1 2	1	Do hospital pressures change following rotavirus vaccine introduction? A retrospective
3 4 5	2	database analysis in a large paediatric hospital in the United Kingdom.
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47 48 49	20	Abbreviated title: Hospital pressures post rotavirus vaccination
50 51	21	Word count: 3248
52 53 54	22	ABSTRACT
55 56	23	Objective Hospitals in the United Kingdom are under increasing clinical and financial
57 58 59	24	pressures. Post introduction of childhood rotavirus vaccination in the UK in 2013, rotavirus
60	25	gastroenteritis (RVGE) hospitalisations reduced significantly. We evaluated changes in

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'hospital pressures' (demand on healthcare resources and staff) following rotavirus vaccine 26

introduction in a paediatric setting in the UK. 27

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

Merseyside, UK. 30

Participants Hospital admissions aged < 15 years. Outcomes were calculated for four 31

32 different patient groups identified through diagnosis coding (ICD-10) and/or laboratory

33 confirmation: all admissions; any infection, acute gastroenteritis; and RVGE.

Methods Hospital pressures were compared before and after rotavirus vaccine 34

35 introduction: these included bed occupancy, hospital-acquired infection rate, unplanned

readmission rate, and outlier rate (medical patients admitted to surgical wards due to lack 36

of medical beds). Interrupted time-series analysis was used to evaluate changes in bed 37 38 occupancy.

Results There were 116,871 admissions during the study period. Lower bed occupancy in 39

the rotavirus season in the post-vaccination period was observed for RVGE (-89%, 95%CI 40

41 73%,95%), acute gastroenteritis (-63%, 95%CI 39%,78%) and any infection (-23%, 95%CI

15%,31%). No significant overall reduction in bed occupancy was observed (-4%, 95%CI -42

1%,9%). No changes were observed for the other outcomes. 43

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

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

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1 2 50	'Strengths and limitations of this study'
3 4 51	This study used 8 years of retrospective routinely collected data from a large
5 6 52 7	paediatric hospital in the United Kingdom.
8 9 53	• This is the first study to examine the effects of a vaccine on wider measures of
10 11 54 12	hospital pressures in the United Kingdom.
13 14 55	• Our analysis highlights the importance of the presentation of data from the full study
15 16 56 17	period in a time series analysis, rather than restricting the results to a "before-after"
18 19 57	comparison.
20 21 58 22	• Our analysis was complicated by inevitable changes in hospital practices over the 8-
23 24 59	year study period, in particular changes in patient flow, laboratory procedures,
25 26 60 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	infection control and clinical coding.

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61 INTRODUCTION

In the context of increasing patient need and constrained resources, the United Kingdom's 62 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 admission rates have been increasing for the past decade; if the increases continue at the 65 current rate an extra 22 hospitals with 800 beds each will be required by 2022.[3] Although 66 highest for the elderly, increases in admission rates are occurring across all age groups.[3] In 67 68 children aged 0-14 years, the number of hospital admission episodes increased from 1.7 to 2.0 million between 2004-05 and 2014-15 [4] and emergency department (ED) attendances 69 70 have risen by approximately 300,000 between 2011-12 and 2014-15,[5] leaving paediatric services with increased demand but a short fall of medical staffing.[6] 71 While the problems the NHS faces are complex, there are ongoing disease prevention 72 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 targeting childhood diseases with a large hospitalisation burden, it is possible that the 75 76 reduction in beds occupied for infections caused by the vaccine target pathogen reduces hospital pressures, and potentially nosocomial infections.[8, 9] 77 78 Prior to vaccine introduction in the UK, rotavirus gastroenteritis (RVGE) was a major cause of hospital admission in young children during the winter/spring months. It was estimated 79 that in children less than 5 years of age, 20% of ED attendances and 45% of hospitalisations 80 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 of RVGE hospitalisations in children. [7, 12, 13] The aim of this study was to assess hospital 85

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pressures at a large UK NHS paediatric hospital pre- and post- rotavirus vaccine introduction
using routinely collected data. As there are no direct measures of hospital clinical pressures
(on healthcare resources and staff), evidenced proxy indicators were used: bed occupancy,
hospital-acquired infection rate, unplanned readmission rate, and rate of outliers (medical
patients admitted to surgical wards).

