

Cost-Effectiveness Analysis of Maternal Immunisation Against Group B Streptococcus (GBS) Disease: a Modelling Study.

Kyriaki Giorgakoudi^{a,1}, Kyriaki.Giorgakoudi@brunel.ac.uk, Catherine O'Sullivan^b, cosulliv@sgul.ac.uk, Paul T. Heath^b, pheath@sgul.ac.uk, Shamez Ladhani^{b,c}, Shamez.Ladhani@phe.gov.uk, Theresa Lamagni^d, Theresa.Lamagni@phe.gov.uk, Mary Ramsay^c, Mary.Ramsay@phe.gov.uk, Hareth Al-Janabi^e, H.AJJanabi@bham.ac.uk, Caroline Trotter^a, clt56@cam.ac.uk

^aDepartment of Veterinary Medicine, University of Cambridge, Cambridge, UK

^bVaccine Institute, Institute of Infection and Immunity, St George's University of London, London, UK

^cImmunisation, Hepatitis and Blood Safety Department, National Infection Service, Public Health England, London UK

^dHealthcare-Associated Infection & Antimicrobial Resistance Department, National Infection Service, Public Health England, London UK

^eInstitute of Applied Health Research, University of Birmingham, Birmingham, UK

Correspondence to:

Kyriaki Giorgakoudi, Kyriaki.Giorgakoudi@brunel.ac.uk

Institute of Environment, Health and Societies, Brunel University London, Uxbridge, UK

¹ Present address: Institute of Environment, Health and Societies, Brunel University London, Uxbridge, UK

1 **Abstract**

2 Background: There is a considerable global burden of invasive group B streptococcal (GBS)
3 disease. Vaccines are being developed for use in pregnant women to offer protection to
4 neonates.

5 Objective: To estimate the potential impact and cost-effectiveness of maternal immunisation
6 against neonatal and maternal invasive GBS disease in the UK.

7 Methods: We developed a decision-tree model encompassing GBS-related events in infants
8 and mothers, following a birth cohort with a time horizon equivalent to average life
9 expectancy (81 years). We parameterised the model using contemporary data from disease
10 surveillance and outcomes in GBS survivors. Costs were taken from NHS sources and
11 research studies. Maternal immunisation in combination with risk-based intrapartum
12 antibiotic prophylaxis (IAP) was compared to the current standard practice of risk-based IAP
13 alone from an NHS and Personal Social Services (health-provider) perspective. We estimated
14 the cases averted and cost per QALY gained through vaccination. One-way sensitivity
15 analysis, scenario analysis and probabilistic sensitivity analysis were performed.

16 Results: An effective maternal immunisation programme could substantially reduce the
17 burden of GBS disease. The deterministic analysis estimated the threshold cost-effective
18 price for a GBS vaccine to be £54 per dose at £20,000 /QALY (£71 per dose at £30,000
19 /QALY). Results were most sensitive to assumptions on disease incidence, sequelae rate and
20 vaccine efficacy. Probabilistic analysis showed 90.66% of iterations fell under the £30,000
21 threshold at a vaccine price of £55. Inclusion of modest prevention of stillbirths and/or,
22 preterm births, carer health impacts, maternal GBS deaths and 1.5% discounting improved
23 cost-effectiveness compared to the base case. Lowering vaccine strain coverage made the
24 vaccine less cost-effective. A key limitation is that the properties of the final GBS vaccine are

25 unknown.

26 Conclusions: Maternal GBS immunisation is expected to be cost-effective, even at a
27 relatively high vaccine price.

28 **Keywords:** Group B Streptococcus; vaccine; infant; pregnancy; infectious disease; cost-
29 effectiveness analysis

30

31 **Introduction**

32 In the UK, group B *Streptococcus* (GBS; *Streptococcus agalactiae*) is a leading cause of
33 meningitis and septicaemia in babies up to 3 months of age. A recent national prospective
34 study showed GBS was responsible for half of all neonatal meningitis cases [1]. Invasive
35 infant GBS disease has a case fatality rate of 5-10% in the UK [1–3], despite the availability
36 of sophisticated neonatal intensive care. Up to 50% of GBS meningitis survivors have
37 adverse neurodevelopmental outcomes [4]. GBS is also implicated as a cause of stillbirth
38 [5,6], pre-term birth [6,7] and maternal sepsis [6,8].

39 GBS is part of the natural flora of the human gastrointestinal and genitourinary tracts.

40 Asymptomatic carriage is common, with 20% of pregnant women in developed countries
41 carrying GBS rectovaginally [9]. Around 50% of infants born to colonised mothers will
42 become colonised and 1% will develop GBS disease [7]. Because maternal colonisation is a
43 necessary stage in the disease process, at least for early onset disease (defined as <7 days of
44 age), intervention strategies have, to date, focussed on prophylactic antibiotics for women in
45 labour targeted on the basis of antenatal screening results and/or identified risk factors [10].

46 The incidence of GBS disease has increased in the UK since 2004 [1,11]; enhanced
47 surveillance studies from the British Paediatric Surveillance Unit (BPSU) reported incidence
48 of 0.72 per 1000 livebirths in 2004 [3] and 0.97 per 1000 livebirths in 2015 [2]. This increase

49 is despite the UK prevention strategy of risk factor-based intrapartum antibiotic prophylaxis
50 (IAP) [12]. The UK has not adopted universal antenatal screening because it is not clear
51 whether the benefits of screening outweigh the harms for the majority of pregnant women
52 [13]. Maternal immunisation strategies offer promise for the prevention of infant GBS
53 disease without reliance on widespread antibiotic use and several vaccine candidates are in
54 development [14].

55 Any new vaccine being considered for introduction into the UK immunisation programme
56 must be supported with evidence of cost-effectiveness. A previous study [15] examined the
57 cost-effectiveness of interventions against infant GBS disease in the UK, including maternal
58 immunisation. This analysis emphasised that further research should prioritise the realisation
59 of a GBS vaccine, although at this time vaccination was still a distant prospect. Other studies
60 on the cost-effectiveness of GBS vaccines have been published more recently, including a
61 study exploring the South African case [16], a study in sub-Saharan Africa [17] and two
62 based in the USA [18,19]. The aim of this paper is to estimate the potential cost-effectiveness
63 of GBS vaccine in the current UK context in order to inform both vaccine development and
64 decision-making once a vaccine is licensed.

65

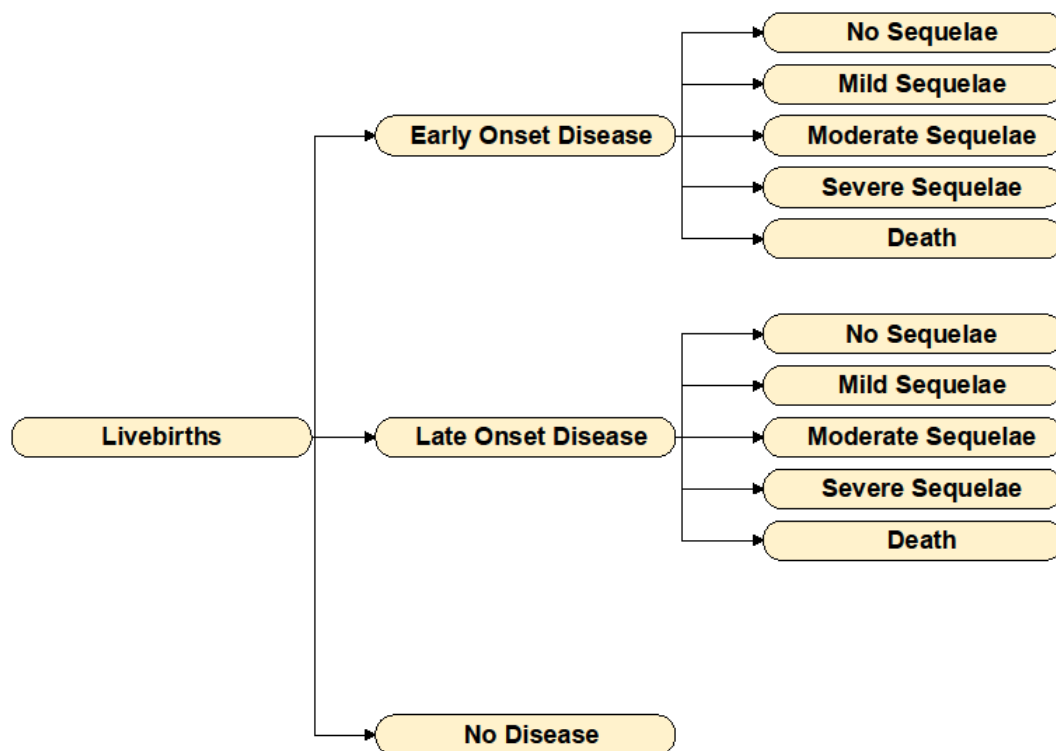
66 **Methods**

67 *Model description*

68 A static decision tree model was developed to account for infant GBS disease and long-term
69 health outcomes, including death, among an annual cohort of UK livebirths (**Error!**
70 **Reference source not found.**). Maternal GBS disease was estimated separately based on the
71 incidence of disease among maternities (excluding miscarriages). Stillbirths were included in

72 the estimation of vaccination costs, however, the potential impact of the vaccine on the
 73 prevention of both stillbirths and preterm births was only explored in scenario analysis.

74 The cohort of livebirths was assumed to be homogenous and was based on 2014 data
 75 reporting 776,352 livebirths in the UK [20–22]. Infants were followed over their lifetime to
 76 enable the inclusion of health outcomes and healthcare costs over this period. The adopted
 77 time horizon was the life expectancy of survivors with no or mild sequelae, which was 81
 78 years [23]. There were 3,563 stillbirths in the UK in 2014 [20,24,25] and these were included
 79 in the estimation of maternal immunisation costs (vaccine purchase and administration).



