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Reactive vaccination as a control strategy for pneumococcal meningitis outbreaks in the African meningitis belt: analysis of outbreak data from Ghana

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Abstract

Streptococcus pneumoniae is increasingly recognised as an important cause of bacterial meningitis in the African meningitis belt. The World Health Organization sets guidelines for response to outbreaks of meningococcal meningitis, but there are no current guidelines for outbreaks where *S. pneumoniae* is implicated. We aimed to evaluate the impact of using a similar response to target outbreaks of vaccine-preventable pneumococcal meningitis in the meningitis belt. Here, we adapt a previous model of reactive vaccination for meningococcal outbreaks to estimate the potential impact of reactive vaccination in a recent pneumococcal meningitis outbreak in the Brong-Ahafo region of central Ghana using weekly line list data on all suspected cases over a period of five months. We determine the sensitivity and specificity of various epidemic thresholds and model the cases and deaths averted by reactive vaccination. An epidemic threshold of 10 suspected cases per 100,000 population per week performed the best, predicting large outbreaks with 100% sensitivity and more than 85% specificity. In this outbreak, reactive vaccination would have prevented a lower number of cases per individual vaccinated (approximately 15,300 doses per case averted) than previously estimated for meningococcal outbreaks. Since the burden of death and disability from pneumococcal meningitis is higher than that from meningococcal meningitis, there may still be merit in considering reactive vaccination for outbreaks of pneumococcal meningitis. More outbreak data are needed to refine our model estimates. Whatever policy is followed, we emphasize the importance of timely laboratory confirmation of suspected cases to enable appropriate decisions about outbreak response.

47 Introduction

48 Following the rollout of the serogroup A conjugate vaccine, MenAfriVac, across the
49 African meningitis belt since 2010, the incidence of meningococcal meningitis due to
50 serogroup A has sharply declined.(1) With an accompanying increase in surveillance quality,
51 it has become increasingly clear that meningitis due to *Streptococcus pneumoniae* (Spn)
52 represents a substantial proportion of the burden of endemic meningitis in this region. In
53 addition to this, localized outbreaks of pneumococcal disease, in excess of normal seasonal
54 activity, have been reported.(2–7)

55 The introduction of a 13-valent pneumococcal conjugate vaccine (PCV13) into
56 Ghana's routine immunization programme as a 3 + 0 schedule in 2013 is expected to have
57 decreased the burden of invasive pneumococcal disease in children aged under five years,
58 based on observations from other African countries.(8) It has been shown in high-income
59 countries that PCVs provide indirect protection against invasive pneumococcal disease to
60 older children and adults and that this is accelerated with the use of catch-up campaigns,
61 however the only country to show indirect benefit without a catch up campaign in older
62 children used a 2 + 1 schedule.(9,10) The scale of indirect effects that might be achieved
63 following routine infant PCV immunisation in African countries is not yet clear. An outbreak
64 of predominantly serotype 1 pneumococcal meningitis in the Brong-Ahafo region of Ghana
65 in late 2015 and early 2016 demonstrated the ongoing vulnerability of older age groups and
66 the continuing potential of Spn to cause meningitis outbreaks in spite of high PCV coverage
67 in infants (94%).(2,11)

68 Outbreaks of meningococcal meningitis in the African meningitis belt trigger a
69 reactive vaccination response, with the public health goal of curtailing the outbreak and
70 thus preventing cases and deaths. It has been suggested that outbreaks of pneumococcal

71 meningitis due to a vaccine-preventable serotype could also merit such a response.(7,12) To
72 quantify the potential benefits of reactive vaccination for pneumococcal meningitis
73 outbreaks we modelled a reactive vaccination response to the Brong-Ahafo pneumococcal
74 meningitis outbreak. Under the current WHO guidelines applied to outbreaks of
75 meningococcal meningitis, when districts exceed a threshold of 10 suspected cases per
76 100,000 population in a week, an epidemic response is triggered.(13) Countries may submit
77 a request to the International Coordinating Group on Vaccine Provision for Epidemic
78 Meningitis Control for supplies of meningococcal vaccines to deploy in affected districts.
79 However, this process takes some time as a request must be completed and reviewed and
80 vaccine stocks must be delivered, often to inaccessible areas. For this model, we considered
81 the potential impact of mass vaccination response in affected districts with PCV13, to see
82 whether similar guidelines may be appropriate for outbreaks of pneumococcal meningitis.

