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Epidemiology of Bacterial Meningitis in the Nine Years Since Meningococcal Serogroup A Conjugate Vaccine Introduction, Niger, 2010–2018

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Abstract

Background.—In 2010, Niger and other meningitis belt countries introduced a meningococcal serogroup A conjugate vaccine (MACV). We describe the epidemiology of bacterial meningitis in Niger from 2010 to 2018.

Methods.—Suspected and confirmed meningitis cases from January 1, 2010 to July 15, 2018 were obtained from national aggregate and laboratory surveillance. Cerebrospinal fluid specimens were analyzed by culture and/or polymerase chain reaction. Annual incidence was calculated as cases per 100 000 population. Selected isolates obtained during 2016–2017 were characterized by whole-genome sequencing.

Results.—Of the 21 142 suspected cases of meningitis, 5590 were confirmed: *Neisseria meningitidis* ([Nm] 85%), *Streptococcus pneumoniae* ([Sp] 13%), and *Haemophilus influenzae* ([Hi] 2%). No NmA cases occurred after 2011. Annual incidence per 100 000 population was more dynamic for Nm (0.06–7.71) than for Sp (0.18–0.70) and Hi (0.01–0.23). The predominant Nm serogroups varied over time (NmW in 2010–2011, NmC in 2015–2018, and both NmC and NmX in 2017–2018). Meningococcal meningitis incidence was highest in the regions of Niamey, Tillabery, Dosso, Tahoua, and Maradi. The NmW isolates were clonal complex (CC)11, NmX were CC181, and NmC were CC10217.

Conclusions.—After MACV introduction, we observed an absence of NmA, the emergence and continuing burden of NmC, and an increase in NmX. Niger's dynamic Nm serogroup distribution highlights the need for strong surveillance programs to inform vaccine policy.

Keywords

epidemiology; meningitis belt; *Neisseria meningitidis*; Niger; molecular surveillance

Niger is located within the meningitis belt of sub-Saharan Africa, which stretches from Senegal to Ethiopia, and has a high burden of meningococcal disease [1, 2]. Meningitis outbreaks typically occur in March, April, or May and are associated with high temperatures and high concentrations of airborne dust [3]. In this region, large-scale outbreaks have historically been due to *Neisseria meningitidis* serogroup A (NmA), leading to the introduction of a meningococcal serogroup A conjugate vaccine (MACV) in 21 countries to-date [4]. Niger was among the first countries to introduce the vaccine, implementing mass campaigns among 1- to 29-year-olds in 2010–2011 (>90% vaccination coverage in the target group); routine vaccination of 9-month-olds started in October 2017 [4, 5].

In addition to NmA, outbreaks caused by *N meningitidis* serogroup W (NmW), X (NmX), and C (NmC) have also been reported in Niger [6-11]. Although previously rare in sub-Saharan Africa, Niger experienced a large-scale NmC outbreak in 2015 in which over 9000 cases were reported. It has been postulated that introduction of a novel, virulent strain into an immunologically naive population, rather than the replacement of non-A serogroups into the ecologic niche left after MACV vaccination, contributed to this outbreak [12]. However, the factors associated with this outbreak, the first major meningitis outbreak in Niger after MACV introduction, are not well understood, underscoring the importance of careful monitoring of the epidemiology of bacterial meningitis in the post-NmA era.

In this report, we describe the epidemiology of bacterial meningitis in Niger during the 9 years since MACV introduction (2010–2018) to assess the incidence of both NmA and non-A serogroups, characterize the dynamics of bacterial meningitis epidemiology, and inform meningococcal vaccine policy in Niger. We also report the results of molecular characterization of meningococcal isolates collected in 2016–2017 to monitor the potential emergence of additional novel strains.

MATERIALS AND METHODS

Surveillance Systems and Data Collection

Data and cerebrospinal fluid (CSF) specimens were collected through routine national surveillance. Thus, Institutional Review Board review was not required by any participating institutions.

Nationwide, population-based meningitis surveillance is conducted through weekly aggregate reporting of suspected meningitis cases and deaths by district. Case-level data on suspected meningitis cases are collected through overlapping surveillance systems: nationwide laboratory surveillance and, since 2014, case-based surveillance in select districts. Laboratory surveillance, in which basic epidemiologic information is also collected, is conducted on all suspected meningitis cases where a CSF specimen available. Case-based meningitis surveillance, in which detailed epidemiologic and laboratory data are collected on each suspected case, has been progressively implemented in 32 of the 72 districts (representing 47% of Niger's population by 2018) and supported by MenAfriNet, an international consortium that aims to strengthen case-based meningitis surveillance, assess changes in meningitis epidemiology and vaccine impact, and inform vaccine policy and development in sub-Saharan Africa [13]. To ensure the surveillance was comparable across all years of this analysis, the laboratory surveillance data were used, which included nationwide information including case age, date of collection, district, region, and laboratory results. In both laboratory and case-based surveillance systems, microbiologic testing of CSF specimens is conducted by the national meningitis reference laboratory at the Centre de Recherche Médicale et Sanitaire (CERMES). Thus, all suspected meningitis cases with CSF specimens are captured in the laboratory surveillance database, and all suspected meningitis cases with CSF specimens from districts participating in case-based surveillance are recorded in both the case-based surveillance and laboratory databases.

The CERMES has performed conventional (gel-based) polymerase chain reaction (PCR) to detect the 3 common bacterial meningitis pathogens (*N meningitidis, Streptococcus pneumoniae*, and *Haemophilus influenzae*) and identify the 5 *N meningitidis* serogroups (A, B, C, W, and Y) since 2002 and implemented an assay to detect serogroup X in 2004 [10]. Subsequently, real-time (rt)-PCR assays for species and serogroup detection were introduced in 2011 and direct rt-PCR assays, which are carried out directly on the primary CSF specimen [14] since 2014–2015. Thus, species and serogroup identification by CERMES was completed using conventional PCR, rt-PCR, or slide agglutination methods throughout the 9-year period of analysis [15, 16]. Any isolate determined to be negative for all 6 serogroups was categorized as non-groupable (NmNG). *Haemophilus influenzae* serotyping was conducted but not available for all years and thus excluded from the analysis.

Data Analysis

For this analysis, the number of suspected meningitis cases in Niger was identified from aggregate surveillance and confirmed cases from nationwide laboratory surveillance. Cases reported from January 1, 2010 to July 15, 2018 were included in the analysis and defined using World Health Organization (WHO) guidelines [17]. A suspected case was defined by

the sudden onset of fever with headache and at least 1 of the following symptoms (stiff neck, altered consciousness, or signs of meningeal irritation). A confirmed case was defined as identification of *N meningitidis, H influenzae*, or *S pneumoniae* by culture, latex test, or PCR in a patient with suspected meningitis.

