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Neisseria Meningitidis C Meningitis Epidemic after Mass Vaccination Campaign against Meningococcus A in the District of Kpendjal: Factors Associated with the Disease, a Case-Control Study

Épidémie de méningite à Neisseria meningitidis C après une campagne de vaccination de masse contre le méningocoque A dans le district de Kpendjal : facteurs associés à la maladie, étude cas-témoins

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Mots-clés : Méningite, *Neisseria meningitidis* C, Togo, Facteurs associés.

ABSTRACT

Background. Meningococcal A meningitis epidemics were classic in Togo. After mass vaccination campaign against meningococcus A, Togo experienced an epidemic of meningitis caused by Neisseria meningitidis C from February 17 to March 30, 2019, in the district of Kpendjal West of the Savana region. Our objective was to identify factors associated with this disease in this district. **Materials and methods**. A matched case-control study on gender and health facility was conducted from January 1 to March 31, 2020, in the district during the period of the epidemic. A case was a person in West Kpendjal district from whom *Neisseria meningitidis* C was isolated by PCR. A control was defined as a person of the same sex as a case, who visited the same health facility during the same period but did not contract meningitis. We identified 35 cases and 140 controls. **Result.** Sex ratio M / F was 1.33. Recovery was without sequelae in the majority of cases (77.14%) and meningitis-related case fatality was 8.57%. Factors associated with the occurrence of meningitis were: meningococcal C vaccine status (ORa = 7,16; 95%CI = [1,02 – 49,79]; p = 0,04), promiscuity (ORa = 7,08; IC 95 % = [2,59 – 19,37]; p = 0,0001) and history of respiratory infection (aOR = 6,44; 95 %CI = [2,17 – 19,10]; p = 0,001). **Conclusion.** We found that history of respiratory infection, promiscuity and meningococcus C vaccination status were all independently associated with acute bacterial Neisseria meningitidis C meningitis during the outbreak in this district. All these factors are modifiable.

RÉSUMÉ

Introduction. La méningite à méningocoque est une urgence de santé publique du fait de la létalité élevée et des séquelles graves. Le Togo a connu une épidémie de méningite à *Neisseria meningitidis* C du 17 février au 30 mars 2019 dans le district de Kpendjal-ouest dans la région des Savanes. Notre objectif était d'identifier les facteurs associés à cette maladie dans ce district. **Méthodes.** Une étude cas-témoin appariée sur le sexe et la formation sanitaire a été menée du 1er janvier au 31 mars 2020 dans le district sur la période de l'épidémie. Nous avons considéré comme cas, une personne du district de Kpendjal-Ouest chez qui le *Neisseria meningitidis* C a été isolé par la PCR. Un témoin correspondait à une personne de même sexe qu'un cas, ayant consulté dans la même formation sanitaire au cours de la même période. **Résultat.** Nous avons retrouvé une prédominance masculine avec un sex-ratio H/F de 1,33. La guérison a été sans séquelles chez 77,14 % des cas et la létalité liée à la méningite de 8,57%. Le statut vaccinal contre le méningocoque C (ORa = 7,16 ; IC 95 %=[1,02–49,79] ; p=0,04), la promiscuité (ORa = 7,08 ; IC 95 %=[2,59–19,37] ; p=0,0001) et l'antécédent d'infection respiratoire (ORa = 6,44 ; IC 95 % =[2,17–19,10] ; p=0,001) étaient des facteurs indépendamment associés à la méningite. **Conclusion.** Les antécédents d'infection respiratoire, la promiscuité et le statut vaccinal contre le méningocoque C étaient tous indépendamment associés à la méningite bactérienne aiguë à Neisseria meningitidis C pendant l'épidémie dans ce district. Tous ces facteurs retrouvés sont modifiables.

