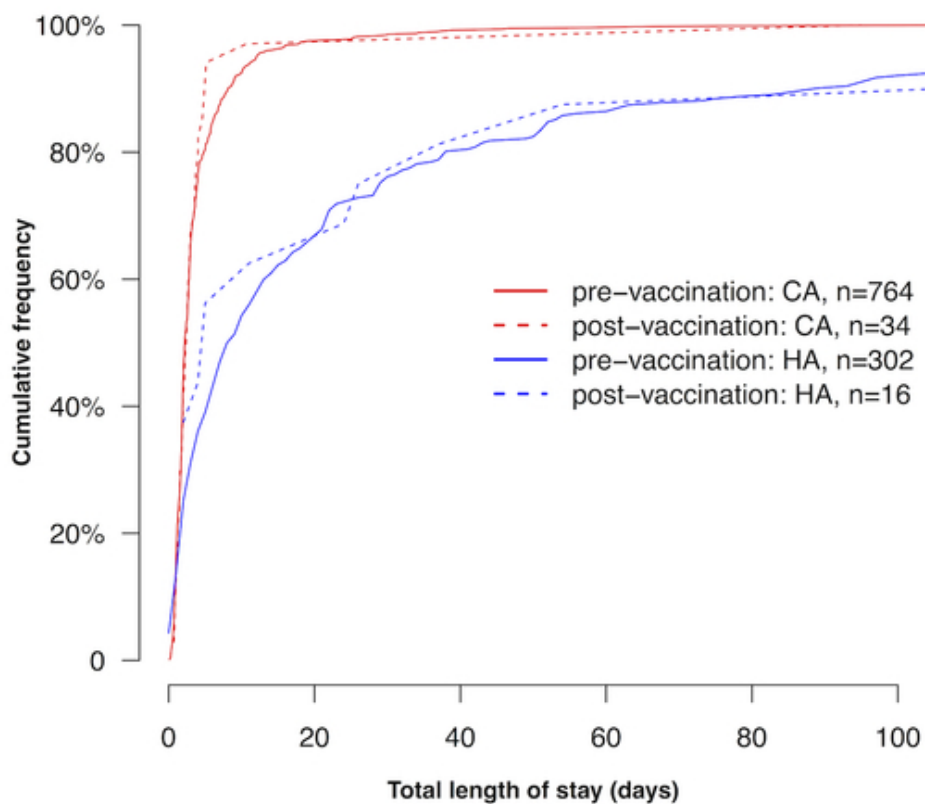


Figure 2. Total length of stay for CA and HA RVGE.

For HA RVGE, length of stay was calculated from date of first positive test.
CA: community-acquired; HA: hospital-acquired.

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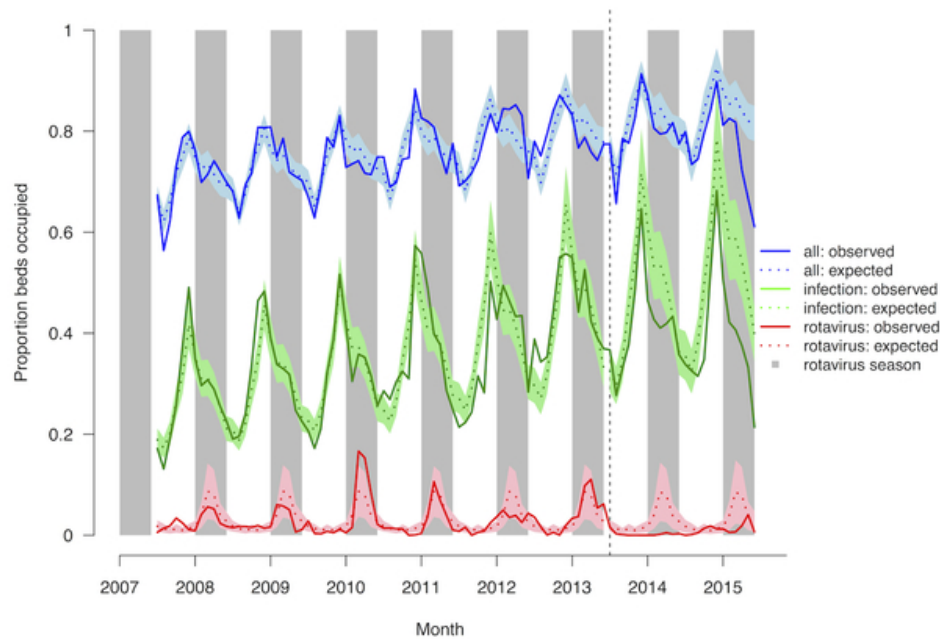


Figure 3. Observed and expected bed occupancy for any admission, any infection and rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

The coloured shading represents the 95% confidence intervals for the expected incidence. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

NHS: National Health Service.

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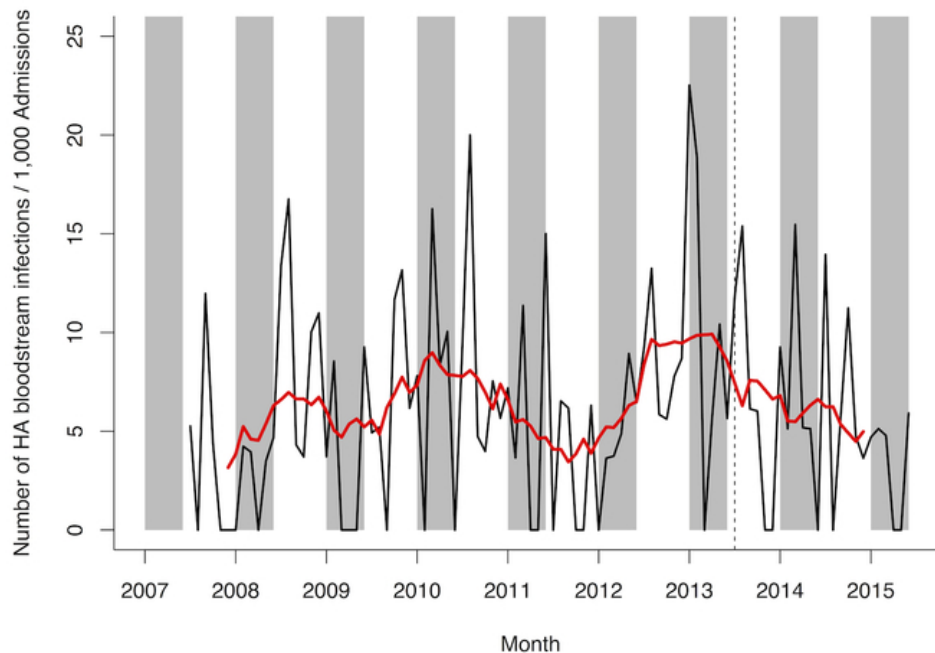


Figure 4. Hospital acquired bloodstream infection rate on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

Black line shows raw data, red line shows smoothed data. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

HA: hospital-acquired; NHS: National Health Service.

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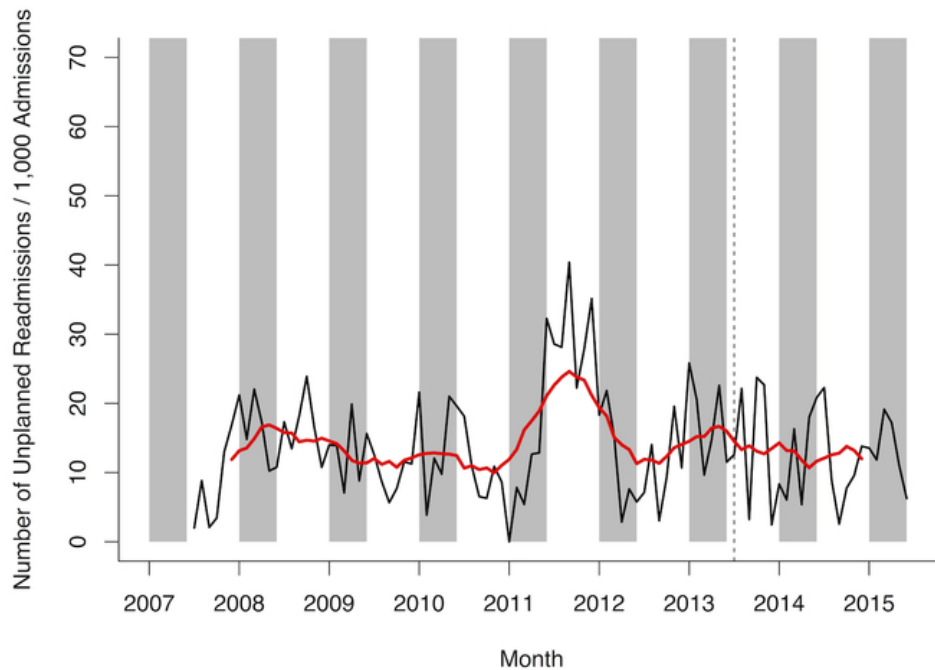


Figure 5. Unplanned readmission rate for any admission on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

Raw data in black, smoothed data in red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

NHS: National Health Service.

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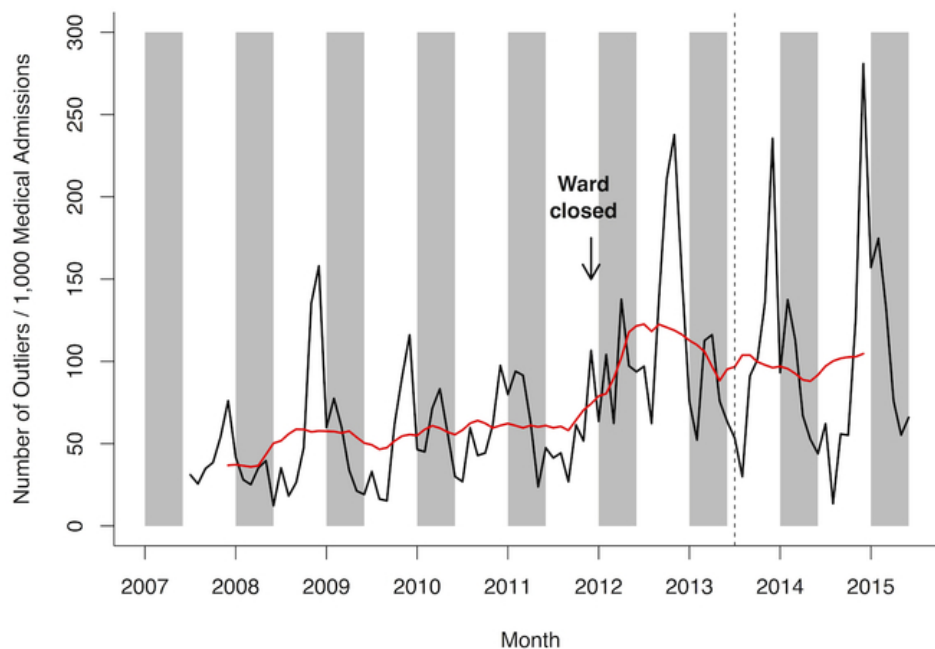


