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Dear Editor,

We follow on from Locke et al.'s recent publication (1) with a paired systematic review of *Streptococcus pyogenes* (GAS) colonisation in lower and middle income countries (LMICs). Like *S. aureus*, GAS causes a spectrum of presentations from asymptomatic colonisation to skin and pharyngeal infections, and potentially fatal invasive disease. Furthermore, GAS causes post-infectious immunological sequelae including rheumatic fever and rheumatic heart disease (RHD), particularly in LMICs. There is increasing evidence that colonisation contributes to the spread of infections (2) and is not immunologically silent (3).

We performed a search using the strategy outlined previously (1), updated to 3/12/24. Studies were included if they: a) presented data on prevalence of GAS colonisation at any body site in healthy individuals in a community setting, b) were available in English language and c) had an available full-text (see PRISMA flowchart, Supplementary Fig. 1). Colonisation was defined as any GAS-positive result in an asymptomatic individual. Data synthesis was conducted as previously described (1), with meta-analyses using random-effects models to estimate pooled prevalence and assess subgroup differences.

57 studies were included, assessing 43155 participants from 56 studies for pharyngeal colonisation and 1039 from two studies for skin colonisation (one study assessed both skin and pharyngeal colonisation). Most studies were conducted in Asia (34/57 studies) and almost all focused on children (53/57 studies). Estimated pooled prevalence was 6.7% for pharyngeal colonisation (95% CI 5.2-8.4%, Supplementary Fig. 2), and 0.9% for skin colonisation (95% CI 0 – 3.3%, Supplementary Fig. 3). Between study heterogeneity was high (I^2 = 98% for pharyngeal colonisation, 86% for skin colonisation).

Subgroup analyses were performed for pharyngeal colonisation, with results detailed in Table 1. Prevalence of pharyngeal colonisation varied significantly by continent (highest in South America, 15%, 95% CI 10.6-20%; lowest in Oceania, 6.0%, 95% CI 4.3-8%), method of detection (combination methods of culture with PCR/antigen testing highest compared to culture/PCR alone), site sampled (highest in oropharynx, 7.6%; 0% in anterior nares), and comparison of children compared with adults (7.1% prevalence among studies only including children, 0% among studies exclusively including adults). However, many of these differences were primarily driven by single studies. No significant effect on prevalence was identified by study decade, proportion of each sex, nor when stratifying age groups into subgroups older and younger than 6 or 10 years. Included countries and prevalence rates are illustrated in Supplementary Fig. 4.

The pooled prevalence of antimicrobial resistance is presented in Figure 1 (n=25/57 studies, with varying number of studies assessing each antibiotic). All isolates tested were sensitive to penicillin (n=23/57 studies), while tetracycline resistance was common (pooled prevalence 50.3%, 95% CI 31.6-69%, n=12/57). Macrolide resistance, and clarithromycin resistance in particular, varied regionally. 17% of 68 isolates tested in two African studies (4,5) were clarithromycin resistant, while rates of clarithromycin reported in two Asian studies ranged from 0% of 17 isolates in Turkey (6) to 96.8% of 94 isolates in China (7).

Our systematic review highlights key gaps in our understanding of GAS colonisation. Despite evidence that skin colonisation contributes to spread of infection (2), and pyoderma can lead to rheumatic fever (8–10), only 2/57 studies assessed skin prevalence, both from western Africa (2,11). There was marked geographic disparity in available colonisation data, with one study each from LMICs in South America (12) and Oceania (13), despite Pacific Island nations having some of the highest estimated death rates from RHD globally (14). Furthermore, the vast majority of studies (53/57) included only paediatric participants, limiting the generalisability of point prevalence estimates to adult populations. Macrolide resistance data are similarly limited, despite recent inclusion of macrolide-resistant GAS on the WHO AMR priority list (15). This echoes findings from a recent review of global prevalence of macrolide-resistant GAS (16).

The role of GAS colonisation in generating protective and pathological immunity is controversial. Although often categorised as a discrete state, colonisation encompasses a dynamic spectrum of infection and host immune response (17). We sought to capture whether studies had assessed serological responses with anti-streptolysin O titres (ASOT). However, only two studies (18,19) reported titres for all participants, using differing cut-off thresholds. One study measured participant ASOT (20), using a negative result (and implied lack of immune reactivity) as a prerequisite for classification of colonisation, illustrating inconsistency in how this is defined. Consensus definitions are needed to ensure future epidemiological studies assessing GAS colonisation provide widely applicable data and to better understand the role of colonisation in immune priming leading to immunological sequelae (3).

