MenAfriCar Consortium, ; , COLLABORATORS; Ali, O; Aseffa, A; Bedru Omer, A; Lema, Ts; Moti Demissie, T; Tekletsion, Y; Worku, A; Guebre Xabher, H; Yamuah, L; Boukary, RM; Collard, JM; Dano, ID; Habiboulaye, I; Issaka, B; Jusot, JF; Ousmane, S; Rabe, I; Daugla, DM; Gami, JP; Gamougam, K; Mbainadji, L; Naibei, N; Narb, M; Toralta, J; Berthe, A; Diallo, K; Keita, M; Coulibaly, A; Onwuchekwa, U; Sow, SO; Tamboura, B; Traore, A; Toure, A; Clark, T; Mayer, L; Amodu, M; Beida, O; Gadzama, G; Omotara, B; Zailani, S; Yahya, Sh; Chandramohan, D; Greenwood, BM; Hassan-King, M; Manigart, O; Nascimento, M; Stuart, JM; Woukeu, A; Basta, NE; Bai, X; Borrow, R; Findlow, H; Alavo, S; Bassene, H; Diallo, A; Dieng, M; Doucour, S; Gomis, JF; Ndiaye, A; Sokhna, Ch; Trape, JF; Bugri, A; Forgor, A; Hodgson, A; Osei, I; Quaye, SL; Williams, J; Wontuo, P; Irving, T; Trotter, CL; Karachaliou, A; Bennett, J; Hill, D; Harrison, O; Maiden, MC; Rebbetts, L; Watkins, E (2016) Household transmission of Neisseria meningitidis in the African meningitis belt: a longitudinal cohort study. The Lancet Global health, 4 (12). e989-e995. ISSN 2214-109X DOI: https://doi.org/10.1016/S2214-109X(16)30244-3

Household transmission of *Neisseria meningitidis* in the African meningitis belt: a longitudinal cohort study

MenAfriCar Consortium*

Summary

Background Information on transmission of meningococcal infection in the African meningitis belt is scarce. We aimed to describe transmission patterns of *Neisseria meningitidis* (meningococcus) in households in the African meningitis belt.

Methods Cross-sectional carriage surveys were done in seven African meningitis belt countries (Chad, Ethiopia, Ghana, Mali, Niger, Nigeria, and Senegal) between Aug 1, 2010, and Oct 15, 2012. Meningococcal carriers identified in these surveys and all available people in their households were recruited into this longitudinal cohort study. We took pharyngeal swabs at first visit and took further swabs twice a month for 2 months and then monthly for a further 4 months. We used conventional bacteriological and molecular techniques to identify and characterise meningococci. We estimated the rates of carriage acquisition and recovery using a multi-state Markov model.

Findings Meningococci were isolated from 241 (25%) of 980 members of 133 households in which a carrier had been identified in the cross-sectional survey or at the first household visit. Carriage was detected subsequently in another household member who was not an index carrier in 75 households. Transmission within a household, suggested by detection of a further carrier with the same strain as the index carrier, was found in 52 of these 75 households. Children younger than 5 years were the group that most frequently acquired carriage from other household members. The overall individual acquisition rate was 2·4% (95% CI 1·6–4·0) per month, varying by age and household carriage status. The mean duration of carriage was 3·4 months (95% CI 2·7–4·4).

Interpretation In the African meningitis belt, transmission of meningococci within households is important, particularly for young children, and periods of carriage are usually of short duration.

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Introduction

The vast majority of infections with *Neisseria meningitidis* (meningococcus) result in asymptomatic or mildly symptomatic pharyngeal carriage rather than invasive disease. Study of carriage is therefore essential to understand patterns of infection in different epidemiological situations and to develop evidence-based strategies for vaccination. Data for vaccination strategies are particularly important because of the availability of protein-polysaccharide conjugate vaccines, which, unlike plain polysaccharide vaccines,[1] are able to reduce carriage and thus transmission, generating herd protection.[2]

