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Title: Follow-up echocardiographic changes in children and youth aged less than 25 years with latent rheumatic heart disease: A systematic review and meta-analysis of global data.

Authors: Carl Francia

Background & Aims: Ascertaining a clear understanding of the natural history of latent rheumatic heart disease (RHD) has been challenging. Studies reporting rates of progression, regression, and persistence (unchanged) at follow-up show conflicting and variable results, partly due to variable prescription of and adherence to antibiotic prophylaxis among studies. Given a fundamental requirement of screening is understanding of latent RHD natural history, this review aims to summarise the current literature on follow-up rates of latent RHD regression, persistence, and progression. For endemic countries with no follow-up studies, our meta-analysis provides some guidance on the expected proportion of these follow-up outcomes.

Methods: A review was conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines. Electronic databases were searched for latent RHD echocardiography follow-up studies which used World Heart Federation diagnostic criteria. A meta-analysis of outcomes was conducted for borderline and mild-definite disease subcategories.

Results: Data for 1618 individuals were included. For borderline cases, 48.51% regressed (95%CI 45.10-51.93), 13.99% progressed (95%CI 9.72-18.25), and 38.61% had persistent (unchanged) disease at follow-up (95%CI 29.68-47.54). For mild-definite cases, 34.01% regressed (95%CI 28.88-39.15), 8.06% progressed (95%CI 3.65-16.90), and 60.23%had persistent disease (95%CI 55.08-67.38).

Conclusions: Borderline and mild-definite latent RHD show variable evolution following initial diagnosis. While 8% of mild-definite and 14% borderline cases had signs of disease progression at follow-up, a third of mild-definite and half of borderline cases had disease regression. Future research should use RHD registry data to study natural history and stratify risk of progression to inform targeted screening for latent RHD, as a workable strategy for disease elimination.