In addition to a consistent concept of colonisation, to meaningfully measure the burden of colonisation and understand its contribution to disease transmission in different settings, consistent methodologies are required. We found that existing studies are heterogeneous, with differing detection methods, populations, and sampling sites - a significant limitation but important finding of our review. As evidenced by the significant effect on GAS prevalence by detection method and sampling site, these methodological differences limit between-country comparisons.

There are several further limitations of this review. In addition to heterogeneity in study methodology and definitions, many geographic areas with high RHD prevalence were underrepresented in included studies. There were insufficient data to investigate prevalence by *emm*-type and to conduct meta-analyses by risk determinants such as recent antibiotic use, household overcrowding or income. Finally, we assessed colonisation as measured by pooled point prevalence. Armitage et al. (2) found a median carriage duration of just 4 days in The Gambia, however, indicating that point prevalence measures may not accurately represent a population GAS colonisation burden. Longer term surveillance with comparison of mean monthly prevalence, for example, would provide a more useful measure of true colonisation prevalence and incidence.

Overall, our study expands upon a previous meta-analysis by Oliver et al. (21), focusing specifically on LMICs where disease burden is greatest, and including more recent studies and evidence on skin colonisation. Our results highlight the heterogeneity of GAS colonisation rates and resistance patterns across LMICs, underscoring the need for targeted prevention strategies. Findings emphasise the importance of improved surveillance with coordinated methods and definitions between settings to allow meaningful comparisons. As efforts towards a vaccine for GAS progress, epidemiological data such as these will be vital to inform prioritisation for delivery and monitoring to understand the potential impact of vaccination on colonisation. Further research on skin colonisation in particular, an understudied source of streptococcal disease, is essential.

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***Table 1**. Results of subgroup meta-analyses for pooled prevalence of Group A streptococcal colonisation. NB– aside from 'Overall prevalence' calculations, subgroup analyses were restricted to studies of pharyngeal colonisation to allow meaningful comparison of prevalence rates (n = 56 studies). PCR = polymerase chain reaction.*

	Subgroup	Studies (n)	Participants (n)	Estimated prevalence	95% CI	P value
Overall prevalence	Pharyngeal	56	43155	6.7	5.2 – 8.4	NA
	Skin	2	1039	0.9	0 – 3.3	
Continent	South America	2	227	15.0	10.6 – 20	0.0007
	Africa	19	10817	6.9	4.7 – 9.6	
	Asia	34	31446	6.3	4.3 – 8.5	
	Oceania	1	665	6.0	4.3 – 8	
Sampling site	Oropharynx	45	37196	7.6	5.7 – 9.7	< 0.0001
	Oral rinse	1	484	6.0	4 – 8.3	
	Nasopharynx	8	5289	4.5	2.1 – 7.8	

	Anterior nares	2	186	0.0	0 – 0.2	
Proportion male sex	0%	2	404	7.8	2.5 – 15.4	0.5937
	0-25%	2	270	3.6	1.3 – 6.5	
	25-50%	20	12918	6.5	4.3 – 9.2	
	50-75%	13	8122	8.5	5 – 12.9	
	No sex data	19	21441	6.1	3.6 – 9.2	
Age group	Children	53	42528	7.1	5.5 – 8.9	< 0.0001
	Both	2	456	1.4	0.3 – 3.1	
	Adults	1	171	0.0	0 – 1	
Decade	1980-1989	2	354	7.6	0 – 32.8	0.1547
	1990-1999	6	4582	11.9	7.5 – 17.2	
	2000-2009	17	22283	6.4	4.1 – 9.2	
	2010-2019	24	13694	6.5	4.5 – 8.8	
	2020-2025	7	2242	4.2	1.1 – 8.7	
Detection method	Culture + PCR	1	496	15.9	12.8 – 19.3	< 0.0001
	Culture + Antigen test	9	6860	8.2	3.7 – 14.1	
	Culture + Antigen test +	1	1257	7.6	6.2 – 9.2	
	Culture	41	32570	6.6	4.8 – 8.6	
	PCR	4	1972	3.2	0.6 – 7.3	

