THESE DE DOCTORAT DE
L'UNIVERSITE PIERRE ET MARIE CURIE

Spécialité

Epidémiologie

ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS : EPIDEMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMEDICALE

Présentée par

Madame MIRABEL Mariana

Pour obtenir le grade de

DOCTEUR de l'UNIVERSITÉ PIERRE ET MARIE CURIE

Cardiopathie Rhumatismale

Prévalence, méthodes diagnostiques, morbidité et mortalité attribuables en Nouvelle Calédonie

soutenue le 12 janvier 2016

devant le jury composé de :
M. JOUVEN Xavier, Professeur des Universités, Directeur de thèse

M. CELERMAJER David, Professor, et M. IUNG Bernard, Professeur des Universités, Rapporteurs

M. COHEN Ariel Aron, Professeur des Universités, M. HAGEGE Alain Albert, Professeur des Universités, M. LAFITTE Stéphane, Professeur des Universités, Examinateurs

Acknowledgments

I dedicate this thesis to my beloved ones. To my husband Gilles who willingly supported me throughout and agreed to moving to the opposite point in the Globe, and to our two marvelous daughters Alice and Chloé who fill me with joy.

Publications arising from this thesis

Published

Mirabel M, Fauchier T, Bacquelin R, Tafflet T, Germain A, Robillard C, Rouchon B, Marijon E, Jouven X. Echocardiography Screening to Detect Rheumatic Heart Disease. *A Cohort Study of Schoolchildren in French Pacific Islands. Int J Cardiol* 2015, 188:89-95.

Mirabel M, Bacquelin R, Tafflet M, Robillard C, Huon B, Corsenac Ph, de Frémicourt I, Narayanan K, Meunier JM, Noel B, Hagège AA, Rouchon B, Jouven X, Marijon E. Screening for Rheumatic Heart Disease: Evaluation of a Focused Cardiac Ultrasound Approach. *Circulation CVI* 2015, 8:e002324.

Mirabel M, Tafflet M, Noël B, Parks T, Axler O, Robert J, Nadra M, Phelippeau G, Descloux E, Cazorla C, Missotte I, Gervolino S, Barguil Y, Rouchon B, Laumond S, Jubeau T, Braunstein C, Empana JP, Marijon E, Jouven X. Newly diagnosed rheumatic heart disease among indigenous populations in the Pacific. *Heart*, 2015;101(23):1901-6

Under Review

Mariana M, Tafflet M, Noël B, Parks T, Braunstein C, Rouchon B, Marijon E, Jouven X. Prevalence of rheumatic heart disease in the Pacific: from subclinical to symptomatic heart valve disease. Submitted, Nov 2015

Articles published, related to the PhD, not in the strict framework of the PhD thesis

Mirabel M, Marijon E, Jouven X. Preventon of Acute Rheumatic Fever and Rheumatic Heart Disease. *Circulation* 2014;130:e35-e37.

Marijon E*, Mirabel M*, Celemajer D, Jouven, X. Rheumatic Heart Disease. *Lancet* 2012;379: 953–64. *first co-authors

Rheumatic heart disease: prevalence, diagnostic tests, and burden of disease in New Caledonia

Cardiopathie Rhumatismale: Prévalence, méthodes diagnostiques, morbidité et mortalité attribuables en Nouvelle Calédonie

Abstract

Rheumatic Heart Disease (RHD) is the leading cause of acquired heart disease in children and young adults worldwide, with significant associated morbidity and mortality. Early secondary prophylaxis may retard the deleterious progression from its antecedent, acute rheumatic fever to permanent heart valve damage, and thus several echocardiographic screening programmes to detect asymptomatic RHD and institute early prophylaxis have been conducted. While effective interventions are available for ameliorating the effects of RHD, research on their use in different settings is scant. Key questions remain regarding the natural history of asymptomatic RHD and the optimal method for early detection. In addition, there is a lack of contemporary estimates of mortality and morbidity among the symptomatic population.

The primary purpose of the thesis was to determine the outcomes of asymptomatic and symptomatic RHD. More specifically, this thesis focuses on the outcomes of asymptomatic RHD diagnosed by means of systematic echocardiography-based screening, and assesses a simplified echo-based protocol for screening in schoolchildren. Population-based and hospital-based estimates of disease burden are provided in this work. Finally, outcomes of symptomatic RHD are depicted in a captive population and factors associated with poor outcomes identified in patients with newly diagnosed RHD.

This thesis has five key findings. Firstly, research methods used for echocardiography-based screening may not be readily translated into public health policies. Secondly, asymptomatic echocardiography-screened RHD has a variable natural history that ranges from regression to a normal state, to persistence of mild disease in the majority of cases. Also, a single screening point in childhood among populations at risk may prove insufficient. Thirdly, a focused hand-held echocardiography protocol shows promising levels of sensitivity and specificity for detecting subclinical RHD by non-experts. Fourthly, hospital-based prevalence estimates are

in keeping with population-based data and confirm the high burden of RHD in New Caledonia. Symptomatic RHD is often revealed by its complications. Finally, the survival rate is 96% at 8 years and the incidence of major cardiovascular events is of 59 per 1,000 patients year in the subset of patients with newly diagnosed RHD and no complications at entry. Factors associated with poor outcomes include the severity of heart valve disease at diagnosis and discontinuation of secondary prophylaxis.

The findings encapsulated in this thesis add to the knowledge of the burden of this disease by providing prevalence figures in the population and from a hospital-based cohort. These studies may have important implications for policy, practice and research related to the management of asymptomatic and symptomatic RHD.