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92 METHODS

93 Setting

Alder Hey Children's NHS foundation Trust (Alder Hey) is located in Liverpool, UK and is one of the largest paediatric hospitals in Europe, with a catchment population of over 7.1 million. Alder Hey provides primary, secondary and tertiary care facilities for >200,000 children each year and has approximately 240 inpatient beds; this study utilized data prior to the opening of a new hospital premises in October 2016. General medicine, general surgery, and a range of specialist services are provided. There is also a large ED. Patients with a suspected or confirmed RVGE are admitted to a room within the cubicle areas of one of the general medical wards. If no beds are available in the general medical wards, cubicle areas in specialized medical wards or surgical wards are used. Data sources Retrospective hospital database analysis (ClinicalTrials.gov NCT03271593) was conducted at Alder Hey. Anonymised bed admission and laboratory data were extracted by the hospital 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

 $\frac{40}{41}$ 108 since changes were made to clinical coding in 2006, and bed availability data were only

43 109 available from February 2006 onwards.44

4546 110 Study population and definitions

We included all inpatients aged 0-14 years admitted between 1st July 2007 and 30th June 2015, who attended at least one ward other than the ED. Excluded from analysis were any patients 15 years or older at time of admission, day patients, and those who were admitted and discharged from the ED or observation unit without attending another ward. Outcomes were calculated for four different patient groups identified through ICD-10 (International Classification of Disease, tenth edition) hospital discharge diagnosis codes:

1 2	117	All admissions
3 4 5	118	• Any infection: Admissions coded as any infection (ICD-10 A00-B99 and J09-J22 in any
6 7	119	diagnostic code) or as non-infectious gastroenteritis (K52.9).[14]
8 9 10	120	• Acute gastroenteritis (AGE): Admissions coded as acute gastroenteritis (ICD-10 A00-
11 12	121	A09 in any diagnostic code) or as non-infectious gastroenteritis (K52.9).[14]
13 14 15	122	• Rotavirus gastroenteritis (RVGE): Admissions coded as rotavirus gastroenteritis (ICD-
16 17	123	10 A08.0 in any diagnostic code) and/or laboratory-confirmed as rotavirus.[14]
18 19 20	124	Laboratory confirmation for RVGE was defined as rotavirus antigen detected by
21 22	125	either immunochromatographic test or by enzyme immunoassay in a faecal
23 24 25	126	specimen of a child with AGE. A distinction was made between community-acquired
26 27	127	(CA) and hospital-acquired (HA) RVGE: HA RVGE was defined as any patient with a
28 29 30	128	positive test for rotavirus infection with a sample date more than 2 days after
31 32	129	admission and no record of diarrhoea or vomiting on admission.[7] Testing for RVGE
33 34	130	was done on clinicians' request. The testing policy for RVGE did not change over the
35 36 37	131	study period.
38 39	132	Diagnosis coding for non-infectious gastroenteritis (ICD-10 K52.9) was included since
40 41 42	133	unspecified gastroenteritis was classified under this code until April 2012.[15]
43 44	134	The pre-vaccination period was defined as 1^{st} July 2007 - 30^{th} June 2013; the post
45 46 47	135	vaccination period was defined as 1^{st} July 2013 – 30^{th} June 2015. The rotavirus season was
48 49	136	defined as 1^{st} January – 31^{st} May; the period when laboratory detection rate in the UK is
50 51 52	137	highest.[16]
53 54	138	Outcomes
55 56 57	139	The following outcomes were calculated:
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1 2	140	• <i>Bed occupancy:</i> number of patients allocated a bed on a specific ward divided by
3 4 5	141	number of available beds at that ward at 12.00 noon. Bed occupancy for any
6 7	142	infection, AGE and RVGE were determined using the definitions above. For HA-RVGE,
8 9	143	only bed occupancy on the ward where the patient tested positive for rotavirus was
10 11 12	144	included. For CA-RVGE, total hospital stay was attributed to rotavirus. Sensitivity
13 14	145	analyses were done with bed availability data collected at 9am and 5pm.
15 16 17	146	• HA bloodstream infection rate: number of HA bloodstream infections per 1,000
18 19	147	admissions with length of stay >2 days. We used indicator organisms to describe HA
20 21 22	148	infection: a HA bloodstream infection was defined as identification of methicillin-
23 24	149	sensitive Staphylococcus aureus or methicillin-resistant Staphylococcus aureus or
25 26 27	150	<i>Escherichia coli</i> or <i>Candida</i> species in a blood sample obtained >2 days after
28 29	151	admission. HA Bloodstream infection rate was used as an outcome measure since, as
30 31 32	152	for other outcome measures such as HA rotavirus, this may be an indicator of how
33 34	153	changes in hospital pressures could influence infection control practices and
35 36 37	154	subsequent nosocomial transmission.
38 39	155	• Unplanned readmission: number of patients with an emergency readmission within 7
40 41	156	days after discharge per 1,000 admissions.[8]
42 43 44	157	• Outlier rate: number of medical patients admitted to a surgical ward per 1,000
45 46	158	admissions. A medical patient was defined as any patient classified under
47 48 49	159	haematology/oncology, general paediatrics, endocrinology, nephrology,
50 51	160	rheumatology, respiratory medicine, dermatology or accident & emergency.
52 53 54	161	Calculations of bed occupancy, HA infection rate, and unplanned readmission rate were
55 56 57 58 59 60	162	restricted to nine general medical wards. Several wards opened or closed during the study

