

# Rheumatic heart disease in Timor-Leste school students: an echocardiography-based prevalence study

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**The known** Rheumatic heart disease (RHD) is a disease of poverty that is highly prevalent in resource-limited settings and among Indigenous Australians and New Zealand Māori. The prevalence of RHD in Timor-Leste has not been described.

**The new** The prevalence of echocardiography-detected RHD in Timor-Leste is comparable with the highest rates in the world. All cases of RHD had previously been undiagnosed.

**The implications** A public health response for preventing and managing RHD in Timor-Leste is urgently needed, including improving the recognition of acute rheumatic fever. Further investigation is required to determine the best approaches for managing RHD detected by echocardiography.

**R**heumatic heart disease (RHD) is a preventable condition that is now extremely rare in high income countries, although its prevalence in indigenous, migrant and refugee populations remains high.<sup>1-4</sup> The prevalence of RHD is also high in low and middle income countries in sub-Saharan Africa, South America, Asia, and the Pacific, where high rates of *Streptococcus pyogenes* (group A streptococcus [GAS]) transmission have been documented.<sup>5,6</sup> Group A streptococcal infections are associated with poverty, and cause a spectrum of disease ranging from skin infections and pharyngitis to invasive disease, including bacteraemia.<sup>5</sup> Acute rheumatic fever (ARF) is a multisystem immune-mediated condition that can follow infection with GAS; GAS pharyngitis is associated with ARF, whereas a link between GAS pyoderma and ARF has been suggested but not confirmed.<sup>7</sup> In RHD, chronic valvular damage results from carditis associated with repeated episodes of ARF. ARF recurrences and the associated progression of valvular disease in established RHD can be effectively prevented by 4-weekly injections of long-acting benzathine penicillin G (BPG).<sup>8,9</sup>

After 24 years of occupation, the people of Timor-Leste voted for independence from Indonesia in 1999; following 3 years of transitional administration by the United Nations, it achieved independence in 2002. During and immediately following the referendum and the subsequent withdrawal of the Indonesian army, 70% of the national infrastructure was destroyed, including 35% of health facilities; the vast majority of clinicians and health managers fled the country.<sup>10</sup> Timor-Leste has been reconstructing its health system ever since. In a setting of limited resources such as Timor-Leste, the importance of research for identifying needs and driving improvements in health service delivery is clear.<sup>11</sup>

## Abstract

**Objectives:** To determine the prevalence of rheumatic heart disease (RHD) in school-aged children and young people in Timor-Leste.

**Design:** Prospective cross-sectional survey. Echocardiography was performed by Australian cardiologists to determine the presence of RHD. Demographic data were also collected. Patients in whom RHD was detected were entered into a register to allow monitoring of adherence to secondary prophylaxis; the first dose of benzathine penicillin G (BPG) was administered on the day of screening.

**Setting:** Schools in urban (Dili) and rural (Ermera) Timor-Leste.

**Participants:** School students aged 5–20 years.

**Outcome measures:** Definite and borderline RHD, as defined by World Heart Federation echocardiographic criteria.

**Results:** 1365 participants were screened; their median age was 11 years (IQR, 9–14 years), and 53% were girls. The estimated prevalence of definite RHD was 18.3 cases per 1000 population (95% CI, 12.3–27.0 per 1000), and of definite or borderline RHD 35.2 per 1000 (95% CI, 26.5–46.4 per 1000). Definite (adjusted odds ratio [aOR], 3.5; 95% CI, 1.3–9.4) and definite or borderline RHD (aOR, 2.7; 95% CI, 1.4–5.2) were more prevalent among girls than boys. Eleven children (0.8%) had congenital heart disease. Of the 25 children in whom definite RHD was identified, 21 (84%) received education and a first dose of BPG on the day of screening; all 25 have since received education about primary care for RHD and have commenced penicillin prophylaxis.

**Conclusions:** The rates of RHD in Timor-Leste are among the highest in the world, and prevalence is higher among girls than boys. Community engagement is essential for ensuring follow-up and the effective delivery of secondary prophylaxis.