Table of Contents

List of Abbreviations and Acronyms

ACC American College of Cardiology

AF Atrial fibrillation

AHA American Heart Association

AMVL Anterior mitral valve leaflet

AR Aortic regurgitation

ARF Acute rheumatic fever

AS Aortic stenosis

ASS-NC Agence Sanitaire et Sociale de Nouvelle Calédonie

AV Aortic valve

CCF Congestive cardiac failure

CHT Centre Hospitalier Territorial de Nouvelle Calédonie

CI Confidence interval

CHD Congenital Heart Disease

CRF Case record forms

DASS Département des Affaires Sanitaires et Sociales

EVASAN Département des Evacuations Sanitaires

FCU Focused Cardiac Ultrasound

FU Follow-up

GAS Group A streptococcus

HR Hazard Ratio

IE Infective endocarditis

INR International Normalized Ratio

IQR Interquartile range

LA Left atrium

LVEDD Left ventricular end diastolic diameter

LVEF Left ventricular ejection fraction

MACE Major cardiovascular events

MR Mitral regurgitation

MS Mitral stenosis

MV Mitral valve

NYHA New York Heart Association

OR Odds ratio

PASP Pulmonary artery systolic pressure

RHD Rheumatic heart disease

SD Standard deviation

TR Tricuspid regurgitation

VHD Valve heart disease

WHF World Heart Federation

WHO World Health Organization

List of Figures

List of Tables

1. Introduction

Rheumatic heart disease (RHD) remains the leading acquired heart disease in the young worldwide.[1] Although prevalence, morbidity and mortality have been recently assessed by the Global Burden of Disease study, the data these estimates are based on are scant.[2, 3] Rheumatic heart disease, a disease of poverty, has almost disappeared from wealthy countries, its burden remains a major challenge in the developing world.[4, 5] According to the 2008 Population Reference Bureau's estimates, approximately 80 to 85% of the children under 15 years of age (around 2 billion) live in areas endemic for RHD and are potentially at risk of developing the disease.[6] Retrospective studies show that RHD is associated with high mortality and substantial morbidity due to sequel such as congestive heart failure (CHF), stroke and infective endocarditis (IE).[7, 8] Yet, contemporary estimates of the burden of disease, especially from different areas where this disease is endemic are scant and largely biased.

Rheumatic heart disease is the result of valvular damage caused by an exaggerated immune response to group A streptococcal (GAS) infections, usually during infancy and childhood.[1, 9, 10] Acute rheumatic fever (ARF) usually occurs 3 weeks after GAS pharyngitis and may involve joint, skin, brain and heart.[11] One-third to half the patients with a first ARF episode present with carditis, with cardiac inflammation mainly involving the valvular endocardium.[12-15] Although the initial attack can lead to severe valvular disease, RHD most often results from cumulative valve damage due to recurrent ARF episodes and thus RHD may be of insidious onset.[5, 16] However, if diagnosed early enough with timeous institution of secondary prophylaxis, the deleterious progression to permanent heart valve damage due to recurrent episodes of ARF need not occur. The concept of early identification of silent rheumatic "minimal" valve lesions has emerged in recent years, because of echocardiography-based detection.[17, 18] This approach was first developed for the diagnosis of subclinical carditis in the setting of ARF.[19, 20] This argument has led to the launch of a multitude of echocardiographic screening studies to document the prevalence of subclinical disease and to institute early therapy in affected individuals.[19, 21] There are, however, several unanswered questions in regards to echocardiography-based screening for RHD. Only short-term studies exist with regard to the use of screening to detect subclinical RHD therefore the prognosis of subclinical RHD remains unknown. Also, screening methods that have been used for research purposes may not be applicable in most settings where RHD remains endemic due to the high cost of equipment and need of experienced users and readers.

This thesis focuses on exploring the outcomes of asymptomatic and symptomatic RHD within the context of increasing numbers of screening programmes and ways for simplified echocardiography-based screening. In this introduction is summarized the current knowledge related to disease estimates for RHD, the morbidity and mortality associated with RHD, and screening methods for early detection of RHD.

1.1. The epidemiology of Rheumatic Heart Disease

Improved living conditions, penicillin use, and access to medical care have radically changed the epidemiology of ARF and RHD in high-income settings.[5] Nevertheless, both prevail in developing nations and some unprivileged, mainly indigenous, populations in affluent countries.[21-24] In 2005, a summary report, commissioned by the WHO, was released on the global burden of Group A streptococcal disease; it encapsulated population-based data relating to ARF and RHD that had been published between 1985 and 2005.[5, 25] The overall burden of RHD was estimated to be 15-20 million prevalent cases, with 282,000 new cases and over 233,000 deaths per year (Figure 1.1). Difficulties with such estimates are mainly related to the lack of comprehensive disease registries, passive survey systems and underreporting of acute and chronic cases.[22, 26]
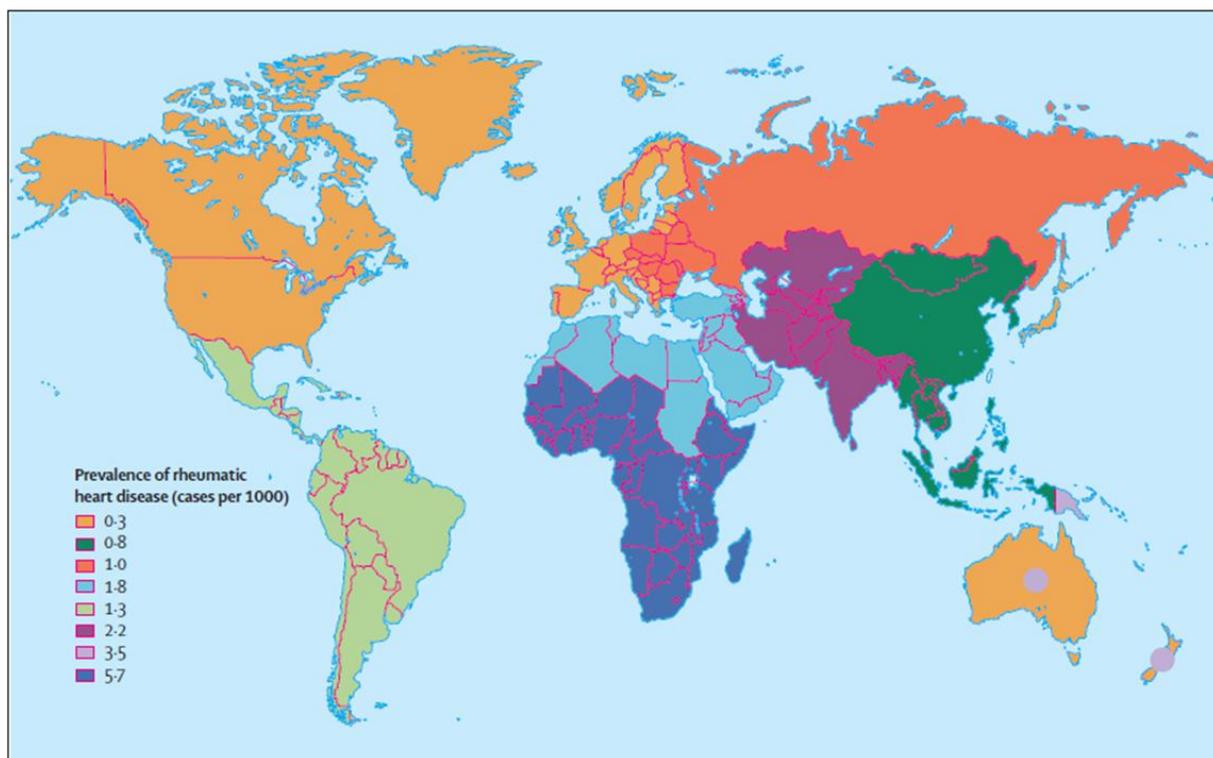
Figure 1.1. Prevalence of rheumatic heart disease.[5]

