

Outbreak of serotype W135 *Neisseria meningitidis* in central river region of the Gambia between February and June 2012: A hospital-based review of Paediatric cases

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Abstract

Background: Meningitis still accounts for many deaths in children especially during epidemics in countries within the African meningitis belt. Between February and May 2012, the Gambia witnessed an outbreak of meningitis in two of its six regions. This study presents a clinical perspective of this outbreak in central river region of the Gambia. It evaluated the outbreak pattern, clinical features, and mortality among suspected cases that presented to the hospital during the outbreak.

Methodology: This is a prospective observational study of suspected cases of meningitis that presented to the pediatric ward of the Bansang Hospital during the outbreak period. Confirmed cases of meningitis were consecutively enrolled, and those with negative blood cultures presenting during the same period were employed as controls.

Result: Two hundred and four suspected cases of meningitis presented to the pediatric ward during the outbreak. Ninety were confirmed as meningitis cases. The W135 strain of *Neisseria meningitidis* was responsible for 89 (98.9%) of meningitis cases seen with an incidence rate of 74.9/100,000 in children (0-14 years) and in-hospital case fatality rate of 7.9%. Highest attack rate was among the 12-49 months age group. Clinical features such as meningeal signs (neck stiffness), conjunctivitis, and joint swelling were seen more in cases than controls. Contact history with relatives, who had fever in previous 2 weeks prior to illness was significantly seen more in cases. Adjusted regression analysis showed 7.5 more likelihood of infection with positive contact history (odds ratio [OR]: 7.2 confidence interval [CI]: [3.39-15.73]). There was no significant difference in death outcome between cases and controls (OR: 0.78 CI: [0.29-2.13]). The double peak wave-like pattern of the epidemic curve noted during this outbreak suggests a disseminated outbreak originating from an index case with propagated spread.

Conclusion: There is need for more effective surveillance and incorporation of vaccine against meningitis into the expanded program on immunization schedule of the Gambia and other countries within the meningitic epidemic belt.

Key words: *Neisseria meningitidis*, W135 strain, Outbreak, Children, Central River Region

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Introduction

Neisseria meningitidis is a known cause of deaths and neurological sequela worldwide. The effect is particularly pronounced in Africa where malnutrition and other infective disease are prevalent. In 1997 alone, 1390 confirmed cases

and 220 deaths were recorded in an outbreak that occurred in the upper river region (URR) of the Gambia.^[1] Due to

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the rapid onset, high-case fatality rate and neurological sequela, a single case constitutes an outbreak and requires a rapid, well-organized public health response which can include antibiotics or vaccination for all residents of those areas, especially those who are/were in close contact with an infected person. Since World War II, such epidemics have been rare in industrialized countries, but they occur periodically in the African meningitis belt and in China.^[2-7] The African meningitis belt extends from Ethiopia in the East, to Senegal in the West within the range of 300-1100 mm annual rainfall. Periodic infections occur in seasonal and annual cycles, while large-scale epidemics occur at greater intervals with irregular patterns in this region.

In countries within the meningitis belt, the estimated incidence for the 20 years period 1970-1992 was about 800,000 cases.^[2] The underlying mechanisms leading to the spread of meningococci and to epidemics of meningococcal disease remain unknown. Carriage rates of 15% can occur during epidemics in Africa.^[8,9] The extreme environmental conditions present in the sub-Saharan meningitis belt during the dry season namely high temperature, low absolute humidity, and the harmattan (a dusty wind that blows from the Sahara) – plus respiratory co-infections due to damage to the mucosal defenses are thought to contribute to enhanced susceptibility to meningococcal disease.^[10]

Between February and May 2012, 10 countries namely Benin, Burkina Faso, Chad, Central African Republic, Côte d'Ivoire, Gambia, Ghana, Mali, Nigeria, and Sudan reported a total of 11,647 meningitis cases including 960 deaths resulting in a case fatality ratio of 8.2%. The outbreaks were mainly caused by the W135 sero-group of *N. meningitidis* bacteria.^[11] In the Gambia, the outbreak occurred mostly in two of its six region as already described in the paper titled - Sero-group W135 meningococcal disease, The Gambia.^[12] This study describes the outbreak of meningitis in the Central River Region (CRR), which was one of the two regions affected and evaluated the outbreak pattern, clinical features and mortality in infected children that presented to the Pediatric section of Bansang Hospital.