Many cross-sectional studies of meningococcal carriage have been done in high-income countries,[3] but few studies have been undertaken of pathways of transmission. Meningococci are transmitted from the pharynx of one person to another via respiratory and throat secretions. Military studies have emphasised the importance of close personal contact in carriage acquisition.[3–7] In the UK, rapid acquisition of meningococcal carriage was reported in university students at the start of term and was associated with smoking, drinking, and intimate kissing.[4,5] Carriage prevalence in contacts of people with meningococcal disease is higher than in general population,[6] but we are aware of only two

longitudinal household carriage studies done in high-income countries.[7,8]

Even less is known about the pattern of transmission of meningococcal infection in the African meningitis belt, where epidemics of meningococcal disease continue to occur.[9] In a 2007 Review[10] we showed that in several surveys, carriage peaked in older children and young adults. Subsequent large cross-sectional carriage surveys in Africa have shown carriage to be consistently highest in children aged 5–14 years,[11] with increased carriage rates in close contacts of people with the disease, suggesting that transmission within households is important.[12] The few longitudinal studies of carriage undertaken in the African meningitis belt have generally reported changes in trends over time at a population level rather than at the individual level, and thus were unable to estimate acquisition and the duration of carriage.[13–17] We are aware of only one previous study that has investigated patterns of transmission of meningococci within households in the African meningitis belt.[18] A 1976 study in northern Nigeria that took place over 11 months found that the duration of carriage was approximately 3 months for all meningococci and 1 month for serogroup A meningococci. Children younger than 10 years were identified as first carriers in a

Research in context

Evidence before this study
We searched PubMed with the terms ([meningococcal OR *Neisseria*] AND [community OR household] AND carriage AND Africa) with no date or language restrictions up to Oct 21, 2015, and searched for early government reports from African meningitis belt countries in the personal archive of BG to identify longitudinal studies of meningococcal carriage in African households. Only one relevant study was identified, which took place in 1976 in northern Nigeria over the course of 11 months. This study followed over 500 residents, estimating the duration of carriage to be around 3 months. Expanding our search to any location, we identified only two further longitudinal household carriage studies, both from the USA.

Added value of this study
To our knowledge this is the first multicentre and multicountry longitudinal meningococcal carriage study.

We address an important knowledge gap by describing the duration and acquisition of meningococci and patterns of transmission in households across the African meningitis belt.

Implications of all the available evidence
Results from this, and the previous study in Nigeria, show that the duration of meningococcal carriage is shorter in the African meningitis belt than in high-income countries. Within-household acquisition is important, with children aged 5–14 years being a common source of transmission, particularly to younger siblings. Chemoprophylaxis to household contacts of an individual with meningococcal disease, a public health intervention not widely used in Africa, should be emphasised as an additional meningitis prevention tool.

household significantly more frequently than were adults, and men were more likely to introduce meningococci into a household than were women.

Because of the paucity of information on meningococcal carriage in the African meningitis belt, members of the African Meningococcal Carriage Consortium (MenAfriCar)[19] undertook a series of carriage surveys aiming to better understand patterns of meningococcal carriage and the impact of a new serogroup A meningococcal conjugate vaccine, MenAfriVac (Serum Institute of India PVT, Pune, India).[20] From Aug 1, 2010, to July 8, 2012, the consortium did 20 cross-sectional carriage surveys in seven African meningitis belt countries involving the collection of more than 48 000 pharyngeal swabs.[11] During these surveys, households in which a meningococcal carrier was identified were recruited for a longitudinal study of household meningococcal transmission; here we report the results of this longitudinal study.

Methods

Cross-sectional carriage surveys

The cross-sectional carriage surveys were conducted in seven countries in the African meningitis belt (Chad, Ethiopia, Ghana, Mali, Niger, Nigeria, and Senegal) in partnership with a national research institution, during the rainy season of 2010 (August to December), the rainy season of 2011 (July to November), and the dry season of 2012 (February to July). Details of the survey methods have been published previously.[19] The sampling frame used was either an updated, ongoing demographic surveillance system (DSS) in sites where a DSS existed or a household census undertaken specifically for the project. Study households were selected by simple random sampling from the DSS or census. Within selected households, individuals stratified by age group (<1 years, 1–4 years, 5–14 years, 15–29 years, and 30 years

or older) were randomly selected until the required sample size had been reached (surveys varied in target size from 2000–6000). Five surveys undertaken in Chad, Mali, and Niger were conducted after the introduction of vaccination with MenAfriVac in participants aged 1–29 years. The MenAfriCar studies were registered with ClinicalTrials.gov, number NCT01119482.