The recently published Global Burden of Disease 2010 Study, reported 345,100 deaths due to RHD in 2010, representing a 25.4% reduction compared with those occurring in 1990, with an age-standardized death rate of 5.2 per 100,000. This represents a 53.1% reduction in the death rate, when compared with the number of deaths that occurred in 1990.[2] Lozano reported that

the number of years lived with disability due to RHD was estimated at 1,430 in 2010 (95% confidence intervals [CI] 944 to 2067) worldwide, a figure that represents up to one fourth of all neoplasms.[27] It is necessary to re-analyze these data, however, due to uncertainties regarding their accuracy. Of particular concern were the clear inconsistencies relating to the epidemiology of the disease, the age groups that are most at risk, and the extreme paucity of incident and mortality data from developing countries. Moreover, a recent report from the Northern Territories in Australia reported little evidence of a decline in the incidence of ARF or RHD.[28]

Inter-regional variability is to be stressed in terms of RHD related mortality. In areas of poor or no medical attention, the natural course of the disease prevails because of poor access to treatment, as cardiac interventions in sub-Saharan Africa (Figure 1.2).[29-31] Mortality rates in these areas may be as high as 20% at 6 years follow-up, as illustrated in a Nigerian paediatric cohort study,[32] or of 12.5% annually, as documented in rural Ethiopia.[8] These are in contrast with more recent mortality reported in Australia where the survival rates are of 96.1% at 5 years among Indigenous Australians.[28] One of the objectives of this thesis is to provide accurate figures in New Caledonia thereby adding to the knowledge on the burden of RHD.
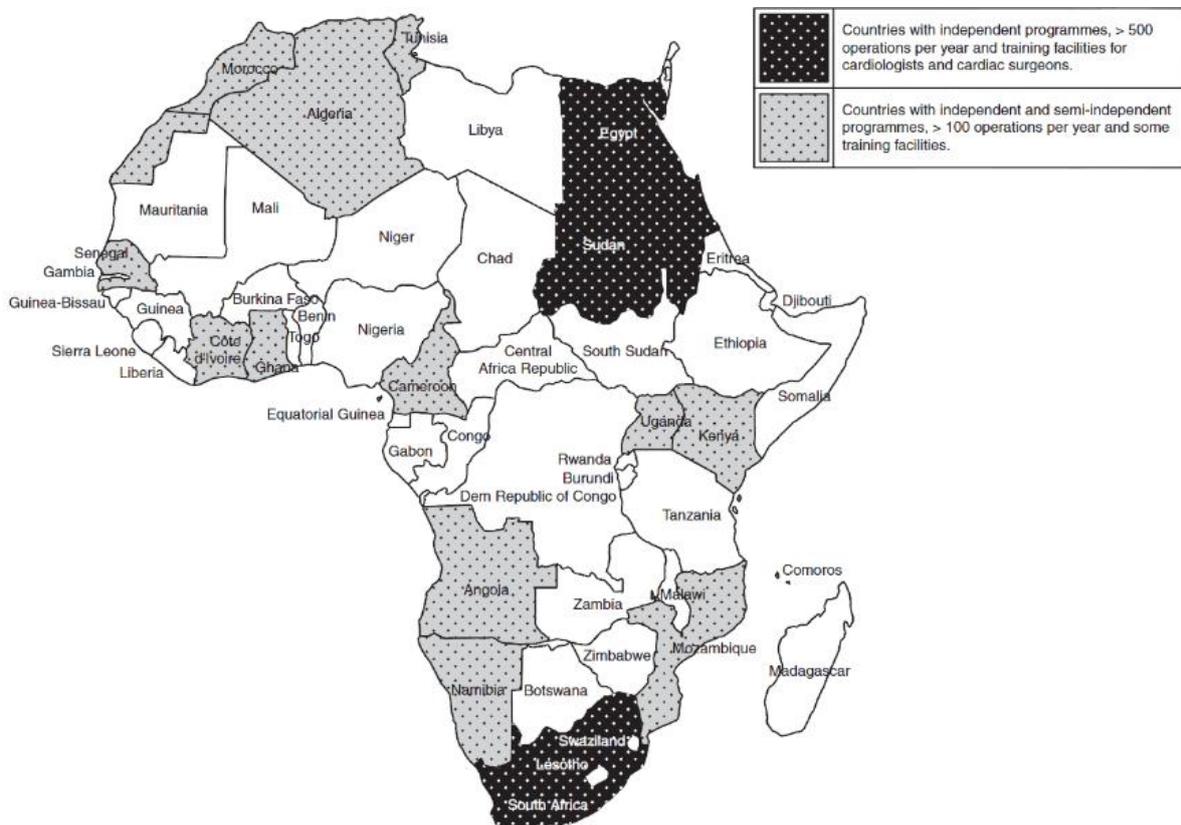
Figure 1.2. Countries with established cardiac surgery programmes in Africa.[29]