Methodology

Study area

The CRR is one of the six regions in The Gambia [Figure 1]. It is divided into North and South banks by the river Gambia with its administrative headquarters in Janjangbureh. The region has an area of about 48,000 km². It shares border with the republic of Senegal on the North and the Southern part and Cassamance to the West. Internally, it is bordered by the

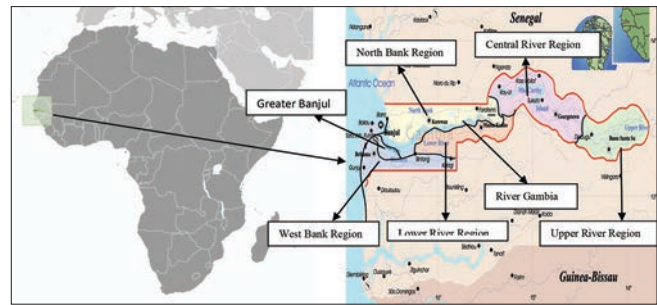


Figure 1: Six regions of the Gambia (study area is colored purple)

Lower River Region (LRR) and Upper River Region (URR) to the West and East, respectively. The 2012 projected population of CRR is 256,990 out of which 120,100 (46.7%) are children 14 years and below.^[13] There are 692 villages located within 11 districts.^[13] The region has 17 primary health care centers, 8 public health facilities, 2 NGO clinics, and one general hospital located in Bansang.^[13] The Bansang Hospital, which is the largest serves as referral center in the region and provides a higher standard of maternal and child health care services compared with other health facilities within the region.^[13]

Study technique and subject

This is a prospective observational study. Routine surveillance by the pneumococcal surveillance project of the Medical Research Council (MRC) for invasive pneumococcal disease is on-going in the region. Blood culture and/or diagnostic lumbar puncture when indicated are performed on suspected cases of sepsis, pneumonia, and meningitis based on study criteria^[14] in children under-five presenting to the Bansang Hospital. However, during the meningitis outbreak blood culture and/or lumbar puncture was done for all patients with suspected meningitis presenting to the pediatric ward of the hospital.

Standard case definition

- Suspected case of acute meningitis was defined as onset of fever (>38.5°C rectal or 38.0°C auxiliary) with a stiff neck (in children above 1 year of age) or bulging fontanelle (in children below 1 year of age) with or without convulsion^[15]
- Confirmed case of acute meningitis is a suspected as defined above with either positive cerebrospinal fluid (CSF) antigen detection for bacterial OR a positive culture of CSF for bacterial organism AND/OR positive blood culture with identification of *N. meningitidis*.^[15]

Data collection

Apart from those presenting to the hospital, suspected cases were also identified by active surveillance carried out in all

districts of the CRR by a joint public health team of the regional health authority and the MRC. The public health team was sent to villages where confirmed meningitis cases had been identified and residents of those villages were informed about the meningitis outbreak. Signs and symptoms of meningitis were explained and the village residents were asked to take any child with similar presentation to the hospital for treatment. Furthermore, public enlightenment via radio was done throughout the CRR during the outbreak period. Health officers in other health facilities in the region were requested to refer all suspected cases to Bansang Hospital for proper evaluation and management.

Based on the pneumococcal surveillance study criteria,^[14] X-ray was done for all patients with suspected pneumonia. Suspected pneumonia was defined as a history of cough or difficulty breathing for <14 days, accompanied by one or more of the following: Raised respiratory rate for age, lower chest wall in drawing, nasal flaring or grunting, oxygen saturation <92%, and focal chest signs (dull percussion note, coarse crackles, and bronchial breathing). Raised respiratory rate for age is defined as rates >60 breaths/min for children <2 months of age, >50 breaths/min for children aged 2-11 months and >40 breaths/min for children aged 12-59 months.^[14] X-ray reading was done by clinician trained using the World Health Organization guidelines for diagnosis of radiological pneumonia.^[16] For patients who presented with associated discharge and/or redness of the eye, vision was assessed using simple confrontational test due to lack of the Snellen chart.

