

Cost-effectiveness analysis of maternal immunisation against group B streptococcus (GBS) disease

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

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4 **Introduction**

5 In the UK, group B *Streptococcus* (GBS; *Streptococcus agalactiae*) is a leading cause of
6 meningitis and septicaemia in babies up to 3 months of age. A recent national prospective
7 study showed GBS was responsible for half of all neonatal meningitis cases [1]. Invasive
8 infant GBS disease has a case fatality rate of 5-10% in the UK [1–3], despite the availability
9 of sophisticated neonatal intensive care. Up to 50% of GBS meningitis survivors have
10 adverse neurodevelopmental outcomes [4]. GBS is also implicated as a cause of stillbirth
11 [5,6], pre-term birth [6,7] and maternal sepsis [6,8].

12 GBS is part of the natural flora of the human gastrointestinal and genitourinary tracts.
13 Asymptomatic carriage is common, with 20% of pregnant women in developed countries
14 carrying GBS rectovaginally [9]. Around 50% of infants born to colonised mothers will
15 become colonised and 1% will develop GBS disease [7]. Because maternal colonisation is a
16 necessary stage in the disease process, at least for early onset disease (defined as <7 days of
17 age), intervention strategies have, to date, focussed on prophylactic antibiotics for women in
18 labour targeted on the basis of antenatal screening results and/or identified risk factors [10].

19 The incidence of GBS disease has increased in the UK since 2004 [1,11]; enhanced
20 surveillance studies from the British Paediatric Surveillance Unit (BPSU) reported incidence
21 of 0.72 per 1000 livebirths in 2004 [3] and 0.97 per 1000 livebirths in 2015 [2]. This increase
22 is despite the UK prevention strategy of risk factor-based intrapartum antibiotic prophylaxis
23 (IAP) [12]. The UK has not adopted universal antenatal screening because it is not clear
24 whether the benefits of screening outweigh the harms for the majority of pregnant women
25 [13]. Maternal immunisation strategies offer promise for the prevention of infant GBS
26 disease without reliance on widespread antibiotic use and several vaccine candidates are in
27 development [14].

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

38

39 **Methods**

40 *Model description*

41 A static decision tree model was developed to account for infant GBS disease and long-term
42 health outcomes, including death, among an annual cohort of UK livebirths (**Error!**
43 **Reference source not found.**). Maternal GBS disease was estimated separately based on the
44 incidence of disease among maternities (excluding miscarriages). Stillbirths were included in
45 the estimation of vaccination costs, however, the potential impact of the vaccine on the
46 prevention of both stillbirths and preterm births was only explored in scenario analysis.

47 The cohort of livebirths was assumed to be homogenous and was based on 2014 data
48 reporting 776,352 livebirths in the UK [20–22]. Infants were followed over their lifetime to
49 enable the inclusion of health outcomes and healthcare costs over this period. The adopted
50 time horizon was the life expectancy of survivors with no or mild sequelae, which was 81

51 years [23]. There were 3,563 stillbirths in the UK in 2014 [20,24,25] and these were included
52 in the estimation of maternal immunisation costs (vaccine purchase and administration).

53

54 **Figure 1. Diagram of decision tree model for base case scenario.** The structure of the model remains
55 the same for both strategies; risk factor-based IAP and maternal immunisation with risk factor-based
56 IAP. Incremental health benefits of the latter strategy were estimated for the annual livebirths
57 population (776,352 in 2014 data) with vaccination costs estimated for both livebirths and stillbirths
58 (3,563 in 2014). The potential impact of strategies on maternal disease (all maternities excluding
59 miscarriage) is estimated separately.

60

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

73 The model was computationally implemented in R using standard packages, and used to
74 investigate costs and benefits of maternal immunisation from the perspective of the NHS and

75 Personal Social Services (health provider). We followed standard methods on cost-
76 effectiveness analysis; the Joint Committee on Vaccination and Immunisation (JCVI), who
77 make vaccine recommendations in the UK, in principle follow NICE methodology although
78 more specific detail on dealing with uncertainty is given [29].

