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ORIGINAL PAPER

β-hemolytic streptococcal throat carriage and tonsillopharyngitis: a cross-sectional prevalence study in Gabon, Central Africa

Sabine Bélard · Nicole Toepfner · Benjamin Arnold · Abraham Sunday Alabi · Reinhard Berner

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Abstract
Background Group A streptococcus (GAS) and possibly other β-hemolytic streptococci (BHS) account for a considerable morbidity and mortality burden in African populations; however, disproportionately little is known about the epidemiology of BHS in sub-Saharan Africa. This study assessed the prevalence of GAS, group G streptococcus (GGS) and group C streptococcus (GCS) carriage and tonsillopharyngitis in a Central African population.
Methods A prospective cross-sectional study was performed to assess the prevalence of and risk factors for BHS carrier status and tonsillopharyngitis in children and adults in Gabon.
Results The overall BHS carrier prevalence was 135/1,005 (13.4 %); carrier prevalence of GAS, GGS, and GCS was 58/1,005 (5.8 %), 50/1,005 (5.0 %), and 32/1,005 (3.2 %), respectively. Streptococcal carriage was associated with school and pre-school age (adjusted OR 2.65, 95 % CI 1.62–4.36, $p = 0.0001$ and 1.90, 95 % CI 1.14–3.17, $p = 0.0141$, respectively). Participants residing in urban areas were less likely carriers (OR 0.52, $p = 0.0001$). The point-prevalence of BHS-positive tonsillopharyngitis was 1.0 % (9/1,014) and 15.0 % (6/40) in school children with sore throat.
Conclusions Non-GAS exceeded GAS throat carriage and tonsillopharyngitis suggesting a yet underestimated role of non-GAS streptococci in BHS diseases.

Keywords Carrier · *Streptococcus pyogenes* · Africa · Tonsillopharyngitis · β-hemolytic streptococci

Introduction

Global mortality due to group A streptococcus (GAS) infections is estimated comparable to that caused by measles and rotavirus [1]. Severe complications of GAS infections are most common in populations with reduced economic status, where prevention as well as treatment programs are less likely to be available or effective and where systems for recording accurate disease burden data are usually absent [1].

Acute non-invasive GAS infections such as GAS tonsillopharyngitis and pyoderma may appear relatively unimportant, but they predispose for subsequent invasive GAS disease and non-suppurative post-streptococcal complications such as acute rheumatic fever (ARF) and rheumatic heart disease (RHD) entailing high morbidity and mortality. The precise role of asymptomatic pharyngeal GAS carriage in the pathogenesis of GAS infections and sequelae remains yet undetermined [2].

Increasingly non-GAS β-hemolytic streptococci [BHS, Lancefield group C and G (GCS and GGS)] are being recognized as human pathogens and their antigenic profile

S. Bélard · A. S. Alabi
Centre de Recherches Médicales de Lambaréné (CERMEL), Lambaréné, Gabon

S. Bélard (✉)
Department of Pediatric Pneumology and Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany
e-mail: sabine.belard@charite.de

S. Bélard · A. S. Alabi
Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany

N. Toepfner · B. Arnold · R. Berner
Department of Pediatrics and Adolescent Medicine, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

overlapping with GAS suggests that GCS and GGS have the capacity of triggering ARF and possibly contribute to the burden of RHD [3] and other non-suppurative post-streptococcal sequelae.

Although populations living in sub-Saharan Africa suffer the highest burden of post-streptococcal sequelae, only very few patchy data are available on the prevalence of BHS carriage and tonsillopharyngitis for this region. Knowledge of local epidemiology is a prerequisite for improving the understanding of the precise disease burden as well as its aetiology and for the development of effective prevention strategies such as vaccines.

This population-based study was conducted to, firstly, assess the prevalence of asymptomatic carriage and tonsillopharyngitis by GAS, GGS, and GCS in a population from Central Africa and secondly, to study risk factors for these conditions.

Methods

This cross-sectional study was performed at the Centre de Recherches Médicales de Lambaréné (CERMEL) in Gabon, Central Africa, and at the research laboratory of the Clinic and Policlinic for Pediatrics and Adolescent Medicine, University Medical Centre Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. Gabon is almost entirely covered with dense rainforest and sparsely populated; infectious diseases contribute considerably to the total morbidity and mortality burden [4]. In 2010 the WHO estimated life expectancy at birth to be 60 years; markers for child health were described with an under-five mortality rate of 69 per 1,000 live births, an underweight rate of 9 % in children under-five and DTP3 immunization coverage in 1-year olds of 38 % [5]. The study was approved by the CERMEL Institutional Review Board. Written informed consent was obtained for all participants prior to any study procedure; for minors a parent or legal guardian provided written consent.

