Prevalence of group A streptococcal carriage in school children from Cape Town: A cross-sectional study and systematic review

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Background. Asymptomatic children can be a major reservoir of pharyngeal group A streptococcus (GAS). The role of GAS carriage causing subsequent infections resulting in the manifestation of clinical symptoms, or being associated with transmission to uninfected individuals, is not entirely clear. Furthermore, data on GAS carriage from countries in Africa remain scant with only a few studies reporting carriage.
Objectives. We performed a cross-sectional study to determine the prevalence of asymptomatic pharyngeal carriage of group A streptococci in school children in Cape Town. We considered our results in the context of a meta-analysis of data of GAS carriage in Africa.
Methods. We conducted a school-based cross-sectional study from 2009 to 2011 in two Cape Town peri-urban communities, enrolling 950 healthy learners. Pharyngeal swabs were obtained from learners and processed at the National Health Laboratory Service (NHLS) microbiology laboratory at Groote Schuur Hospital, Cape Town. Thereafter, we conducted a systematic review through a comprehensive literature search among several sources. Prevalence estimates with 95% confidence intervals (CIs) were determined using a random-effects meta-analysis model.
Results. GAS was isolated from 31 participants corresponding to a carrier rate of 3% (95% CI 2% - 4%). Combining our results with 18 other studies revealed a pooled prevalence of 9% (95% CI 6% - 11%). Regional pooled rates were similar across southern, eastern and northern Africa, of between 9% (95% CI 6% - 11%) and 11% (95% CI 4% - 21%) while countries within Central Africa had a pooled estimate of 7% (95% CI 5% - 9%). Western Africa had the lowest pooled estimate of 2% (95% CI 1% - 2%).
Conclusion. There was a relatively low rate of carriage of GAS in asymptomatic school children residing in South Africa. Pooled prevalence rates revealed regional differences across the African continent as regards the rate of GAS carriage, with the western and northern African regions having rates of GAS carriage that were lower and higher respectively than those of East, Central and southern African countries, which demonstrated similar rates of carriage.

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Streptococcus pyogenes, also known as group A streptococcus (GAS), is a major cause of infections worldwide, commonly causing pharyngitis in children aged 5 - 15 years.[1] Of concern, repeated untreated or inappropriately treated episodes of GAS pharyngitis may result in autoimmune diseases such as acute rheumatic fever (ARF), which may develop into rheumatic heart disease (RHD). The global burden of RHD is estimated to be 33 million prevalent cases, 9 million disability-adjusted life years lost and 275 000 deaths each year.[2-4]

GAS can asymptomatically colonise the upper respiratory tract of children, referred to as GAS carriers; penicillin has been shown not to be effective as the first-line treatment for eradicating GAS carriage.[5] The role of GAS carriage causing subsequent infections resulting in the manifestation of clinical symptoms, or being associated with transmission to uninfected individuals, is not entirely clear.[5-8] Therefore, it is of interest to understand the background prevalence of GAS carriage in communities in comparison with prevalence of GAS in symptomatic pharyngitis in order to interpret the findings of diagnostic tests of true infection appropriately.[9] Finally, knowledge of the *emm* types of GAS recovered from asymptomatic carriers may be useful in the light of recent advances towards the development of multivalent M protein-based streptococcal vaccines.[10]

There is a dearth of recent studies on GAS carriage rates in school-aged children; in South Africa (SA), only three studies exist, conducted more than 25 years ago.[11-13] Among these, carriage among the black population was reported to be 16.8% in an urban setting,[13] 5.2% in lower-socioeconomic households in peri-urban Soweto[11] and 1.62% in participants from a remote traditional community.[13] A study involving mostly grade 3 learners of either mixed or Indian ancestry reported GAS carriage rates >20% in summer and <5% in

spring.[12] The remaining study comprising urban white participants had a carriage prevalence of only 3.4%.[13]

Furthermore, data on GAS carriage from countries in Africa remain scant with only a few studies reporting carriage. An earlier systematic review by Shaikh *et al.*[9] reported a pooled prevalence of GAS carriage of 12% (95% Confidence interval (CI) 9% - 14%) in healthy children <18 years old residing in low- to middle-income countries. This review, unfortunately, did not include African data available at the time, including studies from SA, Ethiopia and Tunisia.[11-21]

We conducted a cross-sectional study to describe the rate of GAS carriage among school children living in Cape Town, SA. Thereafter, we analysed our findings in the context of published data through systematic review and meta-analysis of literature on the prevalence of GAS carriage in children aged 5 - 15 years, residing in African countries,. Our review is essential, given the high burden of acute and chronic complications caused by GAS infections in Africa,[22] and is intended to update the findings of the previous reviews on GAS carriage.