1.2. Rationale, feasibility, means and controversies regarding echo-based screening

The rationale for active surveillance is not only to provide the most accurate epidemiological data of the disease but also to offer early treatment to those affected, especially the large proportion of asymptomatic patients who may subsequently develop advanced RHD. The Council of Europe and WHO recommend screening programmes in the setting of preventable diseases.[33, 34] In most countries, the majority of children are readily accessible through school screening surveys. Under the auspices of the WHO, approximately 15 million children were screened for RHD across 16 countries.[35] Unfortunately the outbreak of HIV and its devastating consequences diverted local priorities in many developing nations and led to discontinuation of funding for many RHD programs.

The first large surveys were based on clinical examination.[36-38] However, cardiac auscultation lacks sensitivity. Small regurgitant volumes, especially mitral regurgitation posteriorly directed jets, may simply not be audible to the human ear. Cardiac examination requires a quiet environment and is time consuming, and to distinguish functional from organic murmurs is far more challenging in clinical practice than in theory.[39, 40] Functional murmurs are very common among children, especially in the presence of fever or anaemia, as may be the case during malaria or sickle cell disease. Auscultation skills require specific training that seemingly are no longer mandatory in medical schools in wealthy countries, where cardiac imaging is readily available.[41] In a three-step screening programme conducted in Tonga, junior and experienced physicians auscultation skills were compared.[20] Even though the more experienced physician had a better ability to detect pathological murmurs, at least half the cases of RHD were missed by auscultation alone.[20]

In addition to the intrinsic limitations of auscultation in detecting valvular disease, cardiac examination may not uniformly occur during follow-up after clinical carditis,[42, 43], and even if practised, most patients with echo-detected RHD have normal findings on auscultation.[15, 43-45] Taken together, these studies demonstrate that clinical examination alone is unable to detect the majority of children with RHD.[46]

Echocardiography as a tool to detect subclinical carditis has emerged after the publications of studies comparing RHD prevalence assessed by ultrasounds versus cardiac auscultation (Figure 1.3).[19, 20, 47-52] Recently reviewed in a meta-analysis by Rothenbüler and colleagues, the pooled prevalence of rheumatic heart disease detected by cardiac auscultation was 2.9 per

1000 people (95% CI 1.7–5.0) and by echocardiography it was 12.9 per 1000 people (95% CI 8.9–18.6).[21]
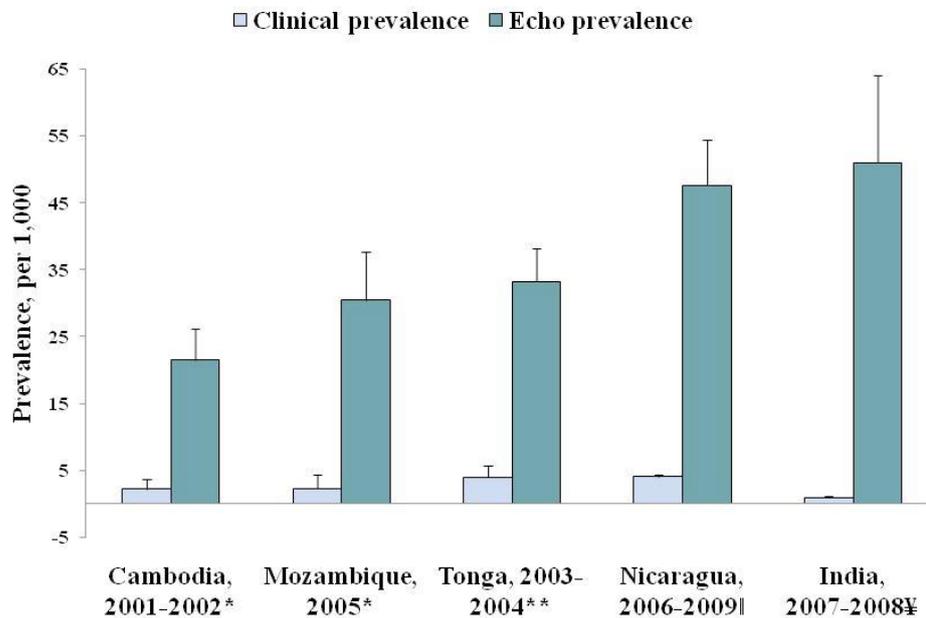
Figure 1.3. Screening using auscultation versus echocardiography.[1]

The interregional variation of RHD prevalence may be due to true differences in the burden of the disease, the sensitivity of the criteria used, or the combination of both. In this context, the World Heart Federation (WHF) released guidelines in 2012 for the diagnosis of RHD in order to standardize echocardiography criteria (Table 2.1.).[53] These criteria consolidated international expert opinion by combining Doppler and morphological features of the left-sided valves. The advent of echo-based screening for RHD led to a new model of the epidemiology of RHD. This includes asymptomatic RHD and symptomatic RHD as a continuum (Figure 1.4).