Household surveys

Longitudinal household surveys were triggered by the identification of a putative carrier during a cross-sectional survey. Within 4 weeks of the identification of a carrier, all members of the carrier's household were invited to participate in the follow-up study. Swabs (sterile, dacron-tipped swabs with plastic shafts) of both the posterior pharynx and tonsils[21] were collected from all consenting members of the household at the first visit and subsequently twice a month for 2 months and then monthly for a further 4 months up to a maximum of nine swabs per person. A questionnaire that asked about the characteristics of the household was administered to the head of the household and a detailed socioeconomic questionnaire was administered to individual participants. Height and weight of each household contact older than 6 months of age were measured, and a pharyngeal swab and a 5 mL blood sample were obtained. On subsequent visits, pharyngeal swabs were taken and a short questionnaire was administered to obtain information on risk factors, including MenAfriVac immunisation status, which might have changed since the last visit.

Identification of a carrier at the study site depended upon conventional microbiology and serogrouping with an agglutination assay.[19] However, confirmatory tests performed using molecular methods undertaken at the Department of Zoology at the University of Oxford (UK) resulted in some isolates being reclassified as capsule-

null organisms and others being not confirmed as meningococci; thus some households were recruited in whom no meningococcal carrier was identified on confirmatory testing. These households formed a control group.

The study was approved by the ethics committee of the London School of Hygiene and Tropical Medicine and by the relevant authorities in each African country (appendix). The head of the household or another responsible adult gave verbal informed consent for the household to be included in the study. Each individual recruited within that household gave written informed consent (signature or thumbprint); a parent or guardian gave written consent for children younger than 18 years, with children older than 12 years additionally asked to give written assent.

Laboratory procedures

Pharyngeal swabs were plated directly onto modified Thayer-Martin agar plates in the field and taken to the laboratory within 6 h of collection where they were incubated for 24–48 h at 37°C in 5% CO_2. Suspected *N meningitidis* colonies identified on the plates were subcultured onto blood agar plates and tested using an oxidase test, followed by a Gram stain. All oxidase-positive, Gram-negative diplococci underwent biochemical testing and those identified as *N meningitidis* on these tests underwent slide-agglutination serogrouping using antisera for serogroups A, W, X and Y, which we had identified *a priori* as the likely most prevalent serogroups. All non-agglutinated strains were classified as non-groupable (NG) by this method.

To confirm the identity of *Neisseria* spp identified by culture techniques, an aliquot of boiled suspensions of Gram-negative oxidase-positive bacteria was sent to the University of Oxford for molecular analysis as described previously.[19] Amplification and sequencing of the *rplF* gene was used to confirm the presence of, and to differentiate between, *Neisseria* spp.[22] Confirmed *N meningitidis* were further characterised by genogroup (including capsule null [cnl] [23]) and *porA* genotype.

Statistical analysis

There were few studies on the rate of meningococcal acquisition in household contacts in Africa to assist in the design of the household studies, but informed presumption was that the household acquisition rate would be around 1% per month.[18] We decided pragmatically that 25 households per survey in rural and urban areas would be the maximum number that the field teams had the capacity to recruit and follow-up. Initially, restriction of recruitment to households of a serogroup A carrier was planned, but because of the paucity of carriers of this serogroup,[11] recruitment was expanded to include carriage of other capsulated meningococci.

Acquisition of carriage was initially defined as a newly identified episode of carriage, preceded by at least one