ARF is not notifiable in Timor-Leste, and its incidence is unknown. The limited capacity of the country for diagnostic microbiology means that the incidence of GAS infections is also unknown, although skin infections (including impetigo) are common.<sup>12</sup> Anecdotal reports from clinicians in Timor-Leste suggest that the number of patients presenting with ARF to health care facilities is small, but that the burden of RHD among children and young people is significant. Many patients present to local health services with end-stage heart disease, but access to surgery is limited. Some East Timorese can undergo cardiac surgery in other countries, funded by charitable organisations such as the East Timor Hearts Fund (ETHF) and Rotary Oceania Medical Aid for Children (ROMAC), but many succumb to their disease while still young.<sup>13</sup>

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## 1 World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease (RHD) in people under 21 years of age (2012)<sup>15</sup>

### Definite rheumatic heart disease

At least one of:

- Pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve
- Mitral stenosis mean gradient  $\geq 4$  mmHg\*
- Pathological aortic regurgitation and at least two morphological features of RHD of the aortic valve†
- Borderline disease of both the aortic and mitral valves‡

### Borderline rheumatic heart disease

At least one of:

- At least two morphological features of RHD of the mitral valve without pathological mitral regurgitation or mitral stenosis
- Pathological mitral regurgitation
- Pathological aortic regurgitation

### Normal echocardiographic findings

All of:

- Mitral regurgitation that does not meet all four Doppler echocardiographic criteria (physiological mitral regurgitation)
- Aortic regurgitation that does not meet all four Doppler echocardiographic criteria (physiological aortic regurgitation)
- An isolated morphological feature of RHD of the mitral valve (for example, valvular thickening) without any associated pathological stenosis or regurgitation
- Morphological feature of RHD of the aortic valve (for example, valvular thickening) without any associated pathological stenosis or regurgitation

\* Congenital mitral valve anomalies must be excluded. † Bicuspid aortic valve, dilated aortic root, and hypertension must be excluded. ‡ Combined aortic and mitral regurgitation in high prevalence regions and in the absence of congenital heart disease is regarded as rheumatic. ◆

No published studies have described the burden of RHD in Timor-Leste. We therefore conducted an echocardiography screening study with the aims of describing the prevalence of RHD in school-aged children and young people in Timor-Leste, and of establishing an RHD register for coordinating secondary prophylaxis for East Timorese people with RHD.

## Methods

Schools were recruited in the capital city of Dili and the inland district of Ermera to obtain a sample population representative of the different geographic regions and a spectrum of socio-economic status in Timor-Leste. A consultation visit to the schools was made 4 months prior to the commencement of screening. A plain language information sheet in Tetum was distributed to parents and families, giving them the opportunity to decline screening of their children. An opt-out approach to consent was adopted because it was strongly preferred by local school principals and community members; this method has been applied successfully in other studies.<sup>14</sup>

All students aged 5–20 years who attended school on the screening days were eligible to participate in the study. Demographic data for all students were collected on a standard form to reduce measurement bias; to maximise accuracy, only study staff fluent in the local language recorded the data. Date of birth, age, number of people in their household, and number of rooms in their home were based on student self-report. All participants were examined for evidence of impetigo or scabies; these results will be reported in a separate article. As the capacity for diagnostic microbiology in Timor-Leste is limited, samples for microbiological testing were not collected.

An echocardiogram was performed by one of five cardiologists (including two paediatric specialists) with a Vivid I or Q machine (GE Healthcare). All children had full screening echocardiograms, including parasternal long axis, parasternal short axis, apical four-chamber, and apical five-chamber views (2D and Doppler).

RHD was classified as borderline or definite according to World Heart Federation criteria (Box 1).<sup>15</sup> Abnormal echocardiograms were flagged during the screening process and immediately reviewed by a paediatric cardiologist, as well as by all five cardiologists at the end of the screening week; a diagnosis of borderline or definite RHD was confirmed only after consensus was reached by at least three of the cardiologists involved in the study. Normal echocardiograms were not reviewed.

## Statistical analysis

Data were entered into an Access 2016 database (Microsoft), and statistical analysis was conducted in Stata 13 (StataCorp). Descriptive statistical analysis was undertaken and the prevalence of RHD estimated with 95% confidence intervals (CIs). Continuous variables that were not normally distributed were compared in Mann–Whitney rank sum tests; differences in binary variables were assessed in  $\chi^2$  tests (univariate analysis). Relative risks (RRs) and 95% CIs were calculated. For multivariate analyses, logistic regression was employed to estimate adjusted odds ratios (aORs) with 95% CIs. Sex, age, and location of screening were included in the logistic regression model because these variables could plausibly influence the prevalence of RHD.  $P < 0.05$  was deemed statistically significant.

Patients with RHD were entered into a register to facilitate monitoring of adherence to subsequent secondary prophylaxis, with the first dose of BPG administered on the day of the study. Patients with heart disease amenable to surgery were referred to ROMAC for possible surgery in Australia.