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period. Changes in ward structure were taken into account in the outcomes calculated by

5 4 5	164	including data according to the wards' opening periods.
6 7	165	Descriptive analysis
8 9 10	166	Data analyses were performed using R version 3.2.0 (R Core Team, Vienna). The number of
11 12	167	admissions for each patient group, length of stay and age of RVGE patients was described
13 14 15	168	pre and post-vaccine introduction during the rotavirus season. Differences between
15 16 17	169	continuous variables were tested using Student's t-test or Wilcoxon rank-sum test if not
18 19	170	normally distributed and $\chi 2$ -test or Fisher's exact test for categorical variables.
20 21 22	171	Statistical analysis
23 24	172	To assess any changes in bed occupancy following rotavirus vaccine introduction,
25 26 27	173	interrupted time-series analysis was used as previously described.[7] Monthly expected bed
28 29	174	occupancy was estimated by fitting a negative binomial regression model to pre-vaccine
30 31 32	175	monthly bed occupancy data, adjusted for seasonality and secular trends using calendar
33 34	176	month and rotavirus year (July to June), respectively. A negative binomial model was chosen
35 36 27	177	to account for overdispersion in the data. This model was used to predict the expected bed
37 38 39	178	occupancy rate in the absence of vaccination, where the post-vaccine introduction change is
40 41	179	expressed by the difference between the expected and observed bed occupancy. To
42 43 44	180	quantify change in average bed occupancy in the rotavirus season as a result of introduction
45 46	181	of the vaccine, a second model included a binary indicator variable for the vaccine period,
47 48 49	182	enabling the computation of risk ratios (RR) and associated 95% confidence intervals (CI).
50 51	183	This second model was restricted to the rotavirus season and adjusted for calendar month
52 53 54	184	and rotavirus year. Percentage change in average bed occupancy was calculated as 100(1 -
55 56	185	RR).
57 58	186	Ethics
59 60		

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187 Ethics approval was provided by the NHS Research Ethics Committee, North East –

188 Newcastle & North Tyneside 2 and by the Alder Hey Children's NHS Foundation Trust

189 Research and Development Department.

190 Patient and public involvement statement

191 This study was conducted using secondary data and there was no new contact with patients

192 throughout the study. No patients were directly involved in designing the research question,

193 conducting the research or interpretation of the research findings. Investigators have

194 presented these findings at national and international events

RESULTS

196 In total, there were 116,871 admissions among 68,838 unique patients at any time in the

197 year during the study period from 1st July 2007 – 30th June 2015. Of those admissions,

198 48,852 occurred during the rotavirus season.

 $_{1}^{0}$ 199 Testing for rotavirus remained stable throughout the pre-vaccination study period, with a

200 median of 509 (IQR=481-539) admissions tested each rotavirus season, of which a median of

201 128 (25.2%) were positive (Figure 1). In the rotavirus seasons following rotavirus vaccine

202 introduction, the proportion of rotavirus-positive test results amongst admissions tested

203 dropped to 3.8% (13/338) and 5.9% (16/272) in 2014 and 2015 respectively.

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

²⁵ 209 vs. 5.0 days post, p=0.88) (Figure 2).

210 Length of stay for all admissions was highest during the respiratory virus season in

November/December and slightly increased from 2007 to 2012 (p<0.001) (Supplementary

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	212	Figure 1). No significant change in length of stay for all admissions was observed for the
	213	period 2012 to 2015 (p=0.21).
	214	Bed occupancy
	215	Figure 3 shows the average monthly bed occupancy for general medical wards for all
	216	admissions, admissions with a diagnosis of any infection, and admissions with a diagnosis of
	217	RVGE. Bed occupancy for AGE is shown in Supplementary Figure 2. Clear seasonal patterns
	218	were observed for total bed occupancy, with highest overall bed occupancy for the
	219	respiratory virus season in November/December, and lowest overall bed occupancy in the
20 21 22	220	summer months. A year-on-year increase was observed for overall bed occupancy over the
22 23 24 25 26 27 28 29 30 31 32	221	study period (p<0.001), from 79% bed occupancy in December 2007 to 90% in December
	222	2014.
	223	Bed occupancy for RVGE showed clear seasonal peaks before introduction of the vaccine,
	224	with highest occupancy shown for February/March. After introduction of the rotavirus
32 33 34	225	vaccine, bed occupancy for RVGE in the rotavirus season was reduced by 89% (95%CI
35 36	226	73%,95%) (Table 1). Bed occupancy for any infectious disease increased year on year in the
37 38 39	227	pre-vaccination period, both within and outside the rotavirus season (p<0.001 and p<0.001
40 41	228	respectively), as did bed occupancy for AGE (p<0.001 within, p=0.04 outside rotavirus
42 43 44	229	season). Post introduction of the vaccine, observed bed occupancy for AGE in the rotavirus
45 46	230	season was reduced by 63% (95%CI 39%,78%) after adjustment for the positive trend in the
47 48 40	231	pre-vaccination period. Observed bed occupancy for any infection in the rotavirus season
49 50 51	232	was reduced by 23% (95%CI 15%,31%). No significant reduction was observed when
52 53	233	considering observed vs. expected bed occupancy for any cause of admission (-4%, 95%CI -
54 55 56	234	1%,9%). Sensitivity analyses with bed availability data taken at 9am and 5pm provided the
57 58 59	235	similar results.