negative swab (appendix). We estimated the rates of carriage acquisition (λ) and loss (ν) using a two-state (infected and uninfected) hidden Markov model, implemented using the MSM package in R version 3.2.1.[24] We estimated the mean duration of carriage as 1/ν. The observations were assumed to be subject to misclassification error and so we used the same statistical package to estimate sensitivity and specificity of swabbing. We investigated covariates affecting transition intensities, including age, sex and whether an individual was from a household with at least one index carrier. We compared different (nested) models with and without covariates using the likelihood ratio statistic. Data from individuals with only one swab through the course of the study were uninformative and thus we excluded these individuals from this analysis. We managed data using the TeleForm system version 10.4.1 (Autonomy,
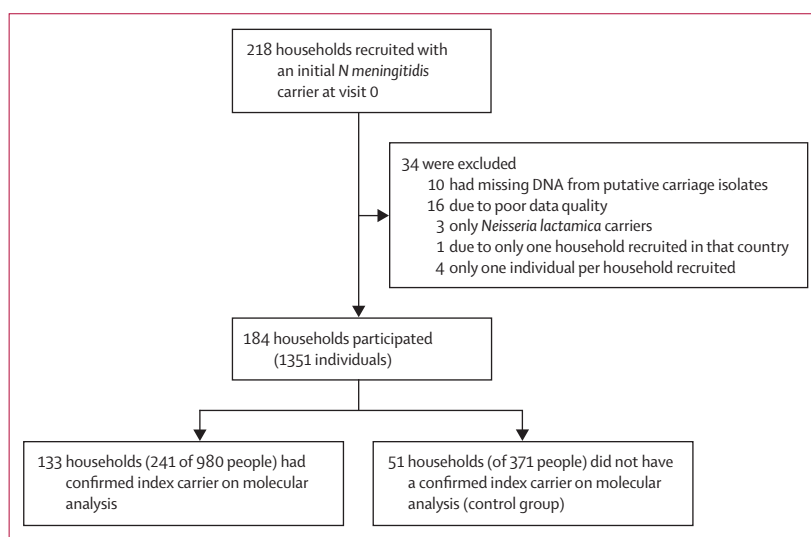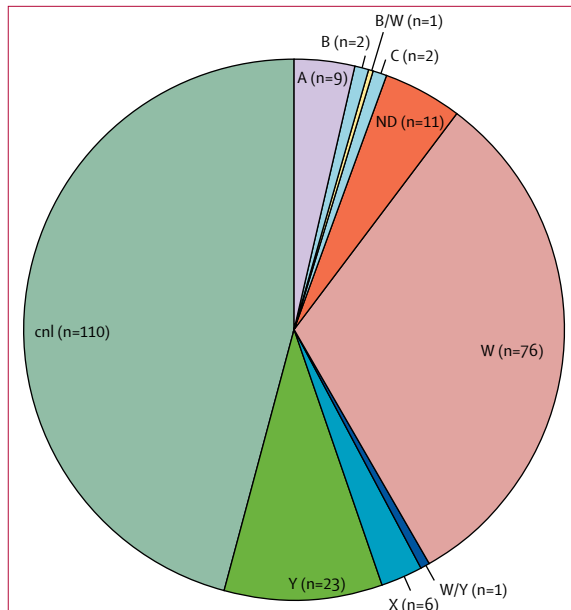
Figure 1: **Study profile**

	2010 (HH1)	2011 (HH2)	2012 (HH3)	Total	Index carrier of *Neisseria meningitidis* in household	
					Yes	No
Chad	0	20*	0*	20	14	6
Ethiopia	20	15	10	45	34	11
Ghana	0	13	9	22	18	4
Mali	22	10*	0*	32	9	23
Niger	40	20*	0*	60	54	6
Nigeria	0	0	0	0	0	0
Senegal	0	5	0	5	4	1
Total	82	83	19	184	133	51

HH=household. *Indicates surveys performed after or during the introduction of MenAfriVac.

Table 1: **Household studies by country and survey year and presence of an index carrier of *Neisseria meningitidis* after full molecular characterisation**

Figure 2: Genogroup of meningococci carried by 241 index carriers
cnl=capsule null meningococci. ND=not determined.

	Acquisition rate per month (%)	Duration of carriage (months)
Overall	2·4% (1·6–4·0)	3·4 (2·7–4·4)
Age group		
0–4 year olds		
Index	7·1% (4·3–11·9)	2·0 (1·3–3·2)
Control	1·5% (0·4–5·1)	1·7 (0·8–3·6)
5–14 year olds		
Index	4·9% (2·9–8·0)	3·8 (2·8–5·0)
Control	1·0% (0·3–3·5)	3·1 (1·6–5·9)
15–29 year olds		
Index	3·5% (1·9–6·3)	5·2 (3·5–7·7)
Control	0·7% (0·2–2·6)	4·2 (2·0–8·9)
30 years and older		
Index	1·6 (0·7–3·8)	4·4 (2·9–6·6)
Control	0·3% (0·1–1·4)	3·6 (1·6–7·7)

Data in parentheses are 95% CI.