Participants were recruited by convenience sampling from rural and urban areas within the province of Moyen-Ogooué. Recruitment, interviews, and sampling took place at the participants' homes which were consecutively approached by researchers within one rainy season. Inclusion criteria were (1) provision of written informed consent and (2) residence within the province of Moyen-Ogooué.

Study procedures

For every participant a one-page questionnaire was completed by the investigator. The first part of the questionnaire recorded demographic data [date of birth, sex, place of residence, and number of household members; the latter to group into three household size categories: low ($n < 5$), middle ($n = 5$–8), and high ($n > 8$) number of household members]. The second and third part of the questionnaire recorded medical history and medical-care seeking behaviour related to tonsillopharyngitis. Subsequently, the McIsaac Score criteria [6] were assessed: presence or absence of (a) axillary body temperature >38 °C, (b) cough, (c) swollen exudative tonsils, (d) swollen cervical lymph nodes. Additionally, participants were examined for clinical signs of rhinitis and conjunctivitis. Finally, participants were interviewed about prior antibiotic drug intake. After completion of the questionnaire and physical examination, a tonsillopharyngeal throat swab was taken for every participant. Specimen collection was done with aseptic swabs (polyurethane foam sponge soaked in Amies agar gel serving as transport medium; TS/5-17, Engelbrecht GmbH, Germany) which were transported to the microbiology laboratory at room temperature for further processing on the same day. For medical conditions encountered in study participants basic medication was provided (antibiotics, topical antifungal creams, or anti-scabies lotion) or recommendation for respective referrals was made.

Laboratory procedures

In the microbiology laboratory of the CERMEL and the Albert Schweitzer Hospital, Lambaréné, Gabon, swabs were inoculated on Columbia blood agar plates and incubated overnight at 37 °C. Colonies presenting with ß-hemolysis and typical streptococcal morphology were isolated and incubated another 24 h before cryopreservation in 30 % glycerol and 70 % Todd Hewitt Broth (BBL™, BD USA) at −20 °C. Subsequently, samples were shipped to Dresden, Germany, where samples were re-cultured and streptococci identified by latex agglutination (Slidex®, Biomerieux). BHS other than GAS were confirmed as non-*pyogenes* species by pyrrolidonyl arylamidase test (PYR, Mast Diagnostic, Germany) and bacitracin DDT resistance analysis (DDT, Biomerieux, France). Voges–Proskauer test (VP, Becton–Dickinson, Germany) and sorbitol fermentation test (SF, Sigma Aldrich, Germany) were used to identify GCS and GGS species.

Case Definitions of GAS, GGS, and GCS streptococcal carriage and tonsillopharyngitis

(1) Carriage: Streptococcal carrier status was defined as isolation of GAS, GGS, or GCS from the throat swab but the absence of any of the three other criteria defining GAS, GGS, or GCS tonsillopharyngitis. For calculations of carrier rates and associations, patients with GAS, GGS, or GCS tonsillopharyngitis were excluded.

(2) Tonsillopharyngitis: BHS-positive tonsillopharyngitis caused by GAS, GGS, and/or GCS was defined as: age ≥3 years, sore throat on the day of assessment, McIsaac score ≥3, and isolation of GAS, GGS, or GCS from the throat swab. Children aged <3 years were excluded for evaluation of tonsillopharyngitis because GAS tonsillopharyngitis is rare in very young children.

Data management and statistics

Sample size calculation was based on the few prevalence data and estimations available for other African countries. Pharyngeal GAS carrier rate was estimated 10–25 % with a maximal carrier rate in school-age children. A total of $n = 1{,}050$ participants were planned to be recruited and stratified to three equally represented age groups indicating different social mixing patterns: pre-school children 0 to <6 years, school children ≥6 to <18 years, and adults ≥18 years ($n = 350$ participants per group).

Data were entered into a data base (Microsoft Office Access 2007) and random data checks were performed before closure of the data base. Subsequently, data were extracted to Microsoft Office Excel 2007 and further analysed using R (R i386 3.0.1). Baseline characteristics were described with summary statistics [mean, median, interquartile range (IQR), and proportions]. Differences between proportions were tested with Pearson's Chi squared test. Two-sided statistical tests were used at alpha = 0.05. Odds ratios (OR) were calculated and regression analysis was performed to assess adjusted associations. All demographic variables (gender, residence, number of household, prior antibiotic drug intake) were considered potential confounders and were included in multivariable regression analysis.