World Heart Federation's Criteria for Echocardiographic Diagnosis of Rheumatic Heart Disease

---

Echo criteria for children ≤ 20 years of age

Definite RHD (either A, B, C or D):

Pathological MR <u>and</u> at least two morphological features of RHD of the MV

MS mean gradient ≥ to 4 mmHg (NB – exclude congenital MV anomalies)

Pathological AR <u>and</u> at least two morphological features of RHD of the AV

Borderline disease of both the aortic and mitral valves

Borderline RHD (either A, B or C):

At least two morphological features of RHD of the MV without pathological MR or MS

Pathological MR

Pathological AR

Normal Echocardiographic findings (all A, B and C);

MR that does not meet all four Doppler criteria (Physiological MR)

AR that does not meet all four Doppler criteria (Physiological AR)

An isolated morphological feature of RHD of the MV or the AV (e.g. vulvar thickening) without any associated pathological stenosis or regurgitation

---

Pathological Regurgitation

Mitral Regurgitation (all four Doppler criteria must be met)	**Aortic Regurgitation** (all four Doppler criteria must be met)
1. Seen in 2 views	1. Seen in 2 views
2. In at least one view jet length ≥ 2 cm	2. In at least one view jet length ≥ 1 cm
3. Peak velocity ≥ 3m/sec	3. Peak velocity ≥ 3m/sec
4. Pansystolic jet for at least one envelope	4. Pandiastolic jet for at least one envelope

---

Morphological features of RHD

Mitral Valve	**Aortic Valve**
1. AMVL thickening ≥ 3mm	1. Irregular or focal thickening
2. Chordal thickening	2. Coaptation defect
3. Restricted leaflet motion	3. Restricted leaflet motion
4. Excessive leaflet tip motion during systole	4. Prolapse

Table 2.1. World Heart Federation Diagnostic criteria for RHD under 20 years of age. See full article for explanatory notes and caveats.[53]
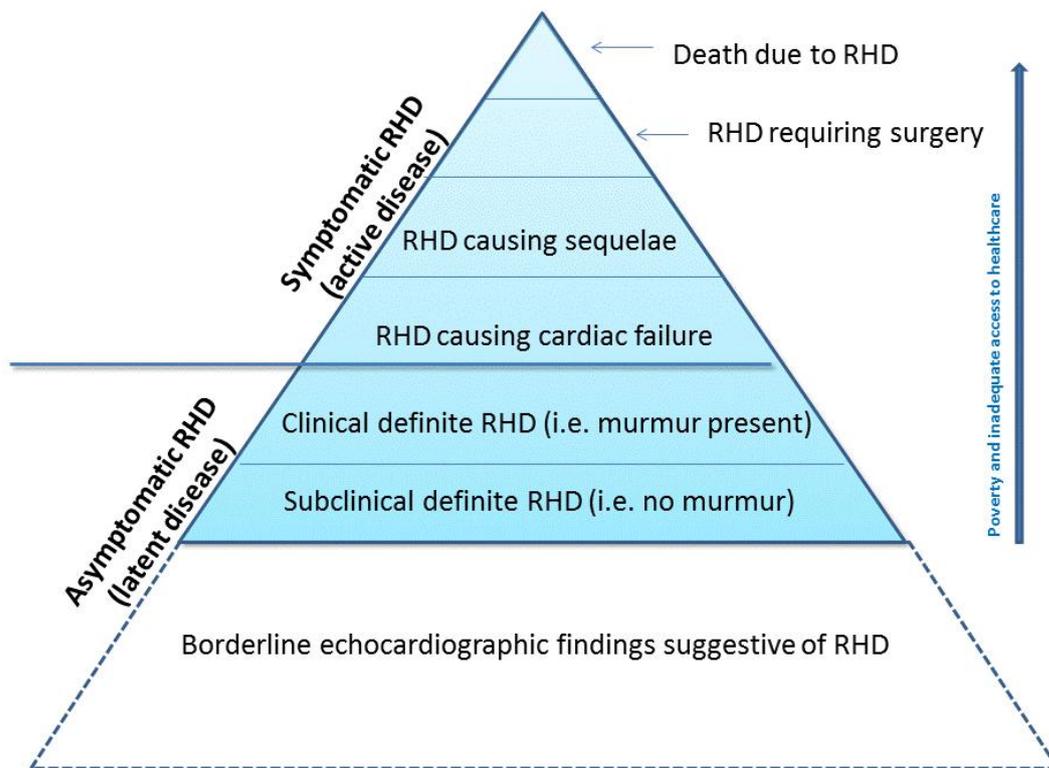
Figure 1.4. Model incorporating asymptomatic and symptomatic disease.[54]

Although echocardiography detects 3 to 10 times more valvular lesions than auscultation, several issues need to be addressed before its implementation. Screening for asymptomatic RHD has given rise to much debate, including around the prognosis of subclinical RHD, the criteria chosen to define RHD, and the impact on public health policies.[55, 56] These debates relate to the ability of developing countries to manage the large numbers of patients who will be detected by means of echocardiography, the appropriate treatment for these patients and the cost-effectiveness of screening for RHD.

The natural history of subclinical RHD in asymptomatic populations without a previous history of ARF is not well characterized. Four studies have reported on the short-term progress of subclinical RHD detected by echocardiography. These studies lacked power to assess clinical endpoints and all focused on the persistence of echocardiographic lesions.[47, 50, 57, 58]

The WHF criteria are based on the best available evidence, its use requires high-end echocardiography machines, experienced users and readers. These technical, and financial,

aspects may prevent use of WHF criteria in low-income settings. Simpler ways to detect RHD need to be validated for screening to be implemented as a public health policy.

In this thesis two distinct studies assess the burden of RHD in New Caledonia by means of a population-based echo-screening programme and a hospital-based cohort of symptomatic RHD patients. In addition, outcomes of children with asymptomatic RHD and a focused cardiac ultrasound approach are also examined.

