Streptococcus pyogenes carriage and infection within households in The Gambia: a longitudinal cohort study

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Summary

Background ***Streptococcus pyogenes*** **causes more than 500 000 deaths per year globally, which occur disproportionately in low-income and middle-income countries. The roles of *S pyogenes* skin and pharyngeal carriage in transmission are unclear. We aimed to investigate the clinical epidemiology and household transmission dynamics of both *S pyogenes* asymptomatic carriage and infection in a high-burden setting.**

Methods **We did a 1-year prospective, longitudinal, household cohort study, recruiting healthy participants from households in Sukuta, The Gambia. Households were eligible if they comprised at least three members, including one child younger than 18 years, and were excluded if more than half of household members declined to participate. Households were identified by random GPS coordinates derived from census data. At monthly visits, pharyngeal and normal skin swabs were collected for *S pyogenes* culture, and sociodemographic data were recorded by interview. Incident pharyngitis and pyoderma infections were captured. Cultured isolates underwent *emm* genotyping. The primary outcome measures were incidence of *S pyogenes* carriage and disease. Additional outcomes were prevalence of *S pyogenes* skin and pharyngeal carriage, *S pyogenes* skin and pharyngeal clearance time, *S pyogenes emm* type, risk factors for carriage and disease events, household secondary attack rate, and *emm*-linked household transmission events. The study is registered on ClinicalTrials.gov, NCT05117528.**

Findings **Between July 27, 2021, and Sept 28, 2022, 442 participants were enrolled from 44 households. The median age was 15 years (IQR 6–28) and 233 (53%) were female. We identified 17 pharyngitis and 99 pyoderma events and 49 pharyngeal and 39 skin *S pyogenes* carriage acquisition events. Mean monthly prevalence was 1·4% (95% CI 1·1–1·9) for *S pyogenes* pharyngeal carriage and 1·2% (0·9–1·6) for *S pyogenes* skin carriage. Incidence was 120 per 1000 person-years (95% CI 87–166) for *S pyogenes* pharyngeal carriage, 124 per 1000 person-years (90–170) for *S pyogenes* skin carriage, 51 per 1000 person-years (31–84) for *S pyogenes* pharyngitis, and 263 per 1000 person-years (212–327) for *S pyogenes* pyoderma. Pharyngeal carriage risk was higher during the rainy season (HR 5·67, 95% CI 2·19–14·69) and in larger households (per additional person: 1·03, 1·00–1·05), as was pharyngitis risk (rainy season: 3·00, 1·10–8·22; household size: 1·04, 1·02–1·07). Skin carriage risk was not affected by season or household size, but was lower in female than in male participants (0·45, 0·22–0·92) and highest in children younger than 5 years compared with adults (22·69, 3·08–167·21), with similar findings for pyoderma (female sex: 0·34, 0·19–0·61; age <5 years: 7·00, 2·78–17·64). Median clearance time after carriage acquisition was 4·0 days for both skin (IQR 3·5–7·0) and pharynx (3·5–7·3). The mean household secondary attack rate was 4·9 (95% CI 3·5–6·3) for epidemiologically linked *S pyogenes* events and 0·74 (0·3–1·2) for *emm*-linked *S pyogenes* events. Of the 204 carriage and disease events, *emm* types were available for 179 (88%). Only 18 *emm*-linked between-visit household transmission events were identified. Pyoderma was the most common source of *S pyogenes* household transmissions in 11 (61%) of 18 *emm*-linked transmissions. Both pharynx to skin and skin to pharynx transmission events were observed.**

Interpretation ***S pyogenes*** **carriage and infection are common in The Gambia, particularly in children. Most events are non-household acquisitions, but skin carriage and pyoderma have an important role in *S pyogenes* household transmission and bidirectional transmission between skin and pharynx occurs.**

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Introduction

Streptococcus pyogenes causes a spectrum of disease from superficial pharyngeal and skin infections to invasive disease. It results in more than 500 000 deaths each year,[1] and an estimated 1·8 million invasive infections, 111 million pyoderma, and 616 million pharyngitis cases

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Research in context

Evidence before this study

In Africa, there is a paucity of research into *Streptococcus pyogenes* and its sequelae, despite a substantial disease burden. We searched PubMed from database inception to Dec 31, 2023, for studies in any language related to *S pyogenes* carriage and infection epidemiology and transmission, using the search terms "Streptococcus", "pyogenes", "GAS", "StrepA", "carriage", "asymptomatic", "colonisation", "pharyngitis", "impetigo", "pyoderma", and "transmission". Few studies of *S pyogenes* have been conducted in Africa. Cross-sectional studies from Uganda, Ethiopia, and Zambia have documented pharyngeal carriage of 10–19% in children younger than 18 years. One review of *S pyogenes* infections in Africa found the pooled prevalence of *S pyogenes*-positive pharyngitis to be 21% and that pyoderma positivity ranged from 32–74%. In Africa, only one study has previously identified *S pyogenes* skin carriage and no longitudinal cohort studies of *S pyogenes* incidence and household transmission have been performed. In contrast to other pathogens, the relationship between *S pyogenes* asymptomatic carriage and infection is not clear. Studies conducted in the Red Lake Indian reservation in the 1960s hinted at the role of skin carriage and infection in transmission, but similar intensive sampling studies have not been repeated. In 2023, a re-analysis using whole-genome sequencing of a surveillance study conducted in Aboriginal communities in Australia has indicated the importance of pharyngeal carriage as a reservoir for *S pyogenes* transmission and shown evidence of throat-to-skin transmission.