Methods

Cross-sectional study

This study was nested within a larger cross-sectional school-based screening study for asymptomatic RHD among healthy learners attending primary and secondary schools in Bonteheuwel and Langa.[23] These two communities are considered to be of lower socioeconomic status and comprise mainly black African (Langa) and mixed ancestry (Bonteheuwel) populations. They are plagued with social problems such as poverty, unemployment, crime, drug and alcohol abuse, poor housing and overcrowding.

The study, performed as part of a larger RHD screening project (Engel *et al.*), recruited participants by convenience sampling over a 3-year period from February 2009 to November 2011. The sample size, set at a minimum of 450 participants per community, was based on published studies in similar SA communities[11,12] for estimation of at least 5% difference of GAS carriage across the two communities within a precision of 5%; additionally, we assumed a 5% non-response rate. School-going children, whose parents provided informed consent, were eligible for participation in the study. We excluded children who had taken antibiotics in the 3 months prior to the study.

A throat swab sample was taken by swabbing the tonsillar and posterior pharyngeal areas; samples were transferred in transport media for processing by the Microbiology Laboratory of the National Health Laboratory Service located at Groote Schuur Hospital. Swabs were inoculated onto 4% sheep blood agar plates according to a standard protocol, inverted and incubated anaerobically at 35ºC for 24 - 48 hours. All cultures of beta-haemolytic colonies were further identified by Gram stain and catalase. Statistical analyses were performed using STATA version 14.0 (Stata Statistical Software: Release 14. StataCorp, USA). Comparisons were made using the χ^2 test or Fisher's exact test. A p-value <0.05 was considered indicative of a statistically significant difference. The study was performed with the approval of the University of Cape Town Faculty of Health Sciences Research Ethics Committee, and informed consent was obtained in writing from a parent or legal guardian of each participant. Forms were provided in the local languages of Afrikaans, English and isiXhosa. In addition, children aged ≥8 years were required to provide assent.

Systematic review

For the systematic review, we employed rigorous methods drawn from the scientific techniques and guidelines offered by the Cochrane Collaboration;[24] (PROSPERO registration number: CRD 42015019589). We considered observational studies such as population-based, cross-sectional, and longitudinal studies. Published and unpublished studies with a population inclusive of healthy children residing in geographic regions confined to the African continent were eligible for inclusion. Studies had to have reported on prevalence of GAS carriage; a participant was deemed a GAS carrier if he/she tested positive for GAS bacteria through a positive rapid antigen detection test (RADT) or positive laboratory throat culture, but demonstrated no clinical signs and symptoms. We excluded publications lacking primary data and/or an explicit description of the methods. Where an eligible study was published in duplicate, the most recent complete version was included.

We developed a comprehensive search strategy that incorporated a combination of free term text items, including carriage, asymptomatic, etc., and medical subject headings (MESH) such as *Streptococcus pyogenes*. In addition, to maximise the likelihood of finding articles from Africa, we applied an African search filter described previously by Pienaar and colleagues.[25] The search was conducted independently by two reviewers (HM, DB) among the following electronic databases: EbscoHost, PubMed and Scopus. Also, we searched the American Society for Microbiology (http://www.asm.org/) websites for additional sources. Furthermore, we searched the proceedings from the XIX Lancefield International Symposium on Streptococci and Streptococcal Disease (http://www.lancefield2014.com). Lastly, searches in Google Scholar complemented the searches, including articles among grey literature. The search strategy was appropriately modified to suit the vocabulary of individual databases. Publication date and language restriction were not applied to searches. To obtain additional publications, we scanned the reference lists of all potential articles retrieved from electronic searches. Also, relevant authors and experts in the field were contacted for additional data. The last manual internet search was conducted on 15 March 2019.

Search results from individual databases, reference searches and unpublished articles were managed with Mendeley referencing software (Mendeley Ltd, UK). Applying the predefined inclusion criteria, we reviewed the titles and abstracts of the full list of potential articles, resolving differences by discussion where necessary. Full text copies of potentially eligible studies were retrieved for detailed evaluation. We extracted relevant data onto a predefined form. We evaluated studies for risk of bias related to internal validity, external validity and generalisability of the study results. An assessment of risk of bias informed the evaluation of heterogeneity in the pooled analysis. We employed the quality assessment tool for evaluating prevalence studies as suggested by Hoy *et al.*[26] and adapted by Werfalli *et al.*,[27] which allows for a composite score to assist with relative comparison between the studies, thereby reducing reviewers' subjectivity. The scoring system tool categorises high-risk studies as those with an overall score of 0 - 5 points, moderate risk as 6 - 8 and low risk >8 points.