Suspected cases of meningitis had diagnostic lumbar puncture done in the sterile procedure room of the Bansang Hospital under aseptic conditions by study clinicians. The samples were sent within 1 hour of collection to the MRC regional laboratory in Basse. Cases were consecutively enrolled from February 1st to May 31st 2012 during the outbreak period. During enrolment, trained research nurses collected information about onset of illness, history of travel or contact with anyone with fever or travel history in the preceding 2 weeks, and immunization history where relevant.^[17] Also, sex, age, weight, and height of cases were also documented. Malaria antigen test and hemoglobin level were done for all suspected cases. For every confirmed meningitis case, patients admitted during the same period with a negative blood culture results was enrolled as control and matched with cases on age and sex. Just like for cases, information on immunization, travel and contact history, weight, and height were also obtained for controls. Admission of patients into the ward was done by medical officers stationed at the outpatient and children emergency sections. Study clinicians were not in any way

involved in admission of patients. Daily temperature and rainfall readings for the period of the outbreak (i.e. February, March, April, May, and June 2012) were obtained from the hydro-meteorological Department of the Ministry of Water Resources, Upper River Regional Office.^[18]

Study specimen and laboratory investigation

Blood sample

Appropriate volume of blood as described in pneumococcal surveillance program (PSP), standard operating procedures^[14] were collected from study patients suspected of having either pneumonia, sepsis, or meningitis inoculated into Bactec fluid medium, were incubated into the (Becton 9050, Becton Dickinson, Erembodegem, Belgium). Antigen test was performed directly on the supernatant of the positive Bactec blood culture after boiling and centrifuging. Sero-grouping was achieved using (Becton Dickinson, Erembodegem, Belgium). Sensitivity and specificity for this kit on serum for *N. meningitidis* W135 is 98.5% and 100%, respectively.^[19]

Cerebrospinal fluid samples

These samples were processed for Gram-stain reaction and for leukocytes (neutrophils and lymphocytes). Cell count was done on all samples using improved Neubauer counting chamber by multiplying the number of white cells in four large squares by $2.5 \times 10^6/L$. Culture performed as indicated above. Antigen detection test was performed on boiled CSF aliquot with the use of BD-Directigen Combo Test (cat in number 252360) following the manufacturer instruction.^[19]

Ethical clearance

This study was done as part of the PSP for which prior ethical clearance had been obtained.^[14] In addition, to this the ethical committees of the hospital management and regional health authority approved this study. Furthermore, verbal and written informed consent were also obtained from the parents and/or the care givers of all study participants before enrolment and performing any invasive procedure.

Data analysis

Data was analyzed using IBM® SPSS version 20.0 (SPSS Inc, Chicago, IL)

Distribution of study variables were computed and tabulated using frequency table. Comparison of these variables between cases and controls was assessed using Chi-squares. Results were presented using percentages, odds ratio, (OR) and 95% confidence intervals (CIs) were appropriate. Bivariate logistic was used to estimate association between identified factors and outcome in cases and controls. For all statistical tests performed, it was ensured that the assumptions for carrying out these specific tests were met. Statistical significance was set at $P < 0.05$.

Results

Between February 1 and May 31, 2012, 204 suspected cases of meningitis were admitted to Bansang Hospital and 90 (44.1%) were confirmed cases of meningitis. Eighty-nine (98.9%) of the confirmed cases had the W135 strain of *N. meningitidis* isolated from either CSF, blood, or both. *Streptococcus pneumoniae* was cultured in the CSF of one of the cases.

Characteristic of study subjects

Seventy-nine (88.8%) of the confirmed cases were children under 5 years of age [Table 1] with the highest attack rate in early school aged 12-49 months. The age range of cases was 1 month-14 years, mean age of 34.9 months and bimodal ages of 12 and 36 months. The male:female ratio of cases was 1.5:1 compared to 1.3:1 for controls ($P = 0.646$). None of the children has had any form of meningitis immunization. The history of other routine vaccination was complete for age in 47.2% of the cases and 45.7% of controls ($P = 0.832$).