80

81 **Figure 1. Diagram of decision tree model for base case scenario.** The structure of the model remains
 82 the same for both strategies; risk factor-based IAP and maternal immunisation with risk factor-based
 83 IAP. Incremental health benefits of the latter strategy were estimated for the annual livebirths
 84 population (776,352 in 2014 data) with vaccination costs estimated for both livebirths and stillbirths

85 (3,563 in 2014). The potential impact of strategies on maternal disease (all maternities excluding
86 miscarriage) is estimated separately.

87

88 The current prevention strategy against infant GBS disease within the UK is one of risk
89 factor-based IAP. The risk factors are a previous baby with GBS disease, maternal GBS
90 carriage discovered during pregnancy, preterm birth, prolonged rupture of membranes,
91 suspected maternal intrapartum infection and pyrexia [26]. Assuming that vaccinated
92 pregnant women will still be provided with IAP in the presence of risk factors, we estimated
93 the incremental cost-effectiveness of a maternal immunisation strategy in combination with
94 risk factor-based IAP using the current standard practice of risk factor-based IAP alone as a
95 comparator. For this reason, any savings that may arise through reduced antibiotic use and
96 associated care were ignored; making our results more conservative. The model choice was
97 based on the assumption that a GBS vaccine will not affect colonisation [27,28] and that
98 maternal immunisation will offer protection for only a single pregnancy which is also a
99 conservative approach in regard to the benefits of a GBS vaccine.

100 The model was computationally implemented in R using standard packages, and used to
101 investigate costs and benefits of maternal immunisation from the perspective of the NHS and
102 Personal Social Services (health provider). We followed standard methods on cost-
103 effectiveness analysis; the Joint Committee on Vaccination and Immunisation (JCVI), who
104 make vaccine recommendations in the UK, in principle follow NICE methodology although
105 more specific detail on dealing with uncertainty is given [29].

106 *Parameter values - Disease*

107 The latest available UK data on GBS disease and sequelae were used to parameterise the
108 model. GBS disease incidence was informed by the most recent BPSU enhanced surveillance

109 study for infants up to 3 months of age [2]. Case fatality rates were based on the same source,
110 while UK-wide data on livebirths and stillbirths were obtained from the Office for National
111 Statistics [22,30–33]. Parameter estimates are presented in Table 1.

112 Preliminary data from a follow-up study of survivors of GBS disease were used to estimate
113 disease after-effects (Heath et al unpublished). Survivors were followed-up 3 to 5 years after
114 recovery with quality of life assessments and neurodevelopmental outcomes. Sequelae
115 stratified by severity (mild, moderate and severe) along with quality-adjusted life year
116 (QALY) loss for each severity group were estimated (Appendix 1). Life expectancy data for
117 the general population [23] and GBS survivors [52–54](Appendix 1) were included in the
118 model to encompass the full lifetime impact of GBS disease on cases.

119 Table 1. Base case parameter values of deterministic analysis and parameter distributions of probabilistic sensitivity analysis.

Parameter	Base value	Distribution	Source
Infant disease			
GBS disease incidence	0.97/1,000 livebirths	unif(0.000873,0.001067)	[2]
EOD incidence	0.58/1,000 livebirths	unif(0.000522,0.000638)	[2]
LOD incidence	0.39/1,000 livebirths	unif(0.000351,0.000429)	[2]
Mortality rate	0.044 (EOD), 0.076 (LOD)	unif(0.0396,0.0484) (EOD), unif(0.0684,0.0836) (LOD)	[2]
Severe sequelae rate	0.055 (EOD), 0.053 (LOD)	unif(0.0495, 0.0605) (EOD), unif(0.0477, 0.0583) (LOD)	Based on Heath et al unpublished
Moderate sequelae rate	0.096 (EOD), 0.092 (LOD)	unif(0.0864, 0.1056) (EOD), unif(0.0828, 0.1012) (LOD)	Based on Heath et al unpublished
Mild sequelae rate	0.341 (EOD), 0.330 (LOD)	unif(0.3069, 0.3751) (EOD), unif(0.297, 0.363) (LOD)	Based on Heath et al unpublished
Quality of life loss for sequelae cases	0.299 (severe), 0.056 (moderate), 0.002 (mild)	Beta(7.475,17.525) (severe), Beta(2.8,47.2) (moderate), Beta(2,998) (mild)	Based on Heath et al unpublished
Life expectancy in years (GBS sequelae)	25 (severe), 71 (moderate), 81 (mild)	Triangular(11, 25, 43) (severe), Triangular(43, 71, 81) (moderate)	Based on: severe [34], moderate-[23,34], mild -[23,34]
Disease diagnoses	EOD: 63.0% (sepsis), 3.1% (meningitis), 23.9% (pneumonia)	Not tested	[2]

	LOD: 63.3% (sepsis), 34.9% (meningitis), 1.8% (pneumonia)	Not tested	[2]
Maternal disease			
Maternal GBS disease incidence	0.27/1,000 maternities	unif(0.000243, 0.000297)	Based on [35]
General population			
Life expectancy (general population)	81		[23]
Livebirths (yearly)	776,352		[20–22]
Stillbirths (yearly)	3,563		[20,24,25]
Vaccine			
Vaccine uptake rate	0.6	Beta(3,2)	[36]
Vaccine efficacy	0.85	unif(0.6,1)	Based on [37,38]
Vaccine strain coverage (pentavalent)	0.962	Triangular(0.8658,.962, 1)	[2]
Vaccine adverse reaction rate	0.01 (GP) and 0.003 (anaphylaxis)	Beta(1,99) (GP) and Beta(3,997) (anaphylaxis)	GP – assumed, no data available Anaphylaxis - [39]
Economic costs (£)			
Healthcare costs per infant case (first 2 years)	11,670.99 (EOD) and 11,993.51 (LOD)	Gamma(24,scale=500)	Resource usage- [40], costs - [41,42]

Annual long-term care costs per case	6,000 (severe), 3,000 (moderate), 1,000 (mild)	Triangular(4000,6000,32000) (severe), Triangular(2000,3000,4000) (moderate), Triangular(500,1000,2000) (mild)	Based on [43–45]
Maternal disease costs	2,475.79	Triangular(367.08, 2475.79, 7341.59)	Based on [35]
Vaccine administration cost per dose	9.80	Not tested	[46]
Vaccine adverse reaction cost	42.42 (GP) and 468.55 (anaphylaxis)	Gamma(220, scale=2.13) (anaphylaxis)	Based on [41,42]
Award per litigation claim	563,241.27	Gamma(5.63,scale=100043)	Based on: base case -[47], distribution- [44,47–50]
Litigation			
Rate of successful litigation claims per infant GBS case	0.0137	unif(0.011,0.0339)	Combination of [2,47–51]
Litigation claim delay	2 years	unif(1,6)	[48]
Number of payments of litigation award	20	unif(15,25)	[44]
Proportion of successful litigation cases being fatalities	0.379	unif(0.3411, 0.4169)	[48]

120 Sources provided for base case values, while wherever possible parameter distributions were also informed by data. More information is available in
121 Appendix 1. GBS: group B *Streptococcus*, EOD: early-onset disease, LOD: late-onset disease, GP: general practitioner

122 Maternal GBS infections were identified by linking laboratory confirmed cases of invasive
123 disease (i.e. GBS isolated from a sterile site) reported to PHE through routine surveillance in
124 England in 2014 to hospital admissions captured through NHS Digital Hospital Episode
125 Statistics (HES). Pregnancy or recent childbirth (within 6 weeks of diagnosis) was identified
126 in HES through assessment of maternity fields, clinical ICD-10 codes, admission method,
127 medical specialty or surgical procedure codes [35]. Maternal GBS disease parameter values
128 were based on HES data on maternal GBS sepsis (Appendix 1) and maternal life expectancy
129 was based on the National Life Tables for the United Kingdom [55].

130 *Parameter values – Costs*

131 All costs were in 2015 £GBP, with estimates from previous years inflated using Hospital and
132 Community Health Services (HCHS) pay and prices index [56].

133 Healthcare costs for infant GBS cases in the first two years of life were based on resource
134 utilisation data by Schroeder et al [40], in combination with NHS Reference data [42] and
135 Unit Costs of Health and Social Care [41]. Details on parameter estimates are given in
136 Appendix 1. Data on long-term sequelae costs are scarce; only one study reporting estimates
137 for healthcare costs for very severe meningitis and sepsis sequelae was identified [43].

138 Litigation costs were sought from the NHS Litigation Authority through a Freedom of
139 Information Request; the available data, however, were not disease-specific (Appendix 1).

140 Estimates used in this study were the result of data synthesis from a number of different
141 sources (Appendix 1). Furthermore, the model includes litigation costs only beyond the
142 product of lost QALYs and ceiling ratio of cost per QALY gained, following current
143 Department of Health practice (Peter Grove personal communication, 24 October 2016).

144 Healthcare costs for maternal GBS disease were derived from the corresponding hospital
145 admission record during which the laboratory diagnosis was made. An average cost per

146 maternal disease case was calculated weighing the relevant HRG codes recorded in HES
147 according to their frequency (Appendix 1).

148 Potential adverse effects of vaccination were also considered. These included both mild
149 effects requiring a GP visit and more serious adverse effects such as anaphylaxis (Appendix
150 1).