To calculate the unadjusted prevalence estimates of streptococcus carriage of children within the age groups of 5 - 15 years, for each study we individually recalculated the reported prevalence and confirmed the numerators and denominators as reported by the authors in 11 studies.[13,16,19-21,28-33] For one study, data pertinent to our target age group were extracted from studies incorporating adults and children.[34] Where data for our target age were reported as part of a wider age range, we included all the data within that category, provided the age did not exceed 25 years,[13,19] the upper end of age-at-risk for rheumatic fever.[35]

Secondly, where sample populations included both symptomatic GAS children and asymptomatic GAS children, we only extracted

information from healthy children/children without any signs or symptoms of disease.[17,36] Thirdly, the earliest full set of results were used where studies reported follow-up data of children over a period of months[12] and years.[14] This was to avoid an over- and underestimation of GAS carriage, that would arise by taking an average of all follow-up data of an individual study.

Using Stata (version 13.1), the Freeman-Tukey double arcsine transformation *metaprop* routine was used to calculate the combined prevalence estimate and standard error across the unadjusted estimates. The Freeman-Tukey stabilises the variance of study-specific prevalence, minimising the influence from studies with extremely small prevalence or extremely large prevalence estimates.[37]

We stratified the aggregated prevalence by region in order to assess similarities and difference within the Africa continent. Our hypothesis was that GAS carriage would differ regionally because of settings and climatic differences. We also evaluated prevalence according to study design in order to assess methodological influences on overall estimates. Our hypothesis was that GAS carriage would not be statistically different across study designs. Furthermore, we evaluated the effect of sample size on the pooled prevalence estimate; estimates reported in two recent large studies by Abdissa *et al.*[28] and Braito *et al.*[21] demonstrated an estimated sample size of 796 as being adequate.[39] Sub-analysis of GAS colonisation risk factors (gender, crowding and seasonality) could not be performed owing to data limitations; these factors are therefore presented as qualitative data. For each study, none of the missing data was relevant to warrant contacting the corresponding authors to request the missing information. We assessed heterogeneity across studies to determine the extent of variation between studies included in the meta-analysis. Heterogeneity was assessed by inspecting the extent of overlap within the forest plots, through the Cochran's χ^2 test (using 10% level of significance), and the I^2 statistic (where 50% or higher values indicate substantial heterogeneity).[40] CIs around heterogeneity estimates were calculated using the *heterogi* command in Stata. Where heterogeneity was statistically significant, we conducted a sensitivity analysis to assess the influence of various study characteristics such as the quality of the study, age of participants and season(s) of participation.

Results

Cross-sectional study

Nine-hundred and fifty healthy learners attending schools within the two communities were enrolled into our study over a 3-year period (2009 - 2011). The median age of the participants was 11 years (range 3 - 24 years); males constituted 43% of the study participants (Fig. 1).

Group A streptococci isolation

GAS was isolated from 31 participants corresponding to a carrier rate of 3.3% (95% CI 2% - 4%) among healthy school-aged learners (Table 1). GAS was recovered from almost all ages of learners (mean (standard deviation) age was 11.09 (3.6) years) with no association between GAS status and age (p=0.628). GAS isolation was not associated with seasonality (p>0.05) or gender (p>0.05). There was a statistically significant difference in the isolation rates of GAS by community, with pupils from Langa having increased odds of having isolated positive culture (odds ratio (OR) 3.13, 95% CI 1.38 - 7.09). Fig. 2 details the *emm* types recovered from our cohort.

Systematic review

The literature search results are reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement.[41] (Appendix, supplementary Fig. 1 details the search results.) We retrieved 1 647 records from electronic database searches which, together with 20 additional references identified through hand searching of relevant reference lists, rendered a total of 1 667 articles. After removal of duplicates, 681 references were assessed for eligibility. Of these, 647 articles were excluded based on title and abstract, leaving 34 articles requiring further evaluation as full-text articles. Finally, 19 studies met our inclusion criteria. Reasons for exclusion were duplicated publication (n=2), irrelevant populations (n=5), objectives (n=5) or outcomes (n=3).

Studies included in the analysis (n=19) comprised 18 peer-reviewed journal articles,[11-21,28-31,33,34,36] together with our school-based cross-sectional study (Table 2). From these studies, 16 were cross-sectional studies, while 3 were longitudinal studies. The study populations ranged from a minimum age of 2 months to a maximum age of 25 years. GAS was diagnosed by microbiological culture of throat swab specimens in all studies except one,[36] which utilised a rapid strep diagnostic method as a means of identifying GAS in the pharynx. Studies were conducted in schools (12 studies[11,12,14,18,20,21,28–33]), clinics/outpatient departments (4 studies[15,17,19,36]), and homes (1 study[34]). Two studies did not state the setting of their sample population.[13,16] All studies were conducted within a range of African regions: southern Africa (6 studies[11–13,15,19,32]), northern Africa (5 studies[14,17,20,29,30]), eastern Africa (5 studies[18,21,28,31,36]), western Africa (2 studies[16,33]) and central Africa (1 study[34]). Studies included in the analysis were conducted in both urban and rural areas or exclusively in urban areas; no studies were conducted exclusively in a rural area.

