Quality of Life Impacts from Rotavirus Gastroenteritis on Children and Their Families in the UK.

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Abstract

Aims

Rotavirus vaccines (RV) are safe and effective but demand significant investment of healthcare resource. In countries with low mortality due to rotavirus, a key component to assessing cost-effectiveness is quantifying the Health Related Quality of Life (HRQoL) lost due to rotavirus acute gastroenteritis (RVAGE).

Methods

Families with children less than six years old with gastroenteritis were recruited from attendees to Bristol Children's Hospital Emergency Department. Stools were tested for viral causes of gastroenteritis. Children's HRQoL was assessed at presentation using Health Utilities Index 2 (HUI2) with visual analogue scale (VAS). The effect of the child's illness on the HRQoL of up to two adult carers was assessed using EQ-5D-5L. Families completed a daily symptom diary to assess time to recovery and within-family transmission.

Results

127 families consented to take part, 84(65%) had rotavirus as the cause of illness.

At the time of attendance, mean paediatric HRQoL with RVAGE was 0.74(HUI2) and 0.42(VAS).

Primary / secondary carer's HRQoL was 0.68/0.80 (EQ5D) or 0.70/0.79 (VAS). The mean number of QALYs lost due to RVAGE was 3.1-3.5 per thousand children and 7.7-8.7 per thousand family units.

In 52% of RVAGE families at least one other member developed a secondary case of gastroenteritis.

For working parents, 69% missed work, for a mean of 2.8 days (95% CI 2.3-3.4).

Conclusions

We have found the HRQoL loss associated with RVAGE in children and their carers to be significantly higher than estimates used for all RV medical attendances in UK cost-effectiveness calculations.

Keywords: Rotavirus; Quality of life; Great Britain; Rotavirus Vaccines; Economic Evaluation

Introduction

Rotavirus is the commonest cause of gastroenteritis in childhood and most children will have suffered from it at least once by the time they are five years old.[1] Although prevalent in all countries, the burden of rotavirus is far from equitable. In developing countries with limited access to healthcare, it is estimated to lead to the deaths of half a million children under the age of five per year.[2] In the early 1980s, vaccination was identified as the only feasible method of controlling rotavirus.[3] A worldwide concerted effort to develop a vaccine has culminated in the licensure of two safe and effective formulations in 2006. The WHO has recommended that all countries[4] introduce RV vaccine into their childhood vaccination schedules.

With the support of international agencies and discounted vaccine prices, in countries with high levels of mortality due to rotavirus, the justification for vaccination is clear. But in those countries where mortality is rare, such as in the United Kingdom (UK), [5] a more formal approach to assessing cost-effectiveness is required. In the UK new vaccines are assessed by the Joint Committee for Vaccination and immunisation (JCVI) using methods based upon the National Institute for health and Care Excellence (NICE) health technology assessment framework. Crucial to cost-effectiveness calculation is an assessment of how the disease affects health related quality of life (HRQoL). When expressed over time as Quality Adjusted Life Years (QALYs) this permits standardised comparisons between different healthcare interventions.

Cost effectiveness is often summarised by the incremental cost effectiveness ratio (ICER) which represents the cost implications per net change in QALYs. In the UK, NICE suggests that an ICER less than £20-30,000 per QALY is likely to be cost-effective. To fully capture the benefits of an intervention, NICE recommends that all direct health benefits (not just those for the patient) should be taken into account. Reviews have found that this is still a relatively uncommon practice, most often applied in health economic assessments of chronic diseases with informal but long term caring commitments such as dementia. [6–8]

Although there have been many assessments of the clinical burden[9–11] and secondary economic costs to families,[12,13] the effects of rotavirus on HRQoL have not been robustly assessed. The analyses of rotavirus vaccine cost effectiveness in the UK [14] as well as in other countries[15,16] are based on data from a single cohort of attendances to Canadian primary care.[17] All found the QALY loss of parents and children to be a major determining factor of vaccine cost effectiveness. As the severity of cases seen in primary care may not be representative of the whole spectrum of rotavirus disease, we sought to determine the effects of more severe rotavirus infection on the HRQoL of a cohort of children and their parents in the UK to help provide additional data to parameterise any future cost effectiveness analyses.