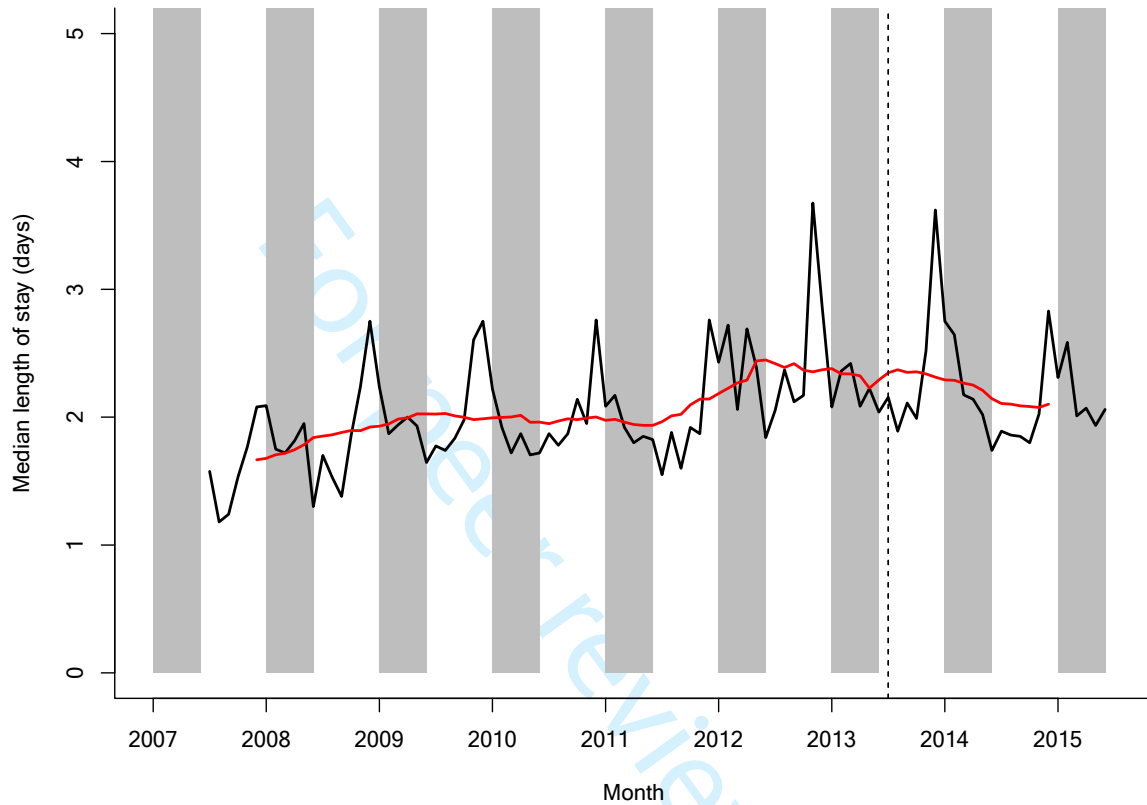
Figure 6. Outlier rate for any admission in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

Raw data in black, smoothed data in red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

NHS: National Health Service.

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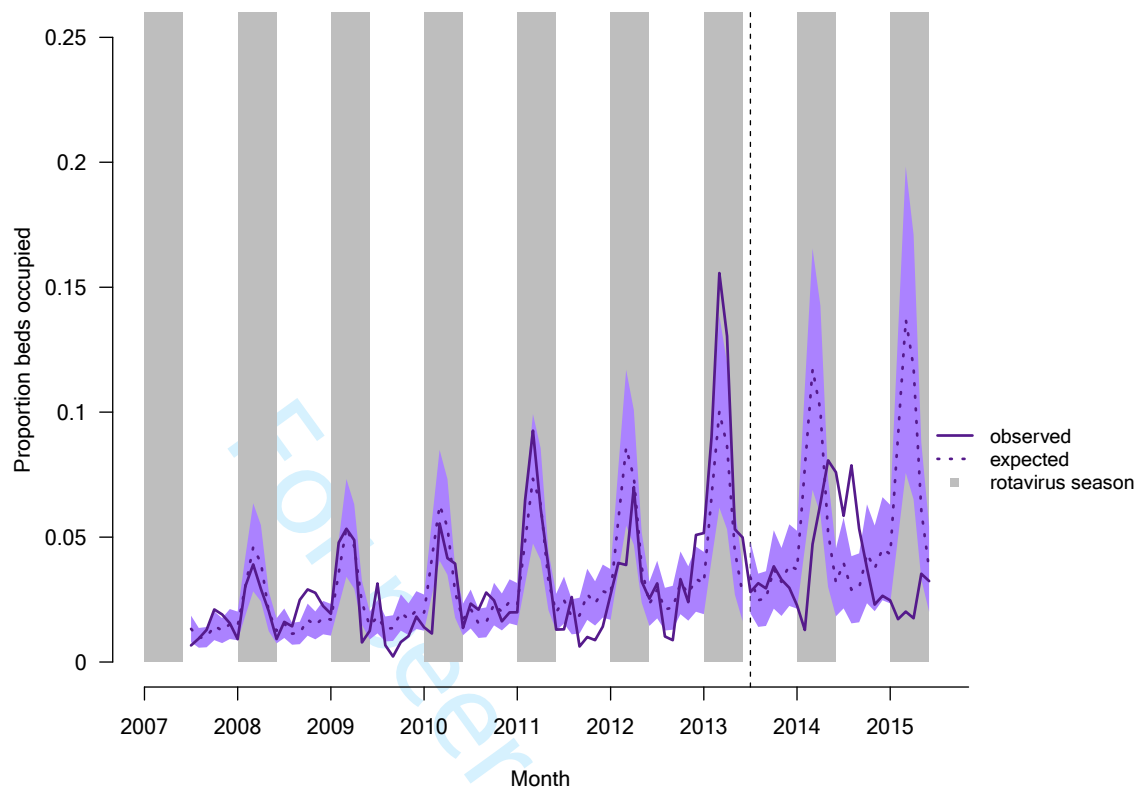
1 Supplementary Material



2

3 **Supplementary Figure 1. Median length of stay (all admissions) on general medical wards in Alder**
 4 **Hey Children's NHS Foundation Trust, July 2007 – June 2015.** Raw data in black, smoothed data in
 5 red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents
 6 the introduction of rotavirus vaccine in the UK in July 2013.

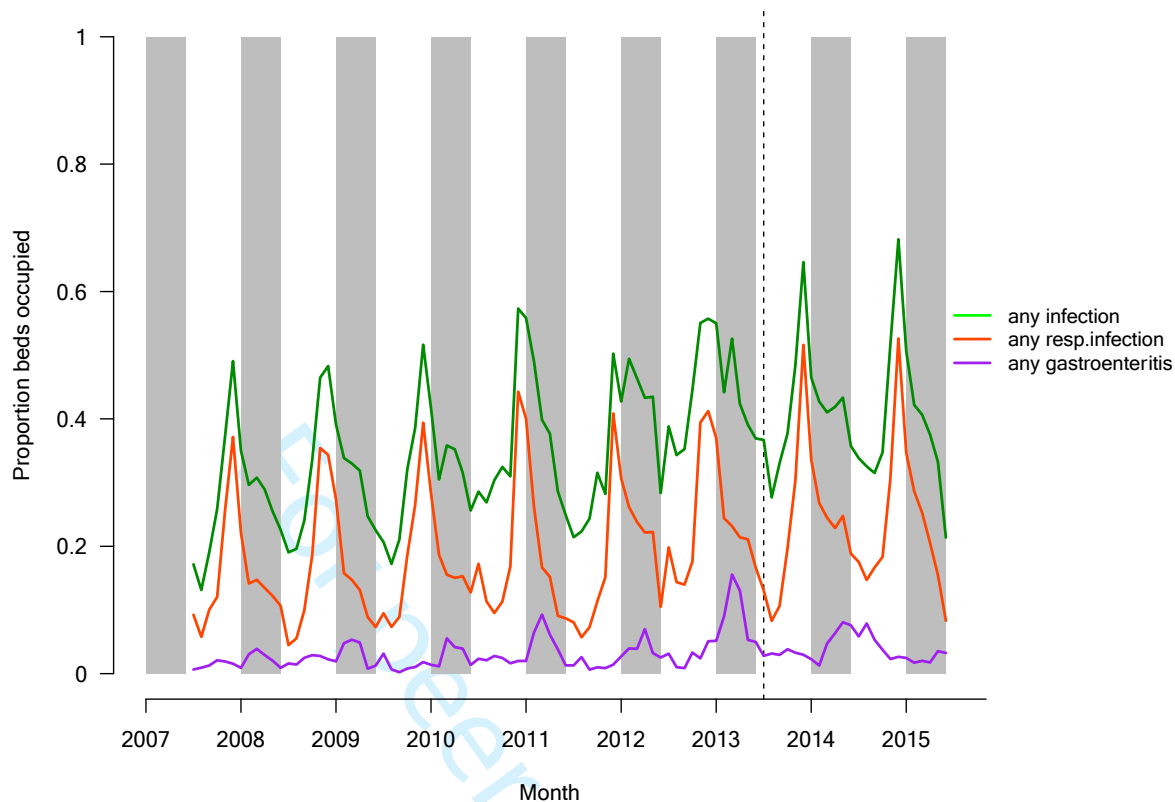
7 *NHS: National Health Service.*



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2 **Supplementary Figure 2. Observed and expected bed occupancy for acute gastroenteritis on**
 3 **general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.** The coloured
 4 shading represents the 95% confidence intervals for the expected incidence. Grey shading
 5 represents the rotavirus season (January-May). The vertical hashed line represents the introduction
 6 of rotavirus vaccine in the UK in July 2013.