83 When discussing disease in the African meningitis belt, it is important to distinguish
84 between seasonal fluctuations in endemic disease, outbreaks - which may be defined as an
85 isolated district surpassing the epidemic weekly incidence threshold, and widespread
86 epidemics, which affect whole regions or countries in a season. For the purposes of this
87 study, we define an outbreak of pneumococcal meningitis using two criteria: i) weekly
88 incidence on the regional or district level of suspected meningitis over a single dry season
89 exceeding some epidemic threshold that reflects the upper bound of dry season endemic
90 incidence, ii) where pneumococcus is the predominant cause. We retain the term “epidemic
91 threshold” for consistency with meningococcal vaccination policy, but do not mean to imply
92 that these events constitute widespread epidemics.

93

94 Methods

95 Line list data on all suspected cases of meningitis reported in the Brong-Ahafo
96 Region between 2 December 2015 (week 49, 2015) and 11 April 2016 (week 15, 2016) were
97 obtained from the Ghana Health Service. Brong-Ahafo is a predominantly rural region
98 located in central Ghana, an area previously considered to be just outside the main
99 meningitis belt. A suspected case of meningitis was defined as any person with sudden
100 onset of fever and one of the following signs: neck stiffness, flaccid neck (in infants), bulging
101 fontanelle (infants) convulsion, or other meningeal signs.(14) We determined the sensitivity
102 and specificity of a variety of incidence thresholds (10, 7, 5, and 3 suspected cases per
103 100,000 per week) for predicting a range of sizes of outbreaks (20, 40, 60, 80, and 100
104 cumulative cases per 100,000). We then modelled reactive vaccination of 5- to 29-year-olds
105 building on methods developed in an earlier paper, using an epidemic threshold of 10
106 suspected cases per 100,000 per week to define the beginning of the outbreak and an
107 endemic threshold of 2 suspected cases per 100,000 per week to define the end of the
108 outbreak.(15) We also performed a sensitivity analysis using a lower epidemic threshold of 3
109 suspected cases per 100,000 per week, which corresponds to the alert threshold for
110 meningococcal meningitis. We chose to target 5- to 29-year-olds because this would
111 effectively extend coverage to all individuals under 30 years of age (we assumed children
112 under the age of 5 years were protected by the routine infant PCV13 vaccine schedule) and
113 because the highest incidence of confirmed pneumococcal meningitis was observed in the
114 10 to 14- and 15to 29-year age groups.

115 As a variety of laboratory tests were used for case confirmation, aetiology was
116 classified according to Table 1. In a large proportion of cases (60%), aetiology could not be
117 definitively determined. For this reason, we modelled true cases of Spn meningitis weekly
118 for each district as

119
$$C_{Spn} = C_{s,i} (1 - p_n) p_{Spn}$$

120 where $C_{s,i}$ is the number of suspected cases reported in week i , p_n is the proportion of CSF
121 samples in the district testing negative (in Table 1, both probable and confirmed negative
122 cases), and p_{Spn} is the proportion of all confirmed cases in the district due to Spn. This
123 modelled case count is hereafter referred to as likely Spn cases. Because there was some
124 uncertainty regarding false negative tests, we performed a sensitivity analysis where p_n is
125 only the proportion of CSF samples in the district testing negative by two or more tests (in
126 Table 1, confirmed negative cases).

127 We then simulated vaccination with PCV13 using the same methods described in
128 Trotter et al 2015, making the following assumptions:

- 129 • 5- to 29-year-olds represent 52% of the population (16)
- 130 • Case fatality ratio for pneumococcal meningitis cases is 23%, as reported for
131 confirmed pneumococcal meningitis cases in this data set
- 132 • 79% of cases of pneumococcal meningitis were caused by PCV13 vaccine-type
133 serotypes (2)
- 134 • A single dose of PCV13 would protect at 90% of individuals 5 to 29 years of age
135 against PCV13 vaccine-type serotypes, giving two weeks for the protection to take
136 effect (17)
- 137 • 5% vaccine wastage

138 One district, Sene West, was excluded from the analysis despite having crossed the
139 epidemic threshold because the majority of confirmed cases were due to Nm.

140 We determined the cases prevented, deaths prevented, number needed to
141 vaccinate to prevent a case (NNV) and number needed to vaccinate to prevent a death

142 (NNVD) for three scenarios: where vaccination occurs immediately, two, and four weeks
143 after crossing the epidemic threshold (lag of zero, two or four weeks, respectively).