151 *Parameter values - Vaccine*

152 The base case scenario considered immunisation of pregnant women in the UK with a
153 pentavalent vaccine (serotypes Ia, Ib, II, III and V). Women of at least 24 weeks of gestation
154 would be offered the vaccine against GBS. Strain coverage by such a vaccine was estimated
155 to be 96.2% based on the latest surveillance data [2] (Appendix 1). Vaccine uptake was set at
156 60% based on information from the pertussis maternal immunisation programme [57]. Data
157 on vaccine efficacy are not currently available so our assumption of 85% was based on
158 reported vaccine efficacy for other conjugate vaccines [37,38] (Appendix 1). Vaccine price is
159 also currently unknown. Here, we tested different vaccine prices with the aim of identifying
160 those for which a GBS vaccine would be cost-effective.

161 The size of the maternities cohort (excluding miscarriages) in combination with the vaccine
162 uptake rate means an estimated 467,949 immunisations will occur annually in the UK. The
163 costs of purchasing and administering the vaccine for this population was estimated in the
164 model.

165 *Parameter values - Discounting*

166 Following JCVI guidelines [29] future costs and health outcomes were discounted at 3.5%
167 and a threshold of £20,000 per QALY gained was applied. A threshold of £30,000 per QALY

168 gained was also explored as well as an alternative scenario of £15,000 per QALY at 1.5%
169 discounting for both future costs and health outcomes.

170

171 *Sensitivity Analysis*

172 Through univariate sensitivity analysis, we explored the effect of individual parameters on
173 the vaccine impact and vaccine cost-effectiveness, while we identified the threshold cost-
174 effective vaccine price for the base parameter values. Parameters were varied by $\pm 50\%$, with
175 some exceptions applying for cases where this variation was beyond their
176 maximum/minimum possible values. We also explored the cumulative effect of groups of
177 parameters - irrespective of disease onset or sequelae severity (overall values of: disease
178 incidence, fatality rate, sequelae rate and cost per sequelae case and combination of: overall
179 disease incidence and vaccine efficacy).

180 Scenario analysis was used to test assumptions excluded from the base case scenario.

181 Prevention of stillbirth and/or premature birth are important potential advantages of maternal
182 immunisation over the current practice of risk factor-based IAP, however, such benefits are
183 currently hypothetical. We tested the potential impact of a GBS vaccine on prevention of
184 stillbirth and premature birth, both in combination and individually. In the investigation of
185 stillbirth prevention, we accounted for averted cases having the life expectancy of healthy
186 survivors. For preterm births, we accounted for the relevant healthcare costs. We also
187 considered other scenarios offering additional health outcomes, including prevention of
188 maternal deaths and effect of disease on the health of carers (predominantly parents; recent
189 economic evaluation studies have accounted for the impact of disease on the quality of life of
190 carers [41–43]). A scenario of decreased vaccine strain coverage, with a trivalent GBS

191 vaccine used instead of the base case scenario assumption of a pentavalent vaccine was also
192 explored. Parameters for all scenarios are available in Appendix 1 (Table 9).

193 Furthermore, Monte Carlo probabilistic sensitivity analysis of 5,000 iterations was carried
194 out. The choice of parameter intervals and distributions (Table 1) was informed by data where
195 possible. Beta distributions were selected for parameters bounded between zero and one and
196 gamma distributions for parameters describing costs. Exceptions were made for parameters
197 which required integer numbers, parameters where detailed data were available and
198 parameters where specific distinctions between the intervals describing sequelae of varying
199 severity (mild, moderate, severe) were needed. In these cases, uniform or triangular
200 distributions were selected.

201

202 **Results**

203 *Deterministic Model Results*

204 In the base case scenario, we estimated that maternal GBS immunisation will prevent 369
205 cases of GBS in infants annually, including 179 cases with sequelae. Twenty one infant
206 deaths will be averted and 103 maternal cases will also be avoided. In total, 563 life years
207 will be gained from averted infant deaths and 232 from averted infant sequelae which would
208 have resulted in premature mortality. The total gain in QALYs from infant disease will be
209 870. Exploration of the base case scenario showed the maximum vaccine price for which
210 immunisation remains cost-effective to be £54 per vaccine dose at £20,000/ QALY gained.
211 The maximum vaccine price when a threshold of £30,000 per QALY was considered was
212 £71.

213 A variety of different vaccine prices were explored and the changing cost per QALY gained
214 is presented in Appendix 2 (Table 1). For our base case scenario, a vaccine price of £54 per
215 dose was adopted. The gross costs of vaccination were estimated at £30.7 million, which
216 includes the costs of buying and administering the vaccine. The net cost of vaccination to the
217 NHS and the PSS will be approximately £17.4 million, accounting for savings from the
218 reduced burden of disease.

219 The cost per QALY gained is £19,953, the cost per infant case prevented £46,987 and the
220 cost per death averted £826,284. The results of the base case scenario are summarised in
221 Table 2.

222 *Sensitivity analysis results*

223 One-way sensitivity analysis identified a number of highly influential parameters (**Error!**
224 **Reference source not found.**), with overall disease incidence and vaccine price having the
225 biggest effect on model results. Vaccine uptake did not alter the incremental cost-
226 effectiveness of the maternal immunisation strategy with risk factor-based IAP in comparison
227 with risk factor-based IAP alone, with both costs and health effects being multiples of this
228 rate and cost per QALY gained remaining unchanged.

229 *Scenario analysis*

230 Several scenarios were explored as alternatives to the assumptions of the base case
231 (Appendix 2, Table 2). Potential prevention of stillbirths and/ or preterm births by the GBS
232 vaccine, for instance, would increase its added benefits, making it more cost-effective. With a
233 theoretical 1% of stillbirths assumed to be vaccine-preventable, the maximum cost-effective
234 vaccine price was £94 (£54 per dose in the base case). A similar percentage of vaccine-
235 preventable (surviving) preterm births had a lesser impact, with the maximum cost-effective

236 price rising to £59. A combination of both resulted in a maximum cost-effective price of
 237 £100.

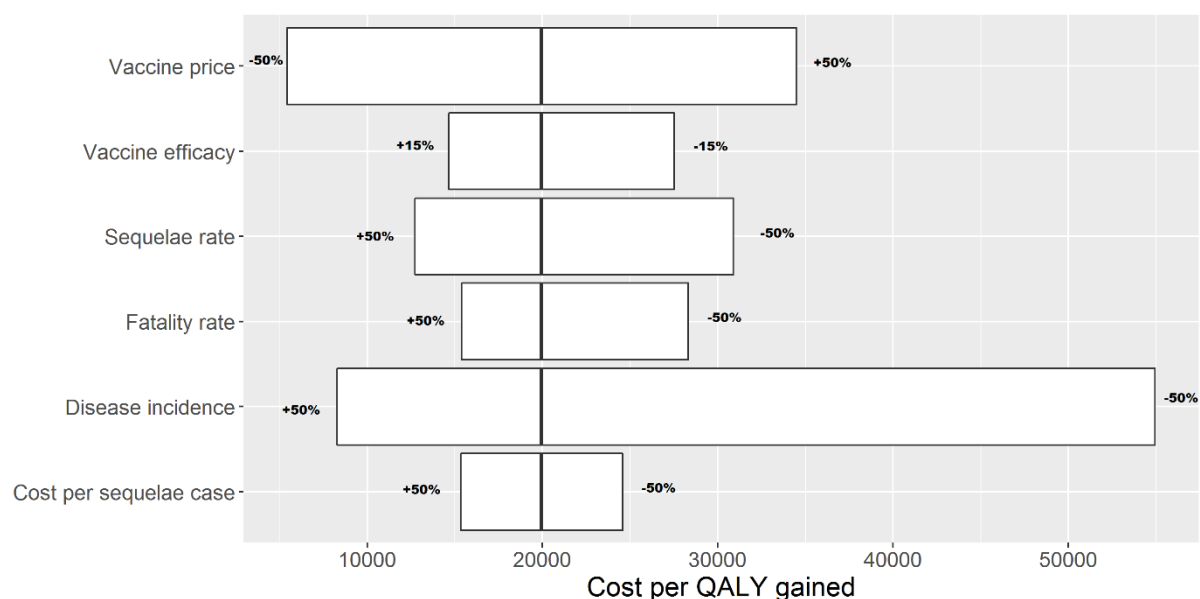
238 Table 2. Deterministic model results for base case scenario.