Crude annual incidence was calculated as the number of suspected or confirmed cases per 100 000 population using district-specific population figures obtained from the Niger Ministry of Health (total population = 21 466 864 persons in 2018). The epidemic threshold was calculated in accordance with WHO guidelines (10 or more suspected cases per 100 000 population per week) [18], and an outbreak is defined as described previously [19]. The case fatality ratios were calculated as the proportion of known deaths among suspected cases reported through the aggregate meningitis surveillance system. For the temporal analysis, the full meningitis season spans epidemiologic weeks 1–24, but the peak meningitis season was defined as epidemiologic weeks 10–20 for this analysis. For the geographical analysis, map shape files for Niger were downloaded from The Humanitarian Data Exchange (https://data.humdata.org/), loaded into R (version 3.5.0), and converted to a spatial vector object using the package rgdal v1.3–6. The spatial vector object was plotted using ggplot2 v3.1.0, and pie charts were overlaid using scatterpie v0.1.2. We investigated the distribution of confirmed cases across 8 age strata (<1, 1–4, 5–9, 10–14, 15–19, 20–24, 25–44, and 45+ years). Two hundred forty-four confirmed cases were missing patient age (*H influenzae* n = 6, *S pneumoniae* n = 40, NmA n = 9, NmC n = 122, NmW n = 39, NmX n = 24, NmNG n = 4) and excluded from the analysis. The χ^2 tests of independence for association between age and pathogen or *N meningitidis* serogroup were calculated using SAS version 9.4. The χ^2 tests of independence (α = .05) for age versus pathogen and age versus *N meningitidis* serogroup were calculated using SAS version 9.4.

Molecular Characterization of Meningococcal Isolates

All available isolates from the 2016 meningitis season (1 NmX, 101 NmC, and 22 NmW) and a subset of isolates from the 2017 season (8 NmX, 30 NmC, and 2 NmW) underwent molecular characterization. For 2017, all available NmX and NmW isolates and at least 2 NmC isolates per district were selected, when available. Isolates were sent to the US Centers for Disease Control and Prevention (CDC) Bacterial Meningitis Laboratory, a WHO Collaborating Centre for Meningitis, for whole-genome sequencing analysis.

Deoxyribonucleic acid (DNA) extractions were conducted using the Gentra Puregene yeast/bacteria DNA extraction kit (QIAGEN) or with a chemagic Prepito instrument (PerkinElmer) using the Cyto Pure Kit. The NEBNext Ultra DNA Library preparation kit was used according to manufacturer specifications to generate genomic libraries. Sequencing was completed at CDC using 250-base pair paired-end reads on a HiSeq 2500 or a MiSeq (Illumina). Raw reads were trimmed to remove adapters and low quality bases before de novo genomic assembly by SPAdes, version 3.7.0 [20]. To identify the sequence type (ST), clonal complex (CC), and PorA and FetA types, sequences for the MLST genes and the fine typing genes (*porA* and *fetA*) were identified by a BLAST search using the PubMLST allele collection (www.pubmlst.org/Neisseria) [21].

RESULTS

From January 1, 2010 through July 15, 2018, 21 142 suspected meningitis cases were reported, with 1842 deaths and an overall case fatality ratio of 8.7% (Table 1). The CERMES tested 15 884 CSF specimens during this period; 5590 CSF specimens (35.2%) were positive for 1 of the 3 bacterial meningitis pathogens. *Neisseria meningitidis* was responsible for the highest disease burden, with 4741 (84.8%) confirmed cases, compared with 721 *S pneumoniae* (12.9%) and 129 *H influenzae* cases (2.3%) (Table 1). *Neisseria meningitidis* serogroups A, C, W, X, and NG were detected during the analysis period, but no cases of serogroup Y or B were identified. Annual variation in the number of *N meningitidis* cases was observed, with 2010 (n = 1033), 2015 (n = 1562), and 2017 (n = 1268) accounting for the highest number of confirmed cases. In addition, there were 3 years (2012–2014) of a historically low disease burden, with fewer than 350 suspected cases and 82 confirmed cases per year.

We observed large annual shifts in the burden of *N meningitidis* compared with *S pneumoniae* and *H influenzae*, which each remained relatively stable (Table 2). Niger had an annual incidence (reported as cases per 100 000 population) ranging between 0.18 and 0.70 for *S pneumoniae* and 0.01 and 0.23 for *H influenzae* during each of the years assessed. In contrast, more than a 100-fold difference in annual incidence was observed for *N meningitidis* (range: 0.06–7.71). Each *N meningitidis* serogroup also exhibited large annual variations in incidence (range: NmA 0.00 to 1.57, NmC 0.00 to 6.37, NmW 0.01 to 4.32, and NmX 0.00 to 1.08).

Temporal Analysis

Highly dynamic patterns of *N meningitidis* serogroups were observed during the 9 years analyzed (Figure 1). The years 2010–2011 exhibited a high burden of NmW meningitis (incidence of 4.32 in 2010 and 2.54 in 2011) and detection of 5 NmA cases during 2011, the second year of MACV mass vaccination campaigns. From 2012 to 2018, no confirmed cases of NmA were identified in Niger. In 2012–2014, fewer than 1000 suspected cases and 200 confirmed cases were identified in all 3 years combined, and the most common pathogens were *S pneumoniae* and NmW (Table 2). Even though *S pneumoniae* was the most common pathogen, the incidence was low (0.18–0.28 in 2012–2014 compared to 0.39–0.70 in 2010–2011 and 2015–2018). *Neisseria meningitidis* serogroup C was detected for the first time during the analysis period in 2014 (n = 9), followed by a high burden of NmC in subsequent years (annual incidence: 1.11–6.37 in 2015–2018). The 2015 meningitis season was associated with an outbreak that included approximately 9000 suspected cases and 1181 confirmed NmC cases (Table 1). In both 2015 and 2016, NmC (82.7%–88.2% of *N meningitidis* cases) and NmW (14.3%–6.8%) were the most common serogroups detected. In 2017–2018, NmC remained the main cause of meningitis (incidence: 4.11 in 2017 and 1.11 in 2018), but an increase in NmX cases was also observed (incidence: 0.96–1.08 in 2017–2018 compared with <0.09 in previous years), with comparable incidences of both NmC and NmX in 2018.

The 3 main bacterial meningitis pathogens exhibited varied degrees of seasonality. *Haemophilus influenzae* exhibited no distinct seasonality. *Streptococcus pneumoniae* cases

were moderately seasonal (44.9% of cases during epidemiologic weeks 10–20 and 70.0% of cases when epidemiologic weeks 5–20 were assessed) along with consistent detection throughout the year (Supplemental Figure 1). In contrast, each *N meningitidis* serogroup exhibited a typical seasonal pattern, with the majority (78.6%) of *N meningitidis* cases occurring between epidemiologic weeks 10–20 (Supplemental Figure 1). In a subset of years, and most prominently in 2017, a small increase in meningococcal meningitis was also observed in epidemiologic weeks 49–53. One interesting feature of the 2015 NmC outbreak was the late onset within the meningitis season (NmC cases peaked in epidemiologic week 19); this contrasted the previous years of high disease burden such as 2010, when NmA and NmW cases peaked during epidemiologic weeks 13 or 16 (Supplemental Figure 1). However, NmC meningitis in subsequent years exhibited an earlier peak in epidemiologic weeks 11 (2016), 14 (2017), and 15 (2018).