About 6.7% of the cases had a positive malaria antigen test compared to 10.5% in controls ($P = 0.347$). Normal hemoglobin concentration was seen in 31.6% of cases and 32.5% of controls ($P = 0.880$). The mean hemoglobin concentration of cases versus controls stratified by age was 15.7 versus 13.76 ± 2.80 ($P = 0.616$) in the neonatal age group, 10.33 ± 1.74 versus 10.0 ± 2.08 ($P = 0.613$) for the infant age group and 9.92 ± 2.28 versus 10.30 ± 2.66 ($P = 0.383$) for the 12-59 months age group. Thirty-six (40.5%) of the cases compared with 9 (7.9%) of control had contact with persons with fever in the preceding 2 weeks of illness ($P = 0.001$). Adjusted logistic regression showed that patients with positive history of contact were 7 times more likely to acquire *N. meningitidis* compared to those without positive history of contact (OR: 7.2, CI: 3.39-15.73). Similarly, 22.4% of cases compared to about 25.4% of control had traveled or lived with relatives who had travelled outside place of residence 2 weeks prior to current illness ($P = 0.624$).

Clinical findings in study participants

Some of the clinical presentations of cases versus controls are shown in Table 2 below. Nonspecific clinical features such as vomiting, malaise, restlessness, feed refusal, diarrhea etc., were not included in the analysis. Joint affectation ($P = 0.001$), meningism ($P = 0.001$), and conjunctivitis ($P = 0.002$) were seen significantly more in cases than controls. All joint swelling seen during the study were in children <5 years of age. The wrist, knee, and ankle were most affected. The joints affectation was bilateral and tender. No joint tap was done because most mothers did not give consent for the procedure.

Table 1: Characteristics of study subject

Characteristics	W135 cases n (%) n=89	Controls n (%) n=114	P value
Immunization status ¹¹			
Complete for age	42 (47.2)	52 (45.7)	0.823
Incomplete for age	47 (52.8)	62 (54.3)	
Malaria parasite ¹²			
Positive	6 (6.7)	12 (10.5)	0.347
Negative	83 (93.3)	102 (89.5)	
Hemoglobin ¹³			
Normal	28 (31.6)	37 (32.5)	0.880
Low	61 (68.4)	77 (67.5)	
X-ray findings ¹⁴			
Normal X-ray	32 (82.1)	45 (88.2)	0.408
End point and/or Non end point consolidation	7 (21.9)	6 (11.8)	
Contact in preceding 2 weeks of illness with person with			
Fever	36 (40.5)	9 (7.9)	0.001
Travel outside region	20 (22.4)	29 (25.4)	0.624
Outcome			
Died	7 (7.9)	13 (11.4)	0.401
Discharged alive	82 (92.1)	101 (88.6)	

¹¹Based on EPI schedule in the Gambia Health Ministry; ¹²Rapid diagnostic test based on antigen detection; ¹³World Health Organization definition of normal Hb levels based on age and sex; ¹⁴X-ray reading based on World Health Organization guidelines. EPI=Expanded Program on Immunization

Table 2: Some clinical features seen in study subjects

Clinical presentation	Cases n (%) n=89	Control n (%) n=114	P value
Fever	84 (94.4)	104 (96.3)	0.394
Cough	39 (43.9)	51 (47.2)	0.896
Convulsion	17 (19.1)	11 (10.2)	0.052
Joint swelling ¹¹	15 (16.9)	2 (1.9)	0.000 ¹²
Skin infection	11 (12.4)	8 (7.4)	0.195
Petechial hemorrhage	1 (1.1)	0 (0.0)	0.901
Meningism	71 (79.8)	1 (0.9)	0.000 ¹²
Conjunctivitis	9 (10.1)	0 (0.0)	0.002 ¹²

¹¹Joint affected were knee, wrist, and ankle joint; ¹²Statistically significant

Two controls had similar swelling and both were also bilateral and in children below 5 years of age. The presentation of conjunctivitis was characterized by bilateral thick conjunctiva redness that was itchy, purulent/clear sticky eye discharge with no apparent visual disturbance. All cases of eye redness developed after cases became ill. Seven of the nine cases were from different households, while two were siblings. Eight of the cases were under 5 years and one was about 7 years old. There was no history of contact with any person with conjunctivitis in the family or immediate vicinity in all nine patients. Eye swab yielded no growth in all cases. The conjunctivitis did not resolve in any of the cases while still on admission. None returned for follow-up.