Added value of this study

This study used frequent microbiological sampling and *emm* typing from normal skin, pharynx, and wounds in a longitudinal household design over 1 year, combined with clinical and sociodemographic data, to understand the clinical and molecular epidemiology of *S pyogenes* over time in an African setting for the first time. We describe a comprehensive overview of the epidemiology of *S pyogenes* in this setting, as well as providing evidence of important transmission routes within households.

Implications of all the available evidence

Various interventional and public health strategies could be applied to African settings to reduce the burden of *S pyogenes*-related disease, and vaccines in development will be an important addition. With so few studies into the natural history of *S pyogenes* carriage and natural infection over time, there is limited understanding of which approaches to use or how to target them. This study builds on studies from other settings and provides evidence for the first time in Africa of the importance of *S pyogenes* skin infections and asymptomatic carriage in household transmission. Evidence from this study will be useful in the design of future surveillance and interventional studies in such settings, which are vital to tackle the burden of *S pyogenes*-related disease globally.

occur globally.[1,2] The largest burden is in low-income and middle-income countries (LMICs), where the post-infection immune-mediated sequelae of acute post-streptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease cause substantial morbidity and mortality.[3] Rheumatic heart disease results in more than 300 000 deaths each year, predominantly in settings where diagnosis and surveillance are poor.[3,4] Despite this burden of mortality, *S pyogenes* receives little attention in global health programmes.[5] The World Health Assembly has now declared *S pyogenes* vaccine development a global research priority and the WHO roadmap for *S pyogenes* vaccines highlighted the lack of understanding of clinical epidemiology and transmission patterns as major research gaps.[6]

Asymptomatic pharyngeal colonisation (carriage) of *S pyogenes* is common and often viewed as inconsequential and not requiring treatment, and *S pyogenes* carriage on normal skin, which is known to increase pyoderma risk, is rarely studied.[7–9] Although data from the UK and Australia suggest that pharyngeal carriage could play a role in onward transmission of *S pyogenes*, its significance and that of skin carriage in Africa are unknown.[10,11]

In The Gambia, the burden of *S pyogenes* disease is largely unknown, although a substantial burden of rheumatic heart disease exists.[12] One cross-sectional study of children younger than 5 years found an 8·8% prevalence of *S pyogenes* pyoderma and suggested an increase in pyoderma risk during the rainy season.[13] Whole-genome sequencing and *emm* typing of Gambian *S pyogenes* isolates has shown a higher diversity of *emm* types than that seen in high-income countries.[9,14,15] The extent of skin carriage is unknown, but one study using quantitative PCR (qPCR) on nasopharyngeal samples from The Gambia showed high rates of *S pyogenes* carriage and an increase in antibody titres to several *S pyogenes* antigens after colonisation.[16] Widespread carriage might contribute to transmission, strain diversity, and immunity in this setting.

Longitudinal studies of *S pyogenes* carriage and infection have not been performed in Africa. We established a household cohort to understand the clinical and molecular epidemiology of *S pyogenes* and factors affecting transmission in this setting.

Methods

Study design and participants

We performed a prospective, longitudinal, household cohort study in the urban area of Sukuta, The Gambia, over a 13-month period in 2021–22. The study protocol has been published previously.[17] In brief, households containing at least three members, including one child younger than

18 years, were eligible for inclusion. Households were excluded if more than 50% of household members declined to participate. All individuals residing in the households were invited to participate, with the exclusion of those with any condition or circumstance that might cause difficulty or discomfort in sample collection, or those deemed by a study team member as unable or unlikely to adhere to the study protocol. Households were identified by random GPS selection (appendix p 14). Random GPS coordinates within the boundaries of Sukuta were derived from 2013 census data using QGIS version 3.12, stratified by low, medium, and high housing density areas. For each set of GPS coordinates, the nearest household was approached for participation, until the target number of households was met.

The study was approved by the Gambia Government/Medical Research Council joint ethics committee and the London School of Hygiene & Tropical Medicine Research Ethics Committee (LEO24005). Written informed consent was provided by adult participants and by parents or guardians for participants younger than 18 years. Children aged 12–17 years provided assent. The study is registered on ClinicalTrials.gov, NCT05117528.

Procedures

Consenting households underwent a baseline monthly visit (MV0) followed by 12 scheduled monthly visits (MV1–12). An open cohort approach was used with new household members able to enrol at any monthly visit. Sociodemographic data were collected at each monthly visit.

At monthly visits, participants were asked to provide an oropharyngeal swab (Copan Transystem 140C, Copan, Brescia, Italy) and a composite normal skin swab from skin surfaces on the arms, legs, and forehead (using flocked nylon fibre swabs, CITOSWAB, Nanjing, China). Participants who acquired new carriage were swabbed from the positive site (oropharyngeal or normal skin swab) at additional weekly visits until two consecutive negatives to estimate clearance time (clearance time cohort). 16 households, randomly selected using the *pps* package in R, underwent weekly intensive visits for 6 weeks during which oropharyngeal swabs and normal skin swabs were taken (intensive sampling cohort). Intensive visits were included in the clearance time and infection incidence analysis, but not the carriage incidence analysis. A wound swab (Copan) was taken when participants exhibited pyoderma. Participants presenting with a sore throat or skin lesions between scheduled visits were seen at unscheduled visits, at which an oropharyngeal swab or wound swab was taken as appropriate to capture incident pharyngitis and pyoderma events. Disease events were treated empirically with antibiotics (appendix p 5). Carriage events were not treated, in line with the Infectious Diseases Society of America guidelines.[9]

Swabs were placed in liquid Amies transport medium (Copan or CITOSWAB) and kept in a cold box until culture the same day. Swabs were plated on Colombia blood agar and beta-haemolytic colonies underwent latex agglutination testing (Prolex, Pro-Lab, Bromborough, UK) for group A *Streptococcus* (appendix p 4). Isolates positive for group A *Streptococcus* were assumed to be *S pyogenes*. Isolates were sent to the Molecular Bacteriology Laboratory (Brussels, Belgium; MBLB) for *emm* typing. Isolates underwent PCR-based *emm* typing as previously described.[18] *Emm* types and subtypes were assigned according to the US Centers for Disease Control and Prevention (CDC) database. New subtypes were assigned by CDC for the newly described sequences (appendix p 4).