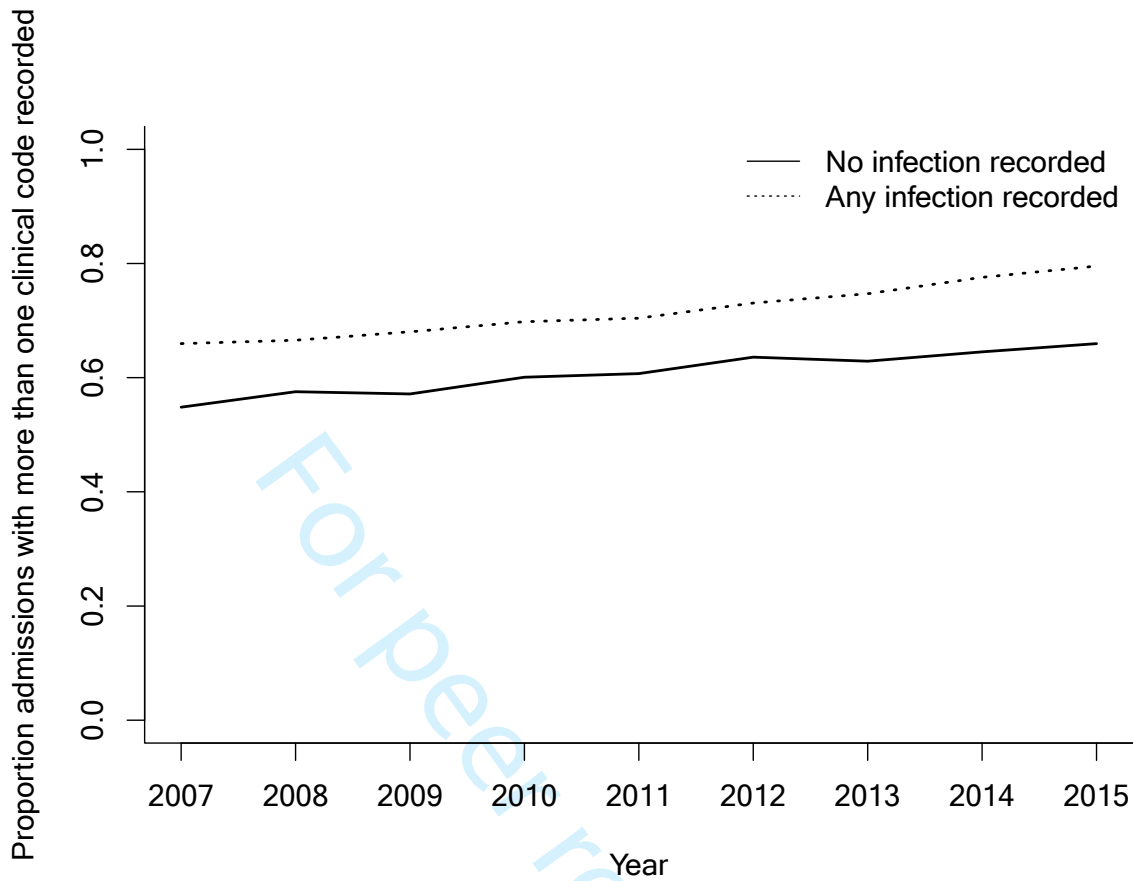
7 *NHS: National Health Service.*



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2 **Supplementary Figure 3. Observed bed occupancy for any infection, any respiratory infection and**
 3 **any gastroenteritis (by clinical coding only) in general medical wards in Alder Hey NHS Foundation**
 4 **Trust, July 2007 – June 2015.** The vertical hashed line represents the introduction of rotavirus
 5 vaccine in the UK in July 2013.

6 *NHS: National Health Service; resp.: respiratory.*



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2 **Supplementary Figure 4. Proportion of admissions to general medical wards for whom more than**
 3 **one clinical code was recorded, Alder Hey NHS Foundation Trust, July 2007 – June 2015**

4 *NHS: National Health Service.*

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Checklist
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	Included “Retrospective hospital database analysis” in abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Included
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Included
Objectives	3	State specific objectives, including any prespecified hypotheses	Included “The aim of this study was to assess hospital pressures at a large UK NHS paediatric hospital pre- and post- rotavirus vaccine introduction using routinely collected data.”
Methods			
Study design	4	Present key elements of study design early in the paper	Included in paragraph ‘data sources’
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Included in paragraph ‘setting’
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Inclusion and exclusion criteria included in paragraph ‘study population and definitions’
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Not applicable for this observational study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Included in paragraphs ‘study population and definitions’ and ‘outcomes’
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment	Included in paragraph ‘data sources’.

measurement		(measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	- 2007 onwards data only included to account for changes in clinical coding (included in paragraph 'data sources') - inclusion of diagnosis coding for non-infectious gastroenteritis (included in paragraph 'study population and definitions')
Study size	10	Explain how the study size was arrived at	Sampling not applicable: this observational study included <i>all</i> patients aged 0-14 years
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Included in paragraphs 'outcomes' and 'statistical analysis'.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Included in paragraphs 'outcomes' and 'statistical analysis'.
		(b) Describe any methods used to examine subgroups and interactions	Included in paragraphs 'outcomes' and 'statistical analysis'.
		(c) Explain how missing data were addressed	Not applicable for hospital database analysis
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	Not applicable for observational study
		(e) Describe any sensitivity analyses	Not applicable

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Included in first paragraph of results
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Median age of participants included. Median length of stay of participants included
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Not applicable
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not applicable
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Not applicable
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Unadjusted estimates included in figures 1-6. Adjusted analysis for bed occupancy included in Table 1.
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Risk ratio translated in decline in bed occupancy in Table 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	- Analysis of clinical coding included in Supplementary figure 4 - Analysis of bed occupancy for infection included in Supplementary figure 3.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Included in first paragraph discussion and conclusions
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Included in discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	Included in discussion

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		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	Included in discussion
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Included in Funding Statement

9
10 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

11
12 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE
13 checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
14 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.
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BMJ Open

Do hospital pressures change following rotavirus vaccine introduction? A retrospective database analysis in a large paediatric hospital in the United Kingdom.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027739.R1
Article Type:	Research
Date Submitted by the Author:	21-Jan-2019
Complete List of Authors:	Heinsbroek, Ellen; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health Hungerford, Daniel; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Public Health England, Field Service – North West, National Infection Service Cooke, Richard; Alder Hey Children's NHS Foundation Trust Chowdhury, Margaret; Alder Hey Children's NHS Foundation Trust Cargill, James; Alder Hey Children's NHS Foundation Trust Bar-Zeev, Naor; Johns Hopkins University Bloomberg School of Public Health, International Vaccine Access Center French, Neil; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health Theodorou, Eleni; GSK Pharma, Health Economics Standaert, Baudouin; GSK Vaccines, Health Economics; a, Cunliffe, Nigel; University of Liverpool, Department of Clinical Infection, Microbiology & Immunology, Institute of Infection and Global Health; Alder Hey Children's NHS Foundation Trust
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Epidemiology, Infectious diseases, Paediatrics, Medical management, Gastroenterology and hepatology
Keywords:	Paediatric infectious disease & immunisation < PAEDIATRICS, nosocomial infections, Hospital, Epidemiology < INFECTIOUS DISEASES, Rotavirus, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

1 **1 Do hospital pressures change following rotavirus vaccine introduction? A retrospective**
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4 **2 database analysis in a large paediatric hospital in the United Kingdom.**

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6 3 Ellen Heinsbroek^a; Daniel Hungerford^a; Richard PD Cooke^b; Margaret Chowdhury^c; James S
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8 4 Cargill^b; Naor Bar-Zeev^a; Neil French^a; Eleni Theodorou^d; Baudouin Standaert^e; Nigel A
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47
48 20 **Abbreviated title:** Hospital pressures post rotavirus vaccination

49
50 21 **Word count:** 3248

51
52 **22 ABSTRACT**

53
54
55 23 **Objective** Hospitals in the United Kingdom are under increasing clinical and financial
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57 24 pressures. Post introduction of childhood rotavirus vaccination in the UK in 2013, rotavirus
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59 25 gastroenteritis (RVGE) hospitalisations reduced significantly. We evaluated changes in

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26 'hospital pressures' (demand on healthcare resources and staff) following rotavirus vaccine
27 introduction in a paediatric setting in the UK.

28 **Design** Retrospective hospital database analysis between July 2007 and June 2015.

29 **Setting** A large paediatric hospital providing primary, secondary and tertiary care in
30 Merseyside, UK.

31 **Participants** Hospital admissions aged < 15 years. Outcomes were calculated for four
32 different patient groups identified through diagnosis coding (ICD-10) and/or laboratory
33 confirmation: all admissions; any infection, acute gastroenteritis; and RVGE.

34 **Methods** Hospital pressures were compared before and after rotavirus vaccine
35 introduction: these included bed occupancy, hospital-acquired infection rate, unplanned
36 readmission rate, and outlier rate (medical patients admitted to surgical wards due to lack
37 of medical beds). Interrupted time-series analysis was used to evaluate changes in bed
38 occupancy.

39 **Results** There were 116,871 admissions during the study period. Lower bed occupancy in
40 the rotavirus season in the post-vaccination period was observed for RVGE (-89%, 95%CI
41 73%,95%), acute gastroenteritis (-63%, 95%CI 39%,78%) and any infection (-23%, 95%CI
42 15%,31%). No significant overall reduction in bed occupancy was observed (-4%, 95%CI -
43 1%,9%). No changes were observed for the other outcomes.

44 **Conclusions** Rotavirus vaccine introduction was not associated with reduced hospital
45 pressures. A reduction in RVGE hospitalisation without change in overall bed occupancy
46 suggests that beds available were used for a different patient population, possibly reflecting
47 a previously unmet need.

48 **Clinical trials identifier** ClinicalTrials.gov NCT03271593

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2 50 **'Strengths and limitations of this study'**

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4 51 • This study used 8 years of retrospective routinely collected data from a large
5
6 52 paediatric hospital in the United Kingdom.
7
8 53 • This is the first study to examine the effects of a vaccine on wider measures of
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10 54 hospital pressures in the United Kingdom.
11
12 55 • Our analysis highlights the importance of the presentation of data from the full study
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14 56 period in a time series analysis, rather than restricting the results to a "before-after"
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16 57 comparison.
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18 58 • Our analysis was complicated by inevitable changes in hospital practices over the 8-
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20 59 year study period, in particular changes in patient flow, laboratory procedures,
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22 60 infection control and clinical coding.
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61 INTRODUCTION

62 In the context of increasing patient need and constrained resources, the United Kingdom's
63 (UK) National Health Service (NHS) faces growing clinical and financial pressures. Currently,
64 the NHS is failing to meet targets for urgent, emergency and planned care.[1, 2] Hospital
65 admission rates have been increasing for the past decade; if the increases continue at the
66 current rate an extra 22 hospitals with 800 beds each will be required by 2022.[3] Although
67 highest for the elderly, increases in admission rates are occurring across all age groups.[3] In
68 children aged 0-14 years, the number of hospital admission episodes increased from 1.7 to
69 2.0 million between 2004-05 and 2014-15 [4] and emergency department (ED) attendances
70 have risen by approximately 300,000 between 2011-12 and 2014-15,[5] leaving paediatric
71 services with increased demand but a short fall of medical staffing.[6]

72 While the problems the NHS faces are complex, there are ongoing disease prevention
73 mechanisms which can help alleviate some of the burden. Vaccines for example, are the
74 most effective defence against infectious diseases.[7] For highly efficacious vaccines
75 targeting childhood diseases with a large hospitalisation burden, it is possible that the
76 reduction in beds occupied for infections caused by the vaccine target pathogen reduces
77 hospital pressures, and potentially nosocomial infections.[8, 9]