Characteristics of the outbreak

Between February and May 2012 over a period of 17 weeks, about 204 suspected cases of meningitis presented to the pediatric ward of the Bansang Hospital. The outbreak had a double peak period in weeks 5 and 8 during which the epidemic threshold of 10 cases/100,000/week^[16] was exceeded [Figure 2]. There was a sharp decline in cases in the 9th week of the outbreak and the decline continued gradually until the 12th week. After the 12th week, incidence rate became constant all through to the 15th week. No new cases were seen on weeks 16 and 17 during which the epidemic was declared over.^[16] However, within the postepidemic period few new cases were identified in weeks 18, 19, 20, and 21 of June 2012. No vaccination campaign was done during the outbreak period due nonavailability of the meningococcal sero-group W135 polysaccharide vaccine in the country.

Analysis of the temperature and rainfall readings during the outbreak periods showed that the rainfall was lowest during the outbreak period and recorded temperature readings were relatively high during the outbreak period [Figure 3].

Incidence was reported from all health district of the CRR with highest concentration in Jahanka and Cassamance which are border villages. The overall incidence rate of W135 meningitis during the outbreak in children 0-14 years was 74.9/100,000 population. Cases were managed with antibiotics based on sensitivity results. Majority of the patient had chloramphenicol or ceftriaxone with adjuvant therapy like dexamethasone and mannitol. The average time of presentation was 3-4 and 1-2 days before and after the region wide public enlightenment campaign, respectively. The average

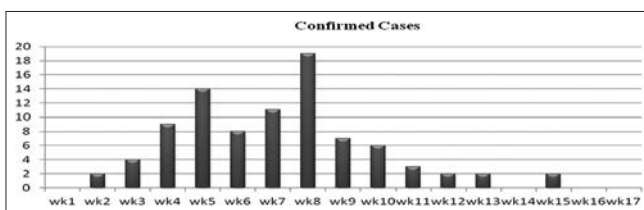


Figure 2: Epidemic curve during outbreak

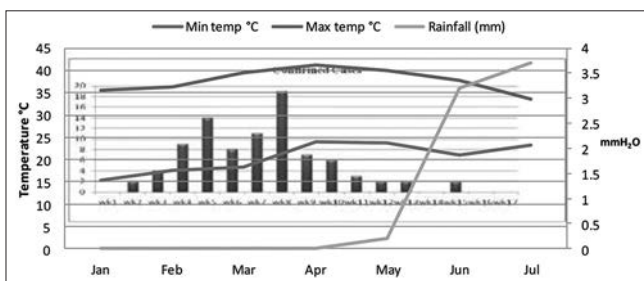


Figure 3: Temperature and rainfall readings in relation to outbreaks epidemic curve

stay in hospital was 7 days (partly due to high patient load and lack of admitting bed spaces) and in-hospital case fatality among patients with confirmed meningitis during outbreak period was 7.9% (7/89) compared to 12.1% (13/114) for controls ($P = 0.401$). There was no significant difference in likelihood of death between cases versus controls (OR = 0.78 CI: [0.29-2.13]). Nationwide vaccination using group ACYW₁₃₅ meningococcal polysaccharide vaccine (manufactured by Zhejiang Tianyuan Bio-Pharmaceutical Company Limited, Lot No. 201111009-2) was done 6 weeks after the outbreak.

Discussion

The meningitis outbreak occurred from February to May 2012. These months were the hottest period of the year with very low humidity which is a well-documented predisposition to meningitis outbreak.^[10] The finding of the study has shown that contact with persons with fever (probably an undiagnosed case) was a significant risk factor for acquiring and transmitting the meningitis infection. As expected, clinical features peculiar to meningitis were significantly higher in cases while the nonspecific features were not significantly different between both groups. The findings of clinical presentations such as fever, neck stiffness, and convulsion are well documented in similar outbreaks which occurred in Burkina-Faso^[20] and Cameroon^[21] but unlike these studies joint swelling and conjunctivitis were seen in significant number of cases during this outbreak.