79 *Parameter values - Disease*

80 The latest available UK data on GBS disease and sequelae were used to parameterise the
81 model. GBS disease incidence was informed by the most recent BPSU enhanced surveillance
82 study for infants up to 3 months of age [2]. Case fatality rates were based on the same source,
83 while UK-wide data on livebirths and stillbirths were obtained from the Office for National
84 Statistics [22,30–33]. Parameter estimates are presented in Table 1.

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

92 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] |

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

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

103 *Parameter values – Costs*

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

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

111 Litigation costs were sought from the NHS Litigation Authority through a Freedom of
112 Information Request; the available data, however, were not disease-specific (Appendix 1).
113 Estimates used in this study were the result of data synthesis from a number of different sources
114 (Appendix 1). Furthermore, the model includes litigation costs only beyond the product of lost
115 QALYs and ceiling ratio of cost per QALY gained, following current Department of Health
116 practice (Peter Grove personal communication, 24 October 2016).

117 Healthcare costs for maternal GBS disease were derived from the corresponding hospital
118 admission record during which the laboratory diagnosis was made. An average cost per maternal
119 disease case was calculated weighing the relevant HRG codes recorded in HES according to their
120 frequency (Appendix 1).

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

123 *Parameter values - Vaccine*

124 The base case scenario considered immunisation of pregnant women in the UK with a
125 pentavalent vaccine (serotypes Ia, Ib, II, III and V). Women of at least 24 weeks of gestation
126 would be offered the vaccine against GBS. Strain coverage by such a vaccine was estimated to be
127 96.2% based on the latest surveillance data [2] (Appendix 1). Vaccine uptake was set at 60%
128 based on information from the pertussis maternal immunisation programme [57]. Data on vaccine
129 efficacy are not currently available so our assumption of 85% was based on reported vaccine
130 efficacy for other conjugate vaccines [37,38] (Appendix 1). Vaccine price is also currently
131 unknown. Here, we tested different vaccine prices with the aim of identifying those for which a
132 GBS vaccine would be cost-effective.

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

136 *Parameter values - Discounting*

137 Following JCVI guidelines [29] future costs and health outcomes were discounted at 3.5% and a
138 threshold of £20,000 per QALY gained was applied. A threshold of £30,000 per QALY gained
139 was also explored as well as an alternative scenario of £15,000 per QALY at 1.5% discounting
140 for both future costs and health outcomes.

141

142 *Sensitivity Analysis*

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

150 Scenario analysis was used to test assumptions excluded from the base case scenario. Prevention
151 of stillbirth and/or premature birth are important potential advantages of maternal immunisation
152 over the current practice of risk factor-based IAP, however, such benefits are currently
153 hypothetical. We tested the potential impact of a GBS vaccine on prevention of stillbirth and
154 premature birth, both in combination and individually. In the investigation of stillbirth
155 prevention, we accounted for averted cases having the life expectancy of healthy survivors. For
156 preterm births, we accounted for the relevant healthcare costs. We also considered other scenarios
157 offering additional health outcomes, including prevention of maternal deaths and effect of disease
158 on the health of carers (predominantly parents; recent economic evaluation studies have

159 accounted for the impact of disease on the quality of life of carers [41–43]). A scenario of
160 decreased vaccine strain coverage, with a trivalent GBS vaccine used instead of the base case
161 scenario assumption of a pentavalent vaccine was also explored. Parameters for all scenarios are
162 available in Appendix 1 (Table 9).