144

145 Results

146 Twenty of the 27 districts of the Brong-Ahafo Region were represented in the line
147 list. The districts had a mean population size of 105,000. Over the 19-week study period,
148 nine of these had cumulative suspected meningitis incidence greater than 20 suspected
149 cases per 100,000; five had cumulative incidence greater than 40 per 100,000; four had
150 cumulative incidence greater than 80 per 100,000, and three had cumulative incidence
151 greater than 100 per 100,000. For predicting larger outbreaks of 60 suspected cases per
152 100,000 and greater, all thresholds had a sensitivity and negative predictive value of 100%,
153 but a threshold of 10 per 100,000 per week had the best positive predictive values and
154 specificity (Figure 1).

155 Five districts (Jaman North, Nkoranza South, Tain, Techiman North, and Wenchi)
156 crossed the epidemic threshold of 10 cases per 100,000 per week, three of which exceeded
157 a cumulative incidence of 100 cases per 100,000 (Figure 2).

158 Sixty six percent of suspected bacterial meningitis cases in the five outbreak districts
159 and 73% of confirmed pneumococcal meningitis cases occurred in 5- to 29-year-olds. Figure
160 3 shows the age distribution of suspected and confirmed incidence of meningitis in the five
161 districts triggering the epidemic threshold.

162 Vaccinating individuals between 5 and 29 years of age in the five eligible districts
163 would have required approximately 284,000 doses of vaccine (Table 3). If a vaccination
164 campaign had been implemented within two weeks of triggering the epidemic threshold of
165 10 suspected cases per 100,000 per week, an estimated number of 36 cases would have

166 been prevented during the outbreak period, placing the number needed to vaccinate to
167 prevent a case at 15,300. With a delay of four weeks, 20 cases might have been prevented,
168 whereas immediate vaccination might have averted 61 cases.

169 Using a lower threshold of 3 cases per 100,000 per week prevents only a few more
170 cases, but raises the number needed the vaccinate to prevent a case significantly because
171 districts with much smaller outbreaks also trigger a response.

172 Using a stricter definition for bacteria negative CSFs results in a much higher
173 estimate of the number of likely Spn meningitis cases (335 cases as opposed to 176 in the
174 five outbreak districts) and a lower number needed to vaccinate to prevent a case (Table
175 S1). With a delay of two weeks, 63 cases might have been prevented, placing the number
176 needed to vaccinate at 8,800, whereas immediate vaccination might have averted 113
177 cases, placing the number needed to vaccinate at 4,800.

178

179 Discussion

180 An incidence threshold of 10 cases per 100,000 seems the most appropriate
181 epidemic threshold for pneumococcal meningitis outbreaks given the limited data available.
182 This threshold would also have been triggered in four of five previous likely outbreaks of
183 pneumococcal meningitis identified in the WHO enhanced meningitis surveillance system
184 (Solanzo, Burkina Faso, 2009; Goundi, Chad, 2009; Karangasso Vigue, Burkina Faso, 2011;
185 Pama, Burkina Faso, 2011).(1) No attempt was made to evaluate different microbiological
186 criteria for defining a pneumococcal outbreak. In this case, a simple majority of confirmed
187 cases due to Spn was required.

188 Excluding the sensitivity analysis, the number needed to vaccinate to prevent a case
189 (NNV) is higher than the range of previous estimates for reactive meningococcal campaigns

190 (3,700 to 11,600 for 2 to 4 week lag),(15) suggesting that reactive vaccination for
191 pneumococcal meningitis outbreaks may be less efficient in preventing cases. Whilst the
192 number needed to vaccinate to prevent a death (NNVD) has not been estimated for reactive
193 meningococcal campaigns, the NNVD is expected to be lower for reactive vaccination in
194 pneumococcal outbreaks given the higher case-fatality rates typically associated with
195 pneumococcal meningitis.(18)

196 It is not certain how quickly immune response would build up after PCV13 in the
197 targeted age groups, however, a clinical trial of naïve 10- to 18-year-olds showed high
198 (>90%) responsiveness one month post-vaccination.(17) A conjugate vaccine like PCV13
199 would also have additional indirect benefits, decreasing carriage and transmission of
200 vaccine-type serotypes where it is used, although realizing the full indirect benefits would
201 take several months.