See **Online** for appendix

For **QGIS** see https://www.qgis.org

S pyogenes events were defined as either disease (presence of *S pyogenes* with clinical symptoms of pharyngitis or pyoderma) or carriage (presence of *S pyogenes* without clinical symptoms; appendix p 2). Weekly visits were excluded from carriage incidence analysis to avoid bias. Baseline events were defined as events occurring at an individual's enrolment visit (whether at MV0 or a later monthly visit).

We defined clearance time as the time from carriage acquisition at a monthly visit or intensive visit until the midpoint between the date of the last positive swab (of the same *emm* type) and the date of the first of the two subsequent negative swabs (appendix p 6). Episodes were excluded if more than one consecutive weekly visit was missed, or if only one negative weekly visit was done at the end of an episode.

Follow-up time for carriage incidence was from enrolment until either MV12 or the midpoint between the last attended monthly visit and the first missed monthly visit. For missed monthly visits, a gap in follow-up was included from the midpoint between the last attended monthly visit and the first missed monthly visit to the midpoint between the last missed monthly visit and the next attended monthly visit. Unscheduled visits, weekly visits, and intensive visits were not included in the carriage incidence follow-up time. For disease incidence, if participants had an unscheduled visit, weekly visit, or intensive visit during a gap in follow-up, an additional 15 days of follow-up time was added (appendix pp 2–3).

We investigated the interaction between the four different event types (pharyngitis, pyoderma, pharyngeal carriage, and skin carriage) using two defined transmission windows to explore transmission within households. *S pyogenes* events that occurred within the same household within a range of 0–2 days were considered within-visit linkages, for which it was not possible to determine directionality of transmission. Events occurring within 3–42 days were considered to represent between-visit linkages. Linkages for which the *S pyogenes* isolates were of different *emm* types were considered epidemiologically linked. Linkages for which the isolates were identical *emm* types were considered *emm*-linked. Concurrent event types occurred when two event types with the same *emm* type were present within 0–2 days in an individual, and event-type changes occurred when two different event types of identical *emm* type occurred in one individual within 3–42 days.

Household secondary attack rate was calculated for between-visit linkages as the proportion of household members swabbed within 3–42 days who had an event in

that time. Household secondary attack rate was calculated for epidemiologically linked events and *emm*-linked events.

Outcomes

The primary outcome of this study was incidence of *S pyogenes* carriage and disease. Additional outcomes were baseline and monthly prevalence of *S pyogenes* skin and pharyngeal carriage, *S pyogenes* skin and pharyngeal clearance time, *S pyogenes emm* type, household secondary attack rate, risk factors for carriage and disease events, and *emm*-linked household transmission events. Monthly prevalence and incidence were stratified by sex and age group (age <5 years, 5–11 years, 12–17 years, and ≥18 years).

Statistical analysis

Detailed sample size considerations are described in the protocol.[17] Briefly, we estimated that 450 individuals would give sufficient power to detect a carriage prevalence of 15% (plus or minus 5%) and risk factors for *S pyogenes* carriage with rate ratios of greater than 2.[17] Data were entered into REDCap.[19] Analysis was performed in R version 4.2.2. Baseline carriage and disease prevalence was calculated as the proportion of participants positive at their enrolment visit with binomial exact 95% CIs. Baseline events were excluded from the incidence and regression analyses. Monthly carriage prevalence was calculated as the proportion of participants swabbed at each monthly visit with carriage with binomial exact 95% CIs. Incidence rates were calculated as events per 1000 person-years with 95% CIs, stratified by sex and age group. Clearance time was described using medians with IQRs and ranges. Wilcoxon rank-sum tests were used for differences in clearance time. The Andersen-Gill extension of the Cox model was used to identify sociodemographic risk factors for disease and carriage (appendix pp 2–3). Hazard ratios (HRs) were calculated in multivariable models including sex, age group, season, and household size (appendix p 2). Age group and sex were added to the model as fixed variables, whereas household size and season were added as time-varying covariates. Household secondary attack rate was calculated with 95% CIs. p values of less than 0·05 were considered to indicate statistical significance.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We recruited 337 participants from 44 households between July 27 and Sept 2, 2021, at MV0. An additional 105 participants from the same households were recruited at subsequent monthly visits, resulting in a total of 442 participants (figure 1). Final visits were conducted between June 28 and Sept 28, 2022. The cohort comprised 256 (58%) children younger than 18 years; the median age was 15 years (IQR 6–28), 233 (53%) were female, and the median household size was seven individuals (IQR 6–10; table 1, appendix p 7). Total follow-up time was 311·4 years (mean 0·71 years per individual [SD 0·34]) for disease events and 307·5 years (mean 0·70 years per individual [0·34]) for carriage events.