Geographic Association

We examined the confirmed cases detected in each district throughout the analysis period (Figure 2A-D). The majority of cases clustered in the southern and western regions of Niger, which are centrally located within the meningitis belt region and have the highest population density (Figure 3A). Very few districts exhibited a pathogen distribution that was distinct from neighboring areas. One exception was the district-level clusters of both NmC (2014) and NmX (2016) cases detected before the first year of widespread disease by each serogroup. All of the 2014 NmC cases were localized in the Dogon-Doutchi district (Figure 2B, denoted by the arrowhead), and the 2015 outbreak spread throughout the southern regions of Dosso, Niamey, and Tillabery. In 2016, the first cluster of NmX cases (n = 10) was detected in Gaya (Figure 2C, denoted by the arrowhead) in addition to 5 cases detected across 4 other districts. By 2017 and 2018, NmX cases were detected throughout most southern and western districts (Figure 2D).

We calculated the annual incidence of meningococcal meningitis (all serogroups) at both the regional and district levels (Figure 3). Five regions (Dosso, Maradi, Niamey, Tahoua, and Tillabery) consistently had a high disease burden and exhibited an annual incidence >1.0 cases per 100 000 during at least 5 of the 9 years assessed (Figure 3A and B). In contrast to the regional trends, the incidence at the district level was quite dynamic, with a large amount of annual variation observed (Figure 3C). In 2010–2011, when NmW was the dominant serogroup nationwide, only the Tillabery region exhibited a meningococcal meningitis incidence >5.0 for both years, with the most affected districts within Tillabery region including Ouallam (13.64 in 2010) and Say (18.51 in 2011) (Figure 3B and C). During the low burden years of 2012–2014, no regions and only a few districts exhibited an incidence >1.0 (Nguigmi, Loga, and Dogon-Doutchi) (Figure 3C). When NmC was the predominant pathogen in 2015 and 2016, the regions of Niamey (incidence 54.54) and Dosso (incidence 21.07) were most affected (Figure 3B). It is interesting that 2017 and 2018, which were both associated with high incidence of NmX and NmC, exhibited distinct geographic distributions. A high disease burden in the regions of Dosso, Niamey, and Tillabery was detected in 2017 (similar to the 2015 and 2016 seasons) but absent in 2018 (Figure 3B). However, an incidence of ~4.5 was noted in the Maradi region in both 2017 and 2018, along with an increased burden in Tahoua (2017 incidence = 5.57) and Zinder (2018 incidence =

2.32). The regional variation between 2017 and 2018 was also readily apparent when the incidence of NmX and NmC were calculated separately (Supplemental Figure 2).

Age Distribution

We detected a significant association between distribution of age at onset and causative pathogen ($P < .001$) (Figure 4A and B). Patient age was reported for 95.6% of confirmed cases. *Haemophilus influenzae* predominantly affected the very young (median age 1 year, interquartile range [IQR], 0–7 years), with 45.1% of cases occurring in those aged <1 year and 83.2% of cases occurring in those aged 9 years. In contrast, *N meningitidis* cases in those aged <1 year were uncommon (4.2% of *N meningitidis* cases); the majority of cases (75.8%) were detected in persons aged 1–14 years (median age of all cases = 9 years; IQR, 5–13 years). *Streptococcus pneumoniae* cases were detected more evenly across all age groups (6.9%–22.0% of cases per age group), with only 49.0% of cases occurring in those aged 1–14 years (median age of all cases = 9 years; IQR, 1–16 years).

Age of onset was similar across the different *N meningitidis* serogroups (Figure 4A and B). The age distribution of NmA and NmC cases was comparable (median 9 years for NmA and 10 years for NmC; IQR = 6–8 years for both). *Neisseria meningitidis* serogroup W had the lowest median age of onset (median 6 years; IQR, 3–12 years). *Neisseria meningitidis* serogroup X (median 8 years; IQR, 5–11 years) was seldom detected in those aged >14 years old (8% compared with 15%–24% for other serogroups).

Molecular Characterization

To monitor the potential emergence of new strains within recent years, the molecular profile (ST) and CC was determined for all isolates collected in 2016 and select isolates from 2017 (Table 3). All 8 NmX isolates were CC181, 131 NmC isolates were CC10217, and 24 NmW isolates were CC11/ST-11. All but one of the NmX isolates were ST-181 (the single isolate of ST-14014 differed by only 1 allele from ST-181). Among NmC isolates, only 1 ST was detected in 2016 (ST-10217), but 3 STs were detected in 2017 (ST-10217, ST-14016, and ST-9367), with each ST only diverging from ST-10217 by a single allele (*adk* for ST-14016 and *fumC* for ST-9367). More specifically, 21 (70%) of the NmC isolates were ST-10217, 8 (27%) were ST-14016, and 1 (3%) was ST-9367.

DISCUSSION

After MACV introduction in 2010–2011, the epidemiology of bacterial meningitis in Niger was marked by an initial reduction in the incidence of suspected meningitis cases to a historically low level, followed by an emergence of large-scale NmC outbreaks and increases in NmX incidence. Notably, no NmA cases were detected after 2011, the year that mass MACV vaccinations concluded, contrasting previous years (NmA comprised 45.7%–98.6% of *N meningitidis* cases per year from 2003 to 2009 [22]), and highlighting the continued, long-term success of this public health intervention. However, serogroups NmW, NmC, and NmX were associated with a high disease burden during this period, indicating that meningococcal meningitis remains an important public health problem and that an affordable, multivalent meningococcal conjugate vaccine may be necessary for the control of

meningococcal disease in Niger. High-quality surveillance systems with strong laboratory confirmation will be critical to monitor this dynamic disease and develop future public health intervention strategies.

Within the analysis period, we detected small district-level clusters of specific meningococcal serogroups in the year before widespread disease (NmC in Dogon-Doutchi and NmX in Gaya), demonstrating that strong surveillance systems are capable of detecting small shifts in serogroup distribution that could have important implications for public health strategies during the following season. Other recent studies have reported the bacterial meningitis cases in Niger at the resolution of the healthcare catchment area [23, 24], but sub-district information was not available for all cases included in this analysis. Because case-based surveillance data were not available for all years, this analysis was limited to the epidemiologic information present within the laboratory surveillance database (which lacked patient outcome and did not have complete sub-district geographic information). However, this limitation can be overcome in the future because case-based surveillance is being progressively implemented throughout Niger, with the support of initiatives like the MenAfriNet Consortium.