2. Methods of the thesis

2.1. Settings

2.1.1. New Caledonia: geographic, social and economic features

New Caledonia is a special collectivity of France located in the southwest Pacific Ocean, divided into three Provinces (Northern, Southern and Loyalty Islands Provinces). The country population was 260 000 according to the 2014 census, with 43,091 children aged 5-14 years (17.5%), among which a majority (44.6%) were indigenous Melanesian, followed by Caucasian (22.5%), Polynesian (10.9%), of mixed origins (13.0%), Asian (1.4%), and other (7.3%). The distribution of ethnic groups is uneven across the archipelago with a majority of indigenous Melanesians residing in the Northern and Loyalty Provinces. Life expectancy is 76 years for those born in 2010. Primary school is universal and mandatory, and attendance is estimated at 86% for primary and pre-primary schools.[59]
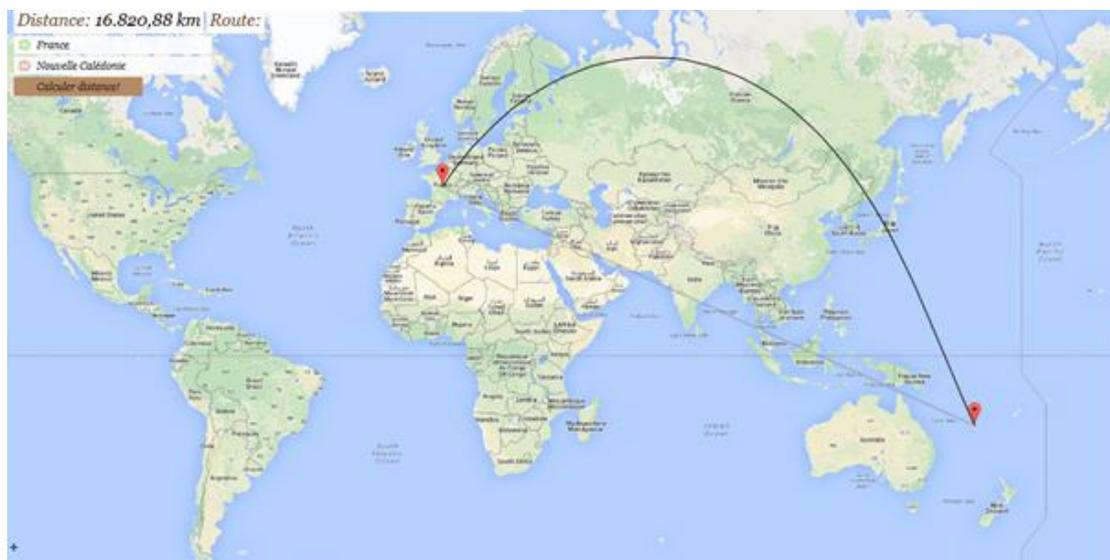
Figure 2.1. World map.

Although classified as a high-income country according to a GDP per capita of 35,298 USD in 2010 (rank 33),[60] with a rapidly growing market economy, major socio-economic disparities prevail within the New Caledonian society. The annual

income per annum is two fold higher in the Southern Province where a majority of the population from European descent lives compared to the other two Provinces (mainly populated by indigenous Melanesians).[61]

Figure 2.2. Map of New Caledonia.

2.1.2. The New Caledonian healthcare system

The healthcare system is similar to that of mainland France. There is universal healthcare coverage through various social security systems according to the level of income of the patient. Diseases such as RHD are universally covered with either no charges to the patient or 100% reimbursement of investigations and treatments related to the condition.

Primary care centres are widespread and cover the entire country. The density of medical Doctors is 223 per 100 000 inhabitants, including general practitioners and specialists. Theses figures vary however according to the region with 274 practioners per 100 000 in the South, 96 per 100 000 in the North and 80 per 100 000 on the Loyalty Islands.[62]

Figure 2.3. Distribution of primary healthcare centres. *Dispensaire stands for primary care centre; Pharmacie, stands for pharmacy.*

Prevention of non-communicable diseases is led by the Agence Sanitaire et Sociale de Nouvelle Calédonie (ASS-NC). This institution has set up a programme of RHD control including awareness campaigns among healthcare workers and the population, recommendations for sore throat detection and treatment, notification of ARF, and a National Register of Secondary Prophylaxis.

As in mainland France, the healthcare system is dual, public and private, the latter being funded by the social security that decides the fares. The Centre Hospitalier Territorial de Nouvelle Calédonie (CHT) is the main hospital for the entire country, the only to provide specialist care including cardiology, infectious diseases, neurology, paediatrics and intensive care.

Heart valve interventions were not available in New Caledonia until 2013. Patients are referred overseas for cardiac surgery and most percutaneous valve procedures. The Département des Evacuations Sanitaires (EVASAN) coordinates and funds all overseas referrals. A national mortality database is held by the Departement des Affaires Sanitaires et Sociales (DASS).

2.2. Study 1. Lessons from the first nationwide echocardiography-based screening programme for Rheumatic Heart Disease and outcomes of asymptomatic Rheumatic Heart Disease

The New Caledonian government declared RHD a public health priority in 2007. The political will to eradicate the condition was driven by the ASS-NC. An echocardiography-based screening program aiming at all 4th graders (i.e., aged 9-10 years) in primary schools was launched from February 2008 after a pilot study carried out in 2007. This survey was meant to be part of a public health prevention program.

All schools in the country (public and private) were included in the survey. The aim was to screen all 4th graders once a year, every year. After obtaining the authorizations of the Ministry of Education, all schools were notified of the date of screening. Visits by healthcare workers were organized prior to the survey in order to inform the children. Parents or guardians were asked to provide written informed consent. The screening included echocardiography, collection of sociodemographic characteristics (sex, date of birth and declared ethnicity), and past history of ARF or known RHD. No second visits were scheduled.

The diagnostic echocardiography protocol comprised two steps. Cardiologists from New Caledonia constituted a working group, acquired and interpreted the echocardiograms. A standardized echocardiography was performed at school in all children who accepted to participate with a written consent from one of the parents. When an abnormality was suspected, children were invited to attend a second examination by an experienced cardiologist at a free of charge clinic either in Nouméa or during outreach clinics in remote locations. Rheumatic heart disease was diagnosed only on the second scan according to predefined criteria agreed among Cardiologists participating in the programme that is detailed below (Section 2.2.4).[63]

All children diagnosed with RHD were offered free of charge secondary prophylaxis and yearly follow-up echocardiograms, and entered the National Register of Secondary Prophylaxis conducted by the ASS-NC. Children with incidental findings of congenital heart disease (CHD) were referred to a specialist clinic and offered intervention accordingly.