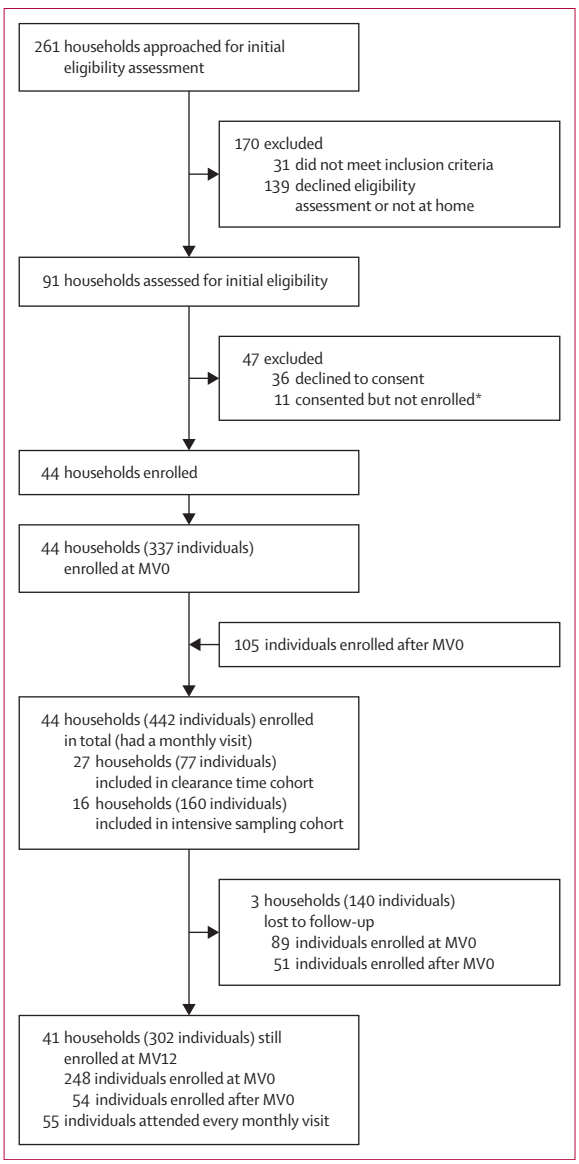

Figure 1: **Study flow diagram**
MV0=baseline monthly visit. MV12=scheduled monthly visit 12. *The study capacity was 44 households; an additional 11 households were kept in reserve in case of withdrawals.

We identified 116 *S pyogenes* disease events (17 pharyngitis and 99 pyoderma) and 88 *S pyogenes* carriage acquisition events (49 pharyngeal and 39 skin). Pyoderma occurred simultaneously with pharyngitis on one occasion, with pharyngeal carriage on three occasions, and with skin carriage on four occasions. No invasive infection events, acute rheumatic fever, or other immune sequelae occurred.

	Participants (n=441*)
Sex	
Male	208 (47%)
Female	233 (53%)
Median age, years (IQR; range)	15 (6–28; 0–85)
Age group, years	
<5	104 (24%)
5–11	79 (18%)
12–17	73 (17%)
≥18	185 (42%)
Ethnic group	
Mandinka	311 (71%)
Wolof	30 (7%)
Fula	43 (10%)
Jola	17 (4%)
Serehule	12 (3%)
Serere	12 (3%)
Manjago	6 (1%)
Non-African	3 (1%)
Other	2 (<1%)
Missing	5 (1%)
Median household size, n (IQR; range)	7 (6–10; 4–37)†

Data are n (%) unless indicated otherwise. *Total cohort was n=442 but demographic information was missing for one participant. †Median household size for each household across all monthly visits.

Table 1: **Sociodemographic characteristics of the cohort**

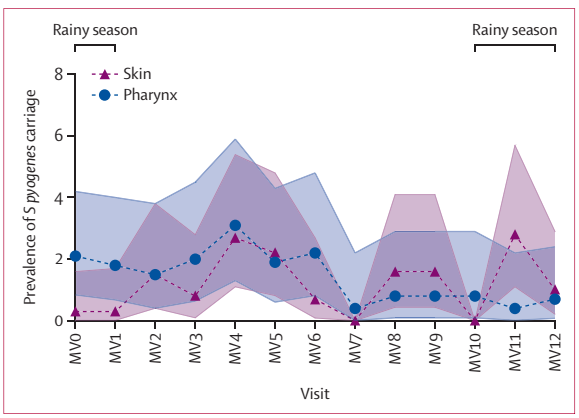

Figure 2: **Prevalence of *S pyogenes* pharyngeal and skin carriage at each monthly visit**

Shaded areas indicate 95% CIs. Carriage prevalence at MV0 is not the same as baseline because baseline included each participant's enrolment visit, which could have been after MV0. *S pyogenes*=*Streptococcus pyogenes*. MV0=baseline monthly visit. MV1–12=scheduled monthly visits 1–12.

Baseline *S pyogenes* pharyngitis prevalence was 0·2% (95% CI 0·0–1·3; one of 442) and pyoderma prevalence was 3·8% (2·3–6·1; 17 of 442). Pharyngeal carriage at baseline was 2·7% (1·4–4·7; 12 of 442) and skin carriage prevalence was 0·2% (0·0–1·3; one of 442; appendix p 8).

Monthly *S pyogenes* pharyngeal carriage prevalence ranged from 0·4% (95% CI 0·01–2·2; one of 249) to 3·1% (1·1–5·4; eight of 261) with a mean of 1·4% (1·1–1·9). Monthly *S pyogenes* skin carriage prevalence ranged from 0·0% (0·0–0·0; none of 249) to 2·8% (1·1–5·7; seven of 248) with a mean of 1·2% (0·9–1·6). There was no clear seasonal trend throughout the study period (figure 2).