202 Serotype 1 was particularly dominant in this outbreak. Seven other studies in the
203 meningitis belt have reported serotype distribution of pneumococcal meningitis cases, all in
204 populations with no PCV use.(3,6,18,20–23) Overall, 45% were serotype 1. Kwambana-
205 Adams 2016 reports a higher proportion of isolates belonging to serotype 1 (67% overall) in
206 the Brong Ahafo outbreak than in the other studies.(2) Among the other studies, there are
207 no marked differences between settings described as “epidemic” or “outbreak” and
208 endemic settings. There are no appropriate data available to support or contradict the
209 hypothesis that outbreaks or clusters of disease tend to be caused by a single serotype
210 because most serotyping data is published as aggregate data over many years.

211 This model is more conservative than the model used to evaluate reactive
212 meningococcal vaccination.(15) Whereas the meningococcal model assumed all cases
213 occurred in individuals under 30 years of age, this model estimates that only 70% of cases

214 occur in the targeted age group. The meningococcal model also assumed that 79% of
215 suspected cases were due to NmW. In addition, the surveillance system relies on a case
216 definition of meningitis; immunisation against Spn may prevent additional cases of
217 pneumonia and septicaemia making these estimates conservative.

218 However, the predictions of this model are highly dependent on the age distribution
219 of cases, the proportion of cases due to Spn, and the overall shape of the incidence curve
220 over time. The data from the Brong-Ahafo outbreak show a particularly strong peak in the
221 15- to 29-year age group, similar to distributions reported from endemic situations.(18) By
222 contrast, the distribution of incidence of Spn meningitis from Traore 2009 peaks sharply in
223 infants but is otherwise fairly even across age groups despite a description in the discussion
224 of “epidemic” patterns.(3)

225 Because many cases had no associated laboratory data, we have chosen to model
226 suspected Spn meningitis cases. As our sensitivity analysis has shown (Table S1), reactive
227 vaccination may be more or less effective depending on underlying assumptions about the
228 true proportion of suspected meningitis cases caused by *S. pneumoniae*. The case-fatality
229 rates in each category support our classification system, with low rates in bacteria-negative
230 cases, intermediate rates in untested cases, and high rates in Spn- and Nm-confirmed cases
231 (Table 1).

232 These predictions are also dependent on how quickly the outbreak progresses. In
233 this outbreak, 14% of suspected cases occurred within four weeks of triggering the epidemic
234 threshold – in other words, 14% of suspected cases would be missed by a reactive response
235 with a lag of two weeks. More suspected cases occurred in the first four weeks of past
236 suspected pneumococcal meningitis outbreaks: 18% in Goundi, Chad in 2009, 28% in

237 Karangasso Vigue, Burkina Faso in 2011, 21% in Pama, Burkina Faso in 2011 and 38% in
238 Solenzo, Burkina Faso in 2009.(1)

239 Our estimates, based on data from the Brong-Ahafo outbreak, suggest that reactive
240 vaccination for pneumococcal meningitis would have prevented fewer cases per dose of
241 vaccine than previous estimates for meningococcal meningitis reactive vaccination (a
242 routine intervention in the African meningitis belt). As the size and duration of outbreaks
243 are likely to vary by country and by year, data from future outbreaks are needed to refine
244 these estimates.

245 It is clear that any reactive response must be timely in order for it to be effective. A
246 particular challenge is ensuring rapid microbiological confirmation of the organism
247 responsible for the outbreak and serotyping of pneumococcal isolates to determine if the
248 outbreak is due to a vaccine-type strain. In Brong-Ahafo, serotyping facilities were initially
249 not available locally and samples were sent to the MRC laboratory in The Gambia, leading to
250 an interval of several weeks before results were available. A technical mission from MRC the
251 Gambia provided support to establish serotyping capacity in Sunyani hospital in Brong-
252 Ahafo during the course of the outbreak. In addition, CDC established PCR capability at
253 Tamali Zonal Public Health Laboratory during the outbreak, which serves Brong-Ahafo. If
254 reactive vaccination for pneumococcal meningitis outbreaks were to be recommended by
255 WHO, it will be important to ensure that other meningitis belt regions also establish and
256 maintain serotyping capacity. Even if reactive vaccination for pneumococcal meningitis
257 outbreaks is not recommended, building laboratory capacity in these regions will benefit
258 health systems more broadly.