Results

Between September 2012 and January 2013 a total of 1,050 participants were recruited and 1,014/1,050 (96.6 %) had evaluable microbiologic examinations. Of the 36 participants excluded from analysis, 24 were excluded due to sample loss following transient incubator dysfunction and 12 were excluded due to contamination of the agar plate.

The age of participants ranged from 2 months to 92 years. Demographic data and distribution of the variables sex, residence, number of household members, and prior antibiotic drug intake are presented in Table 1. BHS were isolated from throat swabs of 144/1,014 (14.2 %) participants. All non-GAS BHS were classified as *S. dysgalactiae* subsp. *equismilis*. GAS were found in 62/1,014 (6.1 %), GGS in 51/1,014 (5.0 %), and GCS in 36/1,014 (3.6 %) participants; five participants had two different streptococci isolated from their throat swabs (GAS/GGS $n = 3$, GAS/GCS $n = 1$, GGS/GCS $n = 1$). Nine participants had BHS-positive tonsillopharyngitis and 135 were streptococcal carriers (Fig. 1).

Pharyngeal streptococcal carriage

The overall pharyngeal streptococcal carrier rate was 135/1,005 (13.4 %) and the GAS, GGS, and GCS carrier rates were 58/1,005 (5.8 %), 50/1,005 (5.0 %), and 32/1,005 (3.2 %), respectively. School children had the highest streptococcal carrier rate of 18.8 %, followed by pre-school children with 13.6 %, and adults with 7.8 %. Total carrier rate and carrier rates for GAS, GGS, and GCS are presented in Table 2.

Pre-school age and school age were significantly associated with streptococcal carriage (adjusted OR 1.90, 95 %

Table 1 Demographics and distribution of variables

	Pre-school children (<6 years) $n = 339$	School children (6 to <18 years) $n = 342$	Adults (≥18 years) $n = 333$	Total $n = 1{,}014$	*p* value
Gender					
Female *n* (%)	153 (45.1)	160 (46.8)	189 (56.8)	502 (49.5)	0.0049
Residence					
Urban *n* (%)	143 (42.2)	123 (36.0)	131 (39.3)	397 (39.2)	0.2503
Number of household members[a]					
Low *n* (%)	65 (19.2)	44 (12.9)	119 (35.7)	228 (22.5)	<0.0001
Middle *n* (%)	150 (44.2)	148 (43.3)	120 (36.0)	418 (41.2)	
High *n* (%)	124 (36.6)	150 (43.9)	94 (28.2)	368 (36.3)	
Antibiotic drug intake during previous month					
Unknown *n* (%)	2 (0.6)	5 (1.5)	3 (0.9)	10 (1.0)	0.1055
Yes *n* (%)	53 (15.6)	34 (9.9)	53 (15.9)	140 (13.8)	
No *n* (%)	284 (83.8)	303 (88.6)	277 (83.2)	864 (85.2)	