The incidence of *S pyogenes* pharyngeal carriage (120 per 1000 person-years; 95% CI 87–166) and skin carriage (124 per 1000 person-years; 90–170) acquisition was similar. For disease events, of 147 episodes of symptomatic pharyngitis, 16 (11%) were *S pyogenes* positive, resulting in an incidence of 51 per 1000 person-years (31–84). Of 170 symptomatic pyoderma episodes, 82 (48%) were *S pyogenes* positive, resulting in an incidence of 263 per 1000 person-years (212–327; table 2).

Incidence of skin carriage was higher in male participants (199 per 1000 person-years, 95% CI 137–290) than female participants (64 per 1000 person-years, 35–116). Similarly, pharyngeal carriage was higher in male participants (162 per 1000 person-years, 107–246) than female participants (87 per 1000 person-years, 53–145). Pharyngeal carriage occurred most frequently in children aged 5–11 years (245 per 1000 person-years, 145–414), whereas skin carriage was most common in children younger than 5 years (239 per 1000 person-years, 156–366).

S pyogenes pyoderma was the most frequently observed event overall. It was more common in male participants (458 per 1000 person-years, 95% CI 358–587) than female participants (109 per 1000 person-years, 70–171) and, in terms of age groups, it was most common in children younger than 5 years (520 per 1000 person-years, 389–694), followed by children aged 5–11 years (412 per 1000 person-years, 276–615). *S pyogenes* pharyngitis was most common in children aged 5–11 years (120 per 1000 person-years, 57–252) and was similar in male and female participants (58 per 1000 person-years, 29–116, *vs* 46 per 1000 person-years, 23–92).

Overall, 33 *emm*-matched pharyngeal carriage episodes in 29 participants and 43 *emm*-matched skin carriage episodes in 39 participants were available. Histograms of clearance time were right-skewed (appendix p 9). Median clearance time was 4·0 days (IQR 3·5–7·0; range 3·0–42·5) for pharyngeal episodes and 4·0 days (3·5–7·3; 3·0–27·5) for skin episodes (p=0·84).

Antibiotics were prescribed at the start of two pharyngeal episodes due to pyoderma occurring concurrently. Antibiotics were given at the end of one episode and in the middle of one episode due to pharyngitis. Pyoderma occurred simultaneously with skin carriage at the start of seven skin episodes, six of which were treated with antibiotics. Of those, five were negative by the next visit. Pharyngitis occurred at the start of one skin episode, which was treated with antibiotics. Overall, antibiotics were given in four (12%) of the 33 pharyngeal episodes, compared with 10 (23%) of the 43 skin episodes (p=0·22). Clearance time length was not significantly affected by antibiotic use (p=0·15 for pharyngeal clearance and p=0·13 for skin clearance).

In multivariable Cox regression models, there was an increased risk of both pharyngeal carriage acquisition (HR 5·67, 95% CI 2·19–14·69, p=0·0004) and pharyngitis

	S pyogenes carriage		*S pyogenes* disease		
	Events	Incidence per 1000 person-years (95% CI)	Symptomatic episodes	Events	Incidence per 1000 person-years (95% CI)
Pharynx or skin					
Overall	75	244 (194–306)	309	97	311 (255–380)
Sex					
Male	49	361 (273–478)	168	70	509 (403–644)
Female	26	151 (103–222)	141	27	155 (106–226)
Age group, years					
<5	36	409 (295–568)	122	48	542 (409–720)
5–11	24	420 (282–627)	81	30	515 (360–736)
12–17	8	197 (98–393)	29	8	194 (97–387)
≥18	7	58 (27–121)	77	11	89 (49–161)
Pharynx					
Overall	37	120 (87–166)	147	16	51 (31–84)
Sex					
Male	22	162 (107–246)	55	8	58 (29–116)
Female	15	87 (53–145)	92	8	46 (23–92)
Age group, years					
<5	15	171 (103–283)	34	2	23 (6–90)
5–11	14	245 (145–414)	42	7	120 (57–252)
12–17	2	49 (12–196)	20	2	48 (12–194)
≥18	6	49 (22–110)	51	5	41 (17–97)
Skin					
Overall	38	124 (90–170)	170	82	263 (212–327)
Sex					
Male	27	199 (137–290)	120	63	458 (358–587)
Female	11	64 (35–116)	50	19	109 (70–171)
Age group, years					
<5	21	239 (156–366)	92	46	520 (389–694)
5–11	10	175 (94–325)	43	24	412 (276–615)
12–17	6	147 (66–328)	9	6	145 (65–323)
≥18	1	8 (1–58)	26	6	49 (22–108)

Incidence events do not include baseline events (positive at enrolment visit). *S pyogenes*=*Streptococcus pyogenes*.

Table 2: **Pharyngeal and skin *S pyogenes* carriage acquisition and disease incidence rates over the study period, stratified by sex and age group**

(3·00, 1·10–8·22, p=0·032) during the rainy season, whereas pyoderma and skin carriage were not affected by season (table 3).

Similarly, for each additional person in a household, we observed an increase in both pharyngeal carriage (HR 1·03, 95% CI 1·00–1·05, p=0·030) and pharyngitis (1·04, 1·02–1·07, p=0·0001) risk, whereas neither pyoderma nor skin carriage showed an association with household size. By contrast, risk of pharyngeal carriage and pharyngitis was not associated with sex, whereas the risk of pyoderma (0·34, 0·19–0·61, p=0·0003) and skin carriage (0·45, 0·22–0·92, p=0·030) was lower in female participants than male participants.

