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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.

Introduction

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

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

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

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

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

Methods

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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

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

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

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

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

Supplementary Information

Table S1. Cases and deaths prevented by reactive vaccination with different times to 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

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Conflict of interest

CLT reports personal fees from GlaxoSmithKline and Sanofi Pasteur, outside the submitted work. All other authors declare no competing interests. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

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Figure 1

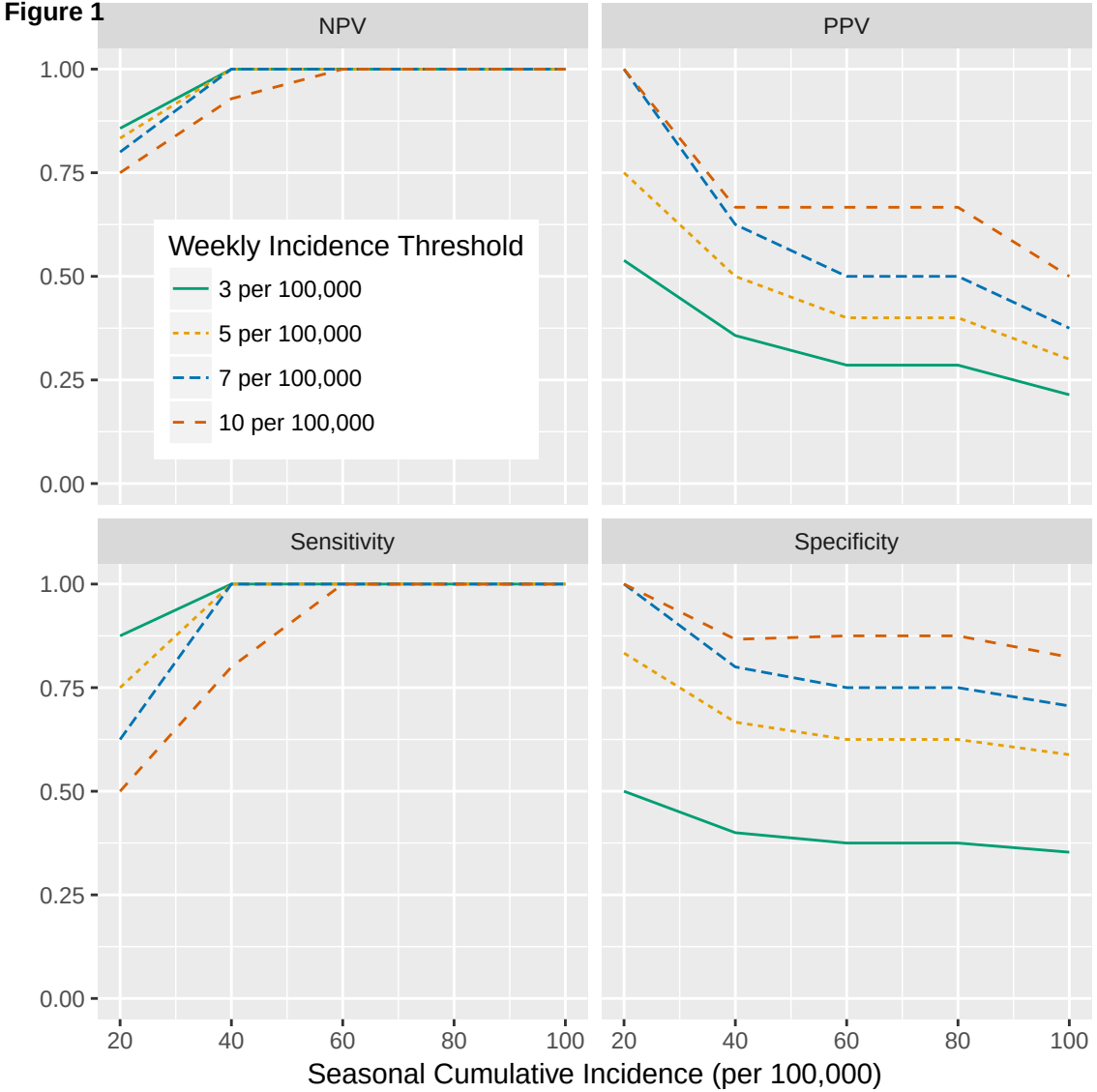

NPV
PPV
Sensitivity
Specificity
1.00
0.75
0.50
0.25
0.00
Weekly Incidence Threshold
3 per 100,000
5 per 100,000
7 per 100,000
10 per 100,000
20
40
60
80
100
Seasonal Cumulative Incidence (per 100,000)