 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

and rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust,

239 July 2007 – June 2015.

Variable	Average be	d occupancy	Crude Risk	Adjusted	Decline in	Р-
	in rotavirus	season	ratio (95%	Risk ratio	bed	value
	(range)		CI)	(95% CI) ¹	occupancy	
	Pre-	Post-	-		(95% CI)	
	vaccinatio	vaccination				
	n					
All	77%	79%	1.03	0.96	4%	0.15
	(70% -	(67% - 87%)	(0.99,1.08)	(0.91,1.01)	(-1%,9%)	
	85%)					
Any	39%	42%	1.09	0.77	23%	<0.00
infection ²	(25% -	(33% - 51%)	(0.95,1.25)	(0.69,0.85)	(15%,31%)	
	56%)					
AGE ²	5%	3%	0.72	0.37	63%	<0.00
	(1% - 16%)	(1% - 8%)	(0.45,1.13)	(0.22,0.61)	(39%,78%)	
RVGE ³	5%	1%	0.18	0.11	89%	<0.00
	(0% - 17%)	(0% - 4%)	(0.09,0.35)	(0.05,0.27)	(73%,95%)	
AGE: acute g	gastroenteriti	s; CI: confidenc	ce interval; NH	S: National Healt	h Service; RVG	E:
rotavirus gas	stroenteritis.					
¹ Adjusted fo	or seasonality	and secular tr	end. ² Diagnos	is of any infectio	n and AGE by (clinical

coding only. ³ Diagnosis of RVGE by clinical coding and laboratory results.

1 2	244	
3 4 5	245	Hospital-acquired (HA) bloodstream infection rate
6 7	246	A decrease in HA bloodstream infection was observed in the post-vaccination period,
8 9 10	247	although this did not appear different from secular trends in the pre-vaccination period
11 12	248	(Figure 4).
13 14 15	249	Unplanned readmission rate
16 17	250	No difference was observed between the unplanned readmission rate in the pre-vaccination
18 19 20	251	period and the post-vaccination period (Figure 5).
20 21 22	252	Outlier rate
23 24 25	253	Clear seasonal patterns were observed for the outlier rate, with the highest peak during the
25 26 27	254	respiratory virus season in November/December, and a secondary peak during the rotavirus
28 29	255	season in January-May (Figure 6). The outlier rate increased in 2012, and remained high
30 31 32	256	throughout 2013-2015, both within and outside the rotavirus season. The increase in outlier
33 34	257	rate is synchronous with the closure of one specific ward, a large general medical ward in
35 36 37	258	November 2011, and the opening of a new medical admission unit (short-stay department
38 39	259	prior to discharge or admission to other wards).
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1 2	260	DISCUSSION
3 4 5 6 7 8 9 10 11 12 13 14	261	This is the first study to examine the effects of national vaccine introduction on wider
	262	measures of hospital pressures in the UK. The introduction of rotavirus vaccine has led to a
	263	large reduction in RVGE hospitalisation,[7] reflected in the reduction in proportion of
	264	admissions tested rotavirus-positive and the reduction in bed occupancy due to RVGE and
	265	AGE as described here. Lower bed occupancy for RVGE and AGE in the rotavirus season
15 16 17	266	post-vaccine introduction was concordant with lower bed occupancy for any infection in the
18 19 20	267	rotavirus season in the post-vaccination period. Despite the reduction in RVGE
20 21 22	268	hospitalisation, overall bed occupancy was not reduced. This suggests that a large, busy NHS
23 24 25	269	Trust, such as Alder Hey, operates at full capacity and that the beds that became available
25 26 27	270	by the reduction of RVGE hospitalisations were occupied by a different patient population,
28 29 30 31 32 33 34 35 36 37	271	probably reflecting a previously unmet need and/or physicians having greater freedom to
	272	admit patients if beds have become available. The absence of a reduction in overall bed
	273	occupancy could explain why reductions in the other proxy measures (HA-infection rate,
	274	unplanned readmission rate, outlier rate) were not observed.
38 39	275	Two other studies have examined hospital pressures since rotavirus vaccination
40 41 42	276	introduction. A study conducted in two Finnish hospitals concluded that bed occupancy for
42 43 44	277	RVGE and AGE decreased since introduction of the vaccine.[17] There is no discussion of
45 46	278	changes in total bed occupancy, or on other proxy measures for hospital pressures following
47 48 49	279	rotavirus vaccine introduction. A study conducted in a general hospital in Belgium (36
50 51	280	paediatric beds) concluded that bed-day occupancy, bed-day turnover and unplanned
52 53 54	281	readmissions for AGE were lower in the post-vaccination compared with the pre-vaccination
55 56	282	periods, and that this resulted in improved quality of care for overall admissions.[8] In our
57 58 59	283	study, the reduction of bed occupancy for RVGE did not result in a change in overall bed
60	284	occupancy or other measures of hospital pressure. No change in hospital length of stay for