Compared with adults, the highest risk of pharyngeal carriage was in children aged 5–11 years (HR 4·80, 95% CI 1·71–13·49) followed by children younger than 5 years (2·92, 1·53–5·58). Skin carriage risk was highest in children younger than 5 years (22·69, 3·08–167·21), followed by children aged 5–11 years (18·44, 2·70–126·08). Pyoderma risk was also highest in children younger than 5 years (7·00, 2·78–17·64) followed by children aged 5–11 years (6·60, 2·77–15·74), but pharyngitis risk was not significantly associated with age (table 3).

Of 252 *S pyogenes*-positive swabs, 227 (90%) were successfully regrown and sent to MBLB for *emm* typing. One isolate failed to regrow, six were regrown but later tested as group G *Streptococcus*, and one isolate previously identified as group G *Streptococcus* was found to be group A *Streptococcus* at MBLB. Among 221 *S pyogenes* isolates that were successfully *emm* typed, 57 different *emm* subtypes were identified, including three new subtypes (data not shown). From the 204 separate carriage and disease events defined earlier, *emm* types were available for 179 (88%).

We identified 128 epidemiologically linked events that occurred 3–42 days after an index event, of which 18 (14%) were of identical *emm* type. Mean household secondary attack rates for transmission linkages are shown in table 4.

We identified 42 within-visit linkages with isolates of the same *emm* type, and 18 between-visit linkages (figure 3). For within-visit linkages, the most common event types that were linked were skin carriage with skin carriage (12 [29%] of 42 linkages), skin carriage with pyoderma (ten [24%] of 42 linkages), and pyoderma with pyoderma (eight [19%] of 42 linkages; appendix p 10). No transmissions between pharyngitis and pyoderma or skin carriage were identified. Of 18 between-visit transmissions identified, pyoderma was the source in 11 (61%), and the median serial interval was 28 days (IQR 15–29). The most common routes of transmission were pyoderma to pharyngeal carriage (three [17%] of 18 linkages), pyoderma to skin carriage (three [17%] of 18 linkages), and pyoderma to pharyngitis (three [17%] of 18 linkages; appendix p 11).

We identified eight occasions on which a different event-type occurred in the same individual within the transmission windows. Concurrent (within-visit) event types in one individual were identified five times, of which four (80%) were concurrent pyoderma and skin carriage and one was concurrent pyoderma and pharyngeal carriage. Three between-visit event-type changes were identified: two from skin carriage to pyoderma and one from pyoderma to pharyngeal carriage. No event-type changes from pharyngeal carriage to pharyngitis occurred (appendix p 13). The longest gap between events of the same *emm* type within a household was 252 days (appendix p 12).

Discussion

The findings of this longitudinal cohort study demonstrate a substantial burden of *S pyogenes* carriage and disease in The Gambia, especially in children. To our knowledge, this is the first evidence from Africa to show bidirectional household transmission of *S pyogenes* between the pharynx and the skin, that both pharyngeal and skin carriage are transmission sources, and that pyoderma is the predominant source of transmission to household contacts. However, the majority of events were not *emm* type-linked household

	S pyogenes carriage				*S pyogenes* disease			
	Pharynx (37 events)		Skin (38 events)		Pharynx (16 events)		Skin (82 events)	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Rainy season	5·67 (2·19–14·69)	0·0004	0·42 (0·09–1·91)	0·26	3·00 (1·10–8·22)	0·032	1·14 (0·34–3·84)	0·83
Sex		0·24		0·030		0·51		0·0003
Male	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Female	0·71 (0·40–1·26)	..	0·45 (0·22–0·92)	..	0·75 (0·31–1·77)	..	0·34 (0·19–0·61)	..
Age group, years		0·0009		0·022		0·055		0·0001
<5	2·92 (1·53–5·58)	..	22·69 (3·08–167·21)	..	0·43 (0·11–1·69)	..	7·00 (2·78–17·64)	..
5–11	4·80 (1·71–13·49)	..	18·44 (2·70–126·08)	..	2·86 (0·95–8·58)	..	6·60 (2·77–15·74)	..
12–17	0·92 (0·18–4·64)	..	16·52 (2·58–106·93)	..	1·15 (0·38–3·43)	..	2·69 (1·18–6·12)	..
≥18	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Household size	1·03 (1·00–1·05)	0·030	1·00 (0·98–1·01)	0·74	1·04 (1·02–1·07)	0·0001	1·01 (1·00–1·03)	0·14

HR and CI values are rounded to two decimal places. p values are rounded to two significant figures (to a maximum of four decimal places). *S pyogenes*=*Streptococcus pyogenes*. HR=hazard ratio.

Table 3: **Multivariable Cox proportional hazards regression models showing the impact of sociodemographic factors on *S pyogenes* carriage acquisition and disease**

transmissions, but rather appeared to be new introductions to the household. These findings provide fundamental insights into the dynamics of *S pyogenes* transmission and will inform intervention strategies to reduce *S pyogenes* transmission and disease.

Although the incidence of *S pyogenes* carriage was similar between the pharynx and the skin, we identified a higher number of pyoderma episodes than pharyngitis episodes. The role of skin infections in the development of acute rheumatic fever has been debated,[20,21] but it is likely that repeated infections of the skin contribute to immune priming ahead of an event that triggers acute rheumatic fever.[22–24] We demonstrate that *S pyogenes* pyoderma is common in the age group most at risk of immune priming and that pyoderma is a key source of household transmission. We observed substantial diversity of *S pyogenes emm* types, consistent with previous findings.[14,15] Exposure of children to the diversity of *S pyogenes emm* types seen in LMICs could be a contributing factor in immune priming for acute rheumatic fever and rheumatic heart disease.[22,25,26] The higher risk of pyoderma in male participants was unexpected and in contrast to previous findings.[13] More work is required to confirm this finding and whether it should influence pyoderma prevention strategies.

