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

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## 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

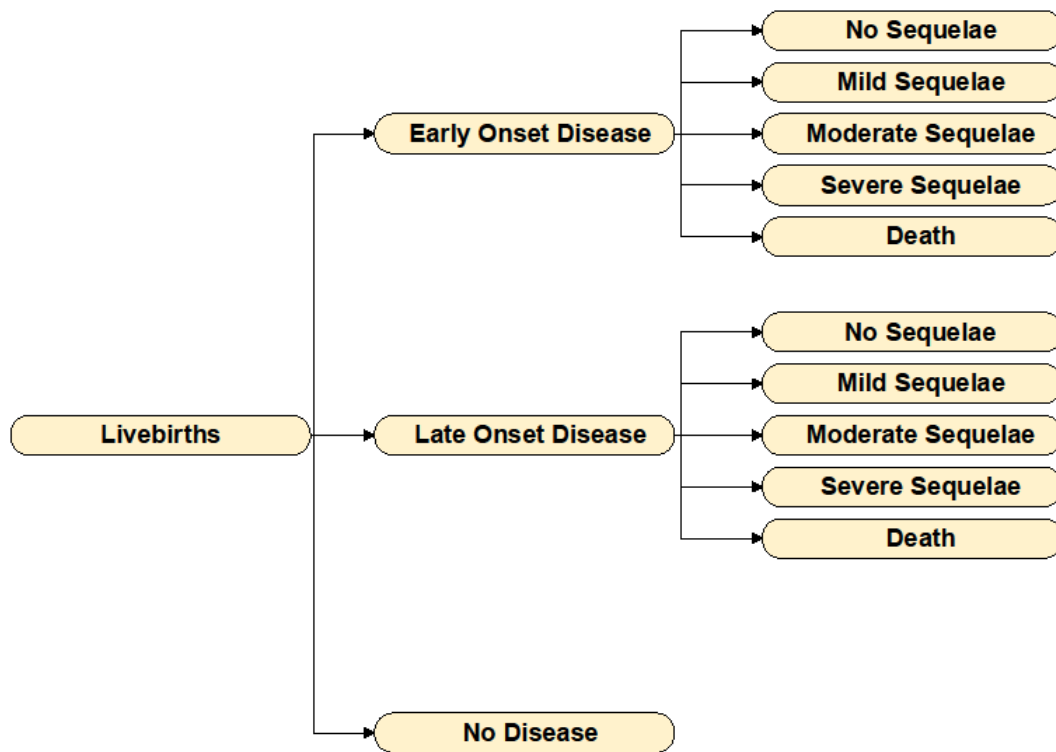
## 66 **Methods**

### 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
<b>Infant disease</b>			
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]
<b>Maternal disease</b>			
Maternal GBS disease incidence	0.27/1,000 maternities	unif(0.000243, 0.000297)	Based on [35]
<b>General population</b>			
Life expectancy (general population)	81		[23]
Livebirths (yearly)	776,352		[20–22]
Stillbirths (yearly)	3,563		[20,24,25]
<b>Vaccine</b>			
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]
<b>Economic costs (£)</b>			
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]
<b>Litigation</b>			
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.