Methods

Children presenting with symptoms of gastroenteritis (>2 loose stools and/or >1 episode of forceful vomiting in the last 24 hours) under six years of age were recruited from the paediatric emergency department of Bristol Royal Hospital for Children. After obtaining informed consent, a short questionnaire assessed childrens' and their carers' quality of life at the point of presentation to hospital and asked for how long symptoms had been present. The impact of the child's illness on the quality of life of the primary, and when present, secondary carer was assessed using the EQ5D-5L[18] using UK 3L-5L crosswalk valuation sets for valuation[19]. Children's HRQoL was assessed using the Health Utilities Index 2 (HUI2)[20] questionnaire with the addition of the EQ5D visual analogue scale (VAS) which is anchored at 0 - "best health you can imagine" to 100- "worst health you can imagine". Clinical severity was assessed using the Vesikari [21] scoring system. This scale was developed for the assessment of rotavirus vaccines and combines the length and frequency of symptoms, degree of dehydration and level of treatment required to assign a score between 0 and 20. In its derivation community cohort of children with rotavirus gastroenteritis the mean score was 11 (standard deviation 3.7); conventionally severe gastroenteritis is defined as a score greater than 10. A stool sample was collected and tested for viral causes of gastroenteritis using routine clinical PCR. Families were asked to complete a daily diary card recording children's symptoms, days of

missed work, childcare and healthcare use until they felt their child had returned to normal health (see appendix 1 for example page). At this point there was a final assessment of the whole family's HRQoL and the diary was returned by post.

Figure 1: Graphical representation of our method of estimating QALY loss.
Point A represents disease onset, point B assessment in the emergency department at nadir HRQoL. Point C, recovery HRQoL – is assumed to represent pre-morbid baseline. Shaded area represents the QALY loss due to rotavirus gastroenteritis.

As rotavirus is usually a transient self limiting illness with no long term effects, we assumed that a child's pre-morbid HRQoL would be the same as their HRQoL once they had recovered from the acute illness. To calculate HRQoL loss we estimated a constant linear decrease from the pre-morbid baseline at reported symptom start to a nadir at point of presentation to the emergency department and then constant improvement to return to baseline by the reported end date. (Figure 1)

Any incomplete domains were scored as perfect health. Non parametric distributions were compared using the Mann -Whitney U test. Confidence intervals for the mean were derived from 1000 bootstrap iterations. Statistical analyses were performed using R.[22]

The study was approved by the South West Central Bristol NRES ethics committee (REC12/SW/0359) and funded through a University Hospitals Bristol NHS Foundation Trust Clinical PhD studentship.

Results

129 families consented to take part in the study, 118 (91%) completed the initial questionnaire and 59 (46%) returned the diary. Of the 84 (65%) found to be rotavirus positive, 77 completed the initial questionnaire and 48 returned the diary. Childrens' median age was 14 months (IQR 10-22m) and 52% were male. Children had been ill for a mean 4 (95%CI 3.5-4.6) / median 4 (IQR 2-5) days before attending the emergency department. 41 (53%) children required hospital admission. The mean

Vesikari score on attendance was 11.2 (SD 2.5 range 5-18) with 66% categorised as severe (score greater than 10).