Conjunctivitis caused by *N. meningitidis* could be concomitant with the systemic meningococcal infection, or in isolation as primary meningococcal conjunctivitis.^[22-24] On average, 10–17% of patients with primary meningococcal conjunctivitis may develop systemic disease, it is, therefore, important to establish a definitive diagnosis in all cases of conjunctivitis^[25] especially in children who can readily transmit the infection to other children in schools and play areas. Whether the cases of conjunctivitis in this study were a co-infection with other organisms like chlamydia^[26] or other *Neisseria* spp. such as *Neisseria gonorrhoea*,^[26] *Neisseria ovis*,^[27] or *Neisseria cinea*^[28] known to cause conjunctivitis or an uncommon presentation of the W135 strain is not clear. While meningitis can cause joint swelling as part of meningococcal septicemia during infection it is, however, not a common presentation of *N. meningitidis*. In a study^[29] in Taiwan in 2006, where the clinical symptoms of different strains of *N. meningitidis* were analyzed in 115 confirmed cases over a 3 years period, athralgia and arthritis were seen in 6 and 20 cases of W135 strain and non-W135 strain, respectively. In the same study,^[29] pneumonia, was also seen

in a significantly higher number of cases in patient whose meningitis was caused by W135 strain compared to those caused by non-W135 strain. In similar, meningitis outbreaks in northern part of Nigeria in 1998 and 2007, allergic presentation like arthritis was also documented in some of the confirmed cases^[30-32] though the identified strains were not mentioned. Whether these presentations (arthritis and conjunctivitis) seen in this study are due to allergic reactions in cases, co-infectivity or a rapidly emerging feature of the W135 strain of *N. meningitidis* is unknown. Studies focusing on clinical presentation in future outbreak will be needed to answer these questions.

The epidemic curve during the outbreak showed a pattern of case detection with an initial slow and progressive infection, and case detection which gradually builds up to a peak followed by a brief fall that rapidly builds up again into another peak of infection and case detection. The infection and case detection, then slowly tapers off until the outbreak was declared over. This double peak wave-like pattern of epidemic curve noted strongly suggested a disseminated outbreak originating from an index case with propagated spread.^[33]

The in-hospital case fatality (7.9%) during the outbreak period seen in this analysis was slightly less but not significantly different from the average case fatality of 8.2% reported from 42 districts of the 10 countries in the African meningitis belt which reported^[11] a total of 960 deaths from 11,647 confirmed cases within the same period. The number of deaths recorded in all affected countries was far lower than the 5352 deaths recorded in similar outbreak which occurred in 2009.^[34] This may have been due to the rapid response to the outbreaks by the Ministries of Health of the various countries in collaboration with International Coordination Group (ICG) that implemented a series of preventive and control measures which included enhancement of surveillance, case management, sensitization of the population, strengthening of cross border collaboration, and provision of vaccines.^[11] The ICG released a total of 11,000 vials of antibiotic (ceftriaxone) and 1,665,673 doses of vaccines to six countries namely Ghana, Sudan, Ivory Coast, Chad, Burkina Faso, and Benin most affected by the epidemic.^[11] This is in addition to vaccines released with the support of Global Alliance for Vaccines and Immunization. The impact of the prompt action of these international agencies together with the ministry of health in these countries further stresses the need for global partnership as well as coordinated surveillance and management system at the national level for effective control of spread and mortality from meningitis during outbreaks.

Limitation

Despite the community wide campaign done during the outbreak advising community residents in the region to immediately take any ill child within their households to the hospital for assessment, being a hospital-based study, the incidence rate that was calculated based on its findings may not be a true reflection of the incidence rate of the disease in the region during the outbreak. Secondly, the contacts mentioned in this survey were either compound or household contacts that had fever within 2 weeks preceding the study subject's illness and presentation to the hospital. Due to logistic reasons, these contacts were not followed-up to ascertain a definite diagnosis of the cause of their febrile illnesses.

Conclusion

This study highlights uncommon clinical features and the contagious nature of the W135 strain of the *N. meningitidis* during epidemic in children. It also shows how fast a single unidentified case can be disseminated very quickly in the community. Therefore, during an epidemic, all ill patients within the community irrespective of the symptoms should be encouraged to present to the hospital for review and the confirmed cases isolated and treated in the hospital to curtail transmission. Government through the appropriate units within the health ministry should as a yearly routine by radio announcement and public health campaigns remind and prepare communities during predisposing (i.e. hot windy with very low humidity) climatic conditions to have high index of suspicion for suspected cases and seek prompt hospital care. Immunization campaigns should also target these high risk periods and border communities. These measures will further reduce mortality during future outbreaks of meningitis which was significantly lower relative to previous outbreaks in the region mainly due to surveillance activity and prompt action by the ICG.

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