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RVGE patients was observed. Median hospital stay for CA RVGE was shorter in Alder Hey

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3 4 5	286	NHS Foundation Trust than reported in the Belgian study (2.2 vs. 4.1 days), suggesting a
6 7	287	difference in management of RVGE cases, and could be an indicator of higher hospital
8 9 10	288	pressure and more rapid patient turnover in Alder Hey.
11 12	289	Several caveats need to be considered when using routinely collected data. Our analysis was
13 14 15	290	complicated by changes in hospital practises, in particular changes in patient flow,
16 17	291	laboratory procedures, infection control and clinical coding. Firstly, several wards relevant
18 19	292	to this study opened or closed during the study period. Although ward closures were
20 21 22	293	accounted for in the bed occupancy analysis, more subtle changes in patient dynamics still
23 24	294	influenced our results. A steep increase was observed for the outlier rate in 2012, with the
25 26 27	295	higher level sustained throughout 2013-2015. The increase in outlier rate is synchronous
28 29	296	with the closure of a large general medical ward in November 2011, and the opening of a
30 31 32	297	new medical admission. It is possible that the change in ward structure led to an increased
33 34	298	bed usage in surgical and specialised medical wards.
35 36	299	Secondly, several changes in laboratory procedures were observed during the study period,
37 38 39	300	most notably the introduction of polymerase chain reaction for the rapid testing of
40 41	301	respiratory pathogens in 2013. Faster diagnosis of respiratory infection could have had
42 43 44	302	implications for patient treatment, isolation practices and patient flow, and could have
45 46	303	influenced the measured hospital pressure outcomes. The number of admissions tested for
47 48 49	304	rotavirus did not change significantly over the study period, which provides confidence that
50 51	305	the drop in RVGE in the post-vaccine era is a real effect, and not caused by a change in
52 53 54	306	testing policy.
55 56	307	Thirdly, there were changes in infection prevention and control (IPC) practices in later years
57 58	308	of the study, including an increase in IPC staff; the introduction of isolation and hand
59 60	309	hygiene posters, bed space dividers screens and infection control enclosure isolation pods;

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291	laboratory procedures, infection control and clinical coding. Firstly, several wards relevant
292	to this study opened or closed during the study period. Although ward closures were
293	accounted for in the bed occupancy analysis, more subtle changes in patient dynamics still
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297	new medical admission. It is possible that the change in ward structure led to an increased
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301	respiratory pathogens in 2013. Faster diagnosis of respiratory infection could have had
302	implications for patient treatment, isolation practices and patient flow, and could have
303	influenced the measured hospital pressure outcomes. The number of admissions tested for
304	rotavirus did not change significantly over the study period, which provides confidence that
305	the drop in RVGE in the post-vaccine era is a real effect, and not caused by a change in
306	testing policy.
307	Thirdly, there were changes in infection prevention and control (IPC) practices in later years
308	of the study, including an increase in IPC staff; the introduction of isolation and hand
309	hygiene posters, bed space dividers screens and infection control enclosure isolation pods;
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and changes in environmental cleaning. Changes in IPC practices will most likely have resulted in changes in HA infection rates – it is difficult to disentangle their effect on HA infection from any effect due to a reduction in hospital pressures post-rotavirus vaccination introduction.

We observed that bed occupancy for any infectious disease increased in the pre-vaccination period, both within and outside the rotavirus season. An increase in bed occupancy for any respiratory infection (supplementary Figure 3) and any gastroenteritis was observed, but neither increase can fully account for the overall increase in any infection. It is possible that the increase in infection observed is due to an artefact of the recording of the data. Supplementary Figure 4 shows that all clinical diagnostic coding increased over the study period. Clinical diagnostic coding increased for both cases with and without any infection recorded. We observed that bed occupancy for any infection in the rotavirus season was lower than the expected bed occupancy for any infection based on pre-vaccination estimates. The increase in any clinical diagnostic coding was sustained in 2014 and 2015, providing confidence that our observation of lower than expected bed occupancy for any infection in the post-vaccination period is a true finding. Our analysis highlights the importance of the presentation of data from the full study period in a time-series analysis, rather than restricting the results to a "before-after" comparison, when there is non-homogeneity in disease management, hospital management and data collection over time. A long-term increase in bed occupancy for any infection could be observed (possibly due to an increase in clinical coding) that predated the introduction of vaccination: taking this ongoing increase in admissions coded as infection into account, a reduction in bed occupancy for any infection can be observed. A further consideration is how changes to the catchment population size and referral

patterns during the study period could affect our findings and their interpretation. There