Health outcomes	Risk factor-based IAP alone (current strategy)	Maternal immunisation with risk factor-based IAP (proposed strategy)	Incremental benefits of proposed immunisation strategy
Infant disease cases	753	384	-369
Infant cases with sequelae	365	186	-179
Infant deaths	43	22	-21
Maternal disease cases	210	107	-103
Life-years lost to infant deaths (discount rate of 3.5% applied)	1,148	585	-563
Life-years lost to infant sequelae which would have resulted in premature mortality (discount rate of 3.5% applied)	473	241	-232
QALY loss (discount rate of 3.5% applied)	1,773	903	-870
Costs (£ millions)	Risk factor-based IAP alone (current strategy)	Maternal immunisation with risk factor-based IAP (proposed strategy)	Incremental costs of proposed immunisation strategy
Maternal immunisation	-	30.7	30.7
Infant GBS disease (both short- and long-term costs)	25.2	12.8	-12.4
Litigation	1.5	0.8	-0.7
Maternal GBS disease	0.5	0.3	-0.2

Total	27.2	44.6	17.4
Cost-effectiveness measures			Incremental cost-effectiveness of proposed immunisation strategy
Cost per QALY gained			19,953
Cost per case prevented			46,987
Cost per death averted			826,284
Cost per life-year gained			21,828

239 Cohort size: 776,352 livebirths, 3,563 stillbirths. Stillbirths were only included in the estimation of
240 immunisation costs. Maternal immunisation parameters: vaccine price = £54/dose, vaccine efficacy =
241 85%, vaccine strain coverage = 96.2%, vaccine uptake rate = 60%. Litigation costs included in the
242 table exclude those already accounted for through lost QALYs (Department of Health practice). IAP:
243 intrapartum antibiotic prophylaxis, QALY: quality-adjusted life year, GBS: group B *Streptococcus*

244



245

246 **Figure 2. Results of one-way (vaccine price, vaccine efficacy) and multi-way (overall: sequelae**
247 **rate, fatality rate, disease incidence and cost per sequelae case) sensitivity analysis.** Base value
248 estimates were varied by $\pm 50\%$ with the exception of vaccine efficacy which was varied by ± 0.15
249 (maximum value = 1). Base case scenario cost per QALY (£19,953) is displayed by the middle line in

250 each bar. Parameters displayed here are those whose alteration had an impact in the cost per QALY of
251 at least 20%. The impact of EOD and LOD incidence is presented here in a cumulative way, though
252 both parameters have an individual effect on the cost per QALY at beyond 20% its base case value
253 (£19,953). QALY: quality-adjusted life year, EOD: early onset disease, LOD: late onset disease

254

255 To date, no maternal deaths caused by GBS have been reported in the UK [35,58].

256 Considering the possibility that some maternal fatalities could occur [59], we accounted for a
257 maternal fatality rate of 1% among maternal GBS cases. The GBS vaccine was only
258 marginally more cost-effective in this scenario with the threshold cost-effective price
259 (rounded to the nearest GBP) remaining the same.

260 We considered the potential effect of health spillovers for cases with sequelae and for
261 fatalities in one of the scenarios we explored, adjusting this for those displaced by funding the
262 intervention [60] (Appendix 1). Results showed the vaccine programme to be more cost-
263 effective, increasing the threshold vaccine price by £6 (Appendix 2, Table 2).

264 A ‘most favourable’ scenario incorporating all of the above increased the threshold vaccine
265 price to £107.

266 The case of a trivalent GBS vaccine (Appendix 1) was explored and compared with the base
267 case assumption of a pentavalent vaccine (Appendix 2, Table 2). The threshold vaccine price
268 at £20k/ QALY was £8 less than the pentavalent vaccine.

269 Finally, an alternative 1.5% discount rate for both future costs and health outcomes with a
270 £15,000/ QALY threshold scenario was explored to reflect discussions on the appropriate
271 threshold [61,62]. Comparing the base case results with this scenario, the vaccine became

272 even more cost-effective (£78 per dose) with the alternative guidelines applied (£54 per dose
273 in the base case).

274 ***Probabilistic sensitivity analysis***

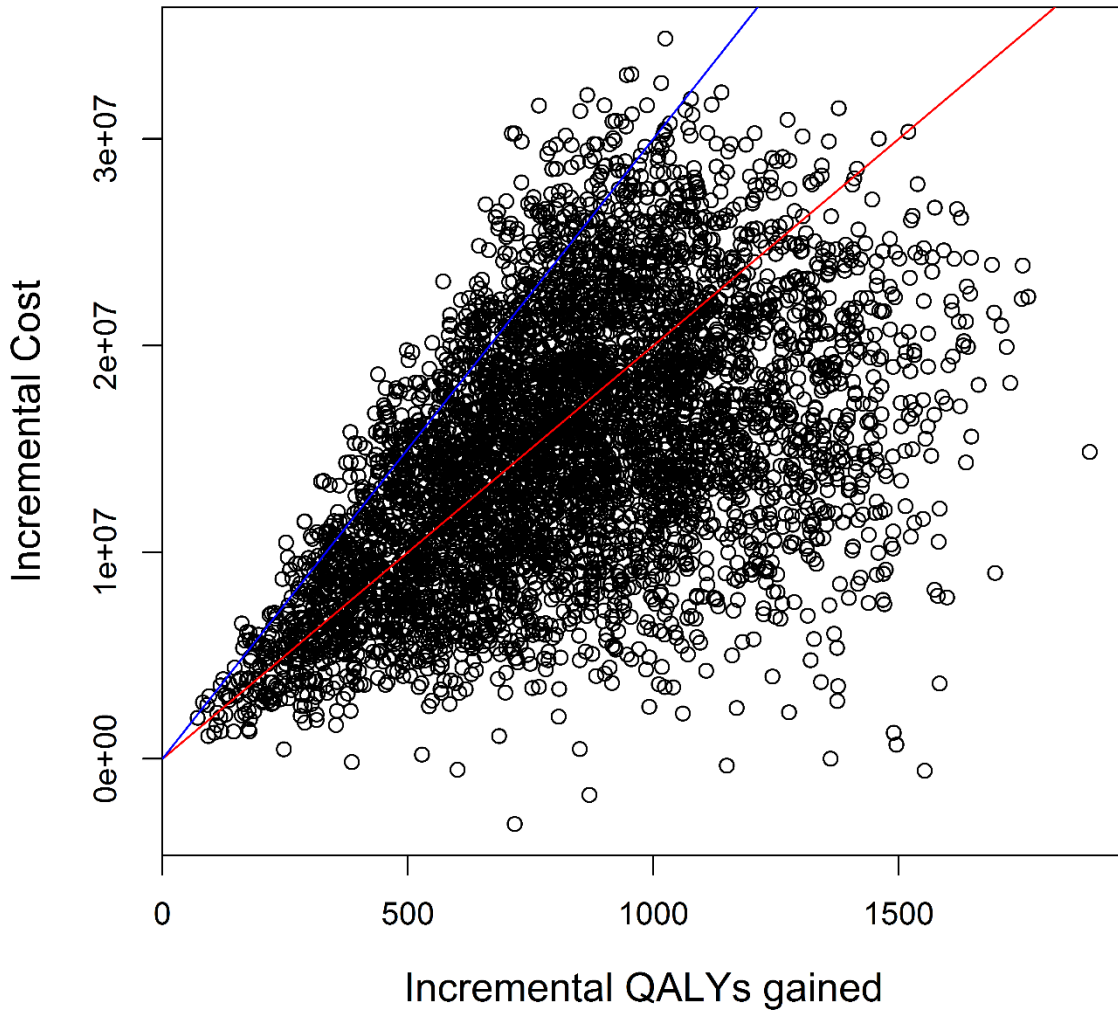
275 Consistency of results for the base case scenario (assuming £54 per dose) was explored in the
276 probabilistic sensitivity analysis, where parameter distributions were set to reflect estimates'
277 variations perceived as realistic. Uncertainty guidelines require at least 90% of iterations to
278 be under the £30,000 threshold [29]. Of the 5,000 iterations that were run, 92.24% fell under
279 the £30,000 threshold of cost per QALY gained (**Error! Reference source not found.**),
280 while a slightly higher vaccine price of £55 per dose showed 90.66% of iterations below the
281 £30,000 threshold. Model outcomes were highly dependent on vaccine price Figure 4.

282

283

284

Cost-effectiveness

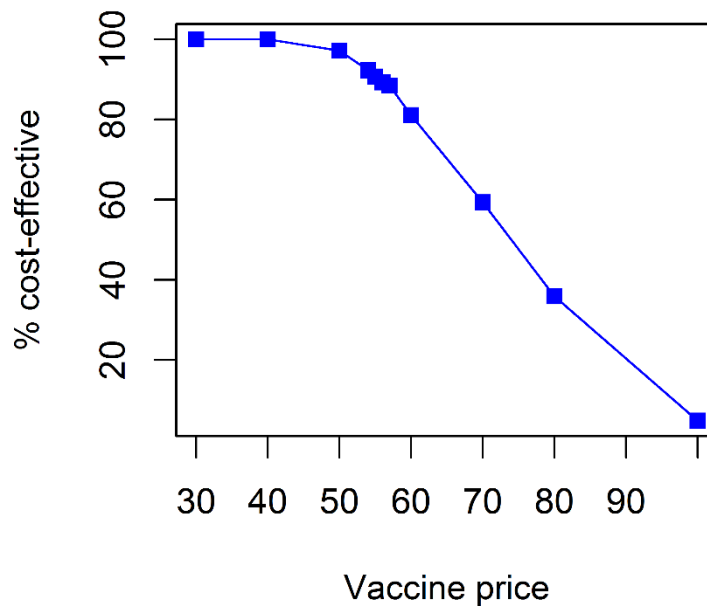


285

286 Figure 3. Monte Carlo probabilistic sensitivity analysis of 33 parameters, 5,000 iterations, for
287 base case scenario. The incremental cost (£) of the maternal immunisation strategy with risk factor-
288 based IAP comparing with that of risk factor-based IAP alone is plotted in the y axis, with the x axis
289 displaying the incremental QALYs gained. Of the 5,000 iterations 92.24% fall below the £30,000
290 ceiling ratio (blue line) of cost per QALY gained and 56.62% below the £20,000 threshold (red line).