## Ethics approval

Ethics approval for the study was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (reference, 2016-2546) and the Instituto Nacional de Saúde in Timor-Leste (reference, MS-INS/DF/DP/V/2016/220). Permission to undertake screening was granted by the Ministério da Educação in Timor-Leste and by the principals of the schools involved.

## 2 Demographic data for people under 21 years of age screened for rheumatic heart disease in Dili or Ermera, Timor-Leste

	Dili	Ermera	Total
Total number	505	860	1365
Sex			
Girls	255 (50.5%)	470 (54.7%)	725 (53.1%)
Boys	250 (49.5%)	390 (45.3%)	640 (46.9%)
Age (years)			
5–9	233 (46.1%)	180 (20.9%)	413 (30.3%)
10–14	269 (53.3%)	351 (40.8%)	620 (45.4%)
15–20	3 (0.6%)	329 (38.3%)	332 (24.3%)
People per household, median (interquartile range)	6 (4–8)	8 (6–9)	7 (6–9)

## Results

A total of 1365 participants aged 5–20 years were screened by echocardiography. Their median age was 11 years (interquartile range [IQR], 9–14 years) and 725 (53%) were girls; the sex distribution was similar for all age groups (data not shown). Five hundred and five children (37%) were screened in Dili, 860 (63%) in the district of Ermera. All students knew their age, but fewer than half were able to report their date of birth. None knew whether they were allergic to penicillin. The median number of residents per household was 7 (IQR, 6–9) (Box 2).

A total of 25 definite and 23 borderline cases of RHD were detected by echocardiography. The estimated prevalence of definite RHD was 18.3 cases per 1000 population (95% CI, 12.3–27.0 per 1000); that of definite or borderline RHD was 35.2 cases per 1000 population (95% CI, 26.5–46.4 per 1000). None of the children in whom RHD was detected had previously been diagnosed with RHD; one had a history of ARF without evidence of carditis and of poor adherence to penicillin prophylaxis. All cases were classified as either mild or moderate, none as severe (Box 3). All borderline and

definite cases included mild or moderate mitral regurgitation. No mitral stenosis was detected. Three children also had mild or moderate aortic regurgitation. Most of the children in whom definite or borderline RHD was detected lived in Ermera, where the estimated prevalence was 43.0 cases per 1000 population (95% CI, 31.2–58.9) (Box 3).

Eleven children (0.8%) had congenital heart disease. Two were referred for surgery (one case of severe aortic stenosis, one of Ebstein's anomaly); nine children had relatively minor cardiac anomalies, including three with haemodynamically insignificant atrial septal defects, two with mitral valve prolapse, two with patent ductus arteriosus, one with dextrocardia, and one with mild pulmonary stenosis.

There was a clear sex difference in prevalence of RHD. There were 27.6 cases of definite RHD per 1000 girls (95% CI, 17.7–42.5) and 7.8 cases per 1000 boys (95% CI, 2.8–18.7) (aOR, 3.6; 95% CI, 1.3–9.5;  $P = 0.012$ ); there were 49.7 cases of definite or borderline RHD per 1000 girls (95% CI, 35.9–68.2) and 18.8 cases per 1000 boys (95% CI, 10.4–32.9) (aOR, 2.7; 95% CI, 1.4–5.2;  $P = 0.004$ ).

Students screened in Ermera appeared more likely to have definite or borderline RHD in the univariate analysis (RR, 2.0; 95% CI, 1.0–3.8;  $P = 0.040$ ), but the multivariate analysis (adjusted for age and sex) detected no significant association between RHD and age or location (Box 4).

Twenty-one children with definite RHD (84%) received BPG and education on the day of screening, and all children were entered into the RHD register for follow-up. Children whose parents were not available on the day of screening did not initially receive BPG, but all children and families have subsequently received education about RHD and the importance of secondary prophylaxis, and have commenced treatment with BPG.

## Discussion

Our echocardiography-based screening study identified a very high prevalence of RHD among young people in Timor-Leste, comparable with the highest documented rates of RHD elsewhere (Box 5).<sup>1,6,16–24</sup> The prevalence of definite RHD in our study (18 cases per 1000 population) is higher than the rate for Fiji (7 cases per 1000), and similar to that in other regional neighbours, including the Top End of Australia (15 cases per 1000 for Indigenous Australians at high risk).<sup>1,18</sup> The prevalence in Timor-Leste may be higher than estimated; we did not detect any cases of mitral stenosis or other forms of severe RHD, and it is possible that students with severe RHD were too unwell to attend school, and therefore not screened. It is also possible that children and young people from poorer families, at greater risk of RHD, do not regularly attend school. The absence of severe RHD in our study contrasts with anecdotal reports of fatal cases managed by Timor-Leste health services, and with the experience of visiting cardiology services,<sup>13</sup> but the morbidity and mortality of severe RHD in Timor-Leste has not been formally documented.