		First assessment n=77		Final Assessment n=48	
		Mean	(95% CI)	Mean	(95% CI)
Child	HUI2	0.735	0.69 - 0.78	0.96	0.94- 0.98
	VAS	0.418	0.37 - 0.46	0.83	0.79- 0.88
Primary carer	EQ5D	0.68	0.61 - 0.74	0.86	0.81 - 0.92
	VAS	0.70	0.65- 0.75	0.84	0.80 - 0.89
Secondary carer	EQ5D	0.80	0.74 - 0.85	0.93	0.90 - 0.96
	VAS	0.79	0.73- 0.85	0.88	0.84 - 0.93

Table 1 of HRQol of child & related adults

Table 1 shows the mean HRQoL of children and carers at presentation and at final assessment in those who returned diaries. At time of presentation to the emergency department, the main domains reported to be affected in children were emotion and pain, with 81% and 64% reporting reduced scores, respectively. In adults the main domains were usual activities and anxiety (with 64% and 62% of cases reporting reduced scores, respectively). There were no significant differences in reported initial HRQoL (p=0.72), disease severity (p=0.92), rate of admission (p=0.23) or length of illness prior to attendance (p=0.5) between those who did and did not return the diaries. Children whose parents returned the diaries tended to be slightly older (median 15.8 vs 11.1 months (p=0.06) than those who did not, but were not significantly different (p=0.2) from the total age distribution of gastroenteritis attendances to the Emergency Department. Families reported their children to remain ill for a mean 5.7 (95%CI 5.1- 6.5) / median of 5.5 (IQR 4-7) additional days following initial interview.

Parents were asked to self allocate as the primary (n=48) or secondary (n=41) carer. In all but one case (where there was a single father), the mother was recorded as primary carer. There were five single mothers families leaving 40 fathers and one grandmother recorded as secondary carers. Within the completed diary cohort, at least one other member developed a secondary case of gastroenteritis in 52% of households. For working carers, 69% missed a mean 2.8 (95% CI 2.3-3.4), median 2.3 (IQR 1.4 -3.8) days of work.

For our primary analysis, in those who returned their diaries, we calculated QALY loss using the last reported HRQoL as baseline, i.e. we assumed that by the end of the study individuals had returned to normal health. For children this equated to a mean loss of 3.1 QALYs per thousand episodes, with mean loss for primary and secondary carers 2.7 and 2.1 QALYS per 1000 episodes respectively.

However 43% of families still reported their child to be unwell in free-text or using the VAS in their last diary entry. Concurrently 44% of carers still reported their HRQoL below standard healthy norms[23] and in free text ten (20%) parents noted that they were suffering from gastroenteritis themselves. To account for this, we carried out a sensitivity analysis (table 2) using the nadir HRQoL reported by all respondents (not just those returning the diaries) and compared it to baseline of perfect health in children and healthy adult UK EQ5D population standard values[23] for age and gender. This resulted in a higher estimated QALY loss for children and the primary carer, although confidence intervals overlapped with our primary estimates.

Analysis	**Population**	**HRQoL comparisions**	**Mean QALY loss per thousand cases (95% CI)**		
			Child	Primary carer	Secondary carer
Primary	Diary returners (n=48)	Difference in individual's first reported HRQoL to the final using triangular function (fig 1a)	3.1 (2.2-4.1)	2.7 (1.2-4.1)	2.1 (1.3-3.0)
Sensitivity	All respondents (n=77)	Difference in individual's first reported HRQoL compared to perfect health in children and population norm for adults	3.5 (2.9-4.1)	3.4 (2.5-4.3)	1.8 (1.0-2.7)

Table 2: Sensitivity analysis comparing our primary analysis to an alternative method of calculating the mean QALY loss / 1000 cases of rotavirus.

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147 Comparing patients who could be discharged from the Emergency department to those that

148 required admission(table 3) we found that families with children requiring admission all reported a

149 trend towards a greater total QALY loss than those who could be discharged, 8.2 vs 4.6 (p=0.18) or 9

150 vs 5.8 QALYS (p=0.08).