1 2	335	has been a small but steady population growth in the surrounding region consistent with a
3 4 5	336	national trend, which could increase demand upon the hospital and dampen any effect of
6 7	337	rotavirus vaccination on reducing these pressures. Finally, the impact of any changes in
8 9 10	338	referral policy during the study period is difficult to quantity as Alder Hey serves a region of
11 12	339	over 7.1 million people.
13 14 15	340	Routinely collected hospital data can be used for the evaluation of a (vaccination) policy, but
16 17	341	our study highlights the difficulty of evaluating a (vaccination) policy in a period with
18 19 20	342	concurrent changes in patient flow, laboratory procedures and IPC practices.
21 22	343	The introduction of rotavirus vaccination has led to a dramatic reduction in hospitalisation
23 24 25	344	for RVGE and thus a reduction in bed occupancy for RVGE. However, overall bed occupancy
25 26 27	345	was not reduced further highlighting the severe strain the NHS is under and that demand is
28 29	346	outstripping capacity. Bed occupancy continues to rise and even a highly effective routine
30 31 32	347	vaccine only freed-up beds which were then filled by admissions, making no overall
33 34	348	headway into reducing the overall pressures the NHS is facing.
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 stages of study conduct. GlaxoSmithKline Biologicals SA also took in charge all costs
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355 **Conflicts of interest**

Rotarix is a trademark of the GSK group of companies.

NC, NF, and DH are in receipt of research grant support from the GSK group of companies 357 for the conduct of the present study. NC has received honoraria for participation in GSK 358 Rotavirus Vaccine Advisory Board Meetings from the GSK group of companies and from 359 360 Watermark Research Partners for participation in independent data monitoring committee of GSK-sponsored clinical trials of Rotavirus vaccine. NC and NF's institution received grant 361 from the GSK group of companies for the conduct of other analysis, not related to the 362 present work. DH received grants from the GSK group of companies and Sanofi Pasteur, and 363 Merck & Co., Inc. (Kenilworth, NJ USA) outside the submitted work. NBZ reports grants from 364 365 the GSK group of companies and from Takeda Pharmaceuticals outside the submitted work. BS and ET are employees of the GSK group of companies. EH, RC, MC and JC have nothing to 366 367 disclose.

368 Authorship and manuscript preparation

369 DH, RPDC, MC, NC, NF designed the study and wrote the protocol. EH performed the
370 analyses and wrote the manuscript. JSC and MC provided data for the study. NBZ provided
371 statistical support. DH, RPDC, MC, JSC, NBZ, NF, NAC provided advice on the understanding

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

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development and editorial support.

381 Data sharing

The results summary for this study (GSK study identifier: 205369 - ClinicalTrials.gov identifier: NCT03271593) is available on the GSK Clinical Study Register and can be accessed at www.gsk-clinicalstudyregister.com. The full data that support the findings of this study are held by Alder Hey Children's NHS Foundation Trust and restrictions apply to the availability of these data as they are not publicly available. Aggregated data may be available from the authors/ Alder Hey Children's NHS Foundation Trust on reasonable request and with permission of Alder Hey Children's NHS Foundation Trust.

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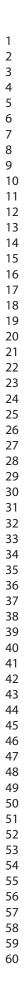
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1 2	434	Figures Captions
3 4 5	435	Figure 1. Number of admissions tested for rotavirus in the rotavirus season in Alder Hey
6 7	436	NHS Foundation Trust, July 2007 – June 2015.
8 9 10	437	NHS: National Health Service.
10 11 12	438	Figure 2. Total length of stay for CA and HA RVGE.
13 14	439	For HA RVGE, length of stay was calculated from date of first positive test.
15 16 17	440	CA: community-acquired; HA: hospital-acquired.
18 19	441	Figure 3. Observed and expected bed occupancy for any admission, any infection and
20 21 22	442	rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust,
23 24	443	July 2007 – June 2015.
25 26 27 28 29	444	The coloured shading represents the 95% confidence intervals for the expected incidence.
	445	Grey shading represents the rotavirus season (January-May). The vertical hashed line
30 31	446	represents the introduction of rotavirus vaccine in the UK in July 2013.
32 33 34	447	NHS: National Health Service.
35 36	448	Figure 4. Hospital acquired bloodstream infection rate on general medical wards in Alder
37 38 39	449	Hey NHS Foundation Trust, July 2007 – June 2015.
40 41	450	Black line shows raw data, red line shows smoothed data. Grey shading represents the
42 43 44	451	rotavirus season (January-May). The vertical hashed line represents the introduction of
45 46	452	rotavirus vaccine in the UK in July 2013.
47 48 49	453	HA: hospital-acquired; NHS: National Health Service.
50 51	454	Figure 5. Unplanned readmission rate for any admission on general medical wards in Alder
52 53	455	Hey NHS Foundation Trust, July 2007 – June 2015.
54 55 56	456	Raw data in black, smoothed data in red. Grey shading represents the rotavirus season
57 58	457	(January-May). The vertical hashed line represents the introduction of rotavirus vaccine in
59 60	458	the UK in July 2013.