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

170

171 **Results**

172 *Deterministic Model Results*

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

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

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

189 *Sensitivity analysis results*

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

196 *Scenario analysis*

197 Several scenarios were explored as alternatives to the assumptions of the base case (Appendix 2,
198 Table 2). Potential prevention of stillbirths and/ or preterm births by the GBS vaccine, for
199 instance, would increase its added benefits, making it more cost-effective. With a theoretical 1%
200 of stillbirths assumed to be vaccine-preventable, the maximum cost-effective vaccine price was
201 £94 (£54 per dose in the base case). A similar percentage of vaccine-preventable (surviving)

202 preterm births had a lesser impact, with the maximum cost-effective price rising to £59. A
 203 combination of both resulted in a maximum cost-effective price of £100.

204 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 |

205 Cohort size: 776,352 livebirths, 3,563 stillbirths. Stillbirths were only included in the estimation of
 206 immunisation costs. Maternal immunisation parameters: vaccine price = £54/dose, vaccine efficacy =

207 85%, vaccine strain coverage = 96.2%, vaccine uptake rate = 60%. Litigation costs included in the table
208 exclude those already accounted for through lost QALYs (Department of Health practice). IAP:
209 intrapartum antibiotic prophylaxis, QALY: quality-adjusted life year, GBS: group B *Streptococcus*

210

211

212 **Figure 2. Results of one-way (vaccine price, vaccine efficacy) and multi-way (overall: sequelae rate,**
213 **fatality rate, disease incidence and cost per sequelae case) sensitivity analysis.** Base value estimates
214 were varied by $\pm 50\%$ with the exception of vaccine efficacy which was varied by ± 0.15 (maximum value
215 = 1). Base case scenario cost per QALY (£19,953) is displayed by the middle line in each bar. Parameters
216 displayed here are those whose alteration had an impact in the cost per QALY of at least 20%. The impact
217 of EOD and LOD incidence is presented here in a cumulative way, though both parameters have an
218 individual effect on the cost per QALY at beyond 20% its base case value (£19,953). QALY: quality-
219 adjusted life year, EOD: early onset disease, LOD: late onset disease

220

221 To date, no maternal deaths caused by GBS have been reported in the UK [35,58]. Considering
222 the possibility that some maternal fatalities could occur [59], we accounted for a maternal fatality
223 rate of 1% among maternal GBS cases. The GBS vaccine was only marginally more cost-
224 effective in this scenario with the threshold cost-effective price (rounded to the nearest GBP)
225 remaining the same.

226 We considered the potential effect of health spillovers for cases with sequelae and for fatalities in
227 one of the scenarios we explored, adjusting this for those displaced by funding the intervention
228 [60] (Appendix 1). Results showed the vaccine programme to be more cost-effective, increasing
229 the threshold vaccine price by £6 (Appendix 2, Table 2).

230 A 'most favourable' scenario incorporating all of the above increased the threshold vaccine price
231 to £107.

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

235 Finally, an alternative 1.5% discount rate for both future costs and health outcomes with a
236 £15,000/ QALY threshold scenario was explored to reflect discussions on the appropriate
237 threshold [61,62]. Comparing the base case results with this scenario, the vaccine became even
238 more cost-effective (£78 per dose) with the alternative guidelines applied (£54 per dose in the
239 base case).

240 *Probabilistic sensitivity analysis*

241 Consistency of results for the base case scenario (assuming £54 per dose) was explored in the
242 probabilistic sensitivity analysis, where parameter distributions were set to reflect estimates'
243 variations perceived as realistic. Uncertainty guidelines require at least 90% of iterations to be
244 under the £30,000 threshold [29]. Of the 5,000 iterations that were run, 92.24% fell under the
245 £30,000 threshold of cost per QALY gained (**Error! Reference source not found.**), while a
246 slightly higher vaccine price of £55 per dose showed 90.66% of iterations below the £30,000
247 threshold. Model outcomes were highly dependent on vaccine price Figure 4.

