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**Title:** DIAGNOSIS OF ACUTE RHEUMATIC FEVER FOR RESEARCH AND SURVEILLANCE: LESSONS FROM LAHORE

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**Background & Aims**: There are few contemporary descriptions of acute rheumatic fever (ARF) from most regions of the world, exacerbating the challenge of reducing the global impact of its consequence, rheumatic heart disease (RHD). In addition, uncertainties remain about the performance of currently available diagnostic criteria in moderate and high-risk populations. Similarly, assessment of evidence of recent streptococcal infection by serology has its limitations. Accordingly, we studied the clinical and serological characteristics of children presenting with ARF recruited to a study of genetic susceptibility set in Lahore, Pakistan, with a view to assessing the performance of the Jones Criteria in this setting.

**Methods**: We prospectively ascertained children with ARF and RHD presenting to the Children's Hospital, Lahore, which provides general and specialist paediatric services to a large area of north-western Pakistan. Recruitment ran during 2019-2022 with interruptions for much of 2020-2021 due to the COVID pandemic. As controls, we recruited children presenting to inpatient and outpatient cardiac services for non-RHD conditions, as well as healthy adult blood donors.

Cases of ARF were recruited based on the diagnosis made by the cardiology team in Lahore before later reassessment by the study team against the 2015 Jones Criteria for moderate and high-risk populations. World Heart Federation echocardiographic criteria were used for cardiac evaluation. Measurement of anti-streptolysin O (ASO) titres was based on an automated immunoassay (Abbott, USA). We considered ASO titres of 250 IU/ml and 276 IU/ml as the upper limit of normal based on local practice and prior work in endemic settings respectively.

**Results**: We recruited 146 cases of ARF diagnosed by the clinical team (median age, 12 years; 61% male), 36 (25%) during a first episode and 110 (75%) during a recurrence. We also recruited 94 children with chronic RHD without current ARF and 248 non-ARF/RHD controls.

Among 146 ARF cases, features at diagnosis included: clinical or echocardiographic evidence of carditis in 139 (95%); polyarthritis, monoarthritis or polyarthralgia in 98 (67%); chorea in seven (5%); subcutaneous nodules in seven (5%). Together, 142 had clinical features sufficient to fulfil the Jones Criteria, while the remaining four had evidence of carditis based on the presence of a rim of pericardial effusion on echocardiography alongside one minor criterion. However, notably, in 20 (14%), the CRP and ESR had fallen below the Jones Criteria thresholds by the time of recruitment (8 first episode; 12 recurrence). In total, 15 (10%) had features of heart failure. Among the 142 with clinical features fulfilling the Jones Criteria, 104 (73%) had evidence of preceding streptococcal infection indicating a confirmed diagnosis of ARF. However, at the time of recruitment, only 71 (50%) had an ASO titre above 250 IU/ml. The remaining 38 (27%) had no confirmation of preceding streptococcal infection. For comparison, considering the higher cut-off of 276 IU/ml, the number with evidence of preceding streptococcal infection at recruitment fell to 64 (45%).

Finally, 22 (32%) RHD and 18 (23%) non-RHD participants also had ASO titres above 250 IU/ml compared to 21 RHD (31%) and 16 (21%) non-RHD participants above 276 IU/ml.

**Conclusions**: Our study has several implications for understanding the challenges of diagnosis of ARF in high risk populations. Especially noteworthy in these data is the predominance of recurrence, the frequency with which falling inflammatory markers confound the diagnosis, and the significant challenge of establishing evidence of preceding streptococcal infection. As a consequence, the diagnosis could be confirmed in less than half of the ARF cases, based on laboratory tests taken at the time of recruitment. Most notably, these findings underscore the significant challenges of confirming the diagnosis of ARF in surveillance and research, especially in the development of future ARF diagnostics.