1 2	459	NHS: National Health Service.
3 4 5	460	Figure 6. Outlier rate for any admission in Alder Hey NHS Foundation Trust, July 2007 –
6 7	461	June 2015.
8 9 10	462	Raw data in black, smoothed data in red. Grey shading represents the rotavirus season
10 11 12	463	(January-May). The vertical hashed line represents the introduction of rotavirus vaccine in
13 14 15	464	the UK in July 2013.
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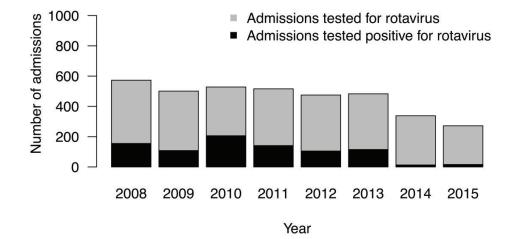
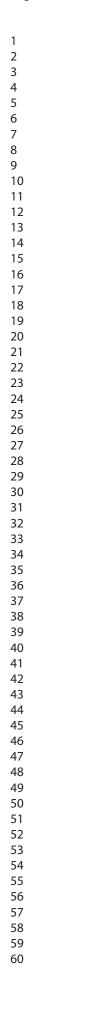


Figure 1. Number of admissions tested for rotavirus in the rotavirus season in Alder Hey NHS Foundation Trust, July 2007 – June 2015. NHS: National Health Service.



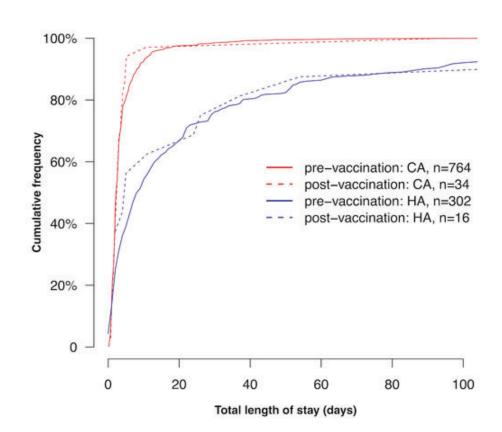
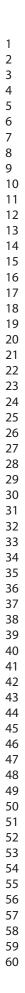


Figure 2. Total length of stay for CA and HA RVGE. For HA RVGE, length of stay was calculated from date of first positive test. *CA: community-acquired; HA: hospital-acquired.*



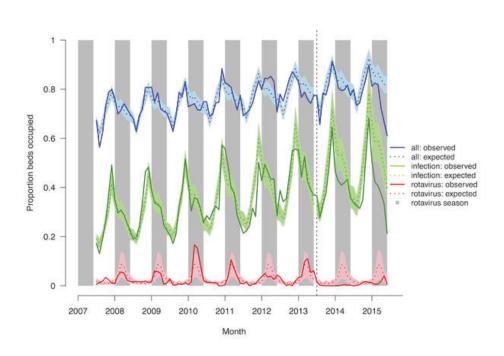


Figure 3. Observed and expected bed occupancy for any admission, any infection and rotavirus gastroenteritis on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

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.*

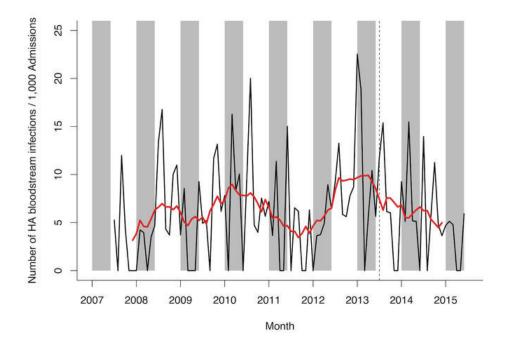


Figure 4. Hospital acquired bloodstream infection rate on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

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.