291 QALY: quality-adjusted life year

292

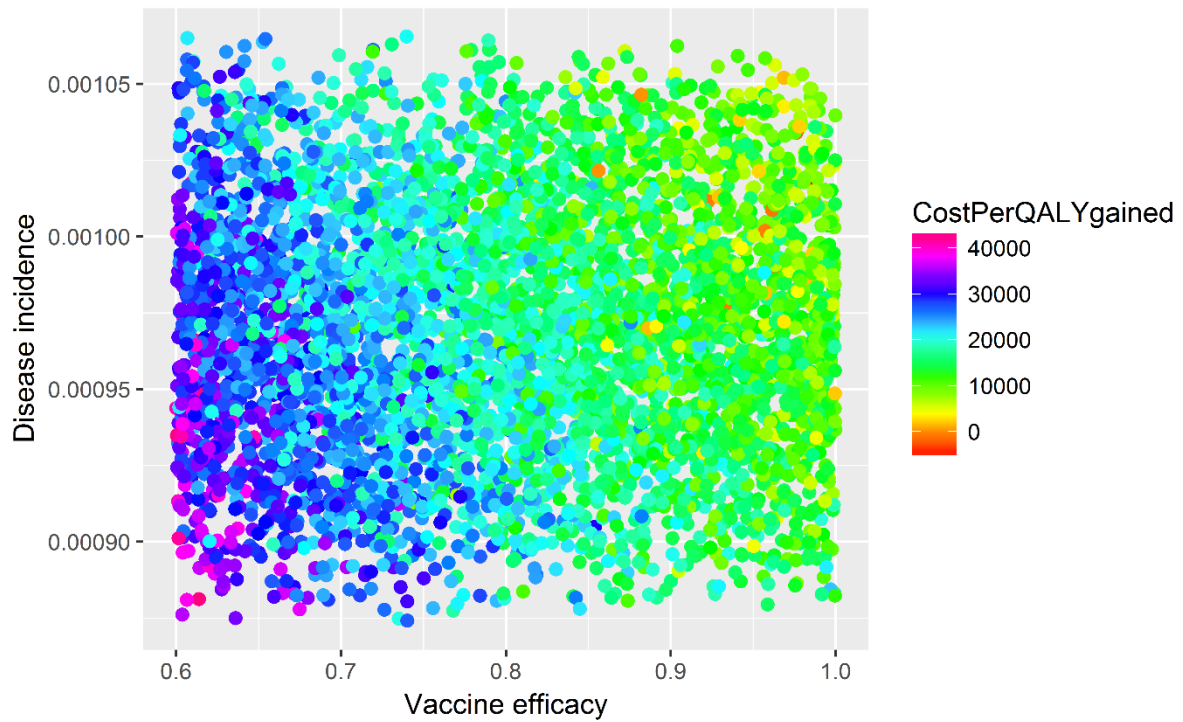


293

294 Figure 4. **Effect of vaccine price (£) on the percentage of Monte Carlo iterations (total of 5,000)**
 295 **for which the immunisation strategy is cost-effective (threshold of £30,000 per QALY gained).**
 296 Discount rate is 3.5% for both future costs and health outcomes. Vaccine price per dose for the base
 297 case scenario is £54. QALY: quality-adjusted life year

298

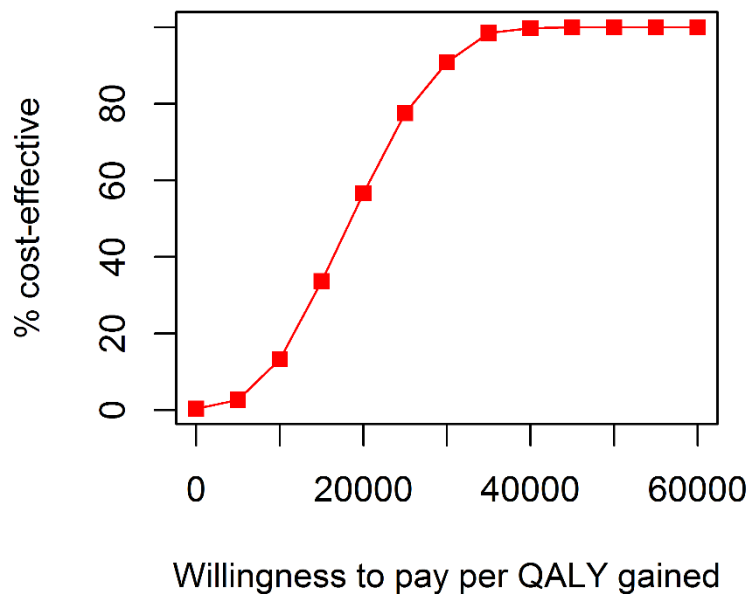
299 Investigating the effect of the interplay between vaccine efficacy and overall disease
 300 incidence on the probabilistic sensitivity analysis results, it is evident that uncertainty in the
 301 cost per QALY gained is mainly driven by vaccine efficacy (The cost-effectiveness
 302 acceptability curve is presented in **Error! Reference source not found.** The latter exhibits
 303 the changing incremental cost-effectiveness of the maternal immunisation strategy with risk
 304 factor-based IAP in comparison with risk factor-based IAP alone for the base case of
 305 parameter values (vaccine price of £54 per dose), for a changing ceiling ratio of cost per
 306 QALY gained.



307

308 **Figure 5. Comparison of overall disease incidence and vaccine efficacy as drivers of vaccine cost-**
 309 **effectiveness, in Monte Carlo probabilistic sensitivity analysis of 5,000 iterations, where other**
 310 **parameter values remain as in base case scenario.** Vaccine price per dose for the base case scenario
 311 is £54. Incremental cost (£) per QALY gained of the maternal immunisation strategy with risk factor-
 312 based IAP comparing with that of risk factor-based IAP alone is represented by nodes of varying
 313 colour depending on value (colour guide on figure's right side). QALY: quality-adjusted life year

Cost-effectiveness acceptability curve



314

315 **Figure 6. Cost-effectiveness acceptability curve of the base case scenario (future costs and health**
316 **outcomes discount rate=3.5%).** The graph displays the percentage of Monte Carlo iterations (total of
317 5,000) for which the immunisation strategy is cost-effective, depending on the willingness of the
318 healthcare system to pay (in £) for each QALY gained. Vaccine price per dose in the base case
319 scenario is £54. QALY: quality-adjusted life year

320

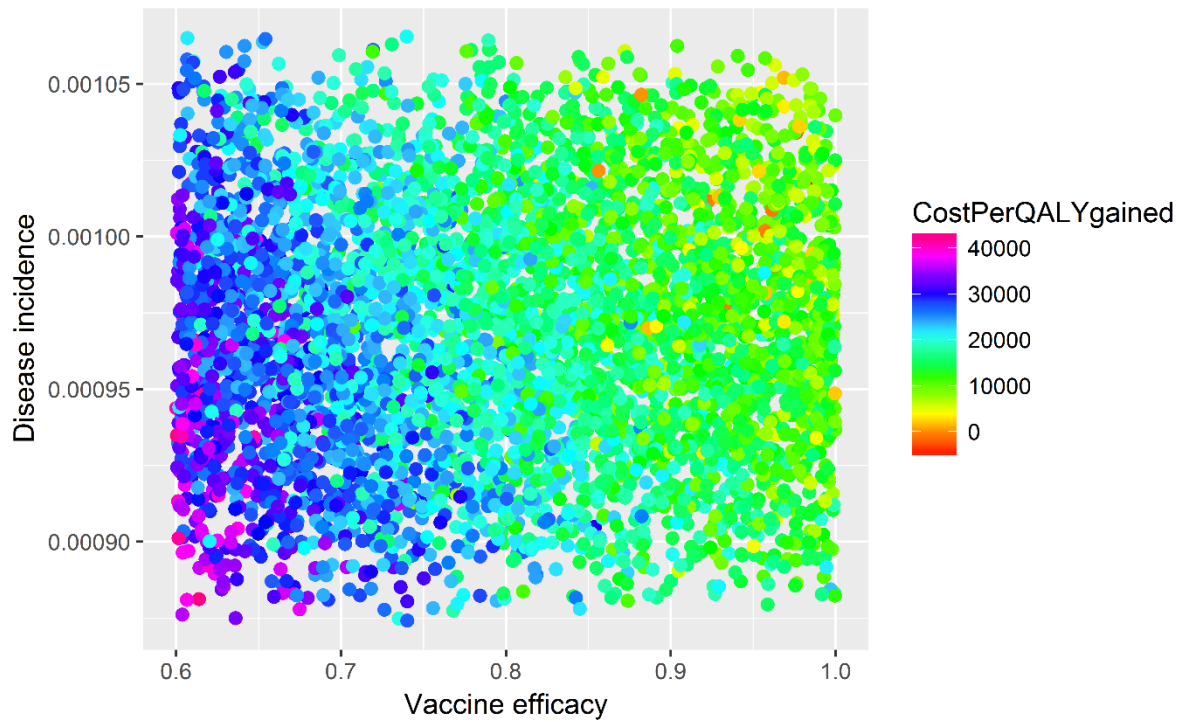
321 **Discussion**

322 *Principal findings*

323 A maternal immunisation strategy with risk factor-based IAP, is highly likely to be a cost-
324 effective intervention against infant GBS disease for the NHS, assuming the availability of a
325 safe, effective vaccine that can be purchased and administered at a reasonable price. The
326 proposed new strategy is compared to the current strategy of risk factor-based IAP alone. In

327 the base case, we estimated that, with 60% coverage, 369 infant cases, 103 maternal cases
328 and 21 infant deaths could be averted in a single birth cohort. Additional benefit would be
329 achieved if coverage were closer to the 75% achieved recently in the maternal pertussis
330 programme [63]. The threshold cost per dose was £54 at £20,000/ QALY; at this price, the
331 uncertainty rules are also met, with 92.24 % of simulations in the probabilistic sensitivity
332 analysis falling below £30,000/QALY. Most of the alternative scenarios we investigated
333 improved the cost-effectiveness of immunisation. Prevention of stillbirths and/ or preterm
334 births would). In contrast with **Error! Reference source not found.**, where both parameters
335 were varied by 50%, here the disease incidence - for which there are recent and reliable data -
336 was only varied by $\pm 10\%$. Vaccine efficacy, on the other hand, for which no data are
337 available, was varied more, with values ranging from 0.6 to 1 to reflect this uncertainty.