Figure 2

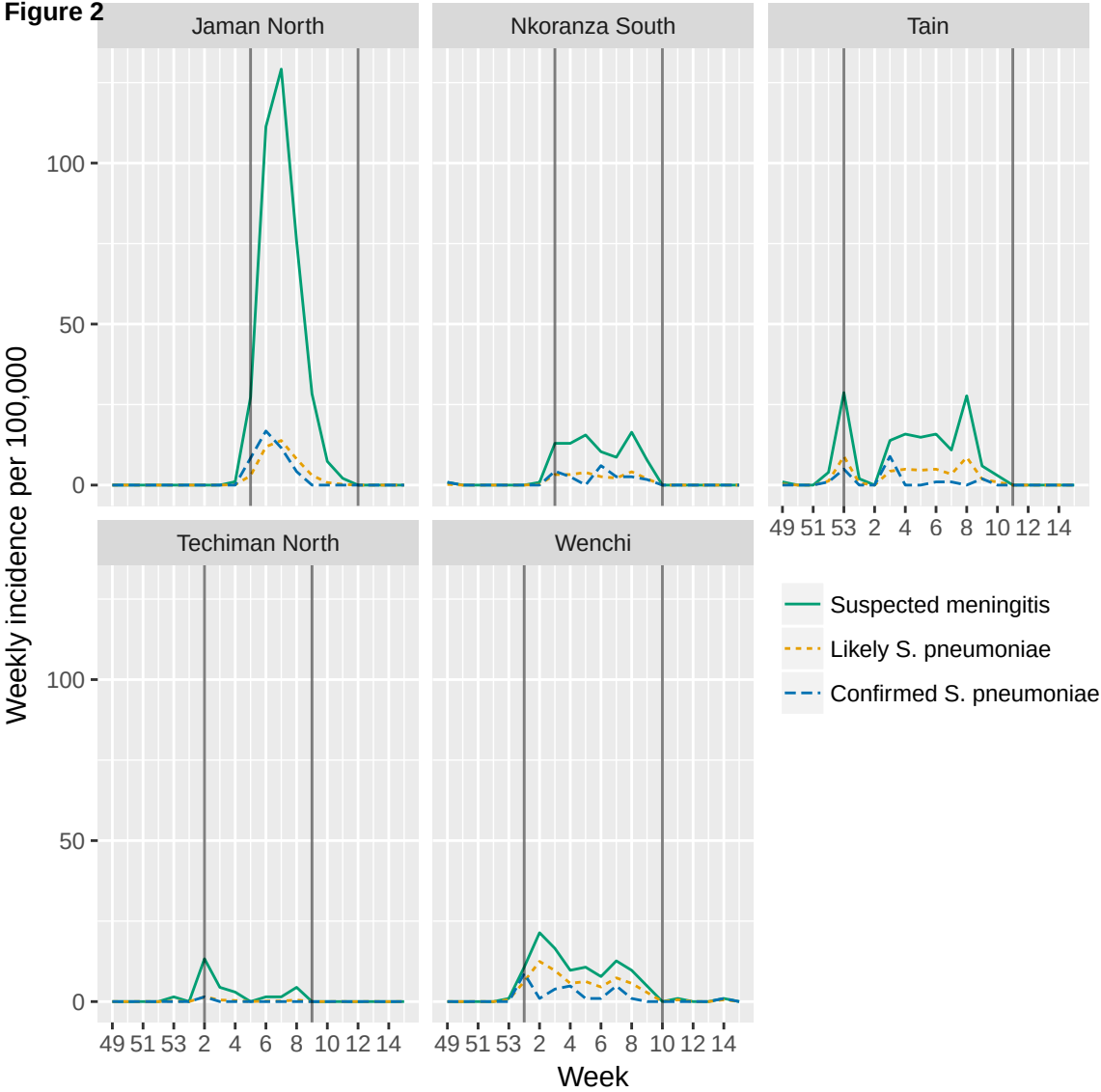
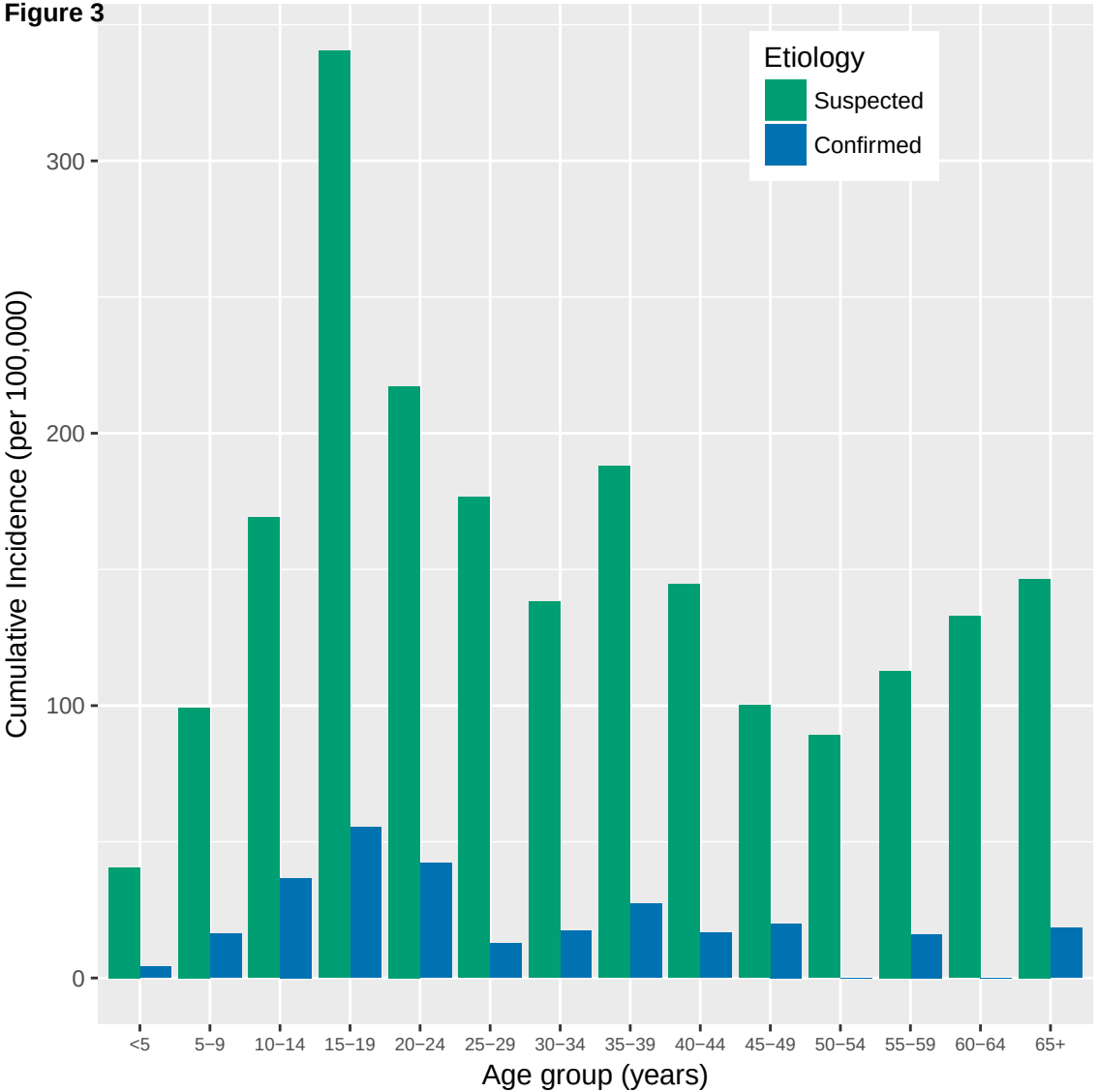

Jaman North
Nkoranza South
Tain
Techiman North
Wenchi
Weekly incidence per 100,000
0
50
100
49 51 53 2 4 6 8 10 12 14
Week
Suspected meningitis
Likely S. pneumoniae
Confirmed S. pneumoniae

Figure 3


Etiology
Suspected
Confirmed
Cumulative Incidence (per 100,000)
0
100
200
300
<5
5–9
10–14
15–19
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
60–64
65+
Age group (years)

Graphical Abstract

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