78 Prior to vaccine introduction in the UK, rotavirus gastroenteritis (RVGE) was a major cause
79 of hospital admission in young children during the winter/spring months. It was estimated
80 that in children less than 5 years of age, 20% of ED attendances and 45% of hospitalisations
81 for acute gastroenteritis (AGE) were due to rotavirus infections.[10] The UK introduced the
82 monovalent two-dose rotavirus vaccination (*Rotarix*, GSK) into the routine childhood
83 immunisation schedule in July 2013. Rotavirus vaccine uptake increased rapidly to over 90%
84 for one dose [11] and early vaccine impact studies suggest a significantly reduced incidence
85 of RVGE hospitalisations in children.[7, 12, 13] The aim of this study was to assess hospital

1 86 pressures at a large UK NHS paediatric hospital pre- and post- rotavirus vaccine introduction
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4 87 using routinely collected data. As there are no direct measures of hospital clinical pressures
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6 88 (on healthcare resources and staff), evidenced proxy indicators were used: bed occupancy,
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9 89 hospital-acquired infection rate, unplanned readmission rate, and rate of outliers (medical
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11 90 patients admitted to surgical wards).
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For peer review only

92 **METHODS**

93 **Setting**

94 Alder Hey Children's NHS foundation Trust (Alder Hey) is located in Liverpool, UK and is one
95 of the largest paediatric hospitals in Europe, with a catchment population of over 7.1
96 million. Alder Hey provides primary, secondary and tertiary care facilities for >200,000
97 children each year and has approximately 240 inpatient beds; this study utilized data prior
98 to the opening of a new hospital premises in October 2016. General medicine, general
99 surgery, and a range of specialist services are provided. There is also a large ED. Patients
100 with a suspected or confirmed RVGE are admitted to a room within the cubicle areas of one
101 of the general medical wards. If no beds are available in the general medical wards, cubicle
102 areas in specialized medical wards or surgical wards are used.

103 **Data sources**

104 Retrospective hospital database analysis (ClinicalTrials.gov NCT03271593) was conducted at
105 Alder Hey. Anonymised bed admission and laboratory data were extracted by the hospital
106 informatics department from routine patient databases. Patient data were extracted for the
107 period July 2000 – June 2015; analysis was restricted to the period July 2007 – June 2015
108 since changes were made to clinical coding in 2006, and bed availability data were only
109 available from February 2006 onwards.

110 **Study population and definitions**

111 We included all inpatients aged 0-14 years admitted between 1st July 2007 and 30th June
112 2015, who attended at least one ward other than the ED. Excluded from analysis were any
113 patients 15 years or older at time of admission, day patients, and those who were admitted
114 and discharged from the ED or observation unit without attending another ward.

115 Outcomes were calculated for four different patient groups identified through ICD-10
116 (International Classification of Disease, tenth edition) hospital discharge diagnosis codes:

- 1 117 • *All admissions*
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- 4 118 • *Any infection:* Admissions coded as any infection (ICD-10 A00-B99 and J09-J22 in any
- 5
- 6 119 diagnostic code) or as non-infectious gastroenteritis (K52.9).[14]
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- 9 120 • *Acute gastroenteritis (AGE):* Admissions coded as acute gastroenteritis (ICD-10 A00-
- 10
- 11 121 A09 in any diagnostic code) or as non-infectious gastroenteritis (K52.9).[14]
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- 14 122 • *Rotavirus gastroenteritis (RVGE):* Admissions coded as rotavirus gastroenteritis (ICD-
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- 16 123 10 A08.0 in any diagnostic code) and/or laboratory-confirmed as rotavirus.[14]
- 17
- 18 Laboratory confirmation for RVGE was defined as rotavirus antigen detected by
- 19 124
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- 21 125 either immunochromatographic test or by enzyme immunoassay in a faecal
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- 23
- 24 126 specimen of a child with AGE. A distinction was made between community-acquired
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- 26 127 (CA) and hospital-acquired (HA) RVGE: HA RVGE was defined as any patient with a
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- 28 128 positive test for rotavirus infection with a sample date more than 2 days after
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- 30
- 31 129 admission and no record of diarrhoea or vomiting on admission.[7] Testing for RVGE
- 32
- 33 130 was done on clinicians' request. The testing policy for RVGE did not change over the
- 34
- 35
- 36 131 study period.

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38 132 Diagnosis coding for non-infectious gastroenteritis (ICD-10 K52.9) was included since

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41 133 unspecified gastroenteritis was classified under this code until April 2012.[15]

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43 134 The pre-vaccination period was defined as 1st July 2007 - 30th June 2013; the post

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45 135 vaccination period was defined as 1st July 2013 – 30th June 2015. The rotavirus season was

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48 136 defined as 1st January – 31st May; the period when laboratory detection rate in the UK is

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50 137 highest.[16]

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52 138 **Outcomes**

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55 139 The following outcomes were calculated:

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- 1
2 140 • *Bed occupancy*: number of patients allocated a bed on a specific ward divided by
3
4 141 number of available beds at that ward at 12.00 noon. Bed occupancy for any
5
6 142 infection, AGE and RVGE were determined using the definitions above. For HA-RVGE,
7
8 143 only bed occupancy on the ward where the patient tested positive for rotavirus was
9
10 144 included. For CA-RVGE, total hospital stay was attributed to rotavirus. Sensitivity
11
12 145 analyses were done with bed availability data collected at 9am and 5pm.
13
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16 146 • *HA bloodstream infection rate*: number of HA bloodstream infections per 1,000
17
18 147 admissions with length of stay >2 days. We used indicator organisms to describe HA
19
20 148 infection: a HA bloodstream infection was defined as identification of methicillin-
21
22 149 sensitive *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* or
23
24 150 *Escherichia coli* or *Candida* species in a blood sample obtained >2 days after
25
26 151 admission. HA Bloodstream infection rate was used as an outcome measure since, as
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28 152 for other outcome measures such as HA rotavirus, this may be an indicator of how
29
30 153 changes in hospital pressures could influence infection control practices and
31
32 154 subsequent nosocomial transmission.
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38 155 • *Unplanned readmission*: number of patients with an emergency readmission within 7
39
40 156 days after discharge per 1,000 admissions.[8]
41
42
43 157 • *Outlier rate*: number of medical patients admitted to a surgical ward per 1,000
44
45 158 admissions. A medical patient was defined as any patient classified under
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47 159 haematology/oncology, general paediatrics, endocrinology, nephrology,
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49 160 rheumatology, respiratory medicine, dermatology or accident & emergency.
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53 161 Calculations of bed occupancy, HA infection rate, and unplanned readmission rate were
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55 162 restricted to nine general medical wards. Several wards opened or closed during the study
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1 163 period. Changes in ward structure were taken into account in the outcomes calculated by
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4 164 including data according to the wards' opening periods.

6 165 **Descriptive analysis**

8 166 Data analyses were performed using R version 3.2.0 (R Core Team, Vienna). The number of
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10
11 167 admissions for each patient group, length of stay and age of RVGE patients was described
12
13 168 pre and post-vaccine introduction during the rotavirus season. Differences between
14
15
16 169 continuous variables were tested using Student's t-test or Wilcoxon rank-sum test if not
17
18 170 normally distributed and χ^2 -test or Fisher's exact test for categorical variables.

21 171 **Statistical analysis**

23 172 To assess any changes in bed occupancy following rotavirus vaccine introduction,
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26 173 interrupted time-series analysis was used as previously described.[7] Monthly expected bed
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28 174 occupancy was estimated by fitting a negative binomial regression model to pre-vaccine
29
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31 175 monthly bed occupancy data, adjusted for seasonality and secular trends using calendar
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33 176 month and rotavirus year (July to June), respectively. A negative binomial model was chosen
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35
36 177 to account for overdispersion in the data. This model was used to predict the expected bed
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38 178 occupancy rate in the absence of vaccination, where the post-vaccine introduction change is
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41 179 expressed by the difference between the expected and observed bed occupancy. To
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43 180 quantify change in average bed occupancy in the rotavirus season as a result of introduction
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45 181 of the vaccine, a second model included a binary indicator variable for the vaccine period,
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47
48 182 enabling the computation of risk ratios (RR) and associated 95% confidence intervals (CI).
49
50 183 This second model was restricted to the rotavirus season and adjusted for calendar month
51
52
53 184 and rotavirus year. Percentage change in average bed occupancy was calculated as $100(1 -$
54
55 185 $RR)$.

57 186 **Ethics**

1 187 Ethics approval was provided by the NHS Research Ethics Committee, North East –
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3
4 188 Newcastle & North Tyneside 2 and by the Alder Hey Children’s NHS Foundation Trust
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6 189 Research and Development Department.
7

8 190 **Patient and public involvement statement**

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11 191 This study was conducted using secondary data and there was no new contact with patients
12
13 192 throughout the study. No patients were directly involved in designing the research question,
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16 193 conducting the research or interpretation of the research findings. Investigators have
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18 194 presented these findings at national and international events
19

20 21 **RESULTS**

22
23 196 In total, there were 116,871 admissions among 68,838 unique patients at any time in the
24
25 197 year during the study period from 1st July 2007 – 30th June 2015. Of those admissions,
26
27
28 198 48,852 occurred during the rotavirus season.
29

30 199 Testing for rotavirus remained stable throughout the pre-vaccination study period, with a
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32
33 200 median of 509 (IQR=481-539) admissions tested each rotavirus season, of which a median of
34
35 201 128 (25.2%) were positive (Figure 1). In the rotavirus seasons following rotavirus vaccine
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37
38 202 introduction, the proportion of rotavirus-positive test results amongst admissions tested
39
40 203 dropped to 3.8% (13/338) and 5.9% (16/272) in 2014 and 2015 respectively.
41

42
43 204 The median age of patients with RVGE was 11 months in the pre-vaccination period, and 22
44
45 205 months in the post-vaccination period ($p=0.06$). Median length of hospital stay for patients
46
47 206 with CA RVGE did not differ between the pre- and post-vaccination period (2.2 vs. 2.4 days,
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49
50 207 $p=0.89$). Median length of stay from RVGE diagnosis to discharge for patients with HA RVGE
51
52 208 was not significantly different between the pre- and post-vaccination period (8.5 days pre
53
54 209 vs. 5.0 days post, $p=0.88$) (Figure 2).
55

56
57 210 Length of stay for all admissions was highest during the respiratory virus season in
58
59 211 November/December and slightly increased from 2007 to 2012 ($p<0.001$) (Supplementary
60

1 212 Figure 1). No significant change in length of stay for all admissions was observed for the
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3
4 213 period 2012 to 2015 ($p=0.21$).

6 214 **Bed occupancy**

8 215 Figure 3 shows the average monthly bed occupancy for general medical wards for all
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10
11 216 admissions, admissions with a diagnosis of any infection, and admissions with a diagnosis of
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13 217 RVGE. Bed occupancy for AGE is shown in Supplementary Figure 2. Clear seasonal patterns
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15
16 218 were observed for total bed occupancy, with highest overall bed occupancy for the
17
18 219 respiratory virus season in November/December, and lowest overall bed occupancy in the
19
20
21 220 summer months. A year-on-year increase was observed for overall bed occupancy over the
22
23 221 study period ($p<0.001$), from 79% bed occupancy in December 2007 to 90% in December
24
25 222 2014.