The continued absence of NmA cases in Niger 7 years after the mass vaccination campaigns highlights the profound impact of the MACV vaccine [6, 7]. However, a few NmA meningitis cases have been reported in the region since 2011 [25, 26]. Burkina Faso, which neighbors Niger to the West, detected 6 NmA cases in persons aged 5–19 years between 2011 and 2015; 5 cases occurred in persons who were unvaccinated, and 1 case was a 9-year-old girl who had received MACV 5 years earlier [25]. Thus, continued support of MACV as part of routine childhood vaccination programs, like the one in Niger that began in 2017, in addition to catch-up campaigns, when appropriate, will be critical to sustain the historically low levels of NmA meningitis [4]. Strong surveillance programs are also essential to supporting these efforts, ensuring identification of any new NmA cases and effective investigation of potential vaccine failures.

The 2015 NmC outbreak, followed by years of sustained high NmC incidence, demonstrates that Niger is still at high risk for meningococcal meningitis, even in the absence of NmA. The NmC ST-10217 strain that caused the outbreak in Niger also caused large outbreaks in Nigeria and smaller outbreaks in Mali and Liberia and was shown to have evolved from a carriage strain ([7, 27-31]), highlighting the potential for emergence of novel, outbreak-prone strains of regional importance. Our molecular characterization demonstrated that isolates from Niger in 2016–2017 all had genetic lineages consistent with those observed elsewhere within the meningitis belt region [32]. Three separate STs were detected in the NmC isolates collected in 2017 (ST-10217, ST-14016, and ST-9367), indicative of increased genetic variation within the outbreak-prone CC10217 compared with prior years (Table 3 and [33]). Our identification of a new ST in multiple NmC cases underscores the continued need for molecular surveillance to detect the emergence of highly invasive strains in the region.

Our analysis also demonstrated that Niger's bacterial meningitis and pathogen distribution remained complex in the post- MACV era, highlighting the importance of strong laboratory

programs. We observed large annual variations in the distribution of *N meningitidis* serogroups and the continued detection of *S pneumoniae* and *H influenzae*. *Neisseria meningitidis* serogroup C, NmW, and NmX each exhibited years of high incidence, and all 3 serogroups have caused prior outbreaks in Niger or surrounding countries, indicating that the outbreak risk remains [7, 9, 10, 27, 28, 34-36]. During each year assessed, more than half of the CSFs tested were negative for all 3 of the main bacterial pathogens, which is consistent with a previous report [6]; multiple factors likely contribute to the low confirmation rate, including but not limited to the broad case definition and challenges in specimen transport leading to decreased specimen quality [37]. Thus, the capacity for rapid and accurate laboratory confirmation remains critical to identifying the causative pathogen and initiating effective and targeted outbreak and vaccination responses.

Although reactive vaccination campaigns remain the primary approach for responding to outbreaks caused by NmW and NmC, global shortages in polysaccharide meningococcal vaccines and the high cost of conjugate vaccines make implementation of effective vaccine campaigns challenging. In addition, there are currently no licensed vaccines available that target serogroup X, which is concerning in light of the increased incidence of NmX in Niger in 2017 and 2018. An affordable, multivalent meningococcal conjugate vaccine (MenACWXY) under development for use in the region is expected to be licensed as early as 2021 [38, 39]. Effective case-based surveillance programs, like the one supported by the MenAfriNet Consortium, and additional evaluations will be important in evaluating the impact of multivalent vaccines on both meningococcal disease and carriage in the region. Data from this analysis will be useful to help inform the need and strategy for implementation of multivalent meningococcal conjugate vaccines in Niger and the surrounding region.

CONCLUSIONS

In summary, the results of our analysis of 9 years of high-quality meningitis surveillance data in Niger, a hyperendemic country of the meningitis belt, demonstrates the remarkable elimination of NmA cases after MACV introduction and the dynamic epidemiology of *N meningitidis*. Altogether, our findings highlight the value of strong surveillance systems and laboratory capacity for accurately assessing the ever-changing epidemiology of meningitis and provides evidence to support development and introduction of the next generation of meningococcal vaccines in sub-Saharan Africa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Molesworth AM, Cuevas LE, Connor SJ, Morse AP, Thomson MC. Environmental risk and meningitis epidemics in Africa. Emerg Infect Dis 2003; 9:1287–93. [PubMed: 14609465]

2. Thomson MC, Molesworth AM, Djingarey MH, Yameogo KR, Belanger F, Cuevas LE. Potential of environmental models to predict meningitis epidemics in Africa. Trop Med Int Health 2006; 11:781–8. [PubMed: 16771998]

3. Jusot JF, Neill DR, Waters EM, et al. Airborne dust and high temperatures are risk factors for invasive bacterial disease. J Allergy Clin Immunol 2017; 139:977–86.e2. [PubMed: 27523432]

4. World Health Organization. Epidemic meningitis control in countries of the African meningitis belt, 2017. Wkly Epidemiol Rec 2018; 93:173–84.

5. Djingarey MH, Diomande FV, Barry R, et al. Introduction and rollout of a new group A meningococcal conjugate vaccine (PsA-TT) in African Meningitis Belt Countries, 2010–2014. Clin Infect Dis 2015; 61(Suppl 5):S434–41. [PubMed: 26553672]

6. Collard JM, Issaka B, Zaneidou M, et al. Epidemiological changes in meningococcal meningitis in Niger from 2008 to 2011 and the impact of vaccination. BMC Infect Dis 2013; 13:576. [PubMed: 24313998]

7. Lingani C, Bergeron-Caron C, Stuart JM, et al. Meningococcal meningitis surveillance in the African Meningitis Belt, 2004–2013. Clin Infect Dis 2015; 61(Suppl 5):S410–5. [PubMed: 26553668]

8. Collard JM, Maman Z, Yacouba H, et al. Increase in *Neisseria meningitidis* serogroup W135, Niger, 2010. Emerg Infect Dis 2010; 16:1496–8. [PubMed: 20735947]

9. Djibo S, Nicolas P, Alonso JM, et al. Outbreaks of serogroup X meningococcal meningitis in Niger 1995–2000. Trop Med Int Health 2003; 8:1118–23. [PubMed: 14641847]

10. Boisier P, Nicolas P, Djibo S, et al. Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in 2006 in Niger. Clin Infect Dis 2007; 44:657–63. [PubMed: 17278055]

11. Sidikou F, Zaneidou M, Alkassoum I, et al. Emergence of epidemic *Neisseria meningitidis* serogroup C in Niger, 2015: an analysis of national surveillance data. Lancet Infect Dis 2016; 16:1288–94. [PubMed: 27567107]

12. World Health Organization. Preparedness for outbreaks of meningococcal meningitis due to *Neisseria meningitidis* serogroup C in Africa: recommendations from a WHO expert consulation. Wkly Epidemiol Rec 2015; 90:633–44. [PubMed: 26591025]

13. Patel JC, Stouffer HM, Diallo AO, et al. MenAfriNet: A network supporting case-based meningitis surveillance and vaccine evaluation in the meningitis belt of Africa. J Infect Dis 2019; 220(Suppl 4):S148–54. [PubMed: 31671453]

14. Vuong J, Collard JM, Whaley MJ, et al. Development of real-time PCR methods for the detection of bacterial meningitis pathogens without DNA extraction. PLoS One 2016; 11:e0147765. [PubMed: 26829233]

15. Sidikou F, Djibo S, Taha MK, et al. Polymerase chain reaction assay and bacterial meningitis surveillance in remote areas, Niger. Emerg Infect Dis 2003; 9:1486–8. [PubMed: 14718100]

16. Chanteau S, Sidikou F, Djibo S, Moussa A, Mindadou H, Boisier P. Scaling up of PCR-based surveillance of bacterial meningitis in the African meningitis belt: indisputable benefits of multiplex PCR assay in Niger. Trans R Soc Trop Med Hyg 2006; 100:677–80. [PubMed: 16359713]

17. World Health Organization. Standard operating procedures for enhanced meningitis surveillance in Africa. Available at: http://wwwmeningvaxorg/files/WHO_SOP_EN_2009pdf. Accessed 23 July 2018.