INTRODUCTION

Meningitis is an inflammation of the protective membranes covering the brain and spinal cord. It can be due to several causes including bacteria such as Neisseria meningitidis [1]. Neisseria meningitidis is a Gram-negative bacterium with 13 serogroups, but six (06) of them (A, B, C, Y, X and W) are known to be at the origin of epidemics of meningitis [2]. According to the World health organization (WHO), 300,000 cases of meningococcal meningitis are recorded each year in the African meningitis belt [3] where it is the source of epidemics, especially in the dry season. It is a medical emergency due to a high case fatality rate and a high frequency of severe sequelae [2]. Early antibiotic treatment is the main measure available to save lives and reduce complications [4]. Active case surveillance allows early detection and treatment of patients in order to avoid epidemics [5]. Reactive vaccination in the event of clustered cases should be early and extended to a large proportion of the population, i.e. subjects aged 01 to 24 years [6]. The introduction of the meningococcal A conjugate vaccine in West Africa in 2010 has changed the profile of meningitis epidemics in this region [7–9]. The risk factors found in the literature are: promiscuity, relocation or vacation in the previous month, recent history of upper respiratory tract infections, and prolonged contact with a patient [10, 11].

In Togo, after a period of six years without meningitis epidemics following the beginning of the mass vaccination campaign against meningococcus A (MenAfriVac (TM)) in 2010, epidemics of meningococcal W meningitis were recorded in three regions in 2016 with 1,975 cases and 127 deaths [12]. From February 17 to March 30, 2019, the district of Kpendjal-West experienced an epidemic of bacterial meningitis due to Neisseria meningitidis of serogroup C. This is the first epidemic linked to this serogroup in Togo. Despite active case-by-case surveillance of meningitis in Togo [13], there are no studies on the factors associated with bacterial meningitis caused by serogroups C, in our country. Our case-control study aimed to identify the factors associated with the occurrence of acute bacterial meningitis caused by Neisseria meningitidis C during the meningitis epidemic in the district of Kpendjal in order to inform public health decision-makers on this serogroup and help improve the effectiveness of response actions against subsequent epidemics linked to Neisseria meningitidis serogroup C.

MATERIALS AND METHODS

This was retrospective study, a matched case-control study on gender and health facility conducted from January 1st, 2020 to March 31st, 2020 over the period February 06th to March 30th, 2019.

The entire population of West Kpendjal district without distinction of sex or age constituted our study population. We included in our study anyone regardless of sex or age present in the district of West Kpendjal during our study period who met our case or control definition. We have excluded in our study all people who have not given their consent to participate in the study.

Operational definitions

Case: any person residing in the district of West Kpendjal during the epidemic period from February 06 to March 30, 2019 and from whom Neisseria meningitidis C was isolated by PCR.

Control: any person of the same sex as a case, who consulted the same health facility as the case from February 6 to March 30, 2019 and not having contracted meningitis.

Considering the variables described in the literature having an association with acute bacterial meningitis due to Neisseria meningitidis such as promiscuity with an Odds Ratio of 3, a study power of 80% and a precision of 5%, the sample simple using the Open Epi software with the Fleiss method is 168 people. After reviewing the registers of health facilities in the West district of Kpendjal and the National Reference Laboratory of the National Institute of Hygiene (NIH), we obtained a total of 35 cases of Neisseria meningitidis C meningitis and we proceeded with an exhaustive sampling of all these cases. To reach the sample size, we considered 4 controls for 1 case by matching on gender and health facility. Hence, our sample size of 175 people including 35 cases and 140 controls.

Cases were identified from the registers of health facilities and the NIH. Controls were selected from the same registers of the same health facilities as the cases, taking into account the matching on gender and health facility. A list of these controls was made and a simple random selection was done using Excel's RANDOM function.

We conducted a documentary review in health facilities through consultation and hospitalization registers, patient records, meningitis case notification forms, and laboratory forms.

We then administered a closed questionnaire to the cases and controls or, when applicable, to the parents of minors and the deceased.

We collected socio-demographic data (health facility of origin, age, sex, socio-professional status, socio-economic status, vaccination status) and the history and lifestyle (history of respiratory infection, history of travel outside the district, history of participation in a group, promiscuity) of the cases and controls.

The variable Vaccination Status was used with the following modalities: Vaccinated; Not vaccinated and Unknown. The data source is the vaccination booklet or card. The subject is considered to be Vaccinated if he/she claims to have received meningococcal ACYW vaccine and has a vaccination card or record booklet that includes information on the administration of the vaccine. The subject is considered Unvaccinated if he/she claimed not to have received the meningococcal vaccine and did not either have a vaccination card or record. Vaccination status is unknown if he/she claimed to have received a dose of vaccine but did not present a card or vaccination record to confirm and specify the type of vaccine.