248

249

250

251

252 **Figure 3. Monte Carlo probabilistic sensitivity analysis of 33 parameters, 5,000 iterations, for base**
253 **case scenario.** The incremental cost (£) of the maternal immunisation strategy with risk factor-based IAP
254 comparing with that of risk factor-based IAP alone is plotted in the y axis, with the x axis displaying the
255 incremental QALYs gained. Of the 5,000 iterations 92.24% fall below the £30,000 ceiling ratio (blue line)
256 of cost per QALY gained and 56.62% below the £20,000 threshold (red line). QALY: quality-adjusted life
257 year

258

259 **Figure 4. Effect of vaccine price (£) on the percentage of Monte Carlo iterations (total of 5,000) for**
260 **which the immunisation strategy is cost-effective (threshold of £30,000 per QALY gained).** Discount
261 rate is 3.5% for both future costs and health outcomes. Vaccine price per dose for the base case scenario is
262 £54. QALY: quality-adjusted life year

263

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

271

272 **Figure 5. Comparison of overall disease incidence and vaccine efficacy as drivers of vaccine cost-**
273 **effectiveness, in Monte Carlo probabilistic sensitivity analysis of 5,000 iterations, where other**
274 **parameter values remain as in base case scenario.** Vaccine price per dose for the base case scenario is
275 £54. Incremental cost (£) per QALY gained of the maternal immunisation strategy with risk factor-based
276 IAP comparing with that of risk factor-based IAP alone is represented by nodes of varying colour
277 depending on value (colour guide on figure's right side). QALY: quality-adjusted life year

278

279 **Figure 6. Cost-effectiveness acceptability curve of the base case scenario (future costs and health**
280 **outcomes discount rate=3.5%).** The graph displays the percentage of Monte Carlo iterations (total of
281 5,000) for which the immunisation strategy is cost-effective, depending on the willingness of the
282 healthcare system to pay (in £) for each QALY gained. Vaccine price per dose in the base case scenario is
283 £54. QALY: quality-adjusted life year

284

285 **Discussion**

286 ***Principal findings***

287 A maternal immunisation strategy with risk factor-based IAP, is highly likely to be a cost-
288 effective intervention against infant GBS disease for the NHS, assuming the availability of a safe,
289 effective vaccine that can be purchased and administered at a reasonable price. The proposed new
290 strategy is compared to the current strategy of risk factor-based IAP alone. In the base case, we
291 estimated that, with 60% coverage, 369 infant cases, 103 maternal cases and 21 infant deaths
292 could be averted in a single birth cohort. Additional benefit would be achieved if coverage were
293 closer to the 75% achieved recently in the maternal pertussis programme [63]. The threshold cost

294 per dose was £54 at £20,000/ QALY; at this price, the uncertainty rules are also met, with 92.24
295 % of simulations in the probabilistic sensitivity analysis falling below £30,000/QALY. Most of
296 the alternative scenarios we investigated improved the cost-effectiveness of immunisation.
297 Prevention of stillbirths and/ or preterm births would). In contrast with **Error! Reference source**
298 **not found.**, where both parameters were varied by 50%, here the disease incidence - for which
299 there are recent and reliable data - was only varied by $\pm 10\%$. Vaccine efficacy, on the other hand,
300 for which no data are available, was varied more, with values ranging from 0.6 to 1 to reflect this
301 uncertainty.

302 The cost-effectiveness acceptability curve is presented in **Error! Reference source not found.**
303 The latter exhibits the changing incremental cost-effectiveness of the maternal immunisation
304 strategy with risk factor-based IAP in comparison with risk factor-based IAP alone for the base
305 case of 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 is
311 £54. Incremental cost (£) per QALY gained of the maternal immunisation strategy with risk factor-based
312 IAP comparing with that of risk factor-based IAP alone is represented by nodes of varying colour
313 depending on value (colour guide on figure's right side). QALY: quality-adjusted life year