28 223 Bed occupancy for RVGE showed clear seasonal peaks before introduction of the vaccine,
29
30 224 with highest occupancy shown for February/March. After introduction of the rotavirus
31
32 225 vaccine, bed occupancy for RVGE in the rotavirus season was reduced by 89% (95%CI
33
34 226 73%,95%) (Table 1). Bed occupancy for any infectious disease increased year on year in the
35
36 227 pre-vaccination period, both within and outside the rotavirus season ($p<0.001$ and $p<0.001$
37
38 228 respectively), as did bed occupancy for AGE ($p<0.001$ within, $p=0.04$ outside rotavirus
39
40 229 season). Post introduction of the vaccine, observed bed occupancy for AGE in the rotavirus
41
42 230 season was reduced by 63% (95%CI 39%,78%) after adjustment for the positive trend in the
43
44 231 pre-vaccination period. Observed bed occupancy for any infection in the rotavirus season
45
46 232 was reduced by 23% (95%CI 15%,31%). No significant reduction was observed when
47
48 233 considering observed vs. expected bed occupancy for any cause of admission (-4%, 95%CI -
49
50 234 1%,9%). Sensitivity analyses with bed availability data taken at 9am and 5pm provided the
51
52 235 similar results.

236 **Table 1:** Average monthly bed occupancy and decline in bed occupancy comparing the pre-
 237 and post-rotavirus vaccination period for any admission, any infection, acute gastroenteritis
 238 and rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust,
 239 July 2007 – June 2015.

Variable	Average bed occupancy		Crude Risk ratio (95% CI)	Adjusted Risk ratio (95% CI) ¹	Decline in bed occupancy (95% CI)	P-value
	Pre-vaccination n	Post-vaccination n				
All	77% (70% - 85%)	79% (67% - 87%)	1.03 (0.99,1.08)	0.96 (0.91,1.01)	4% (-1%,9%)	0.15
Any infection ²	39% (25% - 56%)	42% (33% - 51%)	1.09 (0.95,1.25)	0.77 (0.69,0.85)	23% (15%,31%)	<0.001
AGE ²	5% (1% - 16%)	3% (1% - 8%)	0.72 (0.45,1.13)	0.37 (0.22,0.61)	63% (39%,78%)	<0.001
RVGE ³	5% (0% - 17%)	1% (0% - 4%)	0.18 (0.09,0.35)	0.11 (0.05,0.27)	89% (73%,95%)	<0.001

240 AGE: acute gastroenteritis; CI: confidence interval; NHS: National Health Service; RVGE:
 241 rotavirus gastroenteritis.

242 ¹ Adjusted for seasonality and secular trend. ² Diagnosis of any infection and AGE by clinical
 243 coding only. ³ Diagnosis of RVGE by clinical coding and laboratory results.

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4 245 **Hospital-acquired (HA) bloodstream infection rate**5
6 246 A decrease in HA bloodstream infection was observed in the post-vaccination period,
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8 247 although this did not appear different from secular trends in the pre-vaccination period
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10
11 248 (Figure 4).12
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14 249 **Unplanned readmission rate**15
16 250 No difference was observed between the unplanned readmission rate in the pre-vaccination
17
18 251 period and the post-vaccination period (Figure 5).19
20
21 252 **Outlier rate**22
23 253 Clear seasonal patterns were observed for the outlier rate, with the highest peak during the
24
25 254 respiratory virus season in November/December, and a secondary peak during the rotavirus
26
27 255 season in January-May (Figure 6). The outlier rate increased in 2012, and remained high
28
29 256 throughout 2013-2015, both within and outside the rotavirus season. The increase in outlier
30
31 257 rate is synchronous with the closure of one specific ward, a large general medical ward in
32
33 258 November 2011, and the opening of a new medical admission unit (short-stay department
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37 259 prior to discharge or admission to other wards).
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1 260 **DISCUSSION**

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4 261 This is the first study to examine the effects of national vaccine introduction on wider
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6 262 measures of hospital pressures in the UK. The introduction of rotavirus vaccine has led to a
7
8 263 large reduction in RVGE hospitalisation,[7] reflected in the reduction in proportion of
9
10 264 admissions tested rotavirus-positive and the reduction in bed occupancy due to RVGE and
11
12 265 AGE as described here. Lower bed occupancy for RVGE and AGE in the rotavirus season
13
14 266 post-vaccine introduction was concordant with lower bed occupancy for any infection in the
15
16 267 rotavirus season in the post-vaccination period. Despite the reduction in RVGE
17
18 268 hospitalisation, overall bed occupancy was not reduced. This suggests that a large, busy NHS
19
20 269 Trust, such as Alder Hey, operates at full capacity and that the beds that became available
21
22 270 by the reduction of RVGE hospitalisations were occupied by a different patient population,
23
24 271 probably reflecting a previously unmet need and/or physicians having greater freedom to
25
26 272 admit patients if beds have become available. The absence of a reduction in overall bed
27
28 273 occupancy could explain why reductions in the other proxy measures (HA-infection rate,
29
30 274 unplanned readmission rate, outlier rate) were not observed.
31
32 275 Two other studies have examined hospital pressures since rotavirus vaccination
33
34 276 introduction. A study conducted in two Finnish hospitals concluded that bed occupancy for
35
36 277 RVGE and AGE decreased since introduction of the vaccine.[17] There is no discussion of
37
38 278 changes in total bed occupancy, or on other proxy measures for hospital pressures following
39
40 279 rotavirus vaccine introduction. A study conducted in a general hospital in Belgium (36
41
42 280 paediatric beds) concluded that bed-day occupancy, bed-day turnover and unplanned
43
44 281 readmissions for AGE were lower in the post-vaccination compared with the pre-vaccination
45
46 282 periods, and that this resulted in improved quality of care for overall admissions.[8] In our
47
48 283 study, the reduction of bed occupancy for RVGE did not result in a change in overall bed
49
50 284 occupancy or other measures of hospital pressure. No change in hospital length of stay for

1 285 RVGE patients was observed. Median hospital stay for CA RVGE was shorter in Alder Hey
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3
4 286 NHS Foundation Trust than reported in the Belgian study (2.2 vs. 4.1 days), suggesting a
5
6 287 difference in management of RVGE cases, and could be an indicator of higher hospital
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8
9 288 pressure and more rapid patient turnover in Alder Hey.

10
11 289 Several caveats need to be considered when using routinely collected data. Our analysis was
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13 290 complicated by changes in hospital practises, in particular changes in patient flow,
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16 291 laboratory procedures, infection control and clinical coding. Firstly, several wards relevant
17
18 292 to this study opened or closed during the study period. Although ward closures were
19
20 293 accounted for in the bed occupancy analysis, more subtle changes in patient dynamics still
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22 294 influenced our results. A steep increase was observed for the outlier rate in 2012, with the
23
24 295 higher level sustained throughout 2013-2015. The increase in outlier rate is synchronous
25
26 296 with the closure of a large general medical ward in November 2011, and the opening of a
27
28 297 new medical admission. It is possible that the change in ward structure led to an increased
29
30 298 bed usage in surgical and specialised medical wards.

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32
33 299 Secondly, several changes in laboratory procedures were observed during the study period,
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35
36 300 most notably the introduction of polymerase chain reaction for the rapid testing of
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38 301 respiratory pathogens in 2013. Faster diagnosis of respiratory infection could have had
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40 302 implications for patient treatment, isolation practices and patient flow, and could have
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42 303 influenced the measured hospital pressure outcomes. The number of admissions tested for
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44 304 rotavirus did not change significantly over the study period, which provides confidence that
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46 305 the drop in RVGE in the post-vaccine era is a real effect, and not caused by a change in
47
48 306 testing policy.

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50
51 307 Thirdly, there were changes in infection prevention and control (IPC) practices in later years
52
53 308 of the study, including an increase in IPC staff; the introduction of isolation and hand
54
55 309 hygiene posters, bed space dividers screens and infection control enclosure isolation pods;

1 310 and changes in environmental cleaning. Changes in IPC practices will most likely have
2
3
4 311 resulted in changes in HA infection rates – it is difficult to disentangle their effect on HA
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6 312 infection from any effect due to a reduction in hospital pressures post-rotavirus vaccination
7
8
9 313 introduction.

10
11 314 We observed that bed occupancy for any infectious disease increased in the pre-vaccination
12
13
14 315 period, both within and outside the rotavirus season. An increase in bed occupancy for any
15
16 316 respiratory infection (supplementary Figure 3) and any gastroenteritis was observed, but
17
18 317 neither increase can fully account for the overall increase in any infection. It is possible that
19
20
21 318 the increase in infection observed is due to an artefact of the recording of the data.

22
23 319 Supplementary Figure 4 shows that all clinical diagnostic coding increased over the study
24
25
26 320 period. Clinical diagnostic coding increased for both cases with and without any infection
27
28 321 recorded. We observed that bed occupancy for any infection in the rotavirus season was
29
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31 322 lower than the expected bed occupancy for any infection based on pre-vaccination
32
33 323 estimates. The increase in any clinical diagnostic coding was sustained in 2014 and 2015,
34
35 324 providing confidence that our observation of lower than expected bed occupancy for any
36
37
38 325 infection in the post-vaccination period is a true finding.

39
40 326 Our analysis highlights the importance of the presentation of data from the full study period
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43 327 in a time-series analysis, rather than restricting the results to a “before-after” comparison,
44
45 328 when there is non-homogeneity in disease management, hospital management and data
46
47
48 329 collection over time. A long-term increase in bed occupancy for any infection could be
49
50 330 observed (possibly due to an increase in clinical coding) that predated the introduction of
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52
53 331 vaccination: taking this ongoing increase in admissions coded as infection into account, a
54
55 332 reduction in bed occupancy for any infection can be observed.

56
57 333 A further consideration is how changes to the catchment population size and referral
58
59
60 334 patterns during the study period could affect our findings and their interpretation. There

1 335 has been a small but steady population growth in the surrounding region consistent with a
2
3
4 336 national trend, which could increase demand upon the hospital and dampen any effect of
5
6 337 rotavirus vaccination on reducing these pressures. Finally, the impact of any changes in
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8
9 338 referral policy during the study period is difficult to quantify as Alder Hey serves a region of
10
11 339 over 7.1 million people.

12
13 340 Routinely collected hospital data can be used for the evaluation of a (vaccination) policy, but
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15
16 341 our study highlights the difficulty of evaluating a (vaccination) policy in a period with
17
18 342 concurrent changes in patient flow, laboratory procedures and IPC practices.