[a] Number of household members: low $n < 5$, middle $n = 5$–8, high $n > 8$

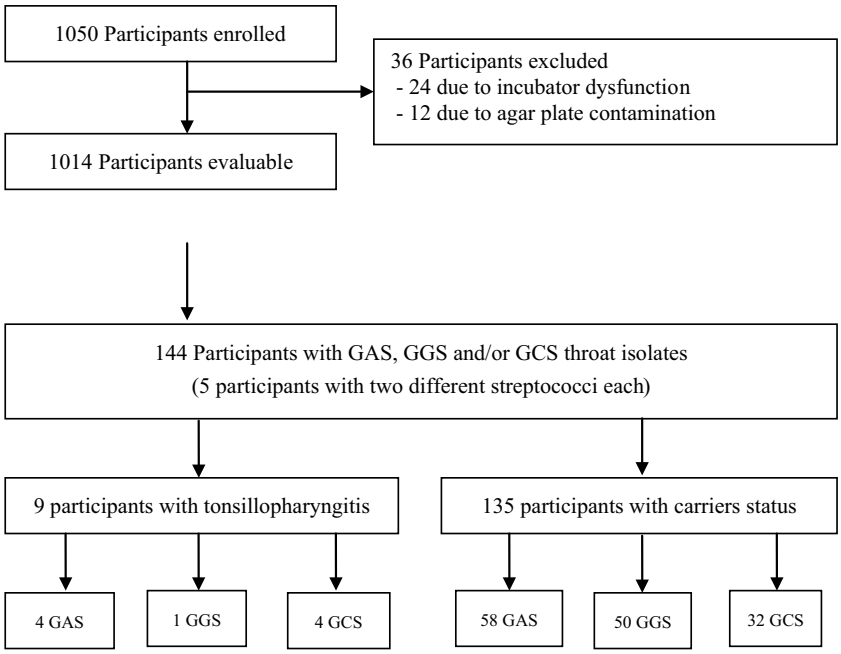

Fig. 1 Study flow of participants with BHS-positive tonsillopharyngitis and BHS carrier status

Table 2 Participants with GAS, GGS and GCS carriage and tonsillopharyngitis

	Pre-school children $n = 339$	School children $n = 342$	Adults $n = 333$	Total $n = 1{,}014$
GAS carrier *n* (%)[a]	20 (5.9)	28 (8.3)	10 (3.0)	58 (5.8)
GAS-positive tonsillopharyngitis *n*	0	3	1	4
GGS carrier *n* (%)[a]	16 (4.7)	22 (6.5)	12 (3.6)	50 (5.0)
GGS-positive tonsillopharyngitis *n*	0	1	0	1
GCS carrier *n* (%)[a]	11 (3.3)	16 (4.8)	5 (1.5)	32 (3.2)
GCS-positive tonsillopharyngitis *n*	2	2	0	4
Overall streptococcal carrier *n* (%)[a]	46 (13.6)	63 (18.8)	26 (7.8)	135 (13.4)
Overall streptococcal tonsillopharyngitis prevalence *n* (%)	2 (1.2)[b]	6 (1.8)	1 (0.3)	9 (1.1)[b]

[a] For calculation of carrier rates participants with tonsillopharyngitis are excluded from the cohort ($n = 1{,}005$)

[b] Children <3 years of age excluded

CI 1.14–3.17, $p = 0.0141$ and 2.65, 95 % CI 1.62–4.36, $p = 0.0001$, respectively). Participants residing in a rural area were more likely to be streptococcal carriers (adjusted OR 1.61, 95 % CI 1.08–2.40, $p = 0.0192$). School children living in rural areas had a streptococcal carrier rate of 20.1 % (43/214). Gender did not influence streptococcal carriage (adjusted OR 0.96, 95 % CI 0.63–1.32, $p = 0.6363$). The number of household members ranged between 1 and 36 (median 7, IQR range 5:11) and was not associated with streptococcal carriage (adjusted OR 1.01, 95 % CI 0.98–1.04, $p = 0.6511$). Antibiotic drug intake during the previous month was reported by 140/1,014 (13.8 %) participants, but did not lower streptococcal carriage (OR 0.72, 95 % CI 0.28–1.88, $p = 0.5059$). Crude and adjusted ORs are presented in Table 3. When looking at ORs for GAS, GGS, and GCS carriage separately, GAS carriage was associated with pre-school and school age; GCS carriage was associated with school age and rural residence; GGS carriage was not associated with any of the above variables (Table 4). The youngest child from whom pharyngeal ß-hemolytic streptococcus (GGS) was isolated was two months old.

BHS-positive tonsillopharyngitis

For participants aged ≥3 years ($n = 841$) and who reported sore throat on the day of assessment (88/841 (10.5 %)), the McIsaac score was calculated. In 29/88 (33 %) participants the McIsaac score was ≥3; in nine (31 %) of these 29 participants GAS, GGS, or GCS was isolated while in 69 % no BHS were recovered. Two of 88 (2.2 %) participants with sore throat had a McIsaac score of four and none of

Table 3 Risk factors for carriage of pharyngeal β-hemolytic streptococci

	Crude OR (95 % CI)	*P* value	Adjusted OR (95 % CI)	*P* value
Age				
Adults	Reference		Reference	
Pre-school children	1.86 (1.12; 3.09)	0.0164	1.90 (1.14; 3.17)	0.0141
School Children	2.72 (1.67; 4.41)	0.0001	2.65 (1.62; 4.36)	0.0001
Gender				
Female	Reference		Reference	
Male	0.96 (0.67; 1.38)	0.8383	0.91 (0.63; 1.32)	0.6363
Residence				
Urban	Reference		Reference	
Rural	1.64 (1.10; 2.43)	0.0140	1.61 (1.08; 2.40)	0.0192
Number of household members	1.02 (0.99; 1.05)	0.1487	1.01 (0.98; 1.04)	0.6511
Antibiotics within preceding month				
No	Reference		Reference	
Yes	0.69 (0.27; 1.77)	0.4378	0.72 (0.28; 1.88)	0.5059