Supplementary Fig. 2 (Appendix) depicts risk of bias as assessed according to the Hoy criteria as modified by Werfalli *et al.*[26,27] Five studies had a low risk of bias,[18,28,30,32,34] while the rest of the studies had a moderate risk of bias. No study was deemed as having a high risk of bias.

This review found an overall prevalence of 9% (95% CI 6% - 11%) for GAS carriage in school children residing in African countries; test for heterogeneity, I^2=97.9%, p<0.0001; 19 studies, n=30 842 (Fig. 3).

The regional pooled rates ranged between 2% and 11% across the five regions of the African continent. Pooled rates were similar across eastern, northern and southern Africa, ranging between 9% and 11% (n=16 studies). There was only one study within Central Africa with a pooled estimate of 7% (95% CI 5% - 9%), while in western Africa (n=2 studies), a lower pooled estimate of 2% (95% CI, 1% - 2%) was observed. The 95% CIs of the pooled estimates between western, eastern, northern and southern Africa combined did not overlap, thus indicating a statistically significant difference (Fig. 4).

Data for estimating the prevalence of GAS carriage by cross-sectional and longitudinal study design were provided by 16 and

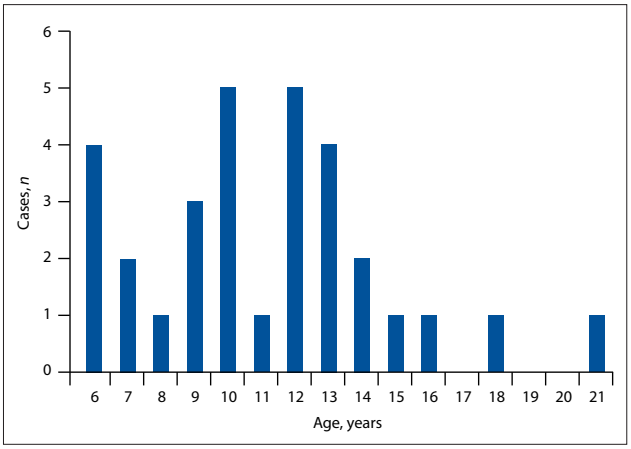

Fig. 1. Age distribution of GAS in asymptomatic school children in Cape Town.

Table 1. Comparison of some of the characteristics of asymptomatic GAS-positive and GAS-negative school children recruited into the study between February 2009 and November 2011

	GAS+, *n* (%)	GAS−, *n* (%)	Total
Age, mean (SD); range	11.1 (3.6); 6 - 21	11.4 (4.0); 3 - 24	-
<9 years	7 (3.1)	218 (96.8)	225 (23.7)
≥9 years	24 (3.3)	701 (96.7)	725 (76.3)
Gender			
Female	15 (2.8)	528 (97.2)	543 (57.2)
Male	16 (3.9)	391 (96.1)	407 (42.8)
School district			
Bonteheuwel	8 (1.6) *	479 (98.3)	487 (51.3)
Langa	23 (5.0)	440 (95.0)	463 (48.7)
Season			
Winter	18 (4.1)	420 (95.9)	438 (46.1)
Summer	13 (2.5)	499 (97.4)	512 (53.9)
Total	31 (3.3)	919 (96.8)	950 (100)

GAS = group A streptococcus; + = positive; − = negative; SD = standard deviation.
* *p*-value <0.05 for association between school district and having a GAS+ status.

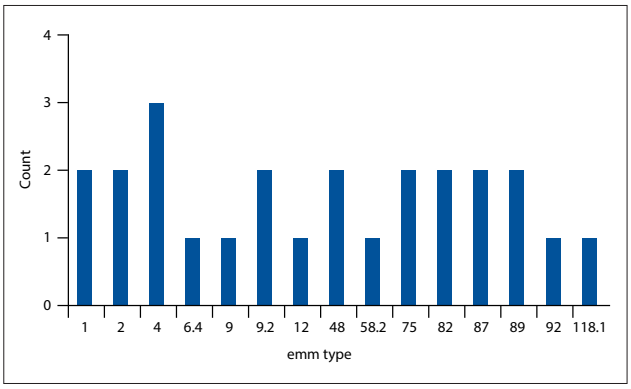

Fig. 2. emm *types recovered from our cohort.*

3 studies, respectively. There was no difference between the pooled prevalence estimates for cross-sectional studies (8% (95% CI 6% - 11%)) and longitudinal studies (9% (95% CI 1% - 26%)); test for heterogeneity between subgroups, p=0.90 (Appendix, supplementary Fig. 3).