18. World Health Organization. Revised guidance on meningitis outbreak response in sub-Saharan Africa. Wkly Epidemiol Rec 2014; 89:580–6. [PubMed: 25538995]

19. Fernandez K, Lingani C, Aderinola OM, et al. Meningococcal meningitis outbreaks in the African meningitis belt after meningococcal serogroup A conjugate vaccine introduction, 2011–2017. J Infect Dis 2019; 220(Suppl 4):S225–32. [PubMed: 31671449]

20. Bankevich A, Nurk S, Antipov D, et al. SPAdes: a new genome assembly algorithm and its applications to single-cell sequencing. J Comput Biol 2012; 19:455–77. [PubMed: 22506599]

21. Jolley KA, Maiden MC. BIGSdb: Scalable analysis of bacterial genome variation at the population level. BMC Bioinformatics 2010; 11:595. [PubMed: 21143983]

22. Manzo LM, Ousmane S, Ibrahim DD, Zaneidou M, Testa J, Mainassara HB. Bacterial meningitis in Niger: an analysis of national surveillance data, 2003–2015. Pan Afr Med J 2018; 30:235. [PubMed: 30574254]

23. Maïnassara HB, Oumarou GI, Issaka B, et al. Evaluation of response strategies against epidemics due to *Neisseria meningitidis* C in Niger. Trop Med Int Health 2017; 22:196–204. [PubMed: 27860062]

24. Paireau J, Mainassara HB, Jusot JF, et al. Spatio-temporal factors associated with meningococcal meningitis annual incidence at the health centre level in Niger, 2004–2010. PLoS Negl Trop Dis 2014; 8:e2899. [PubMed: 24852960]

25. Diallo AO, Soeters HM, Yameogo I, et al. Bacterial meningitis epidemiology and return of Neisseria meningitidis serogroup A cases in Burkina Faso in the five years following MenAfriVac mass vaccination campaign. PLoS One 2017; 12:e0187466. [PubMed: 29095907]

26. Soeters HM, Diallo AO, Bicaba BW, et al. Bacterial meningitis epidemiology in 5 countries in the meningitis belt of sub-Saharan Africa, 2015–2017. J Infect Dis 2019; 220(Suppl 4):S165–74. [PubMed: 31671441]

27. Funk A, Uadiale K, Kamau C, Caugant DA, Ango U, Greig J. Sequential outbreaks due to a new strain of *Neisseria meningitidis* serogroup C in Northern Nigeria, 2013–14. PLoS Curr 2014; 6. doi:10.1371/currents.outbreaks.b50c2aaf1032b3ccade0fca0b63ee518

28. Trotter CL, Lingani C, Fernandez K, et al. Impact of MenAfriVac in nine countries of the African meningitis belt, 2010–15: an analysis of surveillance data. Lancet Infect Dis 2017; 17:867–72. [PubMed: 28545721]

29. Brynildsrud OB, Eldholm V, Bohlin J, Uadiale K, Obaro S, Caugant DA. Acquisition of virulence genes by a carrier strain gave rise to the ongoing epidemics of meningococcal disease in West Africa. Proc Natl Acad Sci U S A 2018; 115:5510–5. [PubMed: 29735685]

30. Bozio CH, Vuong J, Dokubo EK, et al. Outbreak of *Neisseria meningitidis* serogroup C outside the meningitis belt-Liberia, 2017: an epidemiological and laboratory investigation. Lancet Infect Dis 2018; 18:1360–7. [PubMed: 30337259]

31. Sanogo YO, Guindo I, Diarra S, et al. A new sequence type of *Neisseria meningitidis* serogroup C associated with a 2016 meningitis outbreak in Mali. J Infect Dis 2019; 220(Suppl 4): S190–7. [PubMed: 31671437]

32. Topaz N, Caugant DA, Taha MK, et al. Phylogenetic relationships and regional spread of meningococcal strains in the meningitis belt, 2011–2016. EBioMedicine 2019; 41:488–96. [PubMed: 30846392]

33. Kretz CB, Retchless AC, Sidikou F, et al. Whole-genome characterization of epidemic *Neisseria meningitidis* serogroup C and resurgence of serogroup W, Niger, 2015. Emerg Infect Dis 2016; 22:1762–8. [PubMed: 27649262]

34. Broome CV, Rugh MA, Yada AA, et al. Epidemic group C meningococcal meningitis in Upper Volta, 1979. Bull World Health Organ 1983; 61:325–30. [PubMed: 6345014]

35. Mustapha MM, Marsh JW, Harrison LH. Global epidemiology of capsular group W meningococcal disease (1970–2015): multifocal emergence and persistence of hypervirulent sequence type (ST)-11 clonal complex. Vaccine 2016; 34:1515–23. [PubMed: 26876439]

36. Retchless AC, Hu F, Ouedraogo AS, et al. The establishment and diversification of epidemic-associated serogroup W meningococcus in the African Meningitis Belt, 1994 to 2012. mSphere 2016; 1:e00201–16. [PubMed: 27904879]

37. Feagins AR, Vuong J, Fernandez K, et al. The strengthening of laboratory systems in the meningitis belt to improve meningitis surveillance, 2008–2018: a partners' perspective. J Infect Dis 2019; 220(Suppl 4):S175–81. [PubMed: 31671436]

38. LaForce FM, Kulkarni P. Development update on a new African pentavalent ACWYX conjugate vaccine. In: Meningitis Vaccine Project Closure Conference; 2016; Addis Ababa, Ethiopia.