2.2.1. Aims

The aims of this study were threefold:

- To assess the first nationwide echocardiography-based screening programme for RHD in terms of completeness
- To estimate RHD prevalence in schoolchildren in New Caledonia
- To assess the outcomes of asymptomatic schoolchildren with and with no features of RHD on echocardiogram; secondary objectives included the identification of factors associated with the persistence or the progression of RHD.

2.2.2. Study design

This is a retrospective cohort study driven from the yearly RHD echocardiography screening campaigns from February 2008 to December 2011. Cross-sectional follow-up was carried out in 2012.

Inclusion criteria: diagnosis of RHD based on echocardiography following pre-specified criteria detailed below and controls with no RHD at baseline.
Exclusion criteria: subsequent diagnosis of congenital heart disease by an expert.
Data collected: socio-demographic characteristics; heart valve pattern and severity at diagnosis; clinical and echocardiographic measurements at follow-up.

2.2.3. Participants

All children with features of RHD on systematic echocardiography and a subset of matched controls with normal echocardiograms at baseline were eligible for enrolment. Controls attended the same class as cases and were matched according to ethnicity. Matching for same sex was made difficult in remote schools with a limited number of students per class. Two controls per case were aimed at.

2.2.4. Echocardiography protocols

<u>Echocardiography for RHD diagnosis</u>
The acquisition of the initial echocardiograms followed contemporary guidelines and included standard parasternal long and short axis views, apical four, two and three

chamber views. Acquisition was performed in grey-scale and Colour Doppler. Images were not systematically recorded for review.[63]

The initial criteria had been established by a group of senior cardiologists who took part in the RHD programme. These were derived from the WHO criteria and enriched of morphological criteria according to the publication by Marijon et al. These criteria included a combination of at least two morphological changes of the mitral valve and mitral regurgitation, aortic regurgitation or mitral stenosis and are detailed in Table 2.2.

Diagnosis of:	New Caledonia criteria	WHF criteria
Mitral stenosis	• Mean gradient ≥4mmHg Or • Surface area<1.5cm^2	• Mean gradient ≥4mmHg
Pathological mitral regurgitation	• Seen in two views • Jet length ≥2 cm • Pan-systolic jet • Mosaic colour jet with velocity ≥ 2.5 m/s	• Seen in two views • Jet length ≥2 cm • Pan-systolic jet • Velocity ≥3 m/s for one complete envelope
Pathological aortic regurgitation	• Jet length ≥1 cm • Pan-diastolic jet • Mosaic colour jet with velocity ≥ 2.5 m/s	• Jet length ≥1 cm • Pan-diastolic jet • Velocity ≥3 m/s • Seen in two views
Morphological features of the MV	• AMVL thickening >5mm • Chordal thickening • Abnormal mobility of valve leaflets • 'Dog leg' anterior mitral valve leaflet deformity	• AMVL thickening ≥3mm • Chordal thickening • Restricted leaflet motion • Excessive leaflet tip motion during systole
Morphological features of the AV	-	• Irregular or focal thickening • Coaptation defect • Restricted leaflet motion • Prolapse

Table 2.2. Comparison between the New Caledonian and the WHF criteria

Echocardiography protocol at follow-up

Follow-up echocardiograms were performed following a standardized protocol using a portable high-end machine (Vivid I, GE®) with a 1.5-3.6-MHz probe. Frame rates ranged from 25-35 Hz for black-and-white imaging and from 12-18 Hz for colour Doppler. Parasternal long axis and parasternal short axis, apical four chambers, two chamber and three chamber, and subcostal views were acquired and settings optimized according to the WHF recommendations: grey scale without harmonics were recorded in the parasternal long axis view for subsequent measurements of the anterior mitral leaflet, colour Doppler was used in all views, continuous wave Doppler was applied to systematically measure the mean trans-mitral gradient. Echocardiograms were performed either at the ASS-NC, Nouméa, or at outreach clinics in primary health centres by a single operator (the PhD candidate). Rheumatic heart disease diagnosis was based on the WHF criteria following a blinded review of all scans by the PhD candidate using EchoPac® software (GE®) (Table 2.1.).[53]

2.2.5. Data collection and outcomes

Data collection

For each participant, the following data were collected: demographics (age, sex), place of residence (Province, village), ethnicity, number of siblings, maternal employment, maternal education, housing, number of people living in the household, number of bedrooms, usual mode of transport (car *vs.* no car), whether lived over a year away from home (either in boarding schools or with other members of the extended family).

Data on treatment included secondary prophylaxis and its modalities: date of start; drug used (benzathine penicillin G or oral treatment); and periodicity of penicillin injections when applicable.

Outcomes

Participants were classified as having "definite" RHD, "borderline" RHD or no RHD.[53] Persistence of RHD was assessed according to the WHF criteria, including "definite" and "borderline" cases on echocardiogram. Progression of valve disease followed a pre-specified algorithm. Definition of stable valve disease included: unchanged grade of severity of single or multiple valve disease. Definition of

progression of valve disease was based either on the increased grade of isolated valve disease (e.g., mitral regurgitation previously grade 1/4 becoming grade ≥2/4 at follow-up) and/or newly diagnosed mitral regurgitation, aortic regurgitation and/or mitral stenosis.

Clinical endpoints included: a heart murmur at the follow-up clinic (auscultation was performed by the PhD candidate before the echocardiogram); ARF as per the regional guidelines,[64] and/or RHD-related complications (cardiovascular death, heart failure, embolism, infective endocarditis, heart valve intervention using percutaneous approach or surgery). Finally, vital status and cause of death were checked in the national DASS register on August 1st 2013 for all eligible participants. Hospital admission to CHT was also checked for potential participants lost to follow-up.