Onward transmission of *emm* types within households occurred from all four event types (pharyngitis, pyoderma, pharyngeal carriage, and skin carriage). Most events are likely to have originated from a non-household source. Nevertheless, for within-visit transmissions, there was extensive interaction between pyoderma wounds and skin carriage, and pyoderma was the source in most of the between-visit transmissions identified, suggesting *S pyogenes* on the skin could be the predominant source of transmission within households and the main source of event-type change within individuals. Relatively few household transmission events were identified, suggesting

	Index events*	Between-visit (3–42 days) transmissions			
		Epidemiologically linked events†		*emm*-linked events‡	
		Secondary events	Mean HSAR (95% CI)	Secondary events	Mean HSAR (95% CI)
Overall	169	128	4·9 (3·5–6·3)	18	0·74 (0·3–1·2)
Event					
Pharyngeal carriage	40	30	4·6 (1·4–7·8)	2	0·71 (0·0–1·7)
Skin carriage	33	20	6·0 (2·4–9·4)	2	0·58 (0·0–1·5)
Pharyngitis	15	19	6·8 (0·6–12·9)	3	0·80 (0·0–2·0)
Pyoderma	81	59	4·2 (2·4–6·0)	11	0·81 (0·1–1·6)

HSAR=household secondary attack rate. *S pyogenes*=*Streptococcus pyogenes*. *Events at which *emm* type was available and at least one household member was swabbed within 3–42 days. †Any *S pyogenes*-positive event occurring within 3–42 days of the index event. ‡*S pyogenes* positive even with identical *emm* type occurring within 3–42 days of the index event.

Table 4: **Mean HSAR for between-visit transmissions for epidemiologically linked events and *emm*-linked events**

that most acquisitions occur elsewhere. Future research should aim to better understand *S pyogenes* transmission dynamics beyond the household environment.

S pyogenes-positive pharyngitis was rare and served as the transmission source with a frequency similar to that of pharyngeal and skin carriage. Of note, we did not identify any occasions on which an individual was identified as a pharyngeal carrier and then progressed to pharyngitis. On only one occasion was an individual identified as a pharyngeal carrier after an episode of pharyngitis. These findings suggest that in this setting, pharyngitis and pharyngeal carriage do not represent different stages in the natural history of pharyngitis, but rather represent two ends of the symptomatic spectrum of pharyngeal *S pyogenes* infection. There is already increasing recognition that carriage events are not immunologically silent, which indicates that carriage might be implicated in rheumatic heart disease.[16,27] Collectively, these results raise questions about the current advice to leave asymptomatic carriage