Table 2: Rates of acquisition and duration of carriage estimated using a hidden Markov model, with age group and household type included as covariates

Cambridge UK),[19] with a separate database module to link the main study database with genetic laboratory results from the Oxford Bacterial Isolate Genome Sequence (BIGS) database.[25] We used Stata version 12.0 for data cleaning and descriptive analyses.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
218 households were recruited to the study (figure 1). 1351 individuals from 184 households participated in the study (appendix); no data were available for Nigeria. 633 individuals (47%) reported that they had not received a meningitis vaccine in the last 3 years, 502 (37%) reported that they had recently been vaccinated (224 of whom were vaccinated again during the study), and 216 (16%) individuals reported being new vaccine recipients during the course of the study. Most reports of previous vaccination (89%) were recorded in Chad, Mali, and Niger, where mass vaccination with MenAfriVac in participants aged 1–29 years was being undertaken at the time of the follow-up study.

133 (72%) of the 184 households had a confirmed index carrier at visit 0 or visit 1 or both (980 people in household), leaving 51 (28%) households (of 371 people) in which the initial report of isolation of *N meningitidis* was not confirmed on molecular analysis (table 1); these households formed the control group that was used to study external acquisitions.

241 (25%) individuals in the 133 households were index carriers (carrier at visit 0 or 1). 60 households contained more than one index carrier (range one to eight carriers per household). The median age of index carriers was 12 years (IQR 8–23 years) and 133 (55%) were male. cnl was the most common genogroup identified, followed by genogroup W (figure 2). 69 individuals were carriers at both the cross-sectional recruitment visit (visit 0) and first household visit (visit 1). Among these, 56 (81%) carried strains with the same genogroup and *porA* alleles at both visits, and only three (4%) carried definitively different strains between visit 0 and visit 1.

During the course of the 6 month follow-up period, 9809 swabs were obtained from the 1351 participants; 63% individuals provided eight or nine swabs and 86% of individuals provided at least five swabs. The median number of swabs obtained per participant was eight (IQR seven to nine). This number was similar in households with and without an index carrier. The median duration of follow-up from first to last swab was 6·1 months (IQR 5·2–6·6). None of the participants who became a carrier during the period of follow-up are known to have developed meningitis. None of the study sites reported an outbreak of meningitis during the longitudinal follow-up period.

152 (21%) of 739 individuals living with index carriers became a carrier during the course of follow-up. Individuals acquiring carriage were mainly children: 45 (30%) children aged 0–4 years, 52 (34%) children aged 5–14 years, 31 (20%) adults aged 15–29 years, and 24 (16%) adults aged 30 years and older. Subsequent carriers were detected in 75 (56%) of 133 households.

Individual	Household	Baseline vaccine status	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
1	1	0						Vac				
2	2	Vac										
3	3	0										
4	4	0							Vac			
5	5	0							Vac			
6	5	0							Vac			
7	6	0							Vac			
8	6	0							Vac			
9	7	0						Vac				
10	8	0							Vac			
11	8	0							Vac			
12	9	0						Vac				
13	9	0										
14	10	0						Vac				

Figure 3: **Follow-up of serogroup A meningococci carriers and MenAfriVac vaccine status**
Orange indicates group A carriage, yellow indicates carriage of non-A meningococci, blue indicates no carriage, and grey indicates missing swab. Vac=vaccinated.

Among the 371 people in 51 households without an index carrier, 35 (9%) people in 17 households became a carrier during the course of the study. 25 individuals were identified as the first carrier in these households (ie, the person introducing the strain into the household), of whom 15 (60%) were female and ten (40%) male; three (12%) individuals were younger than 5 years, 13 (52%) aged 5–14 years, six (24%) aged 15–29 years, and three (12%) aged 30 years and older.