Further investigation of the morbidity and mortality of RHD in Timor-Leste are needed, and, as RHD had not previously been diagnosed in any of the young people we screened, active case detection and close follow-up is warranted. The World Health Organization has recently renewed its resolution to tackle RHD as an important international health problem requiring a multisectoral

## 3 Estimated prevalence of rheumatic heart disease in people under 21 years of age in Dili or Ermera, Timor-Leste

	Dili		Ermera		Total	
	Cases	Prevalence, per 1000 (95% CI)	Cases	Prevalence, per 1000 (95% CI)	Cases	Prevalence, per 1000 (95% CI)
People with rheumatic heart disease						
Definite	7	13.9 (0.6–28.9)	18	20.9 (13.1–33.1)	25	18.3 (12.3–27.0)
Borderline	4	7.9 (0.2–21.0)	19	22.1 (14.0–34.5)	23	16.8 (11.1–25.3)
Definite or borderline	11	21.8 (11.7–39.0)	37	43.0 (31.2–58.9)	48	35.2 (26.5–46.4)
Severity of definite or borderline rheumatic heart disease						
Mild	10		32		42	
Moderate	1		5		6	
Severe	0		0		0	

CI = confidence interval. ♦

**4 Univariate and multivariate analysis of prevalence of rheumatic heart disease in people under 21 years of age in Dili and Ermera, Timor-Leste**

	Definite rheumatic heart disease				Definite and borderline rheumatic heart disease					
	Cases	Relative risk (95% CI) univariate	P	Adjusted odds ratio* (95% CI) multivariate	P	Cases	Relative risk (95% CI) univariate	P	Adjusted odds ratio* (95% CI) multivariate	P
Sex			0.007		0.012			0.002		0.004
Boys	5 (0.8%)	1		1		12 (1.9%)	1		1	
Girls	20 (2.8%)	3.5 (1.3–9.4)		3.6 (1.3–9.5)		36 (5.0%)	2.6 (1.4–5.0)		2.7 (1.4–5.2)	
Age (years)										
5–9	5 (1%)			1		9 (2%)			1	
10–14	15 (2.4%)			1.9 (0.7–5.3)	0.22	24 (3.9%)			1.7 (0.8–3.7)	0.20
15–20	5 (2%)			1.0 (0.3–3.6)	0.97	15 (4.5%)			1.6 (0.7–3.9)	0.31
Location								0.040		
Dili	7 (1%)	1	0.35	1	0.34	11 (2.2%)	1		1	0.13
Ermera	18 (2.1%)	1.5 (0.6–3.6)		1.6 (0.6–4.0)		37 (4.3%)	2.0 (1.0–3.8)		1.8 (0.8–3.7)	

CI = confidence interval. \* Adjusted for other two factors in table. ♦

response. The WHO recognises that RHD affects a substantial proportion of the world’s most vulnerable populations, and that antibiotic treatment of group A streptococcal infections and secondary prophylaxis for preventing ARF are cost-effective strategies that should be implemented in high burden settings.<sup>25</sup>

Efforts to reduce the prevalence of RHD in Timor-Leste should focus on primordial (reducing risk factors for GAS infection), primary (treating GAS infections to prevent ARF), and secondary prevention (penicillin prophylaxis for people with a history of ARF or established RHD). Access to cardiac surgery (tertiary prevention) is limited to cases amenable to international referral, usually to Australia, Indonesia or Singapore, as cardiac surgery is not currently performed in Timor-Leste.

