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Title: Whole genome sequencing (WGS) to determine the resistome and virulome of GAS to improve management and control of RHD.

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Background & Aims: Streptococcus pyogenes (Group A streptococcus (GAS)) gives rise to various clinical presentations in humans, including the long term sequala, rheumatic heart disease (RHD), which carries a large burden on the African continent. Primary prevention strategies to control RHD include the prompt administration of antibiotics in cases of GAS pharyngitis. Fluctuating trends in the antibiotic resistance patterns of this organism have been reported worldwide. We sought to gain an understanding, using WGS, of the colonization and infection dynamics of GAS, in an attempt to inform disease management strategies and, inter alia, vaccine development.

Methods: Ninety-six GAS isolates, including emm-types commonly isolated from streptococcal pharyngitis, were identified in a prospective surveillance study in Cape Town. After culturing S. pyogenes on Trypticase soy agar supplemented with 5% sheep blood and incubated overnight at 37Â°C in 5% CO2, genomic DNA was extracted and sequenced using the Illumina MiSeq 2000 platform. WGS-analysis pipelines allows for screening for the presence of 24 surface structure, exotoxin, and virulence related gene targets and 21 streptococcal antimicrobial resistance determinants based on gene alleles. We also conducted antimicrobial susceptibility testing (AST) using the Sensititre® STP6F system to determine the minimum inhibitory concentrations of a panel of 20 clinically-relevant antibiotics. Breakpoints were assigned using the CLSI M100-Ed31(2021) guidelines. The AST results were used to validate the sequencing results.

Results: This study has documented the presence of various streptococcal pyrogenic exotoxins and surface proteins in GAS isolates from Cape Town. Ninety percent of isolates contained the hyaluronic acid capsule, which is poorly immunogenic in humans. The most prevalent genes detected among the isolates were, enn (100%), fbaa (100%) and mrp (99%) and prtf2 (87%) and sof (70%). The isolates showed the presence of various streptococcal pyrogenic exotoxins; speG (100%), smeZ (77%), speJ (57%) speC (37%), speH (33%), ssa (26%), speM (19%), speA (18%), speL (17%), speK (14%) and speI (11%). All isolates were negative for the following virulent gene targets: sda1, sic, and rocA. The remaining virulence factors comprised the following: sfb1(58%), nadase_D330G (54%), slaa (16%) and pnga3 (10%) amongst the isolates.

Tetracycline showed the highest rate of resistant isolates with 8.3%, followed by erythromycin (1%), which was confirmed with the AST results. The resistant isolates were mainly obtained from male (77.7%) participants. All 96 isolates were susceptible to moxifloxacin, penicillin, meropenem, ertapenem, cefuroxime, amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, ceftriaxone, linezolid, vancomycin, cefotaxime, clindamycin, daptomycin, cefepime, chloramphenicol and tigecycline. No difference was observed between invasive and non-invasive infection.

Conclusions: In our setting, GAS remains susceptible to routine antimicrobial agents used in our low-resourced setting. Knowledge of the prevalence of resistance and MIC trends of commonly used antibiotics for Streptococcus pyogenes will aid in avoiding therapeutic failures. This study is expected to contribute knowledge to GAS vaccine development efforts, especially in an African setting, and elucidate the role of major virulence factors which may be associated with GAS infection and RHD.