39. Alderson MR, LaForce FM, Meulen AS, Hwang A, Preziosi MP, Klugman KP. Eliminating meningococcal epidemics from the African meningitis belt: the case for advanced prevention and control using next generation meningococcal conjugate vaccines. J Infect Dis 2019; 220(Suppl 4):S274–8. [PubMed: 31671447]

A

B
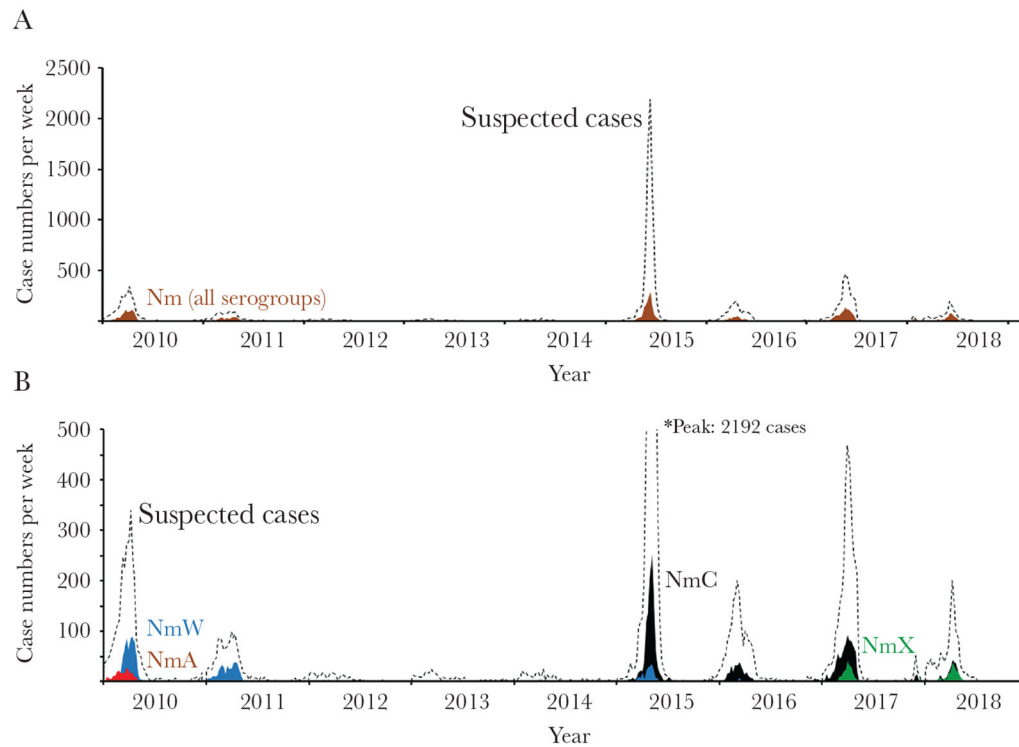
Figure 1.
Suspected meningitis cases and confirmed meningococcal meningitis cases by epidemiologic week, Niger, 2010–18. Suspected cases were compared with all meningococcal meningitis cases (A) and with *Neisseria meningitidis* (Nm) cases classified by serogroup (B). Suspected cases are denoted by the dotted lines, Nm serogroup W (NmW) cases are shown in blue, NmA cases are shown in red, NmC cases are shown in black, NmX cases are shown in green, and all Nm serogroups combined are shown in brown. In B, the * denotes that the suspected cases peaked in 2015 at week 19, with 2192 suspected cases. For 2018, only cases detected in epidemiologic weeks 1–28 are shown.
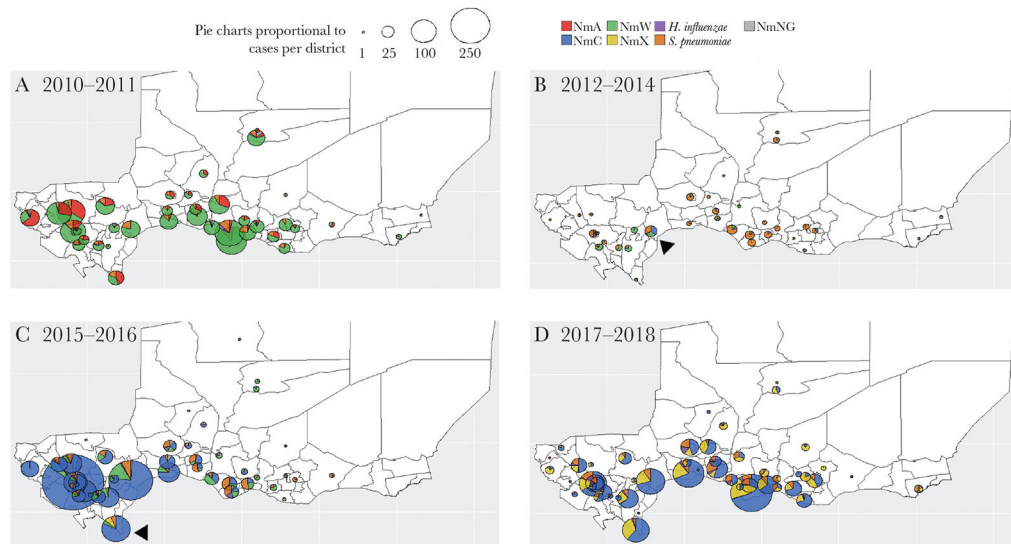
Figure 2.
Confirmed meningitis cases by district, pathogen, and years. The number of confirmed cases detected in each district during 2010–2011 (a), 2012–2014 (B), 2015–2016 (C), and 2017–2018 (D) are depicted as a proportional pie chart. Each pathogen or *Neisseria meningitidis* serogroup is represented by a different color, and the pie chart size reflects the number of cases. The majority of confirmed cases are detected in the southern and western regions of Niger, and this has been consistent over time. The predominant serogroup and causative pathogen has varied widely across multiple years, with nationwide transitions between serogroups observed every few years. The arrowheads denote the cluster of NmC cases detected in the Dogon-Doutchi district in 2014 (B) and the NmX cluster in the Gaya district in 2016 (C). Both NmC and NmX were detected in the majority of districts during the years following these initial clusters.
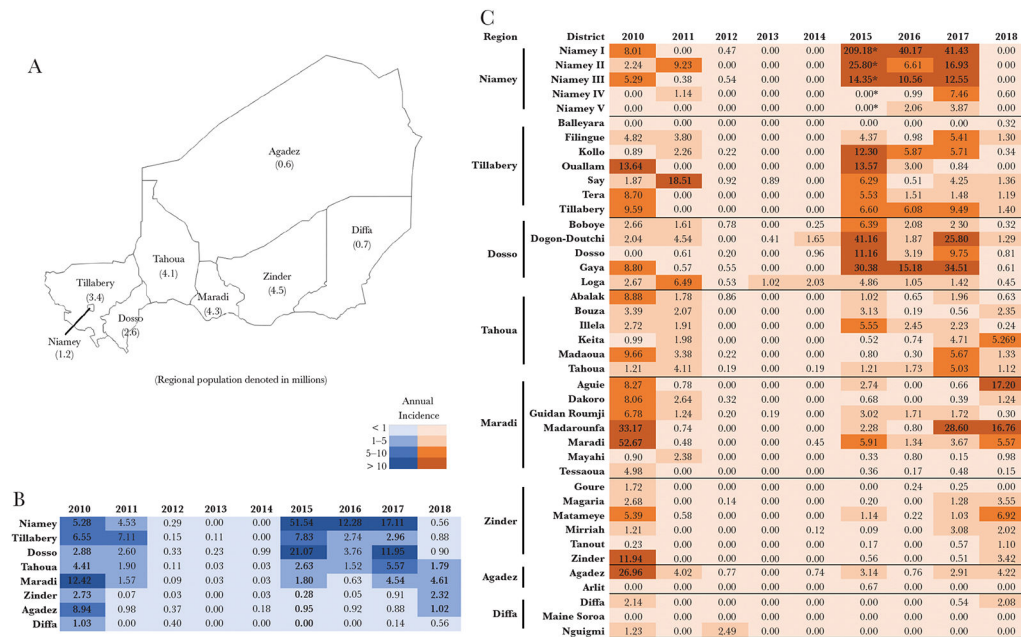
Figure 3.