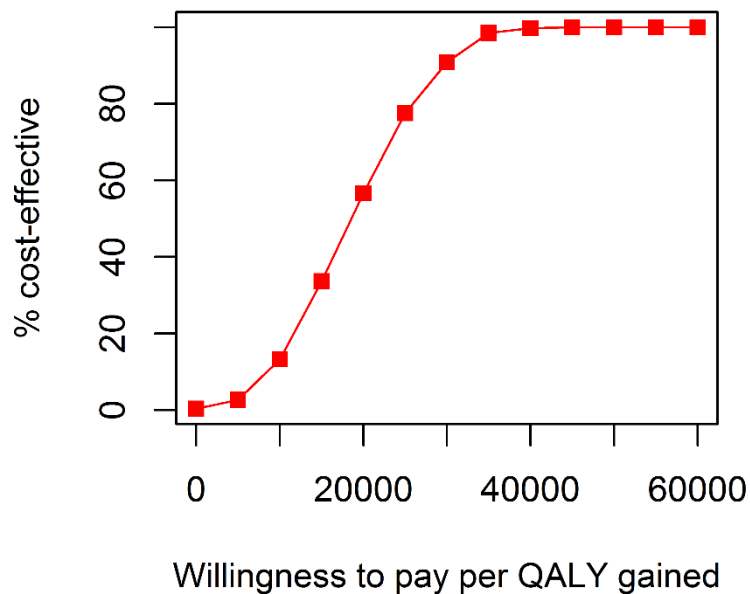
338 The cost-effectiveness acceptability curve is presented in **Error! Reference source not**
339 **found.** The latter exhibits the changing incremental cost-effectiveness of the maternal
340 immunisation strategy with risk factor-based IAP in comparison with risk factor-based IAP
341 alone for the base case of parameter values (vaccine price of £54 per dose), for a changing
342 ceiling ratio of cost per QALY gained.



343

344 **Figure 5. Comparison of overall disease incidence and vaccine efficacy as drivers of vaccine cost-**
 345 **effectiveness, in Monte Carlo probabilistic sensitivity analysis of 5,000 iterations, where other**
 346 **parameter values remain as in base case scenario.** Vaccine price per dose for the base case scenario
 347 is £54. Incremental cost (£) per QALY gained of the maternal immunisation strategy with risk factor-
 348 based IAP comparing with that of risk factor-based IAP alone is represented by nodes of varying
 349 colour depending on value (colour guide on figure's right side). QALY: quality-adjusted life year

Cost-effectiveness acceptability curve



350

351 **Figure 6. Cost-effectiveness acceptability curve of the base case scenario (future costs and health**
352 **outcomes discount rate=3.5%).** The graph displays the percentage of Monte Carlo iterations (total of
353 5,000) for which the immunisation strategy is cost-effective, depending on the willingness of the
354 healthcare system to pay (in £) for each QALY gained. Vaccine price per dose in the base case
355 scenario is £54. QALY: quality-adjusted life year

356

357 **Discussion**

358 *Principal findings*

359 A maternal immunisation strategy with risk factor-based IAP, is highly likely to be a cost-
360 effective intervention against infant GBS disease for the NHS, assuming the availability of a
361 safe, effective vaccine that can be purchased and administered at a reasonable price. The
362 proposed new strategy is compared to the current strategy of risk factor-based IAP alone. In

363 the base case, we estimated that, with 60% coverage, 369 infant cases, 103 maternal cases
364 and 21 infant deaths could be averted in a single birth cohort. Additional benefit would be
365 achieved if coverage were closer to the 75% achieved recently in the maternal pertussis
366 programme [63]. The threshold cost per dose was £54 at £20,000/ QALY; at this price, the
367 uncertainty rules are also met, with 92.24 % of simulations in the probabilistic sensitivity
368 analysis falling below £30,000/QALY. Most of the alternative scenarios we investigated
369 improved the cost-effectiveness of immunisation. Prevention of stillbirths and/ or preterm
370 births would increase vaccine cost-effectiveness, while the prevention of maternal deaths
371 from GBS sepsis would only have a minor impact, as this is considered to be rare. Both a
372 trivalent and a pentavalent vaccine would be cost-effective, with the latter being clearly more
373 attractive for both the health system and vaccine manufacturers. Accounting for the health
374 benefits gained (and displaced) from reducing the strain on carers also makes the vaccine
375 more cost-effective. The cumulative effect of including all vaccine-favourable scenarios more
376 than doubles the threshold vaccine price.

377 *Strengths and limitations*

378 The inclusion of the latest UK surveillance data in this study [2] is a major strength.
379 Moreover, we included preliminary data on outcomes and sequelae among UK infant GBS
380 survivors from an on-going study, an area previously lacking in evidence. We are conducting
381 further research on the relation between quality of life and severity of sequelae in infants with
382 GBS disease. Unlike other studies of the cost-effectiveness of GBS maternal vaccination, we
383 accounted for maternal disease outcomes, litigation costs and health impact on carers. To the
384 best of our knowledge, this is the first cost-effectiveness study on GBS considering displaced
385 health spillover benefits.

386 A key limitation is that we do not yet know the properties of the vaccine. Vaccine efficacy is
387 currently unknown; given the experience with other conjugate vaccines, we would expect a
388 GBS vaccine would demonstrate high efficacy over the course of the infant risk period for
389 both EOD and LOD but this can only be estimated once a vaccine becomes available. We
390 considered vaccination to be necessary in each pregnancy, with no enduring protection from
391 vaccine given in a previous pregnancy. Studies of antibody persistence will be needed to
392 determine whether this is necessary.

393 We did not consider any potential impact of maternal immunisation on maternal GBS
394 colonisation. In one study non-pregnant women who received a GBS conjugate vaccine were
395 found to have a significantly longer time to first vaginal acquisition than women in the
396 control group [27], but no clear effect on colonisation was observed in a pregnancy trial with
397 a different GBS conjugate vaccine [64]. We consider it unlikely that an immunisation
398 programme targeting only pregnant women would have profound effects on the population
399 biology of GBS even if a vaccine did influence carriage and so we chose a static decision tree
400 model rather than a transmission dynamic model. However further research is necessary to
401 fully understand the implications of a vaccine affecting colonisation, e.g. of vaccine selection
402 pressure driving serotype replacement.

403 We did not have good data on the long-term economic cost of sequelae, estimates included in
404 the model are speculative and results suggest they are influential. This issue could be
405 addressed through appropriate follow-up studies of GBS survivors (our current follow-up
406 study addresses prevalence but not cost of outcomes).

407 We investigated the added benefit of a maternal immunisation strategy where IAP is still used
408 when pre-defined risk factors are identified. This does not address any potential savings
409 which accrue if fewer antibiotics are administered and the important but less tangible benefits

410 of reducing selection pressure which could lead to antibiotic resistance. We did not
411 investigate other preventive strategies, such as universal screening for GBS colonisation, as
412 we concentrated on the current UK context.

413 Finally, we also explored the effect of the healthcare system's willingness (and ability) to pay
414 on cost-effectiveness, as a reminder of its influence on the analysis outcomes. We only
415 considered the health provider's perspective, following standard NICE methodology and we
416 did not investigate wider societal costs and benefits.

417 *Comparison with other studies*

418 A previous cost-effectiveness study on GBS disease in the UK [53] showed that a
419 combination of vaccination with IAP for some maternal risk groups was amongst the most
420 cost-effective of the tested strategies. Our analysis uses up-to-date parameter estimates,
421 including increased incidence, and emphasises the added benefits of vaccination with risk-
422 based IAP, rather than comparing a range of screening options. Other studies on the cost-
423 effectiveness of maternal immunisation have been conducted in South Africa [16]; sub-
424 Saharan Africa [17] and the USA [18,19].

425 All of these studies concluded that GBS vaccination could be a cost-effective intervention,
426 but found that disease incidence, vaccine efficacy and vaccine cost were key determinants,
427 with most of the studies also including fatality rates in this list. The studies from the USA
428 [18,19] are more directly comparable to our study, as they investigate the added benefit of
429 vaccination in terms of cost per QALY in a country with sophisticated healthcare. However, a
430 key difference is that they compared vaccination in combination with screening-based IAP
431 versus screening based IAP only (the current US standard of care). This prevents a head-to-
432 head comparison, but it does appear that given the current incidence and standards of care, a
433 UK programme might be more cost-effective than a maternal immunisation programme in the

434 USA. In the future, a model comparison exercise to examine the differences in model
435 assumptions, parameters and results could be of value.

436

437 **Conclusion**

438 A strategy of maternal immunisation in combination with risk-based intrapartum antibiotic
439 prophylaxis against GBS disease in infants up to three months of age is likely to be cost-
440 effective in the UK, offering excellent prospects for reducing the burden of GBS disease.

441

442

443 **Acknowledgements**

444 We thank the following individuals for assistance: Hilary Rattue (St George's Hospital,
445 University of London), Hannah Christensen (University of Bristol), Peter Grove (Department
446 of Health), and Samantha Johnson (University of Leicester).

447

448 **Funding**

449 This study was funded by the Meningitis Research Foundation [project number 1302.0]. The
450 funders had no role in the study design; collection, analysis, and interpretation of data;
451 writing of the report; or decision to submit the article for publication.