The overall acquisition rate and duration of carriage, together with misclassification probabilities, were estimated using a hidden Markov model. The best fitting model was one that included age group and household index status as covariates. The overall estimated acquisition rate of carriage in this model was 2·4% per month (95% CI 1·6–4·0; table 2). Acquisition rates were highest in the youngest children and lowest among older adults (table 2). Acquisition rates were estimated to be between four-times and five-times higher in each age group among households with an index carrier than in those without an index carrier. The estimated mean duration of carriage was 3·4 months overall (95% CI 2·7–4·4) and was lowest in children under 5 years of age (table 2).

Only 20 individuals had a positive swab on six or more occasions: six individuals with group W, six with cnl, four with group Y, one with group B, and three mixed carriers. The estimated duration of carriage in these 20 individuals was 5·8 months (assuming that a single negative swab bordered by positive swabs was a false negative).

The specificity of swabbing in the full dataset was estimated to be very high at 99·2% (95% CI 98·5–99·6), whereas the sensitivity of swabbing was estimated to be much lower at 57·8% (53·5–62·0).

Data were analysed further according to the strain type (genogroup and *porA*) of meningococci within the household. Among the 75 households with both an index carrier and later acquisitions, the index strain was acquired by another household member in 52 households, and a similar strain (with incomplete typing) was acquired in a further five households. Where direct family relationships could be elucidated in these transmission events, sibling to sibling transmission was most common (27 events), followed by child to parent (ten) and then parent to child (six). In the subset of these events where the subsequent carrier was a young child (aged <4 years), most children appeared to have acquired carriage from a sibling (13 of 16 events) rather than a parent (three of 16 events). In 39 households, a completely different strain to the index carrier was acquired by a subsequent carrier.

There was insufficient power to examine the effect of MenAfriVac on acquisition or loss of group A carriage because few group A carriers were identified during the cross-sectional studies.[11] However, 11 individuals identified as group A carriers were vaccinated during the course of follow-up and no further group A carriage was detected after vaccination (figure 3).

Discussion

In 184 households across the African meningitis belt, the overall rate of acquisition of meningococci was 2·4% per month. Within household transmission was important, especially among children aged less than 5 years, who were the group most likely to acquire carriage from other household members. However, acquisition of carriage outside the household was evident from detection of new carriers within households without an index carrier and from examination of strain types. The average duration of carriage was 3·4 months, shorter than is usually found in Europe,[21] and persistent carriers were uncommon. Few previous studies have examined the patterns of

household transmission of meningococci with which our findings can be compared.

The strengths of this study are that it was conducted in six countries across the African meningitis belt, involved both urban and rural populations, included participants across the age spectrum, achieved a high follow-up rate, and used standardised field and laboratory protocols. Thus, the findings are likely to be representative of the pattern of transmission of *N meningitidis* across the African meningitis belt. However, it should be noted that the households recruited were not evenly balanced between countries and survey periods (table 1).

Although common protocols and microbiological methods were used across the different study sites, and characterisation of *Neisseria* spp was confirmed in Oxford using DNA samples, there might have been some differences between laboratories in their ability to detect oxidase-positive Gram-negative diplococci. Additionally we assumed that carriage of the same strain as the index case represented within-household transmission but we cannot rule out external acquisition as the strain type might also have been circulating in the wider community. We also assumed that a newly identified episode of carriage represented acquisition. Due to the infrequent detection of group A carriage we were unable to determine the relative effects of vaccination on reducing the duration of carriage compared with preventing acquisition.[26] There was heterogeneity in carriage duration, with some long-term carriers identified. Index carriers in our study might have been biased towards having longer durations because these individuals would be more likely to be detected in a cross-sectional study than those with shorter duration of carriers; we were not able to adjust for this in our statistical model.