Annual incidence of meningococcal meningitis by region and district. (A) The regional map of Niger. The 2018 population (represented in millions and rounded to the nearest 100 000) is denoted in parentheses for each region. By region (B) and district (C), the annual incidence of *Neisseria meningitidis* cases (all serogroups) in cases per 100 000 are depicted as heat maps. The data for 2018 only includes cases from epidemiologic weeks 1–28. *, The high disease burden in the region of Niamey during the 2015 outbreak made district identification of laboratory-confirmed cases challenging, so district-level incidences during this year may not reflect true geographic association.

B

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Niamey	5.28	4.53	0.29	0.00	0.00	51.54	12.28	17.11	0.56
Tillabery	6.55	7.11	0.15	0.11	0.00	7.83	2.74	2.96	0.88
Dosso	2.88	2.60	0.33	0.23	0.99	21.07	3.76	11.95	0.90
Tahoua	4.41	1.90	0.11	0.03	0.03	2.63	1.52	5.57	1.79
Maradi	12.42	1.57	0.09	0.03	0.03	1.80	0.63	4.54	4.61
Zinder	2.73	0.07	0.03	0.00	0.00	0.28	0.05	0.91	2.32
Agadez	8.94	0.98	0.37	0.00	0.18	0.95	0.92	0.88	1.02
Diffa	1.03	0.00	0.40	0.00	0.00	0.00	0.00	0.14	0.56

C

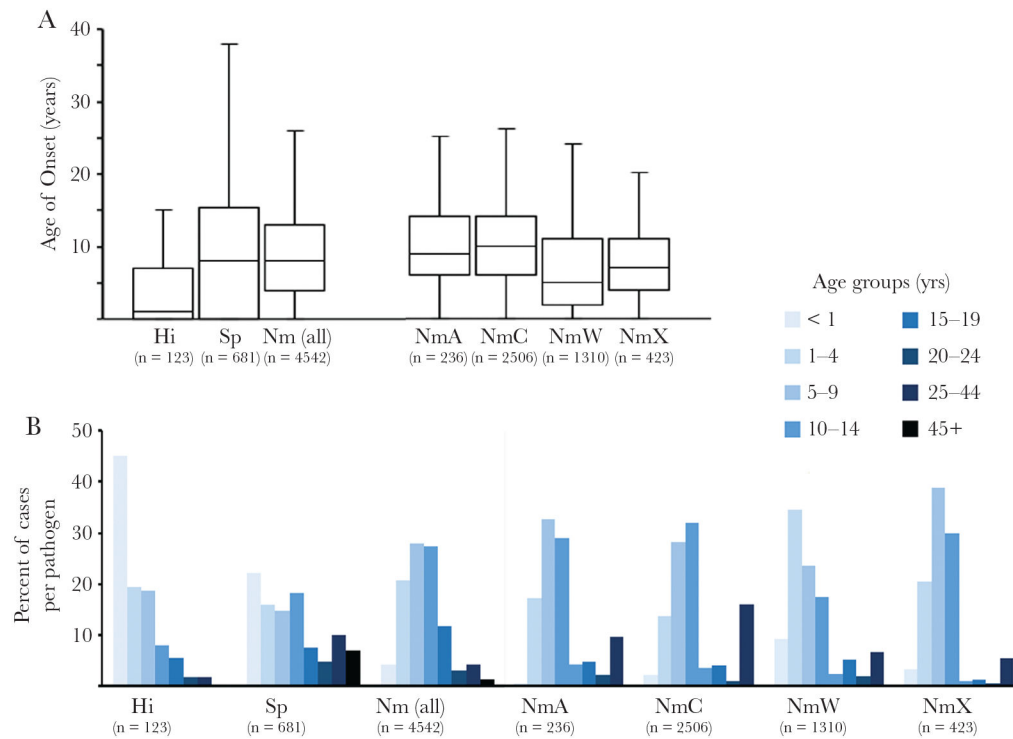| Region	District	2010	2011	2012	2013	2014	2015	2016	2017	2018
Niamey	Niamey I	8.01	0.00	0.47	0.00	0.00	209.18*	40.17	41.43	0.00
	Niamey II	2.24	9.23	0.00	0.00	0.00	25.80*	6.61	16.93	0.00
	Niamey III	5.29	0.38	0.54	0.00	0.00	14.35*	10.56	12.55	0.00
	Niamey IV	0.00	1.14	0.00	0.00	0.00	0.00*	0.99	7.46	0.60
	Niamey V	0.00	0.00	0.00	0.00	0.00	0.00*	2.06	3.87	0.00
Tillabery	Balleyara	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.32
	Filingue	4.82	3.80	0.00	0.00	0.00	4.37	0.98	5.41	1.30
	Kollo	0.89	2.26	0.22	0.00	0.00	12.30	5.87	5.71	0.34
	Ouallam	13.64	0.00	0.00	0.00	0.00	13.57	3.00	0.84	0.00
	Say	1.87	18.51	0.92	0.89	0.00	6.29	0.51	4.25	1.36
	Tera	8.70	0.00	0.00	0.00	0.00	5.53	1.51	1.48	1.19
	Tillabery	9.59	0.00	0.00	0.00	0.00	6.60	6.08	9.49	1.40
Dosso	Boboye	2.66	1.61	0.78	0.00	0.25	6.39	2.08	2.30	0.32
	Dogon-Doutchi	2.04	4.54	0.00	0.41	1.65	41.16	1.87	25.80	1.29
	Dosso	0.00	0.61	0.20	0.00	0.96	11.16	3.19	9.75	0.81
	Gaya	8.80	0.57	0.55	0.00	0.00	30.38	15.18	34.51	0.61
	Loga	2.67	6.49	0.53	1.02	2.03	4.86	1.05	1.42	0.45
Tahoua	Abalak	8.88	1.78	0.86	0.00	0.00	1.02	0.65	1.96	0.63
	Bouza	3.39	2.07	0.00	0.00	0.00	3.13	0.19	0.56	2.35
	Illela	2.72	1.91	0.00	0.00	0.00	5.55	2.45	2.23	0.24
	Keita	0.99	1.98	0.00	0.00	0.00	0.52	0.74	4.71	5.269
	Madaoua	9.66	3.38	0.22	0.00	0.00	0.80	0.30	5.67	1.33
	Tahoua	1.21	4.11	0.19	0.00	0.19	1.21	1.73	5.03	1.12
Maradi	Aguie	8.27	0.78	0.00	0.00	0.00	2.74	0.00	0.66	17.20
	Dakoro	8.06	2.64	0.32	0.00	0.00	0.68	0.00	0.39	1.24
	Guidan Roumji	6.78	1.24	0.20	0.19	0.00	3.02	1.71	1.72	0.30
	Madarounfa	33.17	0.74	0.00	0.00	0.00	2.28	0.80	28.60	16.76
	Maradi	52.67	0.48	0.00	0.00	0.45	5.91	1.34	3.67	5.57
	Mayahi	0.90	2.38	0.00	0.00	0.00	0.33	0.80	0.15	0.98
	Tessaoua	4.98	0.00	0.00	0.00	0.00	0.36	0.17	0.48	0.15
Zinder	Goure	1.72	0.00	0.00	0.00	0.00	0.00	0.24	0.25	0.00
	Magaria	2.68	0.00	0.14	0.00	0.00	0.20	0.00	1.28	3.55
	Matameye	5.39	0.58	0.00	0.00	0.00	1.14	0.22	1.03	6.92
	Mirriah	1.21	0.00	0.00	0.00	0.12	0.09	0.00	3.08	2.02
	Tanout	0.23	0.00	0.00	0.00	0.00	0.17	0.00	0.57	1.10
	Zinder	11.94	0.00	0.00	0.00	0.00	0.56	0.00	0.51	3.42
Agadez	Agadez	26.96	4.02	0.77	0.00	0.74	3.14	0.76	2.91	4.22
	Arlit	0.00	0.00	0.00	0.00	0.00	0.67	0.00	0.00	0.00
Diffa	Diffa	2.14	0.00	0.00	0.00	0.00	0.00	0.00	0.54	2.08
	Maine Soroa	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Nguigmi	1.23	0.00	2.49	0.00	0.00	0.00	0.00	0.00	0.00