452

453 **Conflicts of interest**

454 PTH has received grants from GlaxoSmithKline and Pfizer, outside the submitted work. TL
455 reports a grant from Pfizer to assess the burden of GBS infection, outside the submitted work.
456 MR leads PHE's Immunisation Hepatitis and Blood Safety Department, which provides
457 vaccine manufacturers with post-marketing surveillance reports on pneumococcal and
458 meningococcal infection which the companies are required to submit to the UK Licensing
459 authority in compliance with their Risk Management Strategy. A cost recovery charge is
460 made for these reports. HA reports funding from GlaxoSmithKline to attend a health
461 economics workshop.

462

463 **Contributors**

464 CT conceptualised the study. KG and CT designed the work. KG developed and
465 parameterised the models, carried out all analysis and prepared the first paper draft. KG and
466 CT prepared the final paper draft. CO, PH and TL provided data. All authors critically
467 revised the manuscript and approved the final version. KG is the guarantor of this study.

468

469 Appendix 1: Parameter estimation.

470 Appendix 2: Additional model results.

471

472

473 **References**

474 [1] I.O. Okike, A.P. Johnson, K.L. Henderson, R.M. Blackburn, B. Muller-Pebody, S.N. Ladhani, M.
475 Anthony, N. Ninis, P.T. Heath, E.P. Galiza, others, Incidence, Etiology, and Outcome of Bacterial
476 Meningitis in Infants Aged < 90 Days in the United Kingdom and Republic of Ireland:

- 477 Prospective, Enhanced, National Population-Based Surveillance, *Clin. Infect. Dis.* 59 (2014)
478 e150–e157.
- 479 [2] C. O’Sullivan, T. Lamagni, A. Efstratiou, D. Patel, R. Cunney, M. Meehan, A. Reynolds, R.
480 Campbell, L. Doherty, M. Boyle, E. Davies, P. Heath, P3 Group B Streptococcal (GBS) disease in
481 UK and Irish infants younger than 90 days, 2014–2015, *Arch. Dis. Child.* 101 (2016) A2.
482 doi:10.1136/archdischild-2016-310863.3.
- 483 [3] P.T. Heath, G. Balfour, A.M. Weisner, A. Efstratiou, T.L. Lamagni, H. Tighe, L.A. O’Connell, M.
484 Cafferkey, N.Q. Verlander, A. Nicoll, Group B streptococcal disease in UK and Irish infants
485 younger than 90 days, *The Lancet.* 363 (2004) 292–294.
- 486 [4] R. Libster, K.M. Edwards, F. Levent, M.S. Edwards, M.A. Rench, L.A. Castagnini, T. Cooper, R.C.
487 Sparks, C.J. Baker, P.E. Shah, Long-term outcomes of group B streptococcal meningitis,
488 *Pediatrics.* (2012) peds. 2011-3453.
- 489 [5] C. Nan, Z. Dangor, C. Cutland, M. Edwards, S. Madhi, M. Cunningham, Maternal group B
490 Streptococcus-related stillbirth: a systematic review, *BJOG Int. J. Obstet. Gynaecol.* (2015) n/a–
491 n/a. doi:10.1111/1471-0528.13527.
- 492 [6] J.E. Lawn, F. Bianchi-Jassir, N.J. Russell, M. Kohli-Lynch, C.J. Tann, J. Hall, L. Madrid, C.J. Baker,
493 L. Bartlett, C. Cutland, M.G. Gravett, P.T. Heath, M. Ip, K. Le Doare, S.A. Madhi, C.E. Rubens,
494 S.K. Saha, S. Schrag, A. Sobanjo-ter Meulen, J. Vekemans, A.C. Seale, Group B Streptococcal
495 Disease Worldwide for Pregnant Women, Stillbirths, and Children: Why, What, and How to
496 Undertake Estimates?, *Clin. Infect. Dis.* 65 (2017) S89–S99. doi:10.1093/cid/cix653.
- 497 [7] M. Cunningham, C. Kortsalioudaki, P. Heath, Genitourinary pathogens and preterm birth, *Curr.*
498 *Opin. Infect. Dis.* 26 (2013) 219–230.
- 499 [8] C.D. Acosta, D.A. Harrison, K. Rowan, D.N. Lucas, J.J. Kurinczuk, M. Knight, Maternal morbidity
500 and mortality from severe sepsis: a national cohort study, *BMJ Open.* 6 (2016) e012323.
- 501 [9] G. Kwatra, M.C. Cunningham, E. Merrall, P.V. Adrian, M. Ip, K.P. Klugman, W.H. Tam, S.A. Madhi,
502 Prevalence of maternal colonisation with group B streptococcus: a systematic review and
503 meta-analysis, *Lancet Infect. Dis.* 16 (2016) 1076–1084.
- 504 [10] K. Le Doare, P.T. Heath, An overview of global GBS epidemiology, *Vaccine.* 31 (2013) D7–D12.
- 505 [11] T.L. Lamagni, C. Keshishian, A. Efstratiou, R. Guy, K.L. Henderson, K. Broughton, E. Sheridan,
506 Emerging Trends in the Epidemiology of Invasive Group B Streptococcal Disease in England and
507 Wales, 1991–2010, *Clin. Infect. Dis.* 57 (2013) 682–688. doi:10.1093/cid/cit337.
- 508 [12] Royal College of Obstetricians and Gynaecologists. The prevention of early-onset neonatal
509 group B streptococcal disease., *Green-Top Guidel. No 36.* (2012).
510 http://www.rcog.org.uk/files/rcog-corp/GTG36_GBS.pdf.
- 511 [13] The UK NSC recommendation on Group B Streptococcus screening in pregnancy, 2017.
512 <https://legacyscreening.phe.org.uk/groupbstreptococcus> [Accessed 27 November 2017].
- 513 [14] M. Kobayashi, S.J. Schrag, M.R. Alderson, S.A. Madhi, C.J. Baker, A. Sobanjo-ter Meulen, D.C.
514 Kaslow, P.G. Smith, V.S. Moorthy, J. Vekemans, WHO consultation on group B Streptococcus
515 vaccine development: Report from a meeting held on 27–28 April 2016, *Vaccine.* (2016).
- 516 [15] T.E. Colbourn, C. Asseburg, L. Bojke, Z. Philips, N.J. Welton, K. Claxton, A.E. Ades, R.E. Gilbert,
517 Preventive strategies for group B streptococcal and other bacterial infections in early infancy:
518 cost effectiveness and value of information analyses, *BMJ.* 335 (2007) 655.
519 doi:10.1136/bmj.39325.681806.AD.
- 520 [16] S.-Y. Kim, L.B. Russell, J. Park, J.R. Verani, S.A. Madhi, C.L. Cutland, S.J. Schrag, A. Sinha, Cost-
521 effectiveness of a potential group B streptococcal vaccine program for pregnant women in
522 South Africa, *Vaccine.* 32 (2014) 1954–1963.
- 523 [17] L.B. Russell, S.-Y. Kim, B. Cosgriff, S.R. Pentakota, S.J. Schrag, A. Sobanjo-ter Meulen, J.R.
524 Verani, A. Sinha, Cost-effectiveness of maternal GBS immunization in low-income sub-Saharan
525 Africa, *Vaccine.* (2017). doi:10.1016/j.vaccine.2017.07.108.