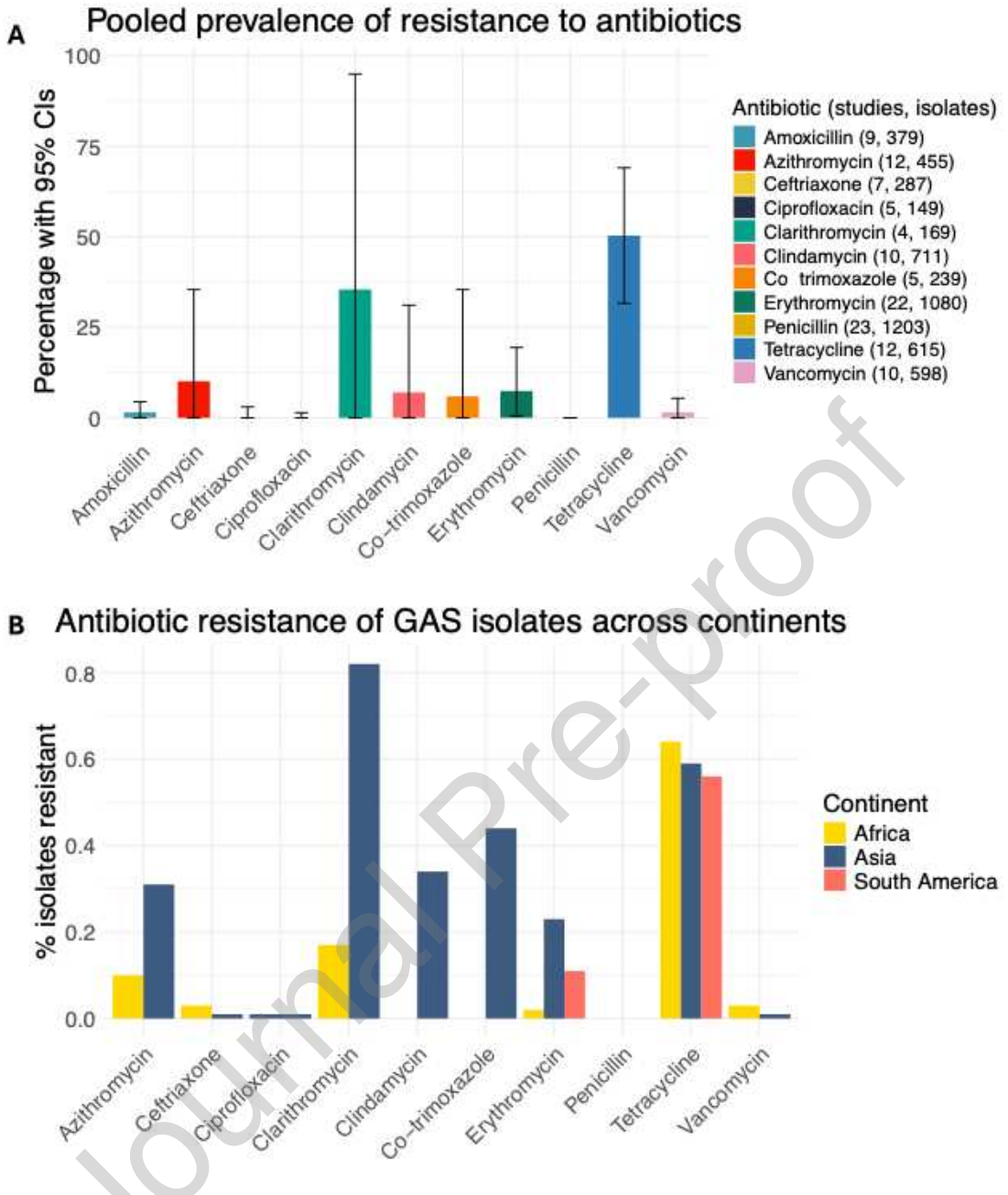

Figure 1*. A: Pooled prevalence of antibiotic resistance by antibiotics (estimate and 95% confidence intervals) with number of studies and tested isolated B: Summary of available antibiotic resistance data (% of isolates tested) by continent*

Declaration of Interest Statement

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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(2) the NIHR Decarbonising the Health and Social Care System Funding Committee

Thomas Darton -
•
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•
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•
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