Eight studies had sample sizes of 796 or greater that together gave a combined prevalence of 4% (95% CI 3% - 7%). This contrasted with the combined estimate of 13% (95% CI 7% - 19%) rendered by inadequately powered studies (n=11 studies). This difference was not statistically significant (test for heterogeneity between subgroups, p=0.1) (Fig. 4).

A limited number of studies reported on risk factors having a possible association with GAS colonisation in children. However, owing to a lack of reporting of the breakdown of prevalence according to possible risk factors, it was not possible to conduct a pooled meta-analysis, and therefore we discuss the findings in a narrative. Two studies, conducted in household residences, found the number living in the household not to be an associated risk factor for GAS carriage.[12,34] Another study, conducted in a school environment, found GAS rates to be significantly higher in children coming from suburbs characterised by lower socioeconomic conditions, including a higher household density.[32]

In 3 studies, no significant difference was found between gender of participants,[28,32,34] while 1 study reported a higher GAS carrier rate in girls compared with boys.[29] Seasonality showed contrasting associations as regards peak GAS carriage. Two studies reported higher GAS carrier rates during the winter months,[14,17] whereas 2 others found a peak prevalence during summer months.[11,12] However, 1 study reported no seasonal variations in carriage rates.[32]

Given the considerable heterogeneity (I^2=98% (95% CI 98% - 99%)), we conducted sensitivity analyses in respect of study quality and age ranges of participants. When quality assessment was considered, studies considered as having a low risk of bias (n=5 studies) had a pooled prevalence of 9% (95% CI 5% - 14%) while studies with moderate risk of bias (n=14 studies) had a pooled prevalence of 8% (95% CI 6% - 11%); this difference was not statistically significant (test for heterogeneity between subgroups, p=0.67). (Appendix, supplementary Fig. 5)

Six studies had a limited age range among their participants,[12,15–18,21] where the age ranges were not inclusive of the whole age range stipulated in our inclusion criteria; therefore we tested the potential contribution to heterogeneity within our meta-analysis, of studies having incomplete age ranges of participants. The sensitivity analysis revealed a pooled prevalence estimate of 7% (95% CI 5% - 10%) within studies that had a complete age range and 12% (95% CI 5% - 21%) in studies having only some of the age ranges within our inclusion criteria. This difference was not statistically significant (test for heterogeneity between subgroups, p=0.21). (Appendix, supplementary Fig. 6)

There were not enough data to analyse the possible influence of seasonality on the heterogeneity.

Discussion

Carriage of GAS in the pharynx of asymptomatic individuals is an important factor in the pathogenesis of these infections and, most importantly, in maintaining the organisms in the population. GAS are human-specific pathogens and other hosts or vectors do not play a major role in the maintenance or spread of the organisms. Therefore, persistence of the organisms on the pharyngeal mucosa or skin is considered a critical determinant for their survival in the human population. It is not surprising that carriage rates ≥10% have been reported in school settings in both industrialised and developing countries.[42-44] In a longitudinal study[5] of carriage in 100 schoolchildren over a 4-year period, it was observed that throughout each of the 4 years, 27 - 32% of the cohort were GAS carriers and the mean prevalence of carriage was 15.9%. In this study, subjects carried a single *emm* type for a mean of 10.8 weeks with a range of

Table 2. Characteristics of included studies

Study ID	Region	Country	Study design	Season of participation	Setting (local, social context)	Inclusion and population description	Site of recruitment	Selection methods	Age, years*
This study	Southern Africa	South Africa	Cross-sectional	All	Peri-urban area of Cape Town	Asymptomatic children of school-going age	Schools	Convenience sampling	6 - 24
Abdissa *et al.*,[28] 2011	Eastern Africa	Ethiopia	Cross-sectional	Hot rainy and cold dry seasons	Gondar and Dire-Dawa are located 750 km north and 540 km south-east of Addis Ababa	Healthy school children living in three major cities of Ethiopia	Schools	Computer-generated random numbers	6 - 14
Bélard *et al.*,[34] 2014	Middle Africa	Gabon	Cross-sectional	One rainy season	Dense rainforest and sparsely populated. Infectious diseases contribute considerably to the total morbidity and mortality burden	Rural and urban residence within the province of Moyen-Ogooué	Participants' homes	Convenience sampling	2 months - 18 years
Braito *et al.*,[21] 2004	Eastern Africa	Tanzania	Cross-sectional	Dry season	Pemba Island is densely populated and divided into four districts that differ from each other in some geographical and economical characteristics	Healthy children living in all the Pemba districts	Schools	Random selection	7 - 10 years
El Kholya *et al.*,[28] 1973	Northern Africa	Egypt	Longitudinal	All	Qalyub district is 20 km north of Cairo	Primary school children	Primary schools	Not stated	6 - 12
Frederiksen *et al.*,[15] 1988	Southern Africa	Zambia	Cross-sectional	Not stated	Two urban areas, a railway clinic and three rural areas in the Choma district. Choma district is situated in the tropical zone of the southern part of Zambia	Healthy infants and children. Mostly attending the under-5 clinics	Clinics	Not stated	Infants and <10
Gaumer *et al.*,[24] 1972.	Northern Africa	Tunisia	Cross-sectional	Spring	Urban	Children from kindergarten, primary and high school	Schools	Not stated	3 - 17
Khemiri *et al.*,[30] 1982	Northern Africa	Tunisia	Cross-sectional	All	Government schools having children from both urban and rural areas	School children	Schools	Not stated	6 - 12
Lawal *et al.*,[33] 1990	Western Africa	Nigeria	Cross-sectional	Not stated	Schools located in zones 1-7 of Lagos, Nigeria	Healthy school children	Schools	Not stated	7 - 12
McLaren *et al.*,[11] 1975	Southern Africa	South Africa	Cross-sectional	Not stated	Soweto lies to the south-western boundary of Johannesburg. The population is mainly black people from different ethnic groups. Most of the population are unskilled workers, but a small middle class also exists	Black children attending crèches and schools of Soweto	Crèches, primary school, higher primary	Randomised	2 - 18