19
20
21 343 The introduction of rotavirus vaccination has led to a dramatic reduction in hospitalisation
22
23 344 for RVGE and thus a reduction in bed occupancy for RVGE. However, overall bed occupancy
24
25 345 was not reduced further highlighting the severe strain the NHS is under and that demand is
26
27 346 outstripping capacity. Bed occupancy continues to rise and even a highly effective routine
28
29 347 vaccine only freed-up beds which were then filled by admissions, making no overall
30
31 348 headway into reducing the overall pressures the NHS is facing.

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2
3
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5
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7
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9
10
11 354 associated with the development and publication of this manuscript.

12
13 355 **Conflicts of interest**

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15
16
17 356 Rotarix is a trademark of the GSK group of companies.

18
19
20
21 357 NC, NF, and DH are in receipt of research grant support from the GSK group of companies

22
23 358 for the conduct of the present study. NC has received honoraria for participation in GSK

24
25 359 Rotavirus Vaccine Advisory Board Meetings from the GSK group of companies and from

26
27 360 Watermark Research Partners for participation in independent data monitoring committee

28
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36
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38
39 366 BS and ET are employees of the GSK group of companies. EH, RC, MC and JC have nothing to

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43 367 disclose.

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49 368 **Authorship and manuscript preparation**

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52 369 DH, RPDC, MC, NC, NF designed the study and wrote the protocol. EH performed the

53
54 370 analyses and wrote the manuscript. JSC and MC provided data for the study. NBZ provided

55
56 371 statistical support. DH, RPDC, MC, JSC, NBZ, NF, NAC provided advice on the understanding

1 372 of the findings. ET and BS provided external advice. All authors approved the final version of
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4 373 the paper for submission.

5
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7

8
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18 379 development and editorial support.
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23 381 **Data sharing**
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25
26 382 The results summary for this study (GSK study identifier: 205369 - ClinicalTrials.gov
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28 383 identifier: NCT03271593) is available on the GSK Clinical Study Register and can be accessed
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30 384 at www.gsk-clinicalstudyregister.com. The full data that support the findings of this study
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32 385 are held by Alder Hey Children's NHS Foundation Trust and restrictions apply to the
33
34 386 availability of these data as they are not publicly available. Aggregated data may be
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36 387 available from the authors/ Alder Hey Children's NHS Foundation Trust on reasonable
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38 388 request and with permission of Alder Hey Children's NHS Foundation Trust.
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1 434 **Figures Captions**

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4 435 **Figure 1. Number of admissions tested for rotavirus in the rotavirus season in Alder Hey**
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6 436 **NHS Foundation Trust, July 2007 – June 2015.**

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9 437 *NHS: National Health Service.*

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11 438 **Figure 2. Total length of stay for CA and HA RVGE.**

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14 439 For HA RVGE, length of stay was calculated from date of first positive test.

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16 440 *CA: community-acquired; HA: hospital-acquired.*

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18 441 **Figure 3. Observed and expected bed occupancy for any admission, any infection and**
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21 442 **rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust,**
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23 443 **July 2007 – June 2015.**

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26 444 The coloured shading represents the 95% confidence intervals for the expected incidence.

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28 445 Grey shading represents the rotavirus season (January-May). The vertical hashed line
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30 446 represents the introduction of rotavirus vaccine in the UK in July 2013.

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33 447 *NHS: National Health Service.*

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35 448 **Figure 4. Hospital acquired bloodstream infection rate on general medical wards in Alder**
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38 449 **Hey NHS Foundation Trust, July 2007 – June 2015.**

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40 450 Black line shows raw data, red line shows smoothed data. Grey shading represents the
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43 451 rotavirus season (January-May). The vertical hashed line represents the introduction of
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45 452 rotavirus vaccine in the UK in July 2013.

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48 453 *HA: hospital-acquired; NHS: National Health Service.*

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50 454 **Figure 5. Unplanned readmission rate for any admission on general medical wards in Alder**
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53 455 **Hey NHS Foundation Trust, July 2007 – June 2015.**

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55 456 Raw data in black, smoothed data in red. Grey shading represents the rotavirus season

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57 457 (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in
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60 458 the UK in July 2013.

1 459 *NHS: National Health Service.*

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4 460 **Figure 6. Outlier rate for any admission in Alder Hey NHS Foundation Trust, July 2007 –**
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6 461 **June 2015.**

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8 462 Raw data in black, smoothed data in red. Grey shading represents the rotavirus season
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11 463 (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in
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13 464 the UK in July 2013.

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For peer review only

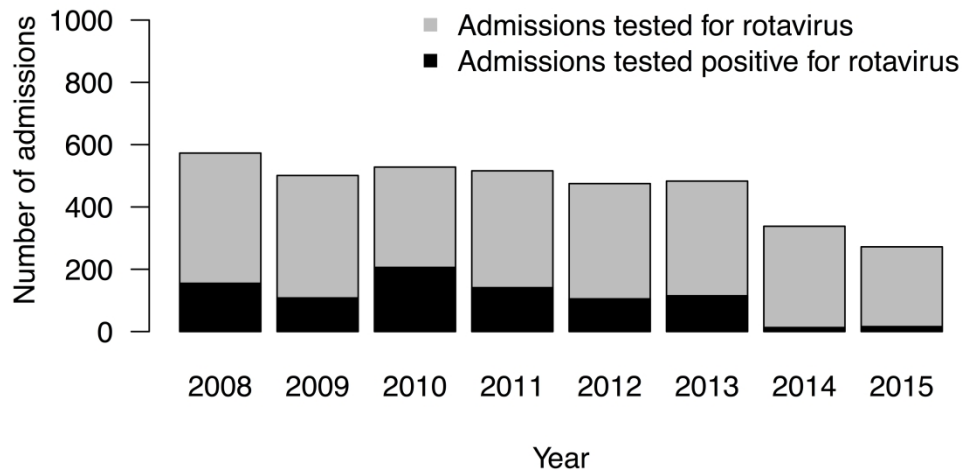


Figure 1. Number of admissions tested for rotavirus in the rotavirus season in Alder Hey NHS Foundation Trust, July 2007 – June 2015.
NHS: National Health Service.

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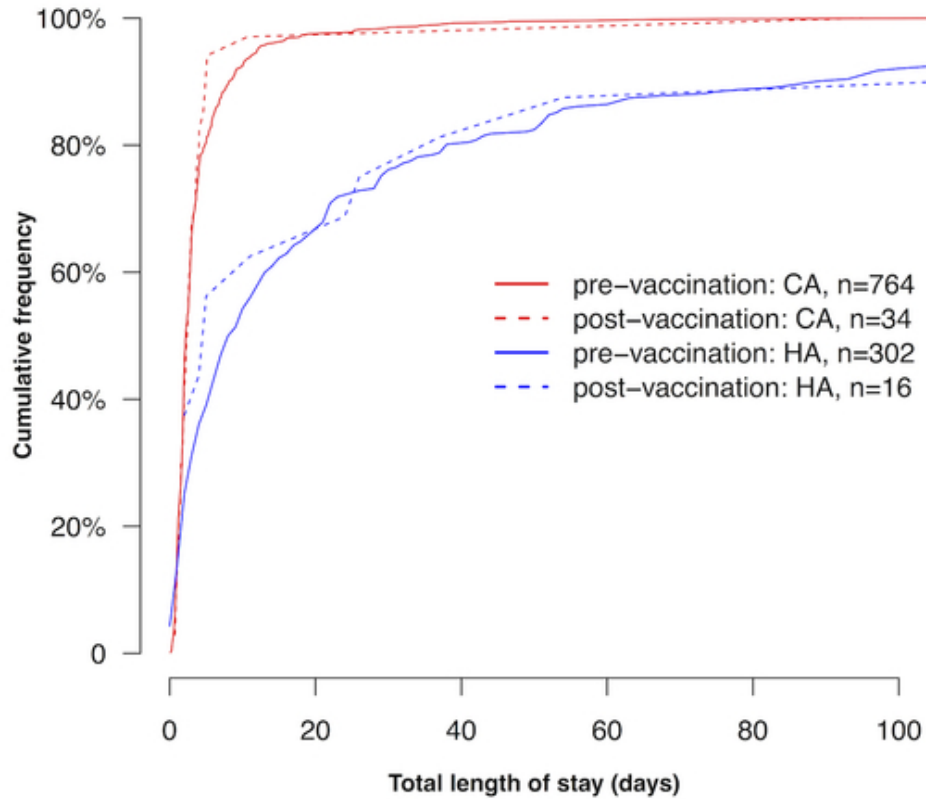


Figure 2. Total length of stay for CA and HA RVGE.

For HA RVGE, length of stay was calculated from date of first positive test.
CA: community-acquired; HA: hospital-acquired.

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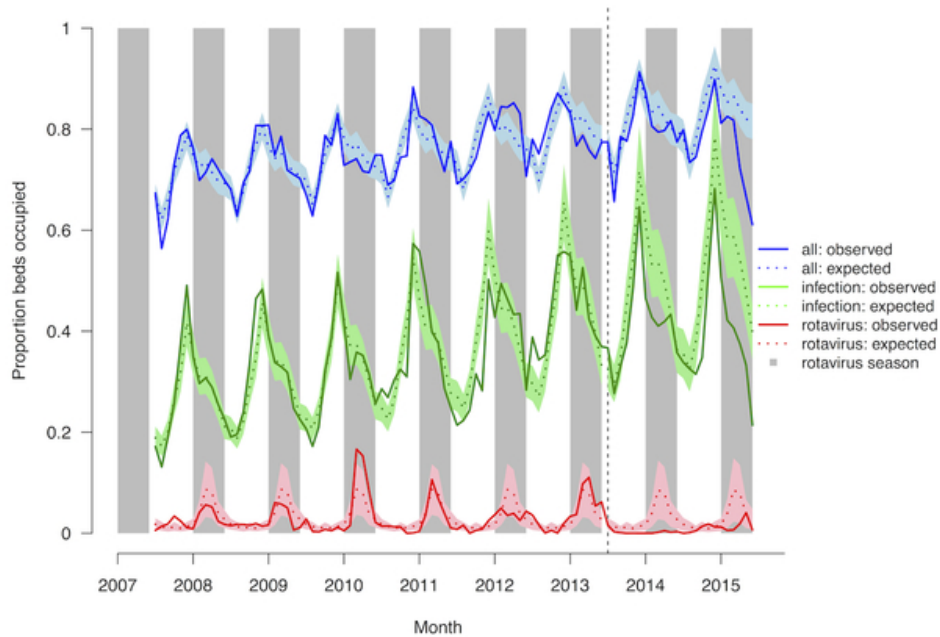


Figure 3. Observed and expected bed occupancy for any admission, any infection and rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

The coloured shading represents the 95% confidence intervals for the expected incidence. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

NHS: National Health Service.