Table 4 Risk factors for pharyngeal GAS, GCS, and GGS carriage

	Adjusted OR	95 % CI	*P* value
GAS			
Pre-school	2.50	(1.11; 5.63)	0.0266
School	3.29	(1.49; 7.30)	0.0033
Rural residence	1.24	(0.69; 2.22)	0.4681
N residents	0.99	(0.94; 1.04)	0.7245
Male	0.67	(0.38; 1.18)	0.1634
GCS			
Pre-school	2.05	(0.69; 6.13)	0.1978
School	3.18	(1.12; 9.04)	0.0303
Rural residence	2.72	(1.10; 6.76)	0.0310
N residents	0.99	(0.93; 1.06)	0.8010
Male	1.58	(0.74; 3.40)	0.2337
GGS			
Pre-school	1.41	(0.63; 3.14)	0.4009
School	1.87	(0.87; 4.04)	0.1094
Rural residence	1.67	(0.87; 3.24)	0.1262
N residents	1.03	(0.98; 1.08)	0.2616
Male	0.95	(0.52; 1.73)	0.8656

these two participants had pharyngeal streptococci isolated. In the population aged ≥3 years the overall point-prevalence of BHS-positive tonsillopharyngitis was thus 1.1 % (9/841). The prevalence of BHS-positive tonsillopharyngitis in all participants with sore throat was 10.2 % (9/88) and 15.0 % (6/40) in school children. Of the nine participants with BHS-positive tonsillopharyngitis six were school-age children, two were pre-school children, and one was an adult (Table 2); 4/9 were female and 7/9 lived in rural areas.

Regarding clinical history of sore throat and related health seeking behaviour in the population aged ≥3 years, 408/841 (48.5 %) participants reported ever having had a sore throat before and 60/408 (14.7 %) confirmed having ever sought medical care for sore throat.

Discussion

Populations from Sub-Saharan Africa are estimated to suffer the highest global burden of RHD [1]. However, there is a striking paucity of data addressing local epidemiology of GAS carriage and primary GAS infections which are established precursory conditions of severe non-suppurative GAS sequelae. Furthermore, there is even less information on the epidemiology of other BHS, namely GGS and GCS, which may also have rheumatogenic potential contributing to post-streptococcal complications. To our knowledge, we present the first data on prevalence of GAS, GGS and GCS carriage and tonsillopharyngitis in a Central African population.

In our study cohort, the GAS carrier rate was highest in school-age children with 8.3 %, a carrier rate similar to the GAS carrier rate of 8.6 and 9.7 % reported for healthy school children from Pemba, Ethiopia, and Nepal [7–9]. Our data thereby confirmed age as risk factor for GAS colonization with the highest GAS carriage rate in school children as reported before [10]. The carrier rate with non-GAS streptococci exceeded the GAS carrier rates in all age groups (overall carrier rate 8.1 vs. 5.8 %) and was also highest in school children with 11.3 %. Again, these findings match with the report from the healthy East African population in Pemba, showing that around two-thirds of pharyngeal BHS isolates are non-GAS (>70 % in Pemba and 61 % in Gabon). Slightly higher non-GAS streptococcal carrier rates were reported from Western Pacific, another region with high prevalence of post-streptococcal sequelae [11]. Although data from tropical countries are limited, the

overall available reports are all pointing towards a relevant prevalence of non-GAS BHS and thereby a possibly underestimated clinical role of non-GAS BHS [11–14].

Unexpectedly, streptococcal carriage was not associated with the number of household members. The particular mobility inherent to the Gabonese population may account for instable household sizes over time and thus balance the risk for carriage. The association of BHS carriage with rural residence was driven by GCS. Further studies are needed to define streptococcal reservoirs beyond the human pharynx; isolated reports on cross-species transmission between humans and pets [15] may indicate a possible role of animals underlying increased carriage rates with rural residence. As anticipated, antibiotic drug intake in the preceding month did not influence GAS carrier status in our cohort underlining ineffectiveness of antibiotics for sustained eradication of streptococcal carriage. Besides, although asymptomatic carriage of BHS being frequently observed, its clinical relevance is unknown as no definite relationship between colonization and GAS, GGS and GCS infections and sequelae has been established so far.