...continued

Table 2. (continued) Characteristics of included studies

Study ID	Region	Country	Study design	Season of participation	Setting (local, social context)	Inclusion and population description	Site of recruitment	Selection methods	Age, years*
Mzoughi *et al.*,[17] 2004	Northern Africa	Tunisia	Cross-sectional	All	Populous district around Sousse	Healthy paediatric patients who were attending outpatient clinics for vaccination	Farhat Hached Hospital and Centre de Protection Maternelle et Infantile	Not stated	2 - 8
Nayiga *et al.*,[31] 2015	Eastern Africa	Uganda	Cross-sectional	Not stated	Wakiso district is in the central region of Uganda. 92% of the population lives in the rural areas compared with 8% living in urban areas	Children aged 5 - 15, attending five primary schools with different socioeconomic status	Schools	Multistage cluster sampling design	5 - 15
Ogunbi *et al.*,[16] 1974	Western Africa	Nigeria	Longitudinal	Dry and wet seasons	Urban	Normal school children	Not stated	Not stated	6
O'Meara *et al.*,[36] 2015.	Eastern Africa	Kenya	Cross-sectional	Not stated	Webuye District Hospital is located in the peri-urban centre of Bungoma East district. Most families engage in farming and small-scale animal husbandry	Afebrile children from the eye clinic, follow-up fractures, or children accompanying parents for other reason	Webuye District Hospital (outpatient)	Not stated	1 - 12
Ransome *et al.*,[12] 1983	Southern Africa	South Africa	Cross-sectional	All	Low socioeconomic classes in Johannesburg and its environs. Approximately 30 pupils per classroom, playgrounds were moderately crowded	Asymptomatic school children	Schools	Not stated	7 - 9
Tewodros *et al.*,[18] 1992	Eastern Africa	Ethiopia	Longitudinal	All	Ethio-Swedish Children's teaching hospital, located in the centre of Addis Ababa	School children without any signs of upper respiratory tract infection	Three public elementary schools located near the Ethio-Swedish Children's Hospital	Randomised	<12
Van Staden *et al.*,[13] 1982	Southern Africa	South Africa	Cross-sectional	Not stated	Traditional black community	Separated tribes living in a community with minimum services and Western influence	Not stated	Not stated	5 – 25
Van Zyl *et al.*,[19] 1981	Southern Africa	South Africa	Cross-sectional	Not stated	Urban area, Pretoria	Blacks and whites living in Pretoria	Outpatient government hospital and private hospital	Not stated	5 – 25
Yazov et al.,[20] 1978	Northern Africa	Ethiopia	Cross-sectional	Humid season	Urban area in Addis-Ababa	Primary and secondary school children from low- and high-income families in Addis-Ababa.	Schools	Not stated	6 - 20

* Unless otherwise specified.