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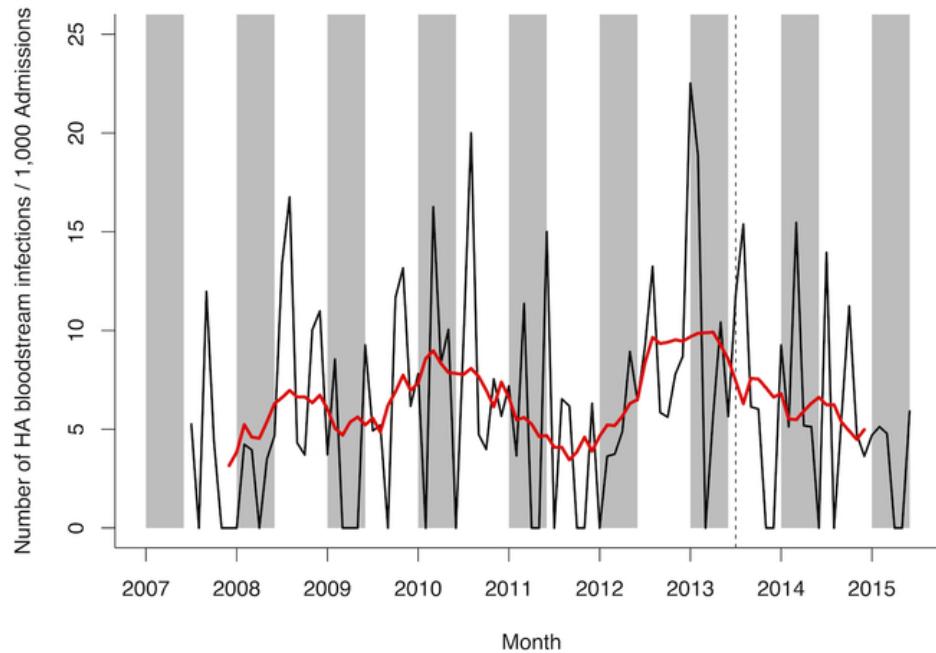


Figure 4. Hospital acquired bloodstream infection rate on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

Black line shows raw data, red line shows smoothed data. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

HA: hospital-acquired; NHS: National Health Service.

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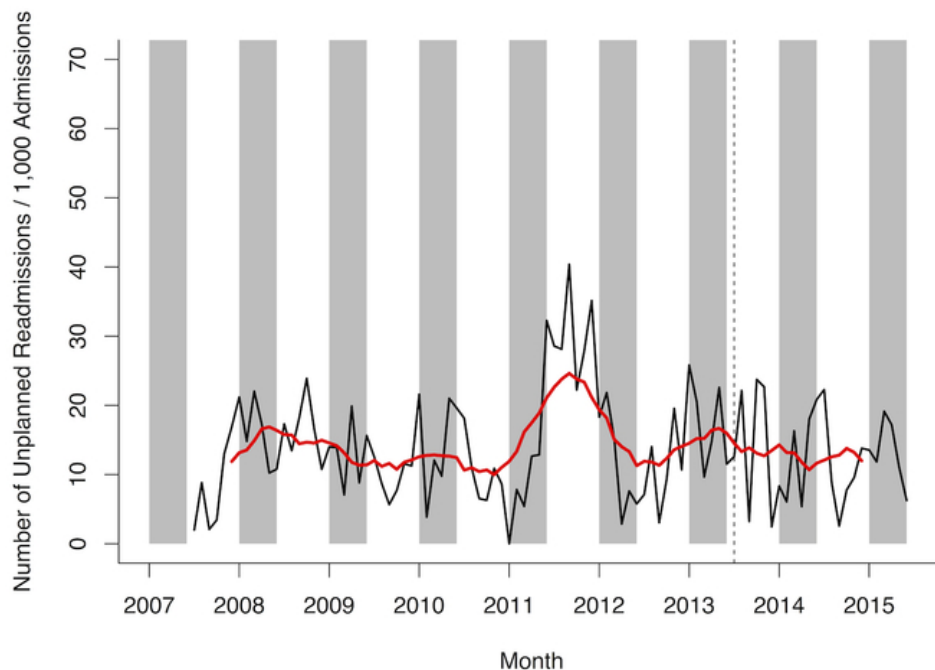


Figure 5. Unplanned readmission rate for any admission on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

Raw data in black, smoothed data in red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

NHS: National Health Service.

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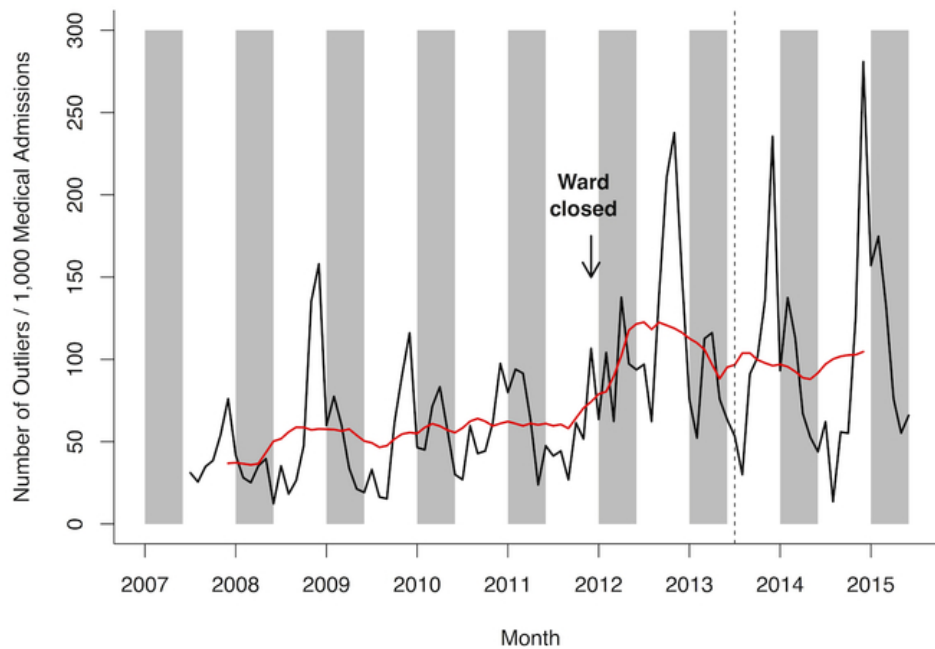


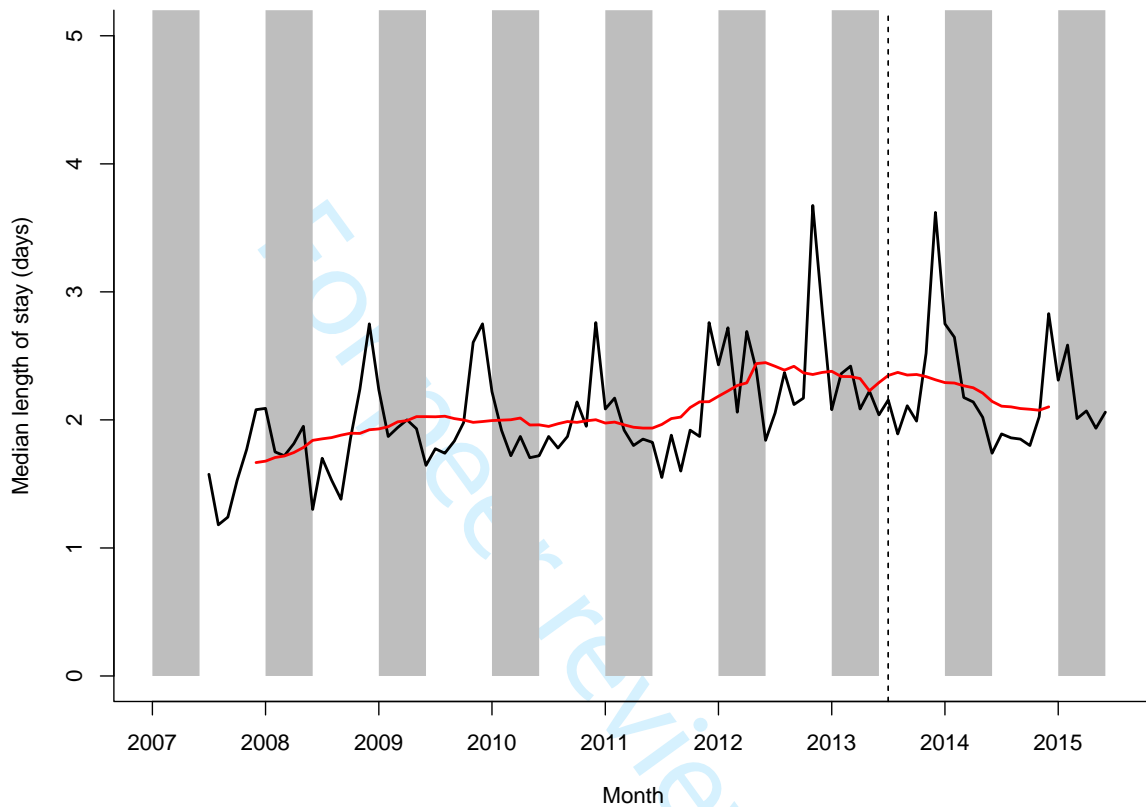
Figure 6. Outlier rate for any admission in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

Raw data in black, smoothed data in red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.

NHS: National Health Service.

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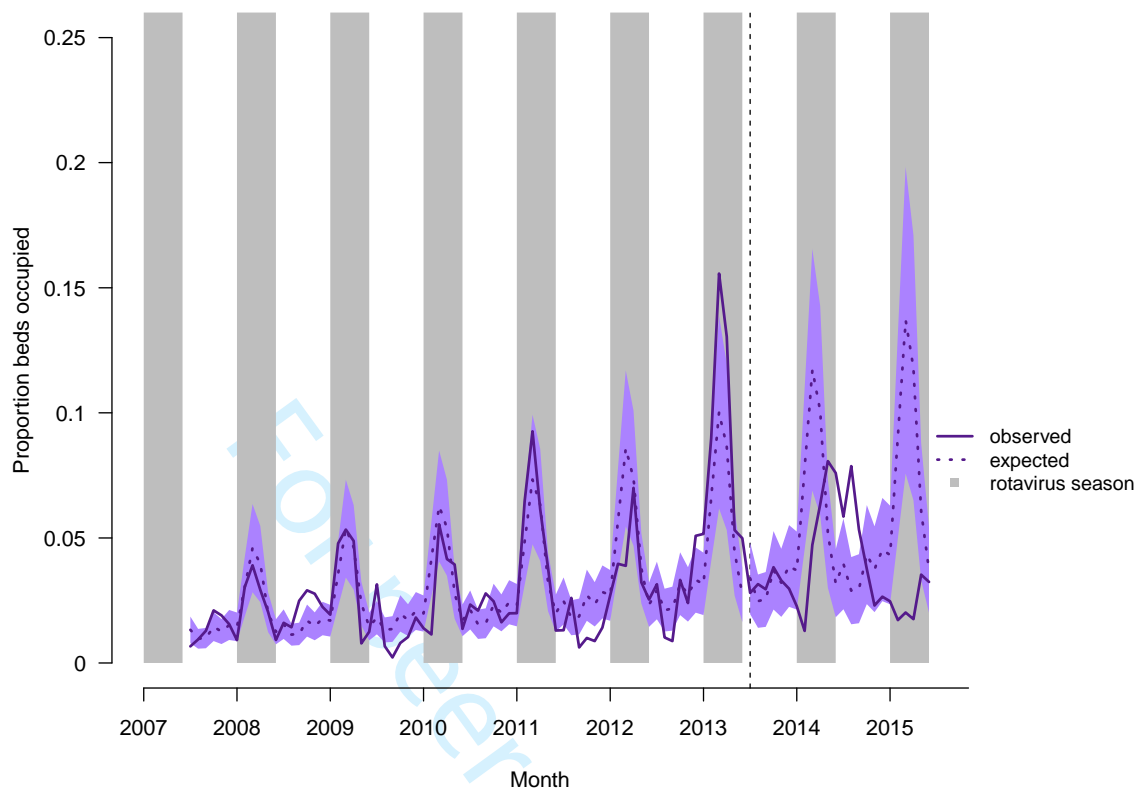
1 Supplementary Material



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3 **Supplementary Figure 1. Median length of stay (all admissions) on general medical wards in Alder**
4 **Hey Children's NHS Foundation Trust, July 2007 – June 2015.** Raw data in black, smoothed data in
5 red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents
6 the introduction of rotavirus vaccine in the UK in July 2013.