Population	**HRQoL comparisions**		**Mean QALY loss per thousand cases (95% CI)**			
			Child	Primary carer	Secondary carer	Family total
Primary analysis Diary returners (n=48)	Difference in individual's first reported HRQoL to the final using triangular function (fig 1a)	Admitted (n=24)	3.4 (1.5-5.3	4.0 (1.6-6.4)	2.8 (1.7-3.9)	8.2 (4.7-11.7)
		Discharged (n=24)	2.9 (2.3-3.4)	1.4 (0.3-2.3)	1.5 (0.2-2.7)	4.6 (2.9-6.3)
		p=	0.91	0.60	0.05	0.18
Sensitivity analysis All respondents (n=77)	Difference in individual's first reported HRQoL compared to perfect health in children and population norm for adults	Admitted (n=36)	3.9 (2.9-4.8)	4.3 (2.8-5.6)	2.4 (1.0-3.7)	9.0 (6.7-11.3)
		Discharged (n=41)	3.0 (2.4-3.7)	2.3 (1.4-3.3)	1.3 (0.3-2.3)	5.8 (4.3-7.3)
		p=	0.33	0.71	0.13	0.08

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152 Table 3: Sub-analysis comparing the mean QALY loss / 1000 cases of rotavirus between those who

153 could be discharged from the emergency department and those who required admission.

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Discussion

This is the first attempt to measure the number of Quality Adjusted Life Years lost due to acute severe rotavirus gastroenteritis in the UK. We have found the QALY loss of children with acute rotavirus attending the paediatric emergency department to be 3.1-3.5 per 1000 cases. The QALY loss per thousand primary / secondary carers was 2.7-3.4 and 1.8-2.1 respectively.

There are just three published studies using a parentally reported preference based method to assess HRQoL during rotavirus infection and only one calculates total QALY loss. A Canadian study of rotavirus burden[24] examined 395 children under the age of three years presenting for outpatient paediatric care. A separately reported HRQoL arm[17] used the HUI2 to assess children and EQ5D for parents at presentation, day 7 and day 14. This found nadir HRQoL of 0.896 (0.874; 0.917) for children and 0.875(0.844; 0.907) for parents. Comparing to a baseline reported HRQoL at day 14 they estimated a QALY loss of 2.2 (95% CI: 1.7; 2.7) and 1.8 (95% CI: 1.0; 2.7) per thousand affected children and parents respectively. This figure was used for all cases seeking medical attention in the cost-effectiveness model[14] instrumental in the UK's 2012 decision to introduction of RV vaccine. Two further studies report the HRQoL at presentation with rotavirus gastroenteritis. Both used the EQ5D for both parent and child (despite there being no validated value sets for children). The first study from Thailand [25] examined hospitalised children and rated the mean child's utility as 0.604 (95%CI: 0.592, 0.615) and parents of 0.618 (95%CI: 0.606, 0.629). The second study from Denmark[26] of all gastroenteritis attendances found median HRQoL of 0.7123 for children, and 0.818 for parents with a median length of illness of 7 days. This was lower in those who required hospitalisation for both the child (0.531) and their parent (0.743) although no significance testing or confidence intervals were reported.

Between countries, different attitudes to health seeking behaviour and accessibility to health services will dictate the severity of cases seen in a particular healthcare setting. In the UK, with the re-organisation of primary care provision, increasing numbers of families now present directly to

the Emergency Department for minor medical illnesses.[27] Thus paediatric emergency departments have a very varied case mix, providing both primary care to self-referrals as well as secondary assessments of more severe cases. Within our cohort only 12% had been referred to hospital by their GP, yet 60% reported that they had already consulted their GP at least once during the episode. Despite 53% requiring admission, our cohort's mean HRQoL was significantly higher than Thai inpatients ($p<0.001$), and most similar to those reported from Danish primary care. Both our HRQoL ($p<0.001$) and sensitivity QALY loss ($p<0.001$) estimates are significantly greater than those measured by Brisson et al[17]. Although underpowered, our subgroup analysis suggests that even patients that could be discharged from the emergency department have a greater QALY loss than in Canadian primary care; with those requiring admission reporting a trend towards greater effects.