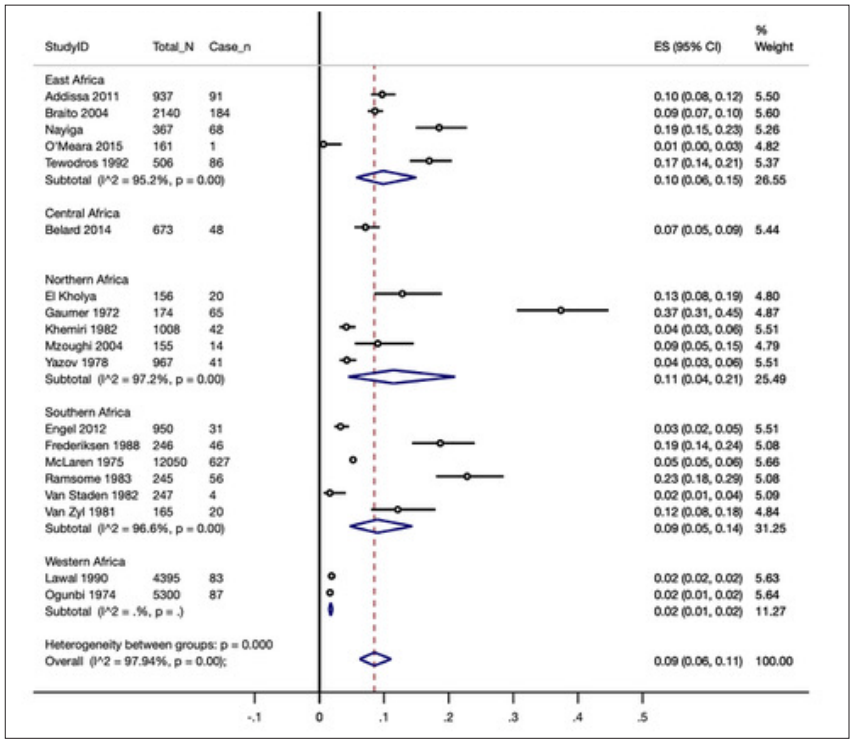

Fig. 3. Streptococcal carriage (%) by region in Africa

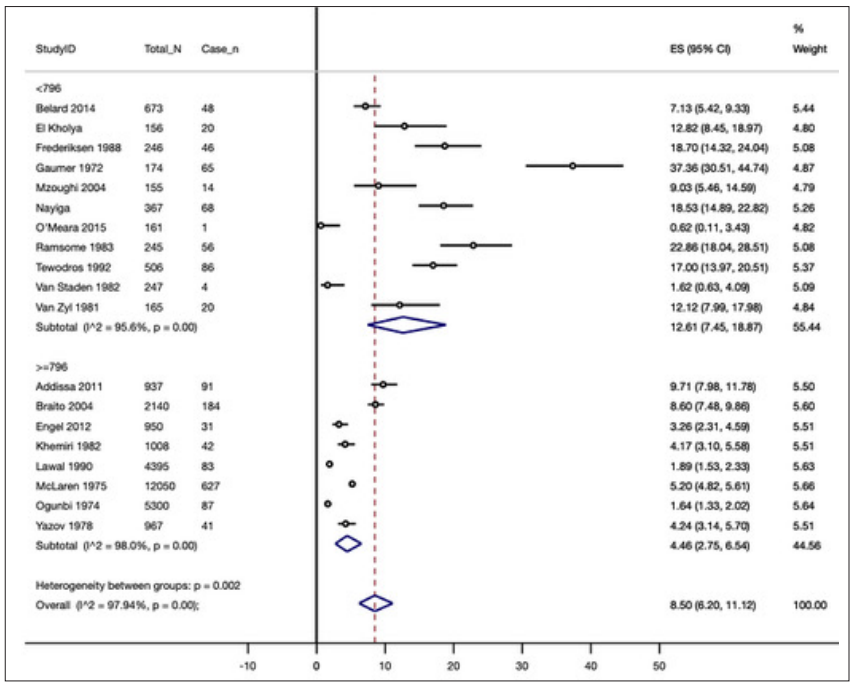

Fig. 4. Prevalence stratified by sample size: Streptococcus carriage in African children.

3 - 34 weeks. In a more recent longitudinal study[45] of school-age subjects with new pharyngeal acquisitions of GAS, 20% of the subjects had persistent carriage of the same *emm* type for 12 weeks or longer, with an average of 23 weeks and a range of 12 - 53 weeks. The latter study was designed to detect changes in serum antibody responses against a panel of GAS antigens following new pharyngeal GAS acquisitions. Of particular interest was the observation that of the subjects who acquired a new *emm* type, 63% were asymptomatic yet mounted an immune response to at least one streptococcal antigen. These episodes most likely represented asymptomatic new infections that previously may have simply been considered carriage of GAS and of little importance in relation to post-streptococcal immune sequelae. Thus, GAS carriage not only reflects the reservoir of circulating strains, but may also be a sampling of organisms that have caused asymptomatic true infections in the majority of the subjects found to have positive cultures.