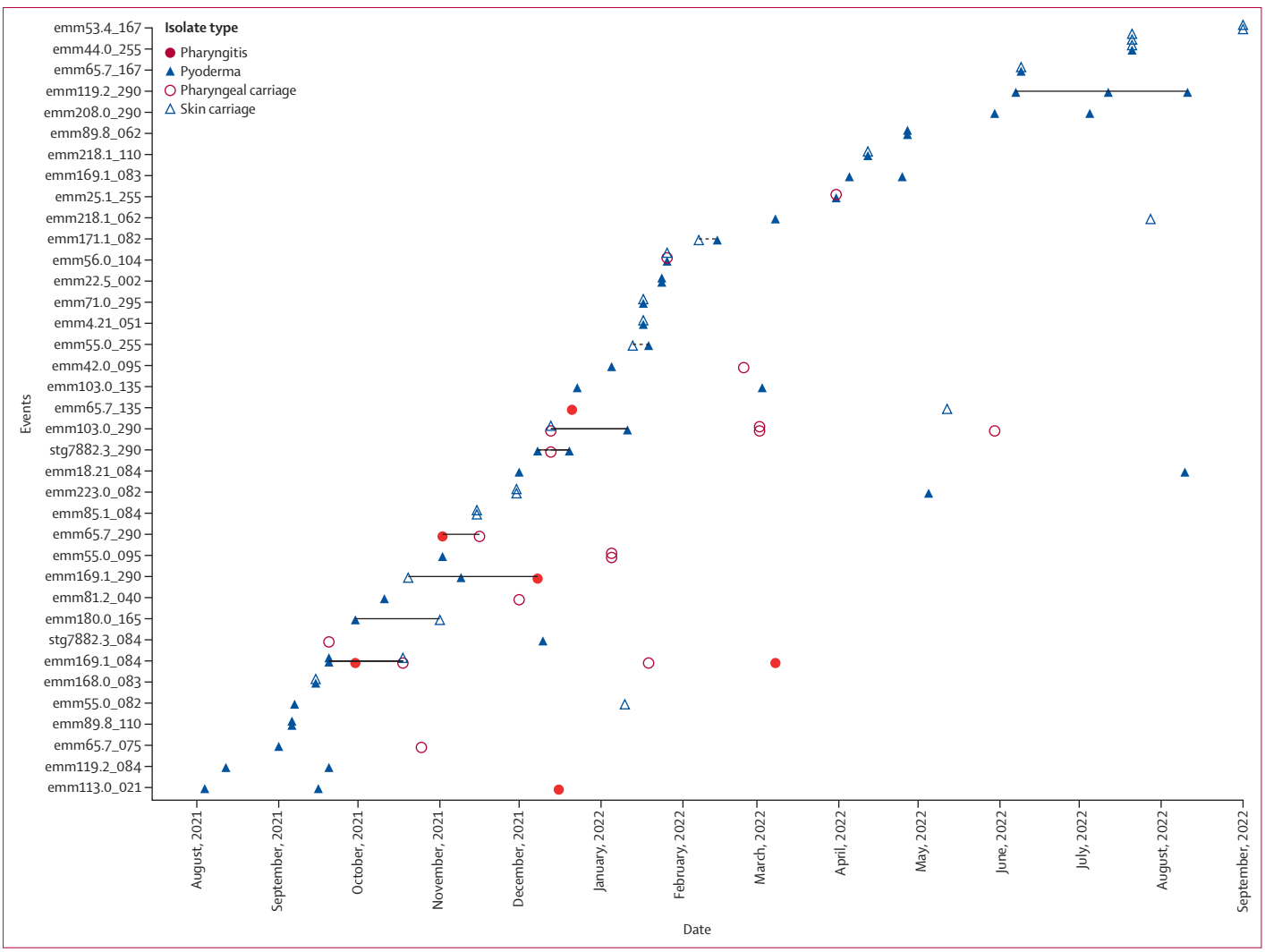

Figure 3: **Household transmission linkage timeline plot of *Streptococcus pyogenes* events across the cohort study period**
Events are grouped by each *emm* type within a household. The y-axis is arranged by date of first isolate, with labels written as *emm* type_household ID. Each point represents an isolate cultured from an individual with pharyngitis, pyoderma, pharyngeal carriage, or skin carriage. Isolates from the same visit are stacked. The solid black lines represent between-visit transmission (3–42 days) linkages of the same *emm* type (note that the lines are stacked in some instances, so not all 18 lines are visible). The dashed black lines represent between-visit event-type changes within the same individual.

untreated in settings at high risk of rheumatic heart disease. Further studies are needed to delineate the impact of treatment of asymptomatic carriage, particularly in LMICs, on transmission and immune responses.

There is an urgent need to identify strategies to reduce *S pyogenes* transmission. Although screening and treating children for *S pyogenes* carriage could potentially reduce transmission, interventions aiming to improve diagnosis and treatment of pyoderma and to increase handwashing with soap could also have a large impact.[28,29] Research is required to understand the impact that such interventions would have on transmission.

Our study has several limitations. First, although we found a considerable degree of presumed transmission with identical *emm* types, *emm* typing does not fully distinguish between *S pyogenes* lineages compared with whole-genome sequencing and pairwise identity at the single nucleotide polymorphism level. Genome sequencing of the isolates collected in this study is planned but these data are not yet available. As such, some presumed transmission events might reflect alternative introductions of separate lineages of the same *emm* type. Second, we actively identified and treated cases of disease and, as a result, the risk of transmission from household infections is probably underestimated. Third, we relied on culture to identify *S pyogenes*. Baseline *S pyogenes* nasopharyngeal colonisation prevalence of children aged 2–4 years in The Gambia using qPCR was 8·1% (95% CI 5·4–11·7) in a previous study[16] compared with 1·9% (95% CI 0·3–7·5) in children younger than 5 years in this study detected by culture. Molecular tests probably would have identified additional *S pyogenes* carriage and disease

events and transmissions. Similarly, a larger cohort would have provided greater confidence around transmission. Fourth, weekly swabbing of clearance time episodes was too infrequent to accurately estimate pharyngeal and skin clearance time and the insensitivity of culture probably led to an underestimated clearance time. Daily swabbing and diagnosis by a molecular method would be required to give a more accurate estimation. Given the short clearance times found for carriage, we probably missed incident carriage events between monthly visits. Fifth, results should be interpreted with caution due to participant absenteeism at monthly visits, the loss of several households to follow-up, and a lack of population demographics for comparison. Finally, clinical reporting of pharyngitis was less than anticipated. We recently conducted a study of health-care-seeking behaviour which suggested that many pharyngitis episodes are not reported.[30] For all of these reasons it is likely that we have underestimated the true burden of *S pyogenes* carriage, disease, and transmission in this setting.

Our study addresses a crucial gap in understanding of the burden of *S pyogenes* in Africa and the importance of pyoderma and asymptomatic carriage in the transmission of *S pyogenes* within households. Further studies to capture the burden of *S pyogenes* and its sequalae more fully in this setting are required and will underpin work towards developing effective vaccines and other interventional tools for the control of *S pyogenes*.

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Contributors

EPA, AJK, AK, TIdS, and MMar were responsible for conceptualisation of the study. EPA, AJK, and GdC curated the data. EPA performed the formal analysis. EPA, AJK, and GdC acquired the main funding, supported by AK, TIdS, MMar, CET, BK, and PRS. EPA, AJK, GdC, ES, FEC, MJ, ABi, HC, IC, BS, and MMan were responsible for the investigations. EPA, AJK, GdC, TIdS, MMar, AK, PRS, and CET developed and designed the methodology. EPA, GdC, MJ, and AJK were responsible for project administration. MMar, TIdS, BK, CET, AK, ABo, and PRS supervised the project. EPA, AJK, GdC, MMar, and TIdS were involved in validation. EPA was responsible for visualisation and the writing of the original draft. EPA, GdC, and AJK accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication. EPA, AJK, GdC, TIdS, MMar, CET, BK, PRS, ES, and FEC assisted with reviewing and editing the manuscript. All authors reviewed and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

The study protocol has been published previously.[17] The REDCap data dictionary and informed consent documents used are in the public domain (https://doi.org/10.5281/zenodo.7463052 and https://doi.org/10.5281/zenodo.7501168). All R code used for analysis in this manuscript is publicly available at https://edwinarmitage.github.io/SpyCATS_primary_analysis.html. Requests for access to individual participant data that underlie the results reported in this Article will be considered on formal request and should be directed to edwin.armitage@lshtm.ac.uk.

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