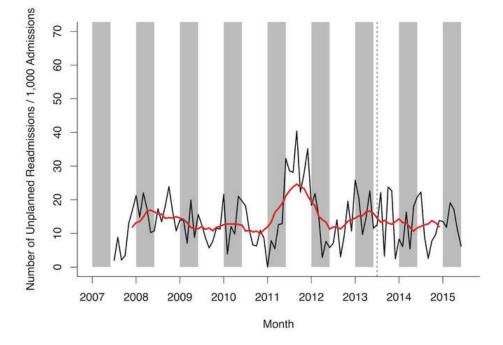


Figure 5. Unplanned readmission rate for any admission on general medical wards in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

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.*

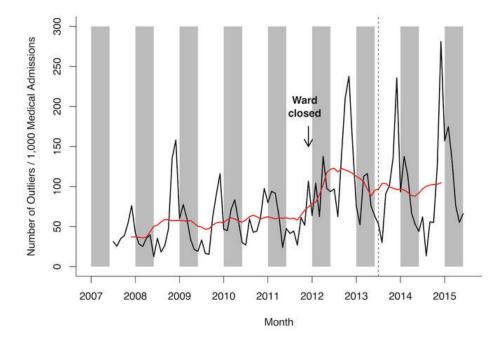
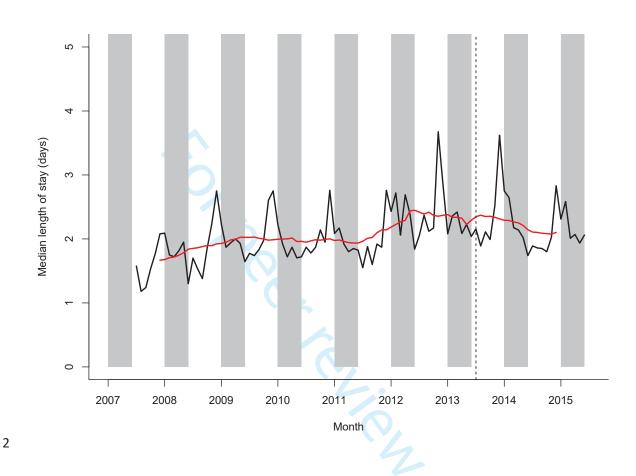


Figure 6. Outlier rate for any admission in Alder Hey NHS Foundation Trust, July 2007 – June 2015.

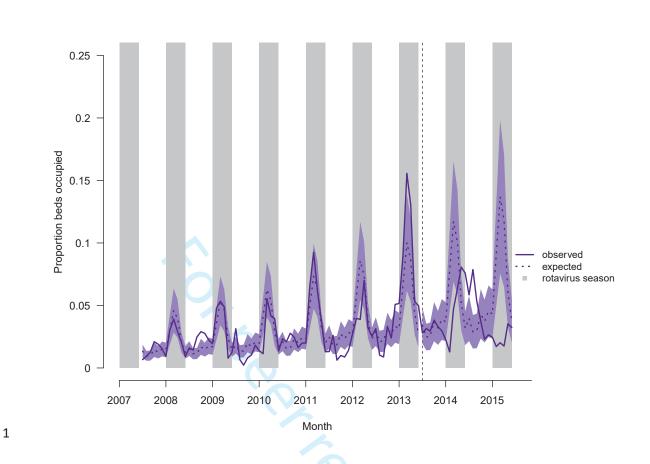
Raw data in black, smoothed data in red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents the introduction of rotavirus vaccine in the UK in July 2013. *NHS: National Health Service.*

1 Supplementary Material



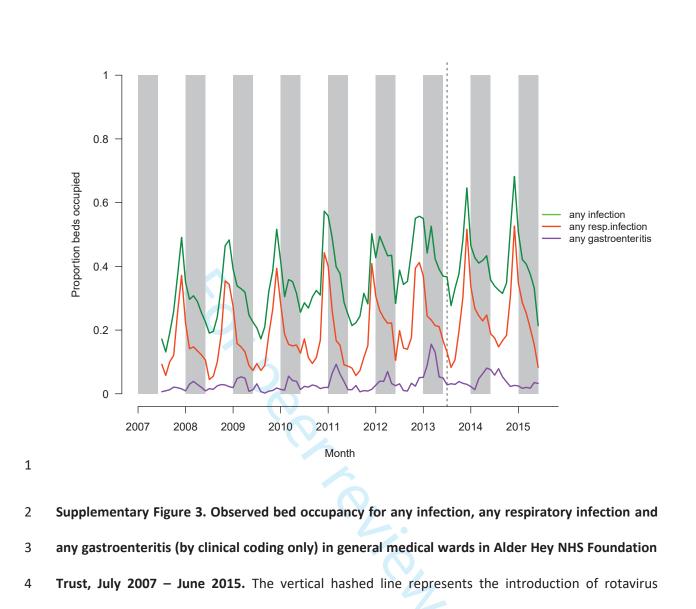
Supplementary Figure 1. Median length of stay (all admissions) on general medical wards in Alder
Hey Children's NHS Foundation Trust, July 2007 – June 2015. Raw data in black, smoothed data in
red. Grey shading represents the rotavirus season (January-May). The vertical hashed line represents
the introduction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

7 NHS: National Health Service.



Supplementary Figure 2. Observed and expected bed occupancy for acute 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.

7 NHS: National Health Service.



5 vaccine in the UK in July 2013.

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