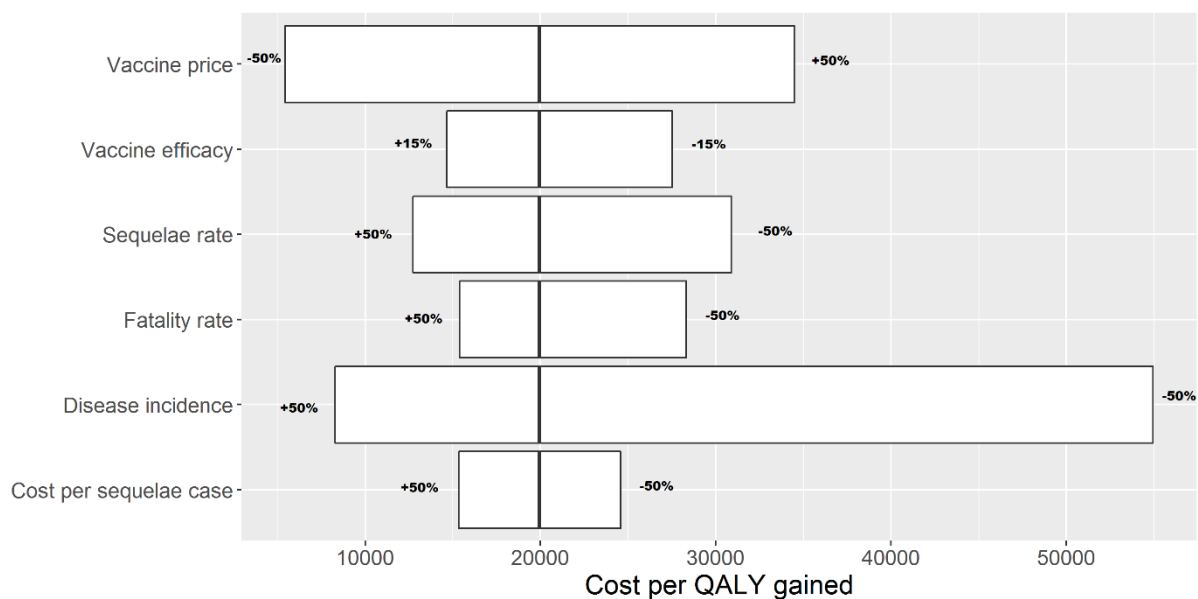
238 Table 2. Deterministic model results for base case scenario.

<b>Health outcomes</b>	<b>Risk factor-based IAP alone (current strategy)</b>	<b>Maternal immunisation with risk factor-based IAP (proposed strategy)</b>	<b>Incremental benefits of proposed immunisation strategy</b>
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
<b>Costs (£ millions)</b>	<b>Risk factor-based IAP alone (current strategy)</b>	<b>Maternal immunisation with risk factor-based IAP (proposed strategy)</b>	<b>Incremental costs of proposed immunisation strategy</b>
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