The main limitation of our study is that in an effort to reduce the burden on families already looking after sick children, rather than require daily diary entry for a fixed period, we allowed carers to report when they considered their child to be recovered and return the diary at that point. It was hoped that this would improve our diary response rate. However despite clear instructions and reminders, many families returned the diaries as soon as diarrhoea had ceased, while commenting that their child had not yet returned to normal in the free text and VAS score. As such our data may both underestimate the length of illness and give a falsely low end baseline HRQoL; to address this we used alternative baselines in a sensitivity analysis, which resulted in slightly higher estimated QALY losses. Our measure of carer HRQoL is likely to have captured both the worry/stress of caring for their child and also any effects of them becoming ill themselves during the time window during which their child was ill. Adult measurements were taken at the (assumed) peak and resolution of child's illness – which will not necessarily correspond to the time course of a carer's disease. Thus carers' QALY loss may well be an underestimate in those who became ill as any acute deterioration is unlikely to have been detected by our method. The differences seen between carers are interesting. By definition the primary carer will have spent more time caring for the ill child, so it is perhaps not

surprising that they felt their quality of life was more affected than the other parent, however the proportion of reported secondary illness was not significantly different 32%/34% (p=1.0) between carers.

In contrast to adults, estimating the HRQoL of pre-school children is problematic[28] as there is simply no validated instrument for this specific age group. We chose to use parentally reported HUI2 as although designed for children over the age of five, it has previously been recommended by NICE[29], UK specific values have been developed[30] and it was the method used in the most widely cited assessment in the literature.[17] This allows direct comparison of our data with those results, and may explain some of the difference in comparison with studies using the adult EQ5D instrument for children.

In comparison to other vaccine preventable diseases (table 4) our findings suggest that on average, an individual episode of rotavirus has only a relatively small HRQoL impact. However the ubiquitous nature of this disease means that this represents a significant population burden especially when the effects on carers are included.

With an increasing number of vaccines being developed but finite healthcare resources, the decision of which ones to introduce can become problematic. For well informed recommendations using our current cost per QALY approach; it is essential that there are accurate data characterising the burden of common childhood illness being collected.

Disease	Child's QALY loss/1000 cases	Incidence in children by age 5
Rotavirus	3.1-3.5	98%[1]
Pneumonia[31]	4	
Chickenpox[32]	4	45%[32]
Influenza[33]	8	67%[34]
Measles[35]	19	<1% with vaccine
Pertussis[36]	97	<1% with vaccine
Meningococcal disease (cases without sequelae)[37]	200	0.05%[38]

Table 4 – QALY loss for childhood vaccine preventable diseases.

Conclusions

Our results suggest that RV gastroenteritis has a significantly higher impact on the quality of life of children and their carers in the UK than previously reported in studies done elsewhere. The results of the first year of vaccination in the UK appear to show a large reduction in rates of disease[39]. Our findings imply the programme will have been more cost effective than previously estimated, since the QALY losses we show in children presenting to the Emergency Department and their families are higher than the estimates used in the cost effectiveness studies which drove the recommendation to introduce the vaccine. These figures may be of value to other European countries still evaluating the cost-effectiveness of introducing rotavirus vaccination.

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Conflicts of interest

RM has received travel bursaries from GSK to attend educational meetings. AF undertakes consultancy and clinical research for all the main vaccine companies, the fees payable to the University of Bristol and University Hospitals Bristol NHS Foundation Trust. CT received a consulting payment from GSK in 2013 for critical review of a health economic model of meningococcal vaccines.

References

[1] Marlow RD, Finn A. The promise of immunisation against rotavirus. Arch Dis Child 2012;97:736–40. doi:10.1136/archdischild-2011-301472.

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

[3] De Zoysa I, Feachem RG. Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunization. Bull World Health Organ 1985;63:569–83.