The date of vaccination of the controls as of the cases is the one marked on the vaccination record. The data source

is the control's vaccination record. This date was either already entered in the consultation register on the consultation day. f it was missing, the investigator looked in the vaccination record keeping only the dates prior to the date of consultation.

We used the plan below for the statistical analysis of our data with the help of Epi info 7.2.1 and Stata / MP 13.1 software.

For the quantitative variables, we calculated means with standard deviation or medians with interquartile range and for the qualitative variables, absolute or relative frequencies and compared the different proportions in each modality with a chi-square test.

For the etiological study, in univariate analysis, we searched for possible statistical associations between acute meningitis caused by Neisseria Meningitidis C and the explanatory variables using simple logistic regression. We calculated crude ORs with 95% confidence intervals and the p-value, the significance level strictly below 0.05. For the multivariate analysis, we selected the variables to be included in the bottom-up multiple stepwise ascending logistic regression model using the 20% significance level in the univariate analysis. We calculated adjusted ORs with their 95% confidence intervals (95% CI) and p-value. For the interpretation of statistical significance, we used the threshold of p strictly less than 0.05.

We obtained authorization to carry out the study from the health authorities of the Ministry of Health and Public Hygiene. The written consent of the participants was obtained by signing, after explanation, the consent form during the interview. During data entry and analysis, the names of respondents were replaced with identifiers so that the results do not include personal information.

RESULTS

Sociodemographic characteristics, background and lifestyle

The median age of cases is 14 years with extremes of 04 and 37 years while in the controls, it was 15 years with extremes of 01 and 61 years. Subjects in the 5-14 years age group were the most represented in both cases and controls, but this difference was not significant (p = 0.2). The M / F sex ratio was 1.33. Fifteen students were in the majority among the cases (42.86%) while among the controls, people who did not practice any paid profession were 53 (37.56%) (p = 0.01). Thirty (85.71%) cases were not vaccinated against meningitis. Socioeconomic status was low in both cases and controls.

The promiscuity which is the fact of sleeping 5 people or more in the same room was found in 22 (62.86%) cases (p = 0.001).

Subjects who had no history of respiratory infection before the onset of signs were predominantly represented in both meningitis cases (18; (51.43%)) and controls (111; (58.57%)) (p = 0.0008). Table 1 summarizes the socio-demographic characteristics of cases and controls in our study.

Table 1: Sociodemographic characteristics of cases and controls during meningitis epidemic due to Nm C in the district of Kpendjal-West in February 2019

Variables	n (%) Cases = 35	n (%) Controls = 140	*p*
Health facility of origin			**0.9**
Tambonga	16 (45.71)	64 (45.71)	
Malgbangou	08 (22.86)	32 (22.86)	
Djignandjoaga	03 (08.57)	12 (08.57)	
Pognon	08 (22.86)	32 (22.86)	
Age groups			**0.2**
Less than 5 years	01 (02.86)	19 (13.57)	
5 to 14 years	18 (51.43)	46 (32.86)	
15 to 29 years	14 (40)	45 (32.14)	
30 years and more	02 (5.71)	30 (21.43)	
Median age	14 (04-37) years	15 (01-61) years	
Sex			**0.9**
Male	20 (57.14)	80 (57.14)	
Female	15 (42.86)	60 (42.86)	
Sex ratio H/F*	1.33	1.33	
Socio-professional status			**0.01**
Trainee	06 (14.14)	05 (03.57)	
Students	15 (42.86)	49 (35.00)	
Liberal profession	03 (08.57	33 (23.57)	
No occupation	11 (31.53)	53 (37.56)	
Socio-economic status			**0.3**
Low	30 (85.71)	128 (91.43)	
Medium	05 (14.29)	12 (8.57)	
Vaccination status			**0.18**
Vaccinated	04 (11.83)	06 (04.29)	
Not vaccinated	30 (85.71)	108 (77.14)	
Unknown	01 (02.86)	26 (18.57)	
Promiscuity			**0.001**
Yes	22 (62.86)	40 (28,57)	
No	13 (37.14)	100 (71.43)	
History of respiratory infection			**0.0008**
Yes	17 (48.57)	29 (20.71)	
No	18 (51.43)	111 (79.29)	
History of participation to a group activity			**0.8**
Yes	24 (68.57)	93 (66.43)	
No	11 (31.43)	47 (33.57)	
History of traveling outside of the district			**0.33**
Yes	07 (20)	19 (13.57)	
No	28 (80)	121 (86,43)	