<b>Cost-effectiveness measures</b>			<b>Incremental cost-effectiveness of proposed immunisation strategy</b>
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  $\pm 0.15$   
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*

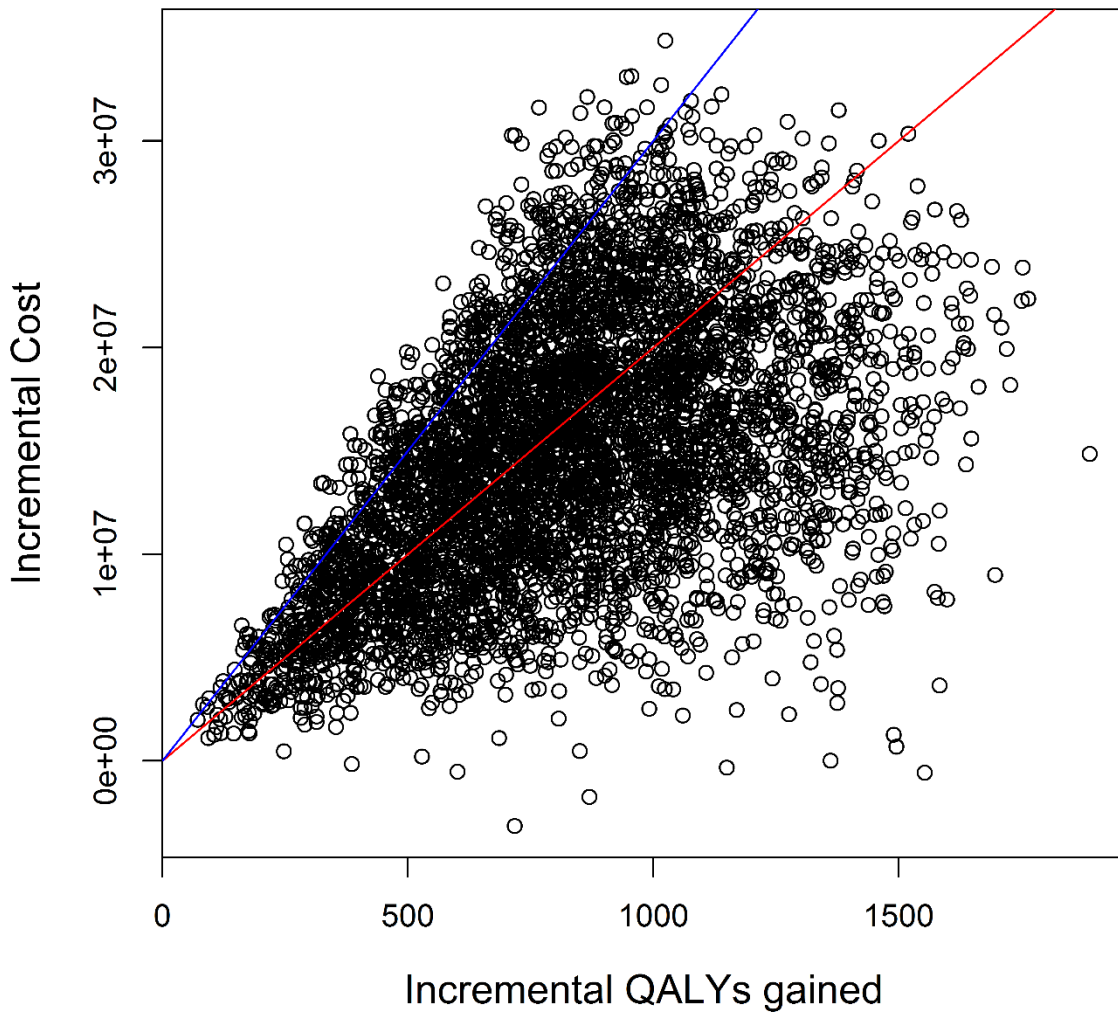
275 Consistency of results for the base case scenario (assuming £54 per dose) was explored in the  
276 probabilistic sensitivity analysis, where parameter distributions were set to reflect estimates'  
277 variations perceived as realistic. Uncertainty guidelines require at least 90% of iterations to  
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