[4] WHO | 18 December 2009, vol. 84, 50 (pp 533–540) n.d. http://www.who.int/wer/2009/wer8451_52/en/index.html (accessed October 25, 2010).

[5] Jit M, Pebody R, Chen M, Andrews N, Edmunds WJ. Estimating the number of deaths with rotavirus as a cause in England and wales. Hum Vaccin 2007;3:23–6.

[6] Goodrich K, Kaambwa B, Al-Janabi H. The inclusion of informal care in applied economic evaluation: a review. Value Health J Int Soc Pharmacoeconomics Outcomes Res 2012;15:975–81. doi:10.1016/j.jval.2012.05.009.

[7] Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. PharmacoEconomics 2013;31:489–500. doi:10.1007/s40273-013-0040-y.

[8] Krol M, Papenburg J, van Exel J. Does including informal care in economic evaluations matter? A systematic review of inclusion and impact of informal care in cost-effectiveness studies. PharmacoEconomics 2015;33:123–35. doi:10.1007/s40273-014-0218-y.

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

[10] Iturriza Gomara M, Simpson R, Perault AM, Redpath C, Lorgelly P, Joshi D, et al. Structured surveillance of infantile gastroenteritis in East Anglia, UK: incidence of infection with common viral gastroenteric pathogens. Epidemiol Infect 2008;136:23–33. doi:10.1017/S0950268807008059.

[11] Iturriza-Gómara M, Elliot AJ, Dockery C, Fleming DM, Gray JJ. Structured surveillance of infectious intestinal disease in pre-school children in the community: “The Nappy Study.” Epidemiol Infect 2009;137:922–31. doi:10.1017/S0950268808001556.

[12] Giaquinto C, Van Damme P, Huet F, Gothefors L, Van der Wielen M, REVEAL Study Group. Costs of Community-Acquired Pediatric Rotavirus Gastroenteritis in 7 European Countries: The REVEAL Study. J Infect Dis 2007;195:S36–44. doi:10.1086/516716.

[13] Lorgelly PK, Joshi D, Iturriza Gómara M, Flood C, Hughes CA, Dalrymple J, et al. Infantile gastroenteritis in the community: a cost-of-illness study. Epidemiol Infect 2008;136:34–43. doi:10.1017/S0950268807008163.

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

[15] Newall A.T., Beutels P., Macartney K., Wood J., MacIntyre C.R. The cost-effectiveness of rotavirus vaccination in Australia. Vaccine 2007.

[16] Bilcke J, Damme PV, Beutels P. Cost-Effectiveness of Rotavirus Vaccination: Exploring Caregiver(s) and ``No Medical Care'' Disease Impact in Belgium. Med Decis Making 2009;29:33–50. doi:10.1177/0272989X08324955.

[17] Brisson M, Sénécal M, Drolet M, Mansi JA. Health-Related Quality Of Life Lost To Rotavirus-Associated Gastroenteritis In Children And Their Parents. Pediatr Infect Dis J 2010;29:73–5. doi:10.1097/INF.0b013e3181b41506.

[18] EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy Amst Neth 1990;16:199–208.