Figure 4.
Distribution for the age of onset for each meningitis pathogen and *Neisseria meningitidis* (Nm) serogroup, Niger 2010–2018. (A) Boxplot depicting the median age of onset in years for each pathogen and Nm serogroup. The χ^2 tests of independence determined that the age of onset and the causative pathogen were significantly associated (*P* < .001). (B) Bargraph depicting the percentage of cases for each pathogen (or *N meningitis* serogroup) that occurred in 8 different age groups (<1, 1–4, 5–9, 10–14, 15–19, 20–24, 25–44, or 45+ years at age of onset).

Table 1.

Suspected and Confirmed[a] Meningitis Cases by Year, Niger, 2010–2018

Year	Suspected Cases	Deaths	CFR[b]	No. CSFs tested	CSFs Positive for Nm, Sp, or Hi	Nm (All)	NmA	NmC	NmW	NmX	NmNG	Sp	Hi	No. Districts That Reached Epidemic Threshold[c]
2010	3025	265	8.8%	2375	1033 (43.5%)	919	242	0	664	1	12	91	23	4
2011	1307	160	12.2%	1034	480 (46.4%)	408	5	0	399	1	3	70	2	0
2012	294	55	18.7%	301	63 (20.9%)	26	0	0	23	0	3	35	2	0
2013	341	51	15.0%	278	46 (16.5%)	10	0	0	10	0	0	31	5	0
2014	337	48	14.2%	398	81 (20.4%)	26	0	9	16	0	1	48	7	0
2015	8991	779	8.7%	4638	1563 (33.7%)	1429	0	1181	204	1	43	121	12	16
2016	1969	146	7.4%	2090	518 (24.8%)	399	0	352	27	15	5	98	21	3
2017	3506	232	6.6%	3652	1269 (34.7%)	1075	0	847	4	223	1	145	48	4
2018[d]	1372	106	7.7%	1129	541 (479%)	449	0	238	2	206	3	81	9	1
All Years	21 142	1842	8.7%	15 884	5594 (35.2%)	4741	247	2628	1349	447	71	721	129	N/A

Abbreviations: CFR, case fatality ratio; CSF, cerebrospinal fluid; Hi, *Haemophilus influenzae*; N/A, not applicable; Nm, *Neisseria meningitidis*; PCR, polymerase chain reaction; Sp. *Streptococcus pneumoniae*.

NOTE: The confirmed cases by pathogen for 2010–2015 have been reported previously [22].

[a] Confirmed cases were defined by either culture or PCR-based methods as Nm, Sp, or Hi.

[b] Case fatality ratios were calculated as the proportion of known deaths among suspected cases reported through the aggregate meningitis surveillance system.

[c] Epidemic threshold defined as 10 or more suspected cases per 100 000 population per week [18].

[d] Only cases reported during epidemiologic weeks 1–28 are reported (collection date January 1-July 15, 2018).

Table 2.

Annual Meningitis Incidence in Cases per 100 000 by Pathogen, Niger, 2010–2018[a]

Suspected or Confirmed Cases	2010	2011	2012	2013	2014	2015	2016	2017	2018
Suspected Cases	19.67	8.31	1.81	2.03	2.00	48.52	10.23	16.98	6.39
Neisseria meningitidis ([Nm] all)	5.98	2.59	0.16	0.06	0.15	7.71	2.07	5.21	2.09
NmA	1.57	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NmC	0.00	0.00	0.00	0.00	0.05	6.37	1.83	4.11	1.11
NmW	4.32	2.54	0.14	0.06	0.09	1.10	0.14	0.02	0.01
NmX	0.01	0.01	0.00	0.00	0.00	0.01	0.08	1.08	0.96
Streptococcus pneumoniae	0.59	0.44	0.22	0.18	0.28	0.66	0.51	0.70	0.39
Haemophilus influenzae	0.15	0.01	0.01	0.03	0.04	0.06	0.11	0.23	0.04

[a]The annual incidence by species for 2010–2015 was reported previously [22].

Table 3.

Molecular Profile of 2016 and 2017 Isolates, Niger

Sequence Type (ST-):PorA Type:FetA Type	No. of 2016 Isolates	No. of 2017 Isolates	Total
NmX: Clonal Complex 181	1	7	8
ST-181:P1-2,10-1:F1-31	1	0	1
ST-181:P1.5-1,10-1:F1-31	0	6	6
ST-14014:P1.5-1,10-1:F5-12	0	1	1
NmC: Clonal Complex 10217	101	30	131
ST-10217:P1.21-15,16:F1-7	101	21	122
ST-14016:P1.21-15,16:F1-7	0	8	8
ST-9367:P1.21-15,16-46:F1-7	0	1	1
NmW: Clonal Complex 11	22	2	24
ST-11:P1.5,2:F1-1	16	2	16
ST-11:P1.5,2:F1-84	6	0	6