The clinical relevance of GAS tonsillopharyngitis as precursor of ARF and RHD is well recognized. In our cohort the diagnosis of tonsillopharyngitis due to BHS was based on the presence of sore throat and a McIsaac score of at least three, a commonly used cutoff for prescription of antibiotics [16, 17, 17]. Because diagnosis on clinical grounds alone cannot reliably differentiate between GAS and viral tonsillopharyngitis, guidelines recommend rapid antigen detection test (RADT) and/or culture [18]. Yet, microbiological tests cannot distinguish between carriage and infection and RADT are only available for GAS. In resource-limited settings where microbiological laboratory infrastructure is often lacking RADT can be particularly useful [19]. The age-adjusted clinical McIsaac score was developed as a simple primary-care management approach to limit the need for microbiological testing in all patients with sore throat, to improve differentiation of streptococcal throat carriage and infection, and to reduce unnecessary antibiotic use [20]. The McIsaac score was recently validated in a large geographically diverse cohort within the USA [21], but its value in populations from tropical areas has not been assessed before. In our study population the McIsaac score performed well in predicting BHS-positive tonsillopharyngitis; 31 % of participants with a McIsaac score of ≥ 3 had a BHS-positive tonsillopharyngitis matching the predicted 35 % probability. The use of the McIsaac score appears particularly valuable not only to limit diagnostic costs to patients with a high pre-test probability of streptococcal tonsillopharyngitis, but also to increase the detection of non-GAS tonsillopharyngitis where RADT is the only microbiological diagnostic test available.

The overall prevalence of BHS-positive tonsillopharyngitis was 1.1 % and 15.0 % in school children who reported sore throat on the day of assessment. Thus, in this cross-sectional survey every seventh school child with sore throat had BHS-positive tonsillopharyngitis being a possible trigger for ARF and would have benefited from antibiotic treatment to prevent ARF. In contrast to previous reports on prevalence of streptococcal tonsillopharyngitis [22] our data were derived from household visits and not from patients presenting with sore throat to healthcare facilities. This may account for the comparatively lower rate of GAS-positive tonsillopharyngitis in our population but may reflect the true burden in the given population more precisely.

The concept of treating suppurative GAS infections with antibiotics to prevent GAS sequelae is widely accepted in industrialized countries where ARF and RHD are rare nowadays. However, the immediate treatment of such superficial GAS infections is a losing game in resource-limited settings. Only few people consult medical health services for sore throat [23]. This was confirmed in our study population where only 5.9 % affirmed having sought medical consultation for tonsillopharyngitis. A comprehensive approach for control of BHS-associated diseases in areas of low health infrastructure is urgently needed.

Our study is limited by the point-prevalence assessment covering one rainy season only as carrier and tonsillopharyngitis rates are known to vary with seasons. Evaluation during the rainy season was chosen because carrier rates are expected to be highest at this time point and the risk of underestimating the true rate would be minimal. A further limit is the small sample size of tonsillopharyngitis patients precluding further analyses on tonsillopharyngitis by different BHS.

While in Sub-Saharan Africa the burden of non-suppurative GAS complications is estimated to be the highest in the world, primary non-invasive GAS infections such as tonsillopharyngitis and pyoderma appear relatively low. This inverse relation calls for hypotheses beyond primary GAS infections as origin of non-suppurative streptococcal sequelae in Africa, although access and adherence to treatment are likely a contributing factor.

Further studies are needed to understand local and precise morbidity and mortality burden due BHS and related complications, describe molecular epidemiology of BHS, and elucidate respective immunologic host responses. This will help to adapt vaccine development and preventive public health approaches for a maximum coverage of populations most in need of preventive strategies.

Conclusion

Pharyngeal GAS, GGS, and GCS are frequently encountered microorganisms in healthy people in Central Africa.

Prevalence of GAS-positive tonsillopharyngitis was relatively low in this population which is estimated to suffer a high burden of RHD. GGS and GCS carriage exceeded GAS carriage; therefore, non-GAS streptococci may play a yet underestimated role in the pathogenesis of ARF and RHD. Further studies on clinical and molecular epidemiology as well as pathogenicity of BHS are needed to tailor urgently needed control strategies.

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Conflict of interest All authors declare no conflict of interest.

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