297 [19] Van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring
298 for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health J Int Soc
299 Pharmacoeconomics Outcomes Res 2012;15:708–15. doi:10.1016/j.jval.2012.02.008.
300 [20] Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function
301 for a comprehensive health status classification system. Health Utilities Index Mark 2. Med
302 Care 1996;34:702–22.
303 [21] Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical
304 severity of diarrhoeal episodes. Scand J Infect Dis 1990;22:259–67.
305 [22] R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R
306 Foundation for Statistical Computing; 2014.
307 [23] Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Centre for Health Economics,
308 University of York; 1999.
309 [24] Sénécal M, Brisson M, Lebel MH, Yaremko J, Wong R, Gallant LA, et al. Measuring the Impact of
310 Rotavirus Acute Gastroenteritis Episodes (MIRAGE): A prospective community-based study.
311 Can J Infect Dis Med Microbiol 2008;19:397–404.
312 [25] Rochanathimoke O, Postma M, Thavorncharoensap M, Riewpaiboon A, Thinyounyong W.
313 PGI35 - Quality Of Life Of Diarrheal Children And Caregivers In Thailand. Value Health
314 2014;17:A368–9. doi:10.1016/j.jval.2014.08.832.
315 [26] Hoffmann T, Iturriza M, Faaborg-Andersen J, Kraaer C, Nielsen CP, Gray J, et al. Prospective
316 study of the burden of rotavirus gastroenteritis in Danish children and their families. Eur J
317 Pediatr 2011;170:1535–9. doi:10.1007/s00431-011-1465-y.
318 [27] Sands R, Shanmugavadivel D, Stephenson T, Wood D. Medical problems presenting to
319 paediatric emergency departments: 10 years on. Emerg Med J EMJ 2012;29:379–82.
320 doi:10.1136/emj.2010.106229.
321 [28] Grange A, Bekker H, Noyes J, Langley P. Adequacy of health-related quality of life measures in
322 children under 5 years old: systematic review. J Adv Nurs 2007;59:197–220.
323 doi:10.1111/j.1365-2648.2007.04333.x.
324 [29] National Institute for Health and Clinical Excellence. Guide to the methods of technology
325 appraisal. 2008.
326 [30] McCabe CJ, Stevens KJ, Brazier JE. Utility scores for the Health Utilities Index Mark 2: an
327 empirical assessment of alternative mapping functions. Med Care 2005;43:627–35.
328 [31] Melegaro A, Edmunds WJ. Cost-effectiveness analysis of pneumococcal conjugate vaccination
329 in England and Wales. Vaccine 2004;22:4203–14. doi:10.1016/j.vaccine.2004.05.003.
330 [32] Brisson M, Edmunds WJ. Varicella vaccination in England and Wales: cost-utility analysis. Arch
331 Dis Child 2003;88:862–9. doi:10.1136/adc.88.10.862.
332 [33] Van Hoek AJ, Underwood A, Jit M, Miller E, Edmunds WJ. The impact of pandemic influenza
333 H1N1 on health-related quality of life: a prospective population-based study. PloS One
334 2011;6:e17030. doi:10.1371/journal.pone.0017030.
335 [34] Sauerbrei A, Langenhan T, Brandstädt A, Schmidt-Ott R, Krumbholz A, Girschick H, et al.
336 Prevalence of antibodies against influenza A and B viruses in children in Germany, 2008 to
337 2010. Euro Surveill 2014;19.
338 [35] Thorrington D, Ramsay M, van Hoek AJ, Edmunds WJ, Vivancos R, Bukasa A, et al. The Effect of
339 Measles on Health-Related Quality of Life: A Patient-Based Survey. PLoS ONE 2014;9:e105153.
340 doi:10.1371/journal.pone.0105153.
341 [36] Van Hoek AJ, Campbell H, Andrews N, Vasconcelos M, Amirthalingam G, Miller E. The Burden
342 of Disease and Health Care Use among Pertussis Cases in School Aged Children and Adults in
343 England and Wales; A Patient Survey. PLoS ONE 2014;9. doi:10.1371/journal.pone.0111807.
344 [37] Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of
345 universal meningitis vaccination (Bexsero) in England: modelling study. BMJ 2014;349:g5725–
346 g5725. doi:10.1136/bmj.g5725.

[38] Ladhani SN, Flood JS, Ramsay ME, Campbell H, Gray SJ, Kaczmarski EB, et al. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. Vaccine 2012;30:3710–6. doi:10.1016/j.vaccine.2012.03.011.
[39] Marlow R.D., Muir P, Vipond B, Trotter C, Finn A. Assessing the impacts from one year of rotavirus vaccination in the UK. Eurosurveillance 2015;accepted.