259 This study does not evaluate the potential impact of mass preventive vaccination, or
260 of extending PCV coverage to older age groups through catch-up campaigns. WHO's

261 Strategic Advisory Group of Experts (SAGE) on Immunization reviewed primary data on PCV
262 vaccine schedules and their impact on carriage and disease, together with evidence from
263 modelling studies on the impact of catch-up campaigns in October 2017
264 (<http://www.who.int/immunization/policy/sage/en/>). Further work may be warranted to
265 quantify the impact of extending PCV to older ages (over 5 years) in preventive campaigns,
266 but this is beyond the scope of this paper.

267 With the roll-out of PCV in the African meningitis belt, the risk of pneumococcal
268 meningitis outbreaks and the need for subsequent reactive vaccination responses may
269 recede as increasing numbers of birth cohorts are protected. The WHO is currently
270 reviewing whether a different vaccination schedule with a subsequent booster dose would
271 be more appropriate for this setting.(12) Meanwhile, this study provides the first evidence
272 that pneumococcal reactive vaccination could prevent cases and save lives during confirmed
273 outbreaks. Additional work is needed to clarify the conditions warranting a response, and
274 the logistical implications of supplying PCV13 for reactive vaccine campaigns.

275 Table 1. Classification of case etiology; frequency and case fatality rates by etiology.

Classification	Criteria	Number of cases	Case fatality rate
Spn	Any test (Pastorex, culture or PCR) indicating Spn or positive gram stain	168	23%
Nm	Any test (Pastorex, culture or PCR) indicating Nm or negative gram stain	40	23%
Indeterminate	Any sample with no test results	209	15%
Probable negative	One test (Pastorex, culture, PCR or gram stain) failing to indicate bacteria in CSF	366	2%
Confirmed negative	Two or more tests (Pastorex, culture, PCR or gram stain) failing to indicate bacteria in CSF	183	0%

276

277 Table 2. Summary of line list data for the 19-week study period by district.

District	Population	Suspected meningitis cases	Confirmed Spn meningitis cases	Confirmed Nm meningitis cases	Epidemic threshold (suspected weekly cases 10 per 10 ⁵) exceeded	Cumulative incidence per 10 ⁵
Asunafo North	143000	14	7	1	No	9.8
Asutifi North	60800	1	0	0	No	1.6
Asutifi South	60600	4	2	1	No	6.6
Atebubu-Amanten	121000	12	3	0	No	9.9
Berekum	149000	2	2	0	No	1.3
Dormaa East	58300	6	1	0	No	10.3
Dormaa Municipal	129000	27	7	1	No	21.0
Jaman South	106000	7	5	7	No	6.6
Kintampo North	109000	11	3	1	No	10.1
Pru	148000	9	3	2	No	6.1
Sene East	69400	5	1	0	No	7.2
Sunyani Municipal	141000	28	9	0	No	19.8
Tano South	89600	4	2	0	No	4.5
Techiman Municipal	169000	77	10	4	No	45.5
Jaman North	95200	364	39	2	Yes	382.3
Nkoranza South	116000	100	24	6	Yes	86.4
Sene West	66800	20	2	0	Yes	29.9
Tain	101000	145	19	12	Yes	143.6
Techiman North	67700	20	1	1	Yes	29.5
Wenchi	103000	110	28	2	Yes	106.9

278

279 Table 3. Cases and deaths prevented by reactive vaccination with different lag time (weeks
 280 between crossing of incidence threshold and implementation of reactive vaccination
 281 campaign).

Incidence threshold	Lag in weeks	Cases prevented (% of total likely Spn [C_{Spn}] cases during outbreak)		Deaths prevented	Number needed to vaccinate to prevent a case	Number needed to vaccinate to prevent a death
10	0	61	35%	14	9100	39100
10	2	36	21%	8	15300	66000
10	4	20	11%	5	27800	120000
3	0	63	32%	15	22500	96900
3	2	40	20%	9	35300	152000
3	4	23	12%	6	60500	261000

282
 283 Figure 1. Negative predictive value (NPV), positive predictive value (PPV), sensitivity, and
 284 specificity of various incidence thresholds (3, 5, 7, and 10 suspected cases per 100,000 per
 285 week) for predicting a range of sizes of outbreaks.