We conducted this cross-sectional study to investigate GAS carriage rates in a population of SA schoolchildren. Our present rate of 3.3% GAS carriage differs from those previously reported in SA settings: 16.8% (urban),[13] 5.2% (lower-socioeconomic peri-urban households)[11] and 1.62% (remote traditional).[13]

Furthermore, we did not observe a seasonal variation between winter and summer isolation rates, which may be related in part to the climatic differences between Cape Town and the other regions in SA where the respective studies were conducted.[12] Prevalence rates of GAS carriage showed no significant difference between male and female participants.

GAS carriage was significantly associated with the Langa school district, having more than three times the odds of GAS carriage (p=0.038) compared with Bonteheuwel. Given that Langa rates poorly in several key indicators of socioeconomic status, the statistically significant higher prevalence observed in Langa may be explained by socioeconomic factors such as overcrowding and lack of suitable housing. This finding corroborates those of earlier studies conducted in SA among urban Black communities,[11,13] historically known to have resided in overcrowded poverty-stricken conditions. Of interest, in our study, carriage of GAS in communities with apparently high rates of rheumatic fever and RHD is remarkably low (overall 3.3%). A similar low carriage rate (3.7%) of GAS was reported in a study from the Northern Territory of Australia.[46]

We analysed our cross-sectional findings in the context of published African data through a meta-analysis. The pooled GAS carriage estimate of 9% (95% CI 6% - 11%) among African schoolchildren was lower than the 12% (95% CI 9% - 14%) previously reported in a systematic review comprising studies in low-, middle- and high-income countries.[9] The low pooled estimate of 2% (95% CI 1% - 2%) in western Africa contrasted significantly with pooled prevalence rates in northern (11%), eastern (10%), southern (9%) and central Africa (7%).

We further considered the impact of sample size on the overall prevalence estimate using n=796 as the cut-off, based on recommended parameters.[39] Adequately powered studies rendered a pooled prevalence estimate of only 4% GAS carriage (n=8 studies), considerably lower than

the combined 12% estimate among smaller inadequately powered studies. Given that studies of pharyngitis report GAS prevalence of >20%,[47] our findings emphasise the association between GAS and pharyngitis, given the low background rate of GAS carriage found within our review.

This meta-analysis presents the first comprehensive synthesis of the prevalence of GAS in children aged 5 -25 residing in Africa, and reveals two important findings: (*i*) there is a relatively low rate of carriage of GAS in asymptomatic schoolchildren residing in Africa; and (*ii*) there are regional differences across the African continent as regards the rate of GAS carriage, with the western and northern African regions having rates of GAS carriage that are lower and higher respectively than those of eastern, central and southern African countries, which demonstrated similar rates of carriage. The data from this review had contradicting results for risk factors, such as gender, seasons and crowding, thought to be associated with GAS colonisation.

In comparison with single studies among schoolchildren in other low-income countries, our pooled rate of GAS carriage was similar to the 10% found in Nepal,[48] which is more than the prevalence of 8.4% found in Chennai, India,[49] but less than the 15% observed in Iraq.[50] Our results were robust regarding study design, with cross-sectional studies and longitudinal studies having similar rates of 8% and 9% respectively, which agree with the overall prevalence. Additionally, considering an assessment of the quality of included studies, they revealed similar rates with 9% for low-risk-of-bias studies and 8% for studies with a moderate risk of bias.

One of the main strengths of this review is the comprehensive search of multiple databases using an African search filter for the first time. We systematically and vigorously assessed all the data available with no language exclusions, using the most recently published standard quality assessment tools for prevalence studies. Furthermore, for the first time in GAS prevalence reviews, double arcsine transformation was used to stabilise the variance of primary studies before pooling, thus limiting the impact of studies with either small or large prevalence on the overall pooled estimates, as well as across major subgroups.

Significant heterogeneity in the prevalence estimates is regarded as a limitation to this systematic review. Attempts to completely explain the heterogeneity were unsuccessful in terms of subgroup analyses. It is difficult to make comparisons between populations unless every effort is made to use standard epidemiological and laboratory efforts in each survey. Therefore, caution must be applied in trying to draw too many conclusions about differences in prevalence rates that are in the same range. Also, four articles were translated into English[13,19,29,30] which might have led to information loss, thus reducing the quality of data extracted.

Conclusions

The findings of this review and primary study provide important baseline information for healthcare workers regarding the carriage of GAS among asymptomatic children in Africa. Given the low rate of GAS carriage, it is highly likely that GAS isolated during pharyngitis plays a pathogenic role.

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Author contributions. MEE conceived of the study. MEE designed the primary study and together with HM and LA, designed the secondary study. JD, AW and BMM gave conceptual advice, interpreted the data and edited the manuscript. MEE implemented and managed the primary study, conducted the analysis with BMM, interpreted the data and wrote the manuscript; HM implemented and managed the secondary study. SN recruited participants and together with LA and DDB collected and managed the data and assisted with the analysis. All authors read and approved the final draft of the manuscript.

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Conflicts of interest. None.

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