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 scenario is
319 £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 safe,
325 effective vaccine that can be purchased and administered at a reasonable price. The proposed new
326 strategy is compared to the current strategy of risk factor-based IAP alone. In the base case, we
327 estimated that, with 60% coverage, 369 infant cases, 103 maternal cases and 21 infant deaths
328 could be averted in a single birth cohort. Additional benefit would be achieved if coverage were
329 closer to the 75% achieved recently in the maternal pertussis programme [63]. The threshold cost
330 per dose was £54 at £20,000/ QALY; at this price, the uncertainty rules are also met, with 92.24
331 % of simulations in the probabilistic sensitivity analysis falling below £30,000/QALY. Most of
332 the alternative scenarios we investigated improved the cost-effectiveness of immunisation.
333 Prevention of stillbirths and/ or preterm births would increase vaccine cost-effectiveness, while
334 the prevention of maternal deaths from GBS sepsis would only have a minor impact, as this is
335 considered to be rare. Both a trivalent and a pentavalent vaccine would be cost-effective, with the
336 latter being clearly more attractive for both the health system and vaccine manufacturers.
337 Accounting for the health benefits gained (and displaced) from reducing the strain on carers also

338 makes the vaccine more cost-effective. The cumulative effect of including all vaccine-favourable
339 scenarios more than doubles the threshold vaccine price.

340 *Strengths and limitations*

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

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

355 We did not consider any potential impact of maternal immunisation on maternal GBS
356 colonisation. In one study non-pregnant women who received a GBS conjugate vaccine were
357 found to have a significantly longer time to first vaginal acquisition than women in the control
358 group [27], but no clear effect on colonisation was observed in a pregnancy trial with a different
359 GBS conjugate vaccine [64]. We consider it unlikely that an immunisation programme targeting

360 only pregnant women would have profound effects on the population biology of GBS even if a
361 vaccine did influence carriage and so we chose a static decision tree model rather than a
362 transmission dynamic model. However further research is necessary to fully understand the
363 implications of a vaccine affecting colonisation, e.g. of vaccine selection pressure driving
364 serotype replacement.

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

369 We investigated the added benefit of a maternal immunisation strategy where IAP is still used
370 when pre-defined risk factors are identified. This does not address any potential savings which
371 accrue if fewer antibiotics are administered and the important but less tangible benefits of
372 reducing selection pressure which could lead to antibiotic resistance. We did not investigate other
373 preventive strategies, such as universal screening for GBS colonisation, as we concentrated on
374 the current UK context.

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

379 *Comparison with other studies*

380 A previous cost-effectiveness study on GBS disease in the UK [53] showed that a combination of
381 vaccination with IAP for some maternal risk groups was amongst the most cost-effective of the

382 tested strategies. Our analysis uses up-to-date parameter estimates, including increased
383 incidence, and emphasises the added benefits of vaccination with risk-based IAP, rather than
384 comparing a range of screening options. Other studies on the cost-effectiveness of maternal
385 immunisation have been conducted in South Africa [16]; sub-Saharan Africa [17] and the USA
386 [18,19].

387 All of these studies concluded that GBS vaccination could be a cost-effective intervention, but
388 found that disease incidence, vaccine efficacy and vaccine cost were key determinants, with most
389 of the studies also including fatality rates in this list. The studies from the USA [18,19] are more
390 directly comparable to our study, as they investigate the added benefit of vaccination in terms of
391 cost per QALY in a country with sophisticated healthcare. However, a key difference is that they
392 compared vaccination in combination with screening-based IAP versus screening based IAP only
393 (the current US standard of care). This prevents a head-to-head comparison, but it does appear
394 that given the current incidence and standards of care, a UK programme might be more cost-
395 effective than a maternal immunisation programme in the USA. In the future, a model
396 comparison exercise to examine the differences in model assumptions, parameters and results
397 could be of value.

398

399 **Conclusion**

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

403

404

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414

415 **Conflicts of interest**

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

423

424 **Contributors**

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

429

430 Appendix 1: Parameter estimation.

431 Appendix 2: Additional model results.

432

433

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