286
 287 Figure 2. Incidence of suspected meningitis, likely and confirmed pneumococcal meningitis
 288 in five districts crossing the epidemic threshold of 10 cases per 100,000. Grey vertical lines
 289 indicate beginning and end of outbreak period.

290
 291 Figure 3. Age distribution of suspected meningitis and confirmed pneumococcal meningitis
 292 incidence in five districts crossing the epidemic threshold of 10 cases per 100,000.

293
 294
 295 Supplementary Information

296 Table S1. Cases and deaths prevented by reactive vaccination with different times to
 297 implementation using strict negative case definition.

Incidence threshold	Lag in weeks	Cases prevented (% of total likely Spn [C_{Spn}] cases during outbreak)		Deaths prevented	Number needed to vaccinate to prevent a case	Number needed to vaccinate to prevent a death
10	0	113	35%	26	4800	20900
10	2	63	19%	15	8800	37800
10	4	30	9%	7	18300	78700

298
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301
 302 Conflict of interest

303 CLT reports personal fees from GlaxoSmithKline and Sanofi Pasteur, outside the submitted
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 305 for the views expressed in this publication and they do not necessarily represent the views,
 306 decisions, or policies of the institutions with which they are affiliated.

307
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398

Figure 1

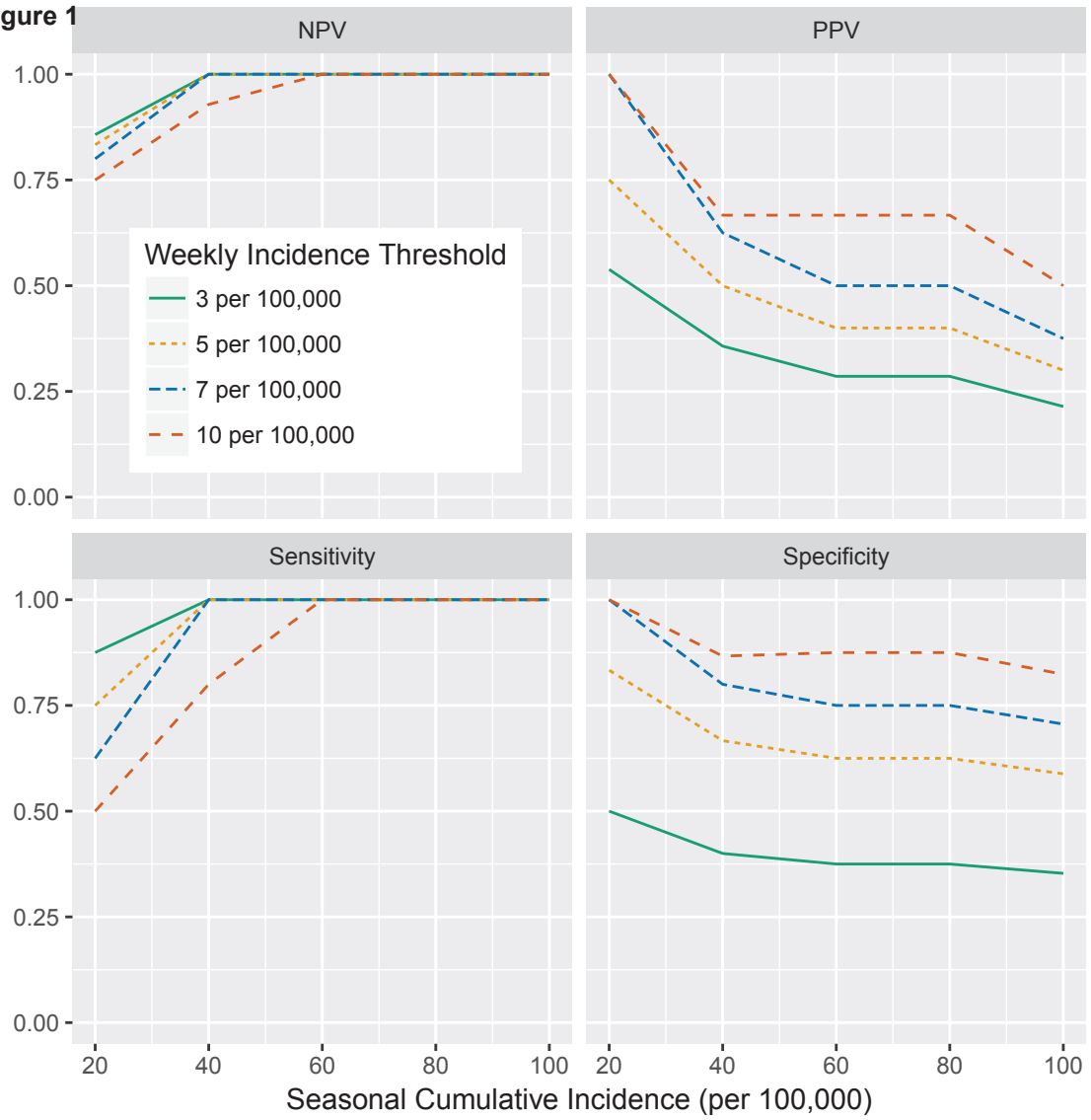


Figure 2

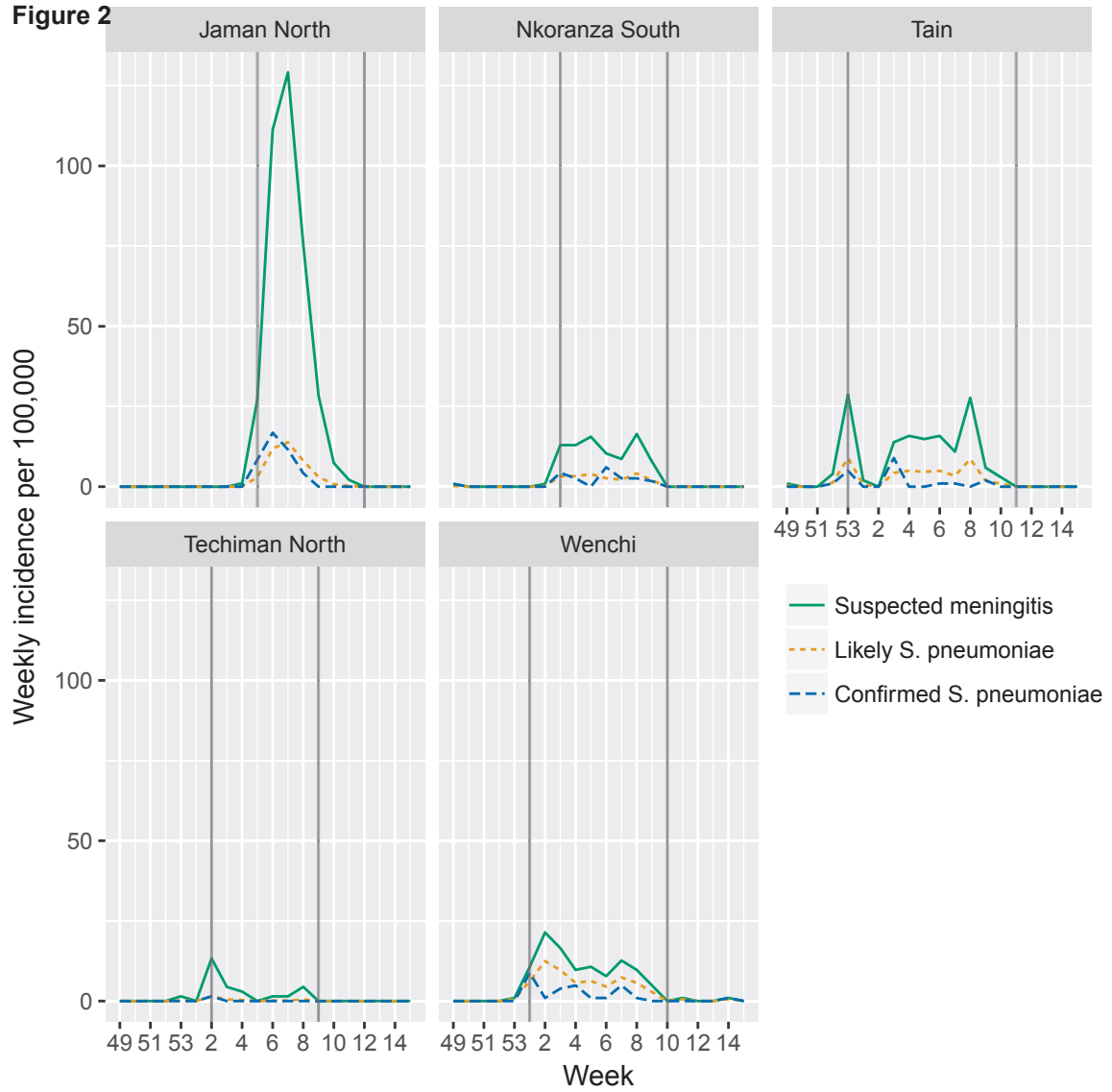
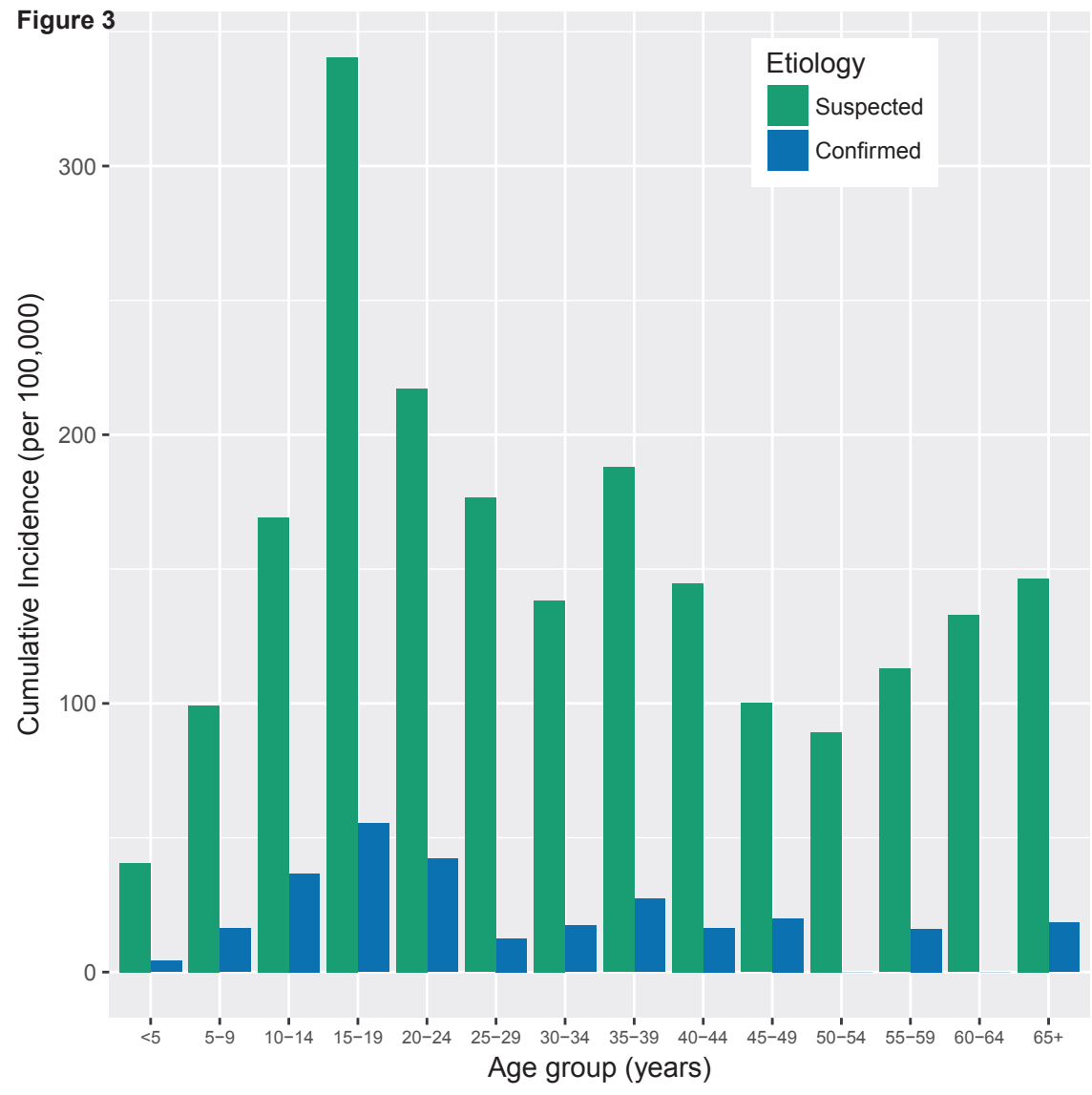


Figure 3



Graphical Abstract

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