- 526 [18] G. Oster, J. Edelsberg, K. Hennegan, C. Lewin, V. Narasimhan, K. Slobod, M.S. Edwards, C.J.
527 Baker, Prevention of group B streptococcal disease in the first 3 months of life: Would routine
528 maternal immunization during pregnancy be cost-effective?, *Vaccine*. 32 (2014) 4778–4785.
- 529 [19] S.-Y. Kim, C. Nguyen, L.B. Russell, S. Tomczyk, F. Abdul-Hakeem, S.J. Schrag, J.R. Verani, A.
530 Sinha, Cost-effectiveness of a potential group B streptococcal vaccine for pregnant women in
531 the United States, *Vaccine*. 35 (2017) 6238–6247. doi:10.1016/j.vaccine.2017.08.085.
- 532 [20] Office for National Statistics. Statistical bulletin: Births in England and Wales, 2014, 2015.
- 533 [21] Northern Ireland Statistics & Research Agency. Vital Statistics. Births. Table 3.10. Live births,
534 stillbirths and maternities, by sex of child, marital status of parents and age of mother, 2012,
535 n.d.
- 536 [22] National Records of Scotland. Vital events Reference Tables 2014. Section 3: Births. Table 3.14;
537 2014., n.d. http://www.nrscotland.gov.uk/_les//statistics/vital-events-reftables/2014/section-3/14-vital-events-ref-tab-3-14.pdf [Accessed 27 May 2016].
- 538 [23] Office for National Statistics. Statistical bulletin: National Life Tables, United Kingdom 2012-
539 2014., 2015.
- 541 [24] Northern Ireland Statistics & Research Agency. Registrar General Annual Report 2014.
542 Stillbirths and Infant Deaths., n.d. Available from :
543 <http://www.nisra.gov.uk/demography/default.asp99.htm> [Accessed 27 May 2016].
- 544 [25] General Register Office for Scotland. Vital events reference tables 2012. Section 4: Stillbirths
545 and infant deaths. Table 4.1, 2013.
- 546 [26] Royal College of Obstetricians and Gynaecologists, Royal College of Obstetricians and
547 Gynaecologists. Group B Streptococcal Disease, Early-onset, (2017).
- 548 [27] National Institute of Allergy and Infectious Diseases (NIAID). A Phase II Randomized, Double-
549 Blinded, Comparative Clinical Trial for a Group B Streptococcus Serotype III-Tetanus Toxoid
550 (GBS III-TT) Vaccine to Prevent Vaginal Acquisition of GBS Type III, (2009).
551 <https://clinicaltrials.gov/ct2/show/study/NCT00128219?term=GBS+studies§=X470156>
552 [Accessed 7 August 2016].
- 553 [28] S.A. Madhi, C.L. Cutland, L. Jose, A. Koen, N. Govender, F. Wittke, M. Olugbosi, A. Sobanjo-ter
554 Meulen, S. Baker, P.M. Dull, Safety and immunogenicity of an investigational maternal trivalent
555 group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2
556 trial, *Lancet Infect. Dis.* 16 (2016) 923–934.
- 557 [29] JCVI. Code of practice June 2013, n.d.
558 [https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224864/JCVI](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224864/JCVI_Code_of_Practice_revision_2013_-_final.pdf)
559 [_Code_of_Practice_revision_2013_-_final.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224864/JCVI_Code_of_Practice_revision_2013_-_final.pdf) [Accessed 27 November 2014].
- 560 [30] Office for National Statistics. Statistical bulletin: Births in England and Wales, 2014, 2015.
- 561 [31] Northern Ireland Statistics & Research Agency. Vital Statistics. Births. Table 3.10. Live births,
562 stillbirths and maternities, by sex of child, marital status of parents and age of mother, 2012,
563 n.d.
- 564 [32] Northern Ireland Statistics & Research Agency. Registrar General Annual Report 2014.
565 Stillbirths and Infant Deaths., n.d. <http://www.nisra.gov.uk/demography/default.asp99.htm>
566 [Accessed 27 May 2016].
- 567 [33] General Register Office for Scotland. Vital events reference tables 2012. Section 4: Stillbirths
568 and infant deaths. Table 4.1; 2013. Available from: [http://www.gro-](http://www.gro-scotland.gov.uk/files2/stats/ve-ref-tables-2012/ve12-t4-1.pdf)
569 [scotland.gov.uk/files2/stats/ve-ref-tables-2012/ve12-t4-1.pdf](http://www.gro-scotland.gov.uk/files2/stats/ve-ref-tables-2012/ve12-t4-1.pdf) [Accessed 30 June 2014]., n.d.
- 570 [34] R.T. Katz, Life expectancy for children with cerebral palsy and mental retardation: implications
571 for life care planning, *NeuroRehabilitation*. 18 (2003) 261–270.
- 572 [35] T. Lamagni, R. Guy, C. Wloch, N. Shetty, V. Chalker, A. Johnson, Estimating the burden of group
573 B streptococcal (GBS) maternal sepsis in England. Federation of Infection Societies (FIS) Annual
574 Conference and the 10th Healthcare Infection Society (HIS) International Conference 2016; 6
575 November 2016; Edinburgh, (n.d.).
- 576 [36] Public Health England, Vaccine Update, Issue 217, 2014.

- 577 [37] G. Amirthalingam, N. Andrews, H. Campbell, S. Ribeiro, E. Kara, K. Donegan, N.K. Fry, E. Miller,
578 M. Ramsay, Effectiveness of maternal pertussis vaccination in England: an observational study,
579 *The Lancet*. 384 (2014) 1521–1528.
- 580 [38] C.L. Trotter, J. McVernon, M.E. Ramsay, C.G. Whitney, E.K. Mulholland, D. Goldblatt, J.
581 Hombach, M.-P. Kieny, Optimising the use of conjugate vaccines to prevent disease caused by
582 *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae*,
583 *Vaccine*. 26 (2008) 4434–4445.
- 584 [39] J. Mohle-Boetani, A. Schuchat, B. Plikaytis, J. Smith, C. Broome, Comparison of prevention
585 strategies for neonatal group b streptococcal infection: A population-based economic analysis,
586 *JAMA*. 270 (1993) 1442–1448. doi:10.1001/jama.1993.03510120064032.
- 587 [40] E.-A. Schroeder, S. Petrou, G. Balfour, O. Edamma, P.T. Heath, The economic costs of Group B
588 *Streptococcus* (GBS) disease: prospective cohort study of infants with GBS disease in England,
589 *Eur. J. Health Econ.* 10 (2009) 275–285.
- 590 [41] L. Curtis, Unit Costs of Health and Social Care 2014, n.d.
- 591 [42] Department of Health. NHS reference costs 2013-2014, n.d.
592 <https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014> [Accessed 27
593 April 2016].
- 594 [43] C. Wright, R. Wordsworth, L. Glennie, Counting the cost of meningococcal disease. Scenarios of
595 Severe Meningitis and Septicemia, *Pediatr. Drugs*. 15 (2013) 49–58.
- 596 [44] H. Christensen, C.L. Trotter, M. Hickman, W.J. Edmunds, others, Re-evaluating cost
597 effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study, *BMJ*.
598 349 (2014) g5725.
- 599 [45] S. Petrou, S. Johnson, D. Wolke, N. Marlow, The association between neurodevelopmental
600 disability and economic outcomes during mid-childhood., *Child: care, health and development*.
601 39 (2013) 345–357.
- 602 [46] NHS Employers. Vaccination and immunisation programmes 2016/17. Guidance and audit
603 requirements, May 2016, n.d. [http://www.nhsemployers.org/
604 /media/Employers/Documents/Primary](http://www.nhsemployers.org/media/Employers/Documents/Primary) [Accessed 1 June 2016].
- 605 [47] NHS Litigation Authority. Freedom of Information Request F/2649., (n.d.).
- 606 [48] J.E. Raine, An analysis of successful litigation claims in children in England, *Arch. Dis. Child*. 96
607 (2011) 838–840.
- 608 [49] G. Sen, J. Keene, J. Raine, An analysis of successful litigation claims in childhood fatalities in
609 England, *Eur. J. Pediatr.* 171 (2012) 1657–1660.
- 610 [50] Meningitis Research Foundation. Response to the JCVI interim position statement on the use
611 of Bexsero meningococcal B vaccine in the UK, (n.d.).
- 612 [51] D. Holt, S. Halket, J. De Louvois, D. Harvey, Neonatal meningitis in England and Wales: 10 years
613 on, *Arch. Dis. Child.-Fetal Neonatal Ed.* 84 (2001) F85–F89.
- 614 [52] R.T. Katz, Life expectancy for children with cerebral palsy and mental retardation: implications
615 for life care planning, *NeuroRehabilitation*. 18 (2003) 261–270.
- 616 [53] T. Colbourn, C. Asseburg, L. Bojke, Z. Philips, K. Claxton, A. Ades, R. Gilbert, Prenatal screening
617 and treatment strategies to prevent group B streptococcal and other bacterial infections in
618 early infancy: cost-effectiveness and expected value of information analyses., *Health Technol.*
619 *Assess.* 11 (2007).
- 620 [54] R.K. Eyman, H.J. Grossman, R.H. Chaney, T.L. Call, The life expectancy of profoundly
621 handicapped people with mental retardation, *N. Engl. J. Med.* 323 (1990) 584–589.
- 622 [55] Office for National Statistics. National Life Tables: United Kingdom. 2015., (n.d.).
- 623 [56] L. Curtis, A. Burns, Unit Costs of Health and Social Care 2015. Personal Social Services Research
624 Unit, The University of Kent, (n.d.).
- 625 [57] Public Health England, Vaccine Update, Issue 217, 2014.

- 626 [58] A. Kalin, C. Acosta, J.J. Kurinczuk, P. Brocklehurst, M. Knight, Severe sepsis in women with
627 group B Streptococcus in pregnancy: an exploratory UK national case-control study, *BMJ Open*.
628 5 (2015) e007976.
- 629 [59] J. Hall, N.H. Adams, L. Bartlett, A.C. Seale, T. Lamagni, F. Bianchi-Jassir, J.E. Lawn, C.J. Baker, C.
630 Cutland, P.T. Heath, M. Ip, K. Le Doare, S.A. Madhi, C.E. Rubens, S.K. Saha, S. Schrag, A.
631 Sobanjo-ter Meulen, J. Vekemans, M.G. Gravett, Maternal Disease With Group B Streptococcus
632 and Serotype Distribution Worldwide: Systematic Review and Meta-analyses, *Clin. Infect. Dis.*
633 65 (2017) S112–S124. doi:10.1093/cid/cix660.
- 634 [60] H. Al-Janabi, J. Van Exel, W. Brouwer, J. Coast, A Framework for Including Family Health
635 Spillovers in Economic Evaluation, *Med. Decis. Making*. 36 (2016) 176–186.
636 doi:10.1177/0272989X15605094.
- 637 [61] The Department of Health Guidance Manual to Impact Assessments, (2015).
- 638 [62] K. Claxton, S. Martin, M. Soares, N. Rice, E. Spackman, S. Hinde, N. Devlin, P.C. Smith, M.
639 Sculpher, Methods for the estimation of the National Institute for Health and Care Excellence
640 cost-effectiveness threshold., *Health Technol. Assess. Winch. Engl.* 19 (2015) 1.
- 641 [63] Public Health England. Pertussis Vaccination Programme for Pregnant Women: vaccine
642 coverage estimates in England, April to August 2014, n.d.
643 <https://www.gov.uk/government/publications/pertussis-immunisation-in-pregnancy-vaccine-coverage-estimates-in-england-october-2013-to-march-2014/pertussis-vaccination-programme-for-pregnant-women-vaccine-coverage-estimates-in-england-april-to-august-2014#results> [Accessed 29 September 2017].
- 644
645
646
647 [64] S.A. Madhi, C.L. Cutland, L. Jose, A. Koen, N. Govender, F. Wittke, M. Olugbosi, A. Sobanjo-ter
648 Meulen, S. Baker, P.M. Dull, Safety and immunogenicity of an investigational maternal trivalent
649 group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2
650 trial, *Lancet Infect. Dis.* 16 (2016) 923–934.