**H/F = man/woman*

Statistical links between the explanatory variables and Nm C meningitis in West Kpendjal district in February 2019

Table 2 shows the result of the univariate analysis between acute meningitis and the other variables in our study. Thus, socio-professional status (OR = 13.19, 95% CI = [2.47 - 70.42]; p = 0.007), promiscuity (OR = 4.23; 95% CI = [1.94-9.20]; p = 0.0003) and a history of respiratory infection (OR = 3.61; 95% CI = [1.65 - 7.87]; p = 0.0008) were statistically associated with acute bacterial meningitis caused by Neisseria meningitidis C.

Table 2: Univariate analysis between explanatory variables and Nm C meningitis epidemic in Kpendjal-West district in February 2019

Variables	crude OR (95% IC)	p
Age groups		**0.2**
Less than 5 years	1	
5 to 14 years	7.43 [0.92 – 59.91]	
15 to 29 years	5.91 [0.72 – 48.19]	
30 years and more	1.26 [0.10 – 14.94]	
Socio-professional status		**0.007**
Liberal profession	1	
Students	3.36 [0.90 – 12.54]	
Trainee	13.19 [2.47 -70.42]	
No occupation	2.28 [0.59 – 8.79]	
Socio-economic status		**0.31**
Low	1	
Medium	1.77 [0.58 – 5.43]	
Vaccination Vaccination status		**0.19**
No	1	
Yes	2.40 [0.63 – 9.07]	
Promiscuity		**0.0001**
Yes	1	
No	4.23 [1.94- 9.20]	
History of respiratory infection		**0.0008**
No	1	
Yes	3.61 [1.65 – 7.87]	
History of participation to a group activity		**0.8**
No	1	
Yes	1.10 [0.49 – 2.43]	
History of traveling out of the district		**0.33**
No	1	
Yes	1.59 [0.61 – 4.15]	

Independent association with Nm C meningitis in Kpendjal West district in February 2019

According to the final obtained model presented in Table 3, factors independently associated with acute bacterial Neisseria meningitidis C meningitis during the meningitis epidemic in the health district of Kpendjal-West in February 2019 are: meningococcus C vaccination status (OR = 7.16; 95% CI = [1.02 - 49.79]; p = 0.04), promiscuity (OR = 7.08; 95% CI = [2.59 - 19.37]; p = 0.0001) and a history of respiratory infection (OR = 6.44; 95% CI = [2.17 - 19.10]; p = 0.001).

Table 3: Independent associated factors with Neisseria meningitidis C meningitis at Kpendjal West in February 2019

Variables	OR (95% IC)	p
Promiscuity		**0.0001**
Yes	1	
No	7.08 [2.59 – 19.37]	
History of respiratory infection		**0.001**
Yes	1	
No	6.44 [2.17 – 19.10]	
Vaccination status		**0.04**
Yes	1	
No	7.16 [1.02 – 49.79]	
Socio-professional status		**0.08**
Liberal profession	1	
Students	8.06 [1.29 – 50.16]	
Trainee	12.06 [1.53 – 94.69]	
No occupation	8.75 [1.37 – 55.59]	
Age groups		**0.88**
Less than 5 years	1	
5 to 14 years	0.14 [0.01 – 1.04]	
15 to 29 years	0.18 [0.01 – 1.91]	
30 years and more	0.70 [0.04 – 10.37]	

DISCUSSION

History of respiratory infection, promiscuity, and meningococcal C vaccination status were independently identified as associated with acute bacterial meningitis caused by Neisseria meningitidis C in our study.

Promiscuity

Promiscuity is most often caused by a large number of people in dwellings and this is a factor that favors the spread of human-to-human transmission diseases, including bacterial meningitis [14]. Hadjichristodoulou [10] in a case-control study on risk factors for meningococcal diseases in children in Greece also found that promiscuity was a risk factor for the onset of meningococcal disease. These studies are consistent with our results, as the majority of our cases were students with a median age of 14 years. The district of Kpendjal-West is mainly agricultural and the habitat is traditional. In addition, several households live together in the same compound, which results in a large number of people for few rooms, leading to overcrowding.