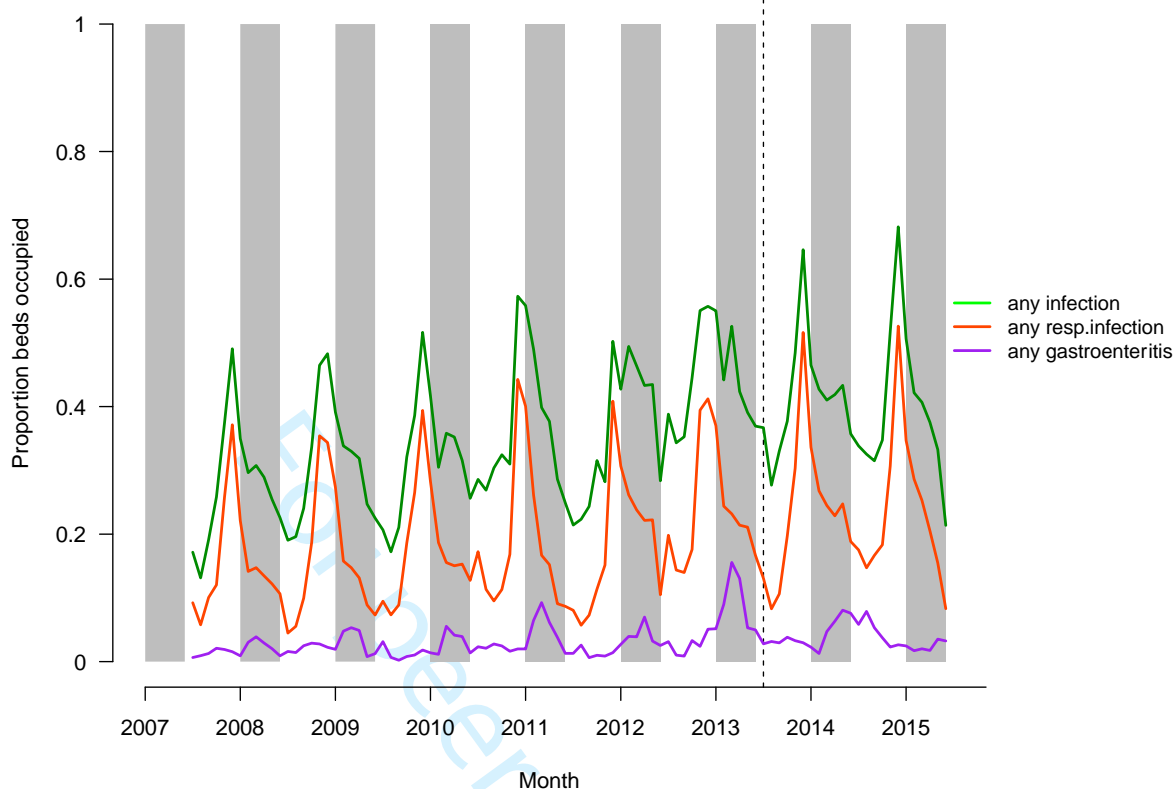
7 *NHS: National Health Service.*



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2 **Supplementary Figure 2. Observed and expected bed occupancy for acute gastroenteritis on**
 3 **general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.** The coloured
 4 shading represents the 95% confidence intervals for the expected incidence. Grey shading
 5 represents the rotavirus season (January-May). The vertical hashed line represents the introduction
 6 of rotavirus vaccine in the UK in July 2013.

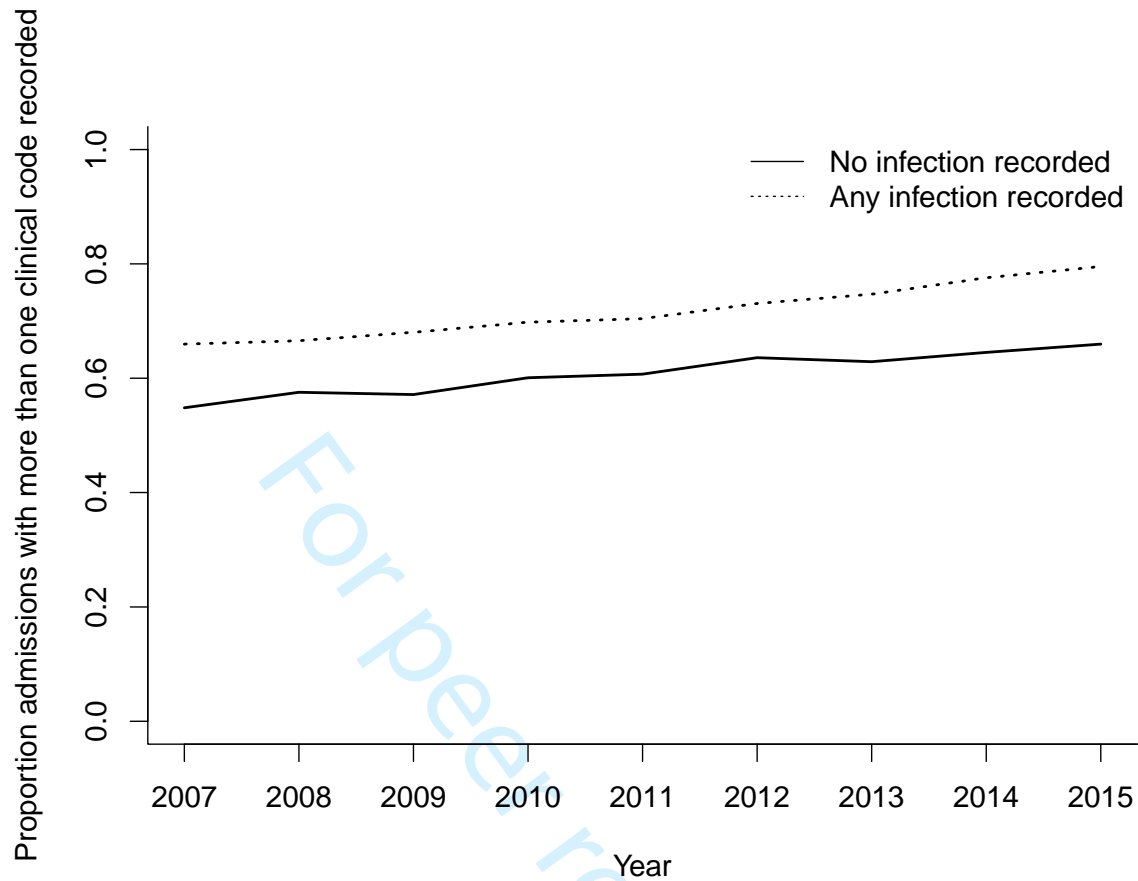
7 *NHS: National Health Service.*



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2 **Supplementary Figure 3. Observed bed occupancy for any infection, any respiratory infection and**
 3 **any gastroenteritis (by clinical coding only) in general medical wards in Alder Hey NHS Foundation**
 4 **Trust, July 2007 – June 2015.** The vertical hashed line represents the introduction of rotavirus
 5 vaccine in the UK in July 2013.

6 *NHS: National Health Service; resp.: respiratory.*



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2 **Supplementary Figure 4. Proportion of admissions to general medical wards for whom more than**
3 **one clinical code was recorded, Alder Hey NHS Foundation Trust, July 2007 – June 2015**

4 *NHS: National Health Service.*

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Checklist
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Included "Retrospective hospital database analysis" in abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Included
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Included
Objectives	3	State specific objectives, including any prespecified hypotheses	Included "The aim of this study was to assess hospital pressures at a large UK NHS paediatric hospital pre- and post- rotavirus vaccine introduction using routinely collected data."
Methods			
Study design	4	Present key elements of study design early in the paper	Included in paragraph 'data sources'
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Included in paragraph 'setting'
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Inclusion and exclusion criteria included in paragraph 'study population and definitions'
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Not applicable for this observational study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Included in paragraphs 'study population and definitions' and 'outcomes'
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment	Included in paragraph 'data sources'.

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measurement

(measurement). Describe comparability of assessment methods if there is more than one group

Bias	9	Describe any efforts to address potential sources of bias	- 2007 onwards data only included to account for changes in clinical coding (included in paragraph 'data sources') - inclusion of diagnosis coding for non-infectious gastroenteritis (included in paragraph 'study population and definitions')
Study size	10	Explain how the study size was arrived at	Sampling not applicable: this observational study included <i>all</i> patients aged 0-14 years
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Included in paragraphs 'outcomes' and 'statistical analysis'.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Included in paragraphs 'outcomes' and 'statistical analysis'.
		(b) Describe any methods used to examine subgroups and interactions	Included in paragraphs 'outcomes' and 'statistical analysis'.
		(c) Explain how missing data were addressed	Not applicable for hospital database analysis
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	Not applicable for observational study
		(e) Describe any sensitivity analyses	Not applicable

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Included in first paragraph of results
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Median age of participants included. Median length of stay of participants included
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Not applicable
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not applicable
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Not applicable
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Unadjusted estimates included in figures 1-6. Adjusted analysis for bed occupancy included in Table 1.
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Risk ratio translated in decline in bed occupancy in Table 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	- Analysis of clinical coding included in Supplementary figure 4 - Analysis of bed occupancy for infection included in Supplementary figure 3.

Discussion

Key results	18	Summarise key results with reference to study objectives	Included in first paragraph discussion and conclusions
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Included in discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	Included in discussion

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multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability	21	Discuss the generalisability (external validity) of the study results	Included in discussion
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Included in Funding Statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.