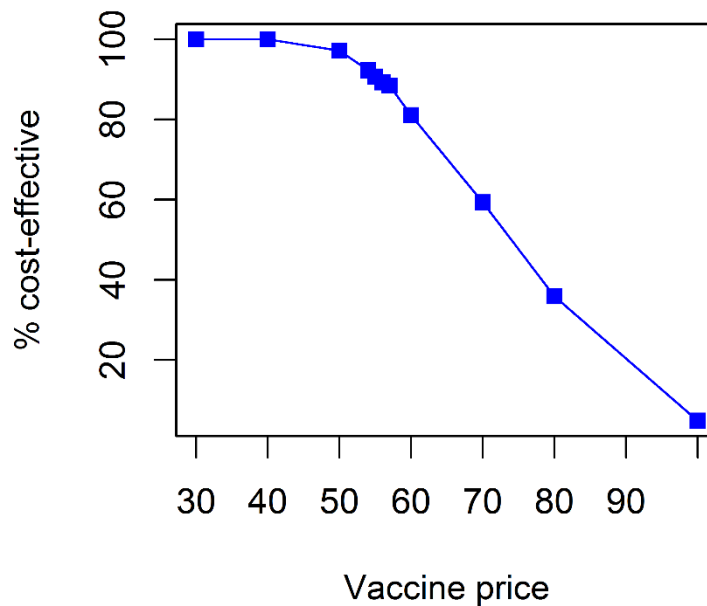


285

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

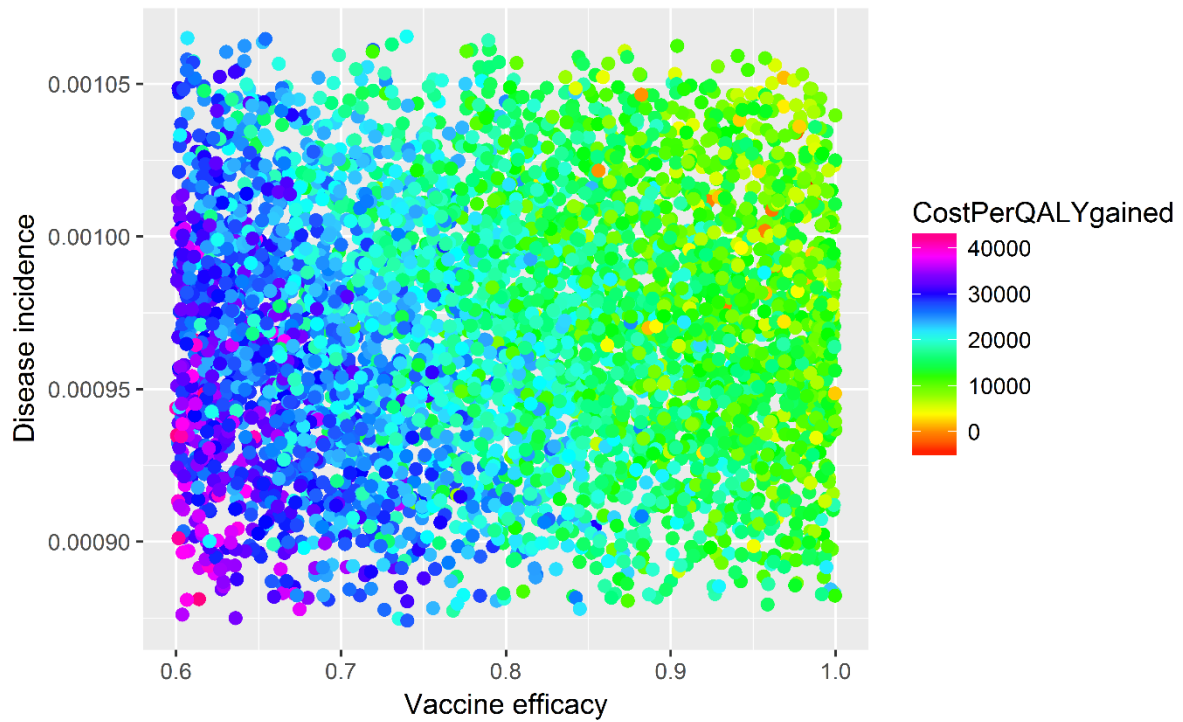


293

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

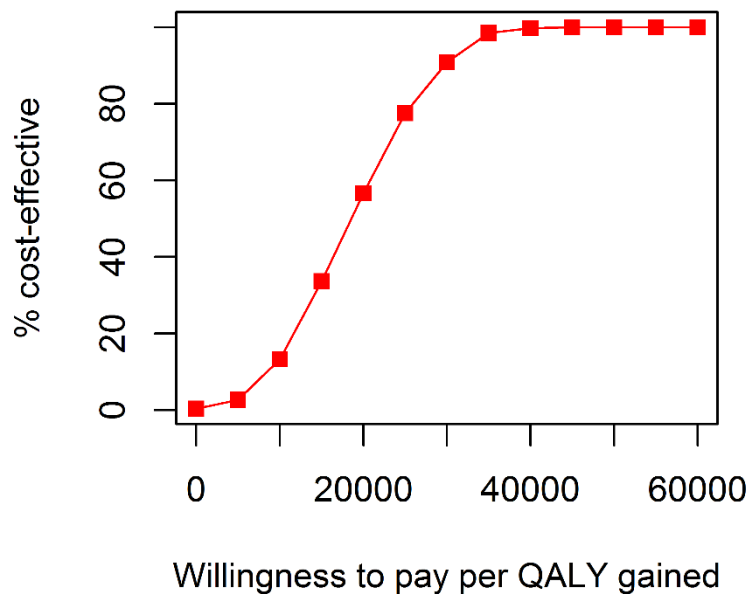
299 Investigating the effect of the interplay between vaccine efficacy and overall disease  
 300 incidence on the probabilistic sensitivity analysis results, it is evident that uncertainty in the  
 301 cost per QALY gained is mainly driven by vaccine efficacy (The cost-effectiveness  
 302 acceptability 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**