We have reported previously that the prevalence of carriage detected during cross-sectional surveys in African meningitis belt countries is generally lower than in high-income countries.[11] Although this might reflect a lower incidence of infection (perhaps predisposing to epidemics), the short duration of carriage identified in this study, and in the only other previous study of carriage duration in Africa,[18] will also affect prevalence. Why the duration of carriage would be less in the African meningitis belt than in high-income countries is uncertain. This finding could be a reflection of a higher background level of immunity, although this hypothesis would not fit with a predisposition to epidemics. An alternative explanation is inhibition by other bacteria present in the nasopharynx, and it is of note that the shortest duration of carriage in the MenAfriCar consortium study was in children younger than 5 years among whom carriage of *N lactamica* was highest.[27,28] *N lactamica* has recently been shown to inhibit colonisation with *N meningitidis* in young adults.[29] Another striking difference in carriage is that there is a similar prevalence in children and young adults in Africa[11] compared with marked peaks in older teenagers and adults in high-income countries.[3]

Widespread deployment of MenAfriVac has, so far, proved highly successful in suppressing outbreaks of epidemics caused by serogroup A meningococci. However, outbreaks due to other serogroups continue to occur, with the most recent example being the 2015 epidemic of serogroup C disease in Niger.[9] Until an affordable multivalent vaccine is available, other control measures will be needed. Our findings indicate that substantial spread of meningococci occurs within households so that prophylaxis of household contacts after a case of meningococcal meningitis, recommended policy in the meningitis belt outside epidemics,[30] could be given greater priority. However, given that acquisition of infection from outside of the household also occurs, vaccination of the whole population of affected communities will be needed to prevent transmission completely and the findings from this study will help to guide decisions on the age groups who should be given priority.

MenAfriCar consortium

Armauer Hansen Research Institute, Addis Ababa, Ethiopia—Oumer Ali, Abraham Aseffa (principal investigator), Ahmed Bedru Omer, Tsehaynesh Lema, Tesfaye Moti Demissie, Yenenesh Tekletsion, Alemayehu Worku, Haimanot Guebre Xabher (deceased), Lawrence Yamuah. Centre de Recherche Médicale et Sanitaire (CERMES), Niamey, Niger (Member of the International Network of Pasteur Institutes)—Rahamatou Moustapha Boukary, Jean-Marc Collard (principal investigator), Ibrahim Dan Dano, Ibrahim Habiboulaye, Bassira Issaka, Jean-François Jusot, Sani Ousmane, Issoufa Rabe. Centre de Support en Santé International (CSSI), N'Djamena, Chad—Doumagoum Moto Daugla (principal investigator), Jean Pierre Gami, Kadidja Gamougam, Lodoum Mbainadji, Nathan Naibei, Maxime Narbé, Jacques Toralta. Centre pour les Vaccins en Développement, Bamako, Mali—Abdoulaye Berthe, Kanny Diallo, Mahamadou Keita, Adama Coulibaly, Uma Onwuchekwa, Samba O Sow (principal investigator), Boubou Tamboura, Awa Traore, Aliou Toure. Centers for Disease Control, Atlanta, GA, USA—Tom Clark, Leonard Mayer. Department of Community Medicine, University of Maiduguri, Maiduguri, Nigeria—Mary Amodu, Omeiza Beida, Galadima Gadzama, Babatunji Omotara (principal investigator), Sambo Zailani, Shuaibu Yahya. Faculty of Infectious Disease, London School of Hygiene & Tropical Medicine, London, UK—Daniel Chandramohan, Brian M Greenwood (principal investigator), Musa Hassan-King, Olivier Manigart, Maria Nascimento, James M Stuart, Arouna Woukeu. School of Public Health, University of Minnesota, Minneapolis, MN, USA—Nicole E Basta. Public Health England Vaccine Evaluation Unit, Manchester, UK—Xilian Bai, Ray Borrow, Helen Findlow. Institut de Recherche pour le Développement, Dakar, Senegal—Serge Alavo, Hubert Bassene, Aldiouma Diallo (principal investigator), Marietou Dieng, Souleymane Doucouré, Jules François Gomis, Assane Ndiaye, Cheikh Sokhna, Jean François Trape. Navrongo Health Research Centre, Navrongo, Ghana— Akalifa Bugri (deceased), Abudulai Forgor (deceased), Abraham Hodgson (principal investigator), Isaac Osei, Stephen L Quaye, John Williams, Peter Wontuo. University of Bristol, UK—Thomas Irving. University of Cambridge, UK—Caroline L Trotter, Andromachi Karachaliou. University of Oxford, UK—Julia Bennett, Dorothea Hill, Odile Harrison, Martin C Maiden, Lisa Rebbetts, Eleanor Watkins.

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