History of respiratory infection

During a local respiratory, bacteria can find their way into the blood and eventually cross the blood-brain barrier to infect the cerebrospinal fluid, resulting in edema and meningeal inflammation [16, 17]. According to the WHO, during the dry season, between December and June, dust-laden winds, cold nights and upper respiratory tract infections combine to damage the nasopharyngeal mucosa, increasing the risk of meningococcal disease [2, 18]. It should be noted that respiratory infections are frequent during the dry season in Togo, as the days of this season are characterized by dusty winds, high temperatures and low humidity. These conditions lead to ruptures of the nasopharyngeal mucous membranes, thus increasing the risk of respiratory tract infections [14]. These lesions of the nasopharyngeal mucosa in the context of asymptomatic meningococcal carriage in the same area promote the passage of the bacteria through the blood-brain barrier to colonize the cerebrospinal fluid. Hadjichristodoulou in Greece [10] found in his study that a recent history of upper respiratory tract infection was a risk factor for meningococcal infection. Similarly, Zelalem [15] found in his study in Ethiopia an association between the degree of meningococcal carriage in the nasopharynx and the history of tonsillectomy

Meningococcal C vaccine status

Vaccination against Neisseria meningitidis has been around for over 40 years [19]. It remains the best way to fight meningitis epidemics, especially in countries where the risk of an epidemic is high, such as those in the African meningitis belt [20].

In Togo, tetravalent meningococcal vaccine ACWY is used for vaccination against meningococcal meningitis. Outside of epidemic periods, when a case of meningococcal meningitis is detected, a vaccine response around the case is carried out with a vaccine containing the identified serogroup. This limits the spread of the disease and the outbreak of the epidemic. Only meningococcus A vaccination is done routinely.

In our study, 94.29% of subjects were not vaccinated against meningococcus C. 11.42% of cases in our study received a tetravalent meningococcal vaccine ACWY a few days before the onset of the disease and this during the vaccine response around the first cases of the epidemic.

In his study, Merabet [21] found that sick children who were vaccinated accounted for 5.57%. The higher proportion of sick vaccinated subjects in our study could be explained by the fact that these individuals would be incubating at the time of the vaccine administration, because they had already been in contact with a sick person. In a case-control study of the effectiveness of meningococcal C conjugate vaccine in an epidemic in El Salvador in 2010, Cardoso [6] showed that a rapid vaccine response that included individuals up to 24 years of age, was an effective way to control meningococcus C epidemics. Chow [22] in Nigeria in his study on the third consecutive epidemic of meningococcal C meningitis in northern Nigeria from 2013 to 2015 advocate the use of a long-lasting meningococcal conjugate vaccine to limit the occurrence of epidemics.

The limits of the study are that our study was based on cases admitted to health facilities; Cases (and/or deaths) who did not consult could have escaped us. So, our sample is not representative of the population of the district; the results of the study cannot be extrapolated to the entire population of the district. Memory bias in data collection related to the time elapsed between the end of the epidemic and the start of data collection, especially among controls.

CONCLUSION

Our study focused on the factors associated with acute bacterial meningitis caused by Neisseria meningitidis C in the district of Kpendjal-West in February 2019. The study found that history of respiratory infection, promiscuity and meningococcus C vaccination status were all independently associated with acute bacterial Neisseria meningitidis C meningitis during the outbreak in this district. These factors are modifiable by public health actions that can be undertaken to improve the prevention of this disease in the district.

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Authors' contributions

PEA conceived, designed, analyzed data; he wrote and prepared the final draft of the manuscript.

PKY contributed in the interpretation of results, in the writing and the finalization of the manuscript.

PKY, JK, **PKY, JK**, **ML, HA, TAT, OS** and **NM**: provided comments on the study design and reviewed the manuscript.

All authors have read and approved the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Main merits and interested audience

Our results will allow us to make proposals to improve the fight against meningococcal meningitis in the Savannah region, because despite the small number of our sample of cases, our case-control study methodology allowed us to find independent associations between meningitis C and three explanatory factors which have been found in other studies in Africa and elsewhere in the world.

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