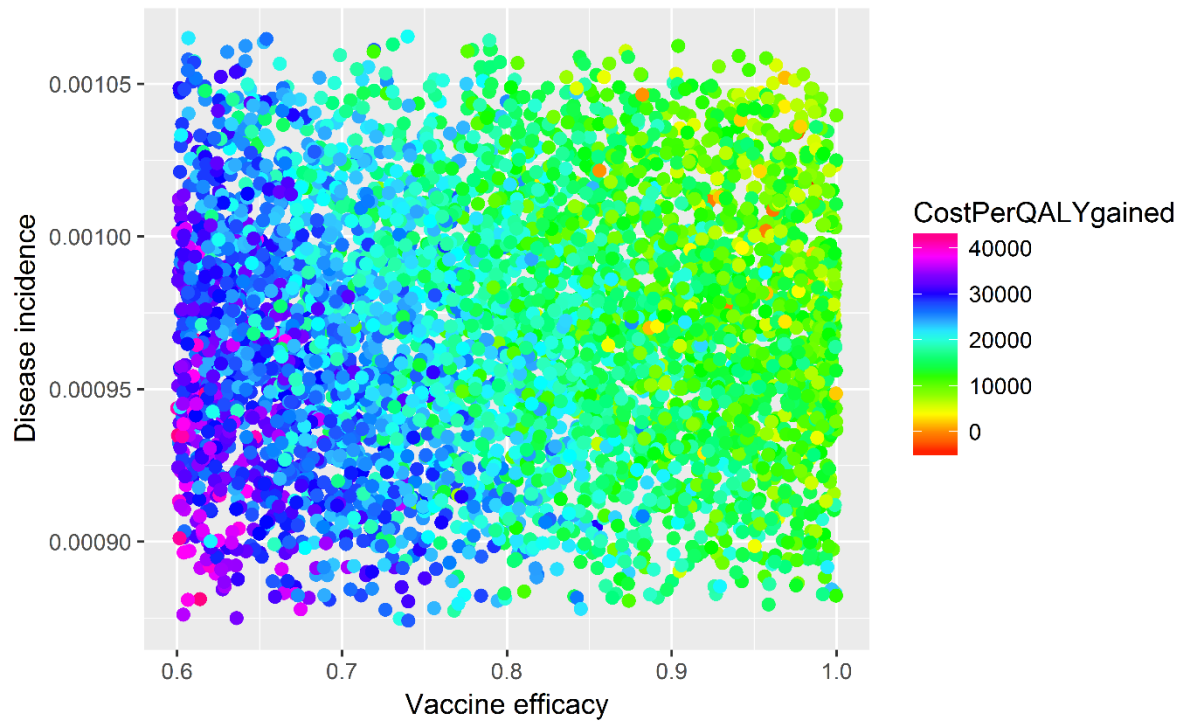
### 322 *Principal findings*

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.

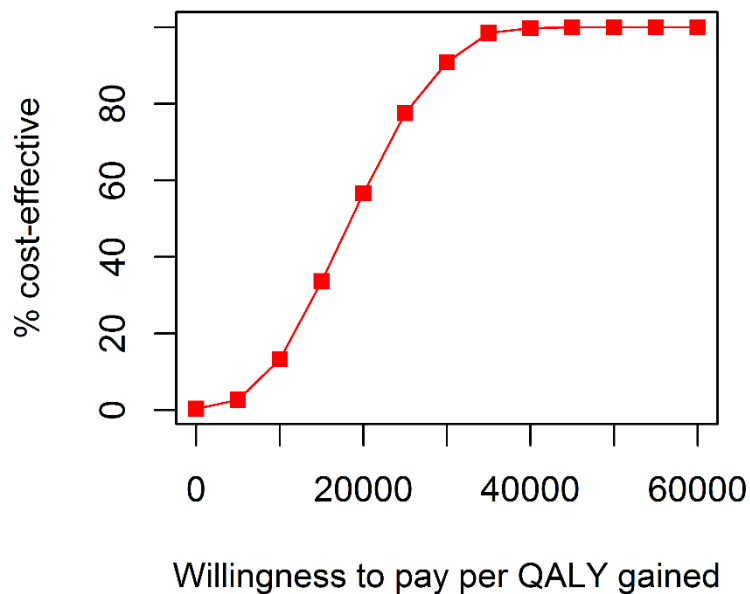
338 The cost-effectiveness acceptability curve is presented in **Error! Reference source not**  
339 **found.** The latter exhibits the changing incremental cost-effectiveness of the maternal  
340 immunisation strategy with risk factor-based IAP in comparison with risk factor-based IAP  
341 alone for 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

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352 **outcomes discount rate=3.5%).** The graph displays the percentage of Monte Carlo iterations (total of  
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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  
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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

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447

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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

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