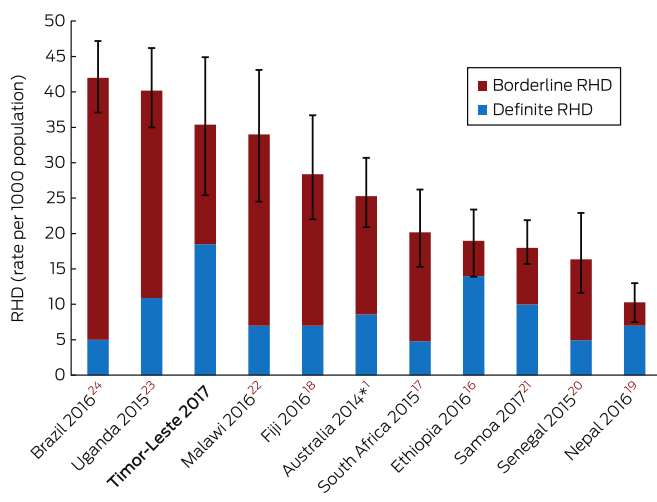
Household sizes in this cohort were large, consistent with census data from Timor-Leste, and domestic crowding is a known risk factor for RHD.<sup>26</sup> Access to health care services is limited, particularly in regional areas. Ermera, like much of Timor-Leste, is a mountainous area with very poor roads in some parts. Delivering BPG regularly is challenging, but has been successfully undertaken since our screening study. Our study has shown that it is possible to screen for and diagnose RHD, immediately enter patients into a register, provide education, and commence BPG prophylaxis on the same day. However, we relied on volunteer cardiologists with specialist skills in the echocardiographic diagnosis of RHD, and it would be difficult to reproduce this approach to screening on a large scale.

Registries for the surveillance and follow-up of patients with established RHD have been shown to be effective in reducing morbidity and mortality, especially when incorporated into national disease surveillance networks.<sup>25</sup> Increasing the available information on disease burden by active surveillance could provide the impetus for providing more resources to the Timorese health care system, leading to long term improvement of local cardiac services, as well as to improving the chances of those with established RHD of undergoing surgery overseas. Most importantly, an effective register facilitates the delivery of penicillin prophylaxis that can halt the progression of RHD and prevent the sequelae of heart failure and death.<sup>8,9</sup>

We found that that risk of RHD in Timor-Leste is greater for girls. This is similar to findings in Australia and other parts of the world,<sup>1,27</sup> although a significant sex difference was not detected by a recent meta-analysis.<sup>6</sup> The cause of the sex difference is yet to be determined. The risk of morbidity and mortality during pregnancy and childbirth is very high in women with RHD, and increases with successive pregnancies.<sup>5</sup> Catholicism is common in Timor-Leste, a country with a median household size of 5.7 people;<sup>28</sup> access to contraception is limited, and societal opposition to its use significant.<sup>29</sup> The prevalence of RHD among pregnant women in Timor-Leste is unknown, but multiple pregnancies in a setting of high prevalence RHD may place women and babies at increased risk of adverse outcomes and death.

There were several limitations to our study. Screening was only conducted in two districts of Timor-Leste. The prevalence of RHD

**5 Prevalence in recent studies of definite and borderline rheumatic heart disease in young people detected by echocardiography according to World Heart Federation criteria**



\* Indigenous Australian population at high risk of rheumatic heart disease. All studies reported prevalence for people under 21 years of age, except the South African study (24 years or younger). ♦

in other districts may be different, but we expect that enrolling subjects from both an urban and a rural district resulted in a sufficiently representative sample for producing meaningful results. We enrolled only children and young people attending school, and those from poorer families or too sick to go to school will not have been included in our sample. The children screened in Ermera were older than those screened in Dili, but neither age nor location were significant factors in the multivariate analysis.

The cardiologists performing the echocardiograms provided a diagnosis during screening, and there was no external review of the images by a blinded cardiologist. However, a diagnosis was only provided after consensus among three of the five cardiologists was reached; it is very unlikely that the burden of RHD was overestimated. On the other hand, unremarkable echocardiograms were not reviewed, so it is possible that some cases were missed and the prevalence therefore underestimated. Some uncertainty regarding the clinical significance of borderline RHD remains, but recent studies have found that children with borderline RHD are more likely to have ARF, progression of their valvular lesions, and later development of definite RHD.<sup>30</sup> Nevertheless, echocardiography screening for RHD case detection remains controversial, as there is no evidence that screening leads to improved outcomes.

## Conclusion

We found a significant burden of undetected RHD in our sample of young people, particularly among girls and young women. Our finding of a large burden of undetected disease indicates that active case detection is needed in Timor-Leste. The health system of Timor-Leste needs to be improved to increase the capacity of health workers to recognise and manage ARF and RHD. The nascent RHD register needs to be expanded, and further investigations in Timor-Leste and elsewhere are required to better define the role and practice of echocardiography screening, and to guide secondary prophylaxis for patients in whom RHD is detected by screening.

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