2.2.6. Bias

The work presented here yields a number of biases. Estimation of prevalence was likely to be conservative given the absence of scheduled new visits for absentees the day of the survey. The criteria for the diagnosis of RHD varied throughout the study. The initial recordings had not been kept at the ASS-NC therefore cases could not be reclassified according to WHF criteria published in 2012 (i.e., 4 years after the start of the survey). Similarly, normal echocardiograms at baseline could not be reviewed therefore children diagnosed with initially normal examinations may have had some minor abnormalities. At follow-up clinical events were collected retrospectively with a risk of memory bias. Finally, admission to the single paediatric facility (CHT) and death could be checked on but severe heart valve disease could not be ruled out in those lost to follow-up.

2.2.7. Statistical methods

All participants' characteristics were described as median [IQR], mean [SD] or proportions, as appropriate. Prevalence estimates were computed. Categorical variables were compared using chi-square test or Fisher's exact test, and continuous variables using Student t-test or Wilcoxon rank sum test, as appropriate. As a supplementary analysis, odds ratio (OR) and relative risks (RR) for diagnosis of RHD at follow-up and their 95% Confidence Intervals were calculated, stratified for year of

diagnosis (chi-square of Mantel Haentzel). A two-sided P value of less than 0.05 was considered to indicate statistical significance. Patients lost to follow-up were not included in the analysis. All data were analysed with the use of Statistical Analysis System software (version 9.3).

2.2.8. Ethics

Ethical clearance was granted from the Bordeaux and French Overseas Protection Committee and the French Institute of Medical Research and Health. The study complies with the declaration of Helsinki. All children and their parents/guardians gave informed consent.

2.3. Study 2. Screening for Rheumatic Heart Disease: Evaluation of a Focused Cardiac Ultrasound (FCU) Approach

2.3.1. Aims

The objective was to compare a FCU approach to the reference approach for the diagnosis of RHD. The FCU approach includes the combination of: (i) a pocket-size echocardiography machine, (ii) non-expert staff; and (iii) a simplified set of echocardiographic criteria.

The study comprises two parts with different objectives:
Part 1: to assess different diagnostic criteria directly on the pocket-echocardiography devices compared to reference WHF criteria in a selected population (high RHD prevalence).
Part 2: to test the FCU approach (including the simplified criteria driven from Part 1) in school-children (lower prevalence, real conditions) compared to the reference approach recommended by the WHF.

2.3.2. Study design

This prospective imaging study comprises two parts. We first tested different set of echocardiographic criteria for RHD to be used for FCU among selected children with

and without RHD in March 2013 (Part 1 of the study). We then prospectively evaluated the feasibility and performance of a FCU approach among a population of school children (4th graders aged 9-10 years in Nouméa, the capital city, and its suburbs) from April to August 2013 in schools during the yearly screening programme (Part 2).

2.3.3. Participants

Participants for Part 1 were recruited through previous yearly echo-screening campaigns conducted in New Caledonia since 2008 (then aged 9-10 years). Participants in part 1 included children with subclinical RHD and children with previously normal echocardiograms.[63] Part 1 was undertaken at the ASS-NC. Schoolchildren taking part in the yearly screening programme in Nouméa and its suburbs in April-July 2013 were offered to participate in Part 2 of this study.

2.3.4. Echocardiography protocols

The reference approach is identical to the methodology described in Section 2.2.4. Briefly, cardiologists performed standard echocardiograms with a portable machine (Vivid I, GE®, Milwaukee, WI) following a predefined acquisition protocol. An experienced reader (the PhD candidate) reviewed the studies using WHF criteria, blinded to clinical data.

The FCU approach was defined by the evaluation of on-site screening using a pocket echocardiography device, carried out by two nurses trained specifically for the purpose of the study. The pocket-echo machine used was the V-scan (General Electrics, GE®, Medical Systems, version1.2, Milwaukee, WI), with a 1.7-MHz to 3.4-MHz transducer. The V-scan offers regular greyscale imaging and colour blood flow mode with a 75° imaging sector. Grey-scale and Colour Doppler parasternal long axis and parasternal short axis, apical four chambers, two chamber and three chamber views were acquired, saved on the device's micro-SD card and transferred to a computer. Distance measurements were performed during the examination using a caliper.

Each participant underwent three echocardiograms the same day in a randomly allocated order, blinded to the child's diagnosis and to the other sonographer's findings: two independent examinations by nurses using FCU and one examination by a cardiologist on-site. Each participant was assigned a unique research identification number, which could be used to link the imaging studies to the research participant.

2.3.5. Training sessions

Two nurses with no previous experience in echocardiography underwent focused training for the recognition of left-sided valve abnormalities. The aim and stepwise methodology used for training the nurses are based on the training schemes supported by the WHF and that were under way at the time of the study.[65] The objectives of the training scheme were to gradually: (i) introduce the basic knowledge in cardiovascular physiology and cardiac anatomy; (ii) recognize the long and short axis parasternal, and all 3 apical transthoracic views, the four chambers and the four cardiac valves; (iii) acquire the views in grey scale and use colour Doppler; (iv) recognize morphological changes of the mitral valve (thickening of the anterior leaflet and of the chordae, restriction of the posterior and anterior leaflet, prolapse of the tip of the mitral leaflet); (v) detect the presence of mitral and/or aortic regurgitation; (vi) measure the maximum mitral regurgitation length using the caliper function on the device.

Training included theoretical lectures for 3 days, followed by 30 hours 2 to 1 hands-on sessions (with normal volunteers followed by sessions with patients at the echocardiography laboratory at CHT) in February 2013. Further tailored tutorship was undertaken after a preliminary assessment of the nurses' capacities, after completion of part 1. Nurses then reviewed a set of 50 of their scans with an experienced reader (PhD candidate) and undertook 12-hours practical sessions (one to one sessions) addressing the pitfalls of each nurse (acquisition, interpretation). Nurses were not asked to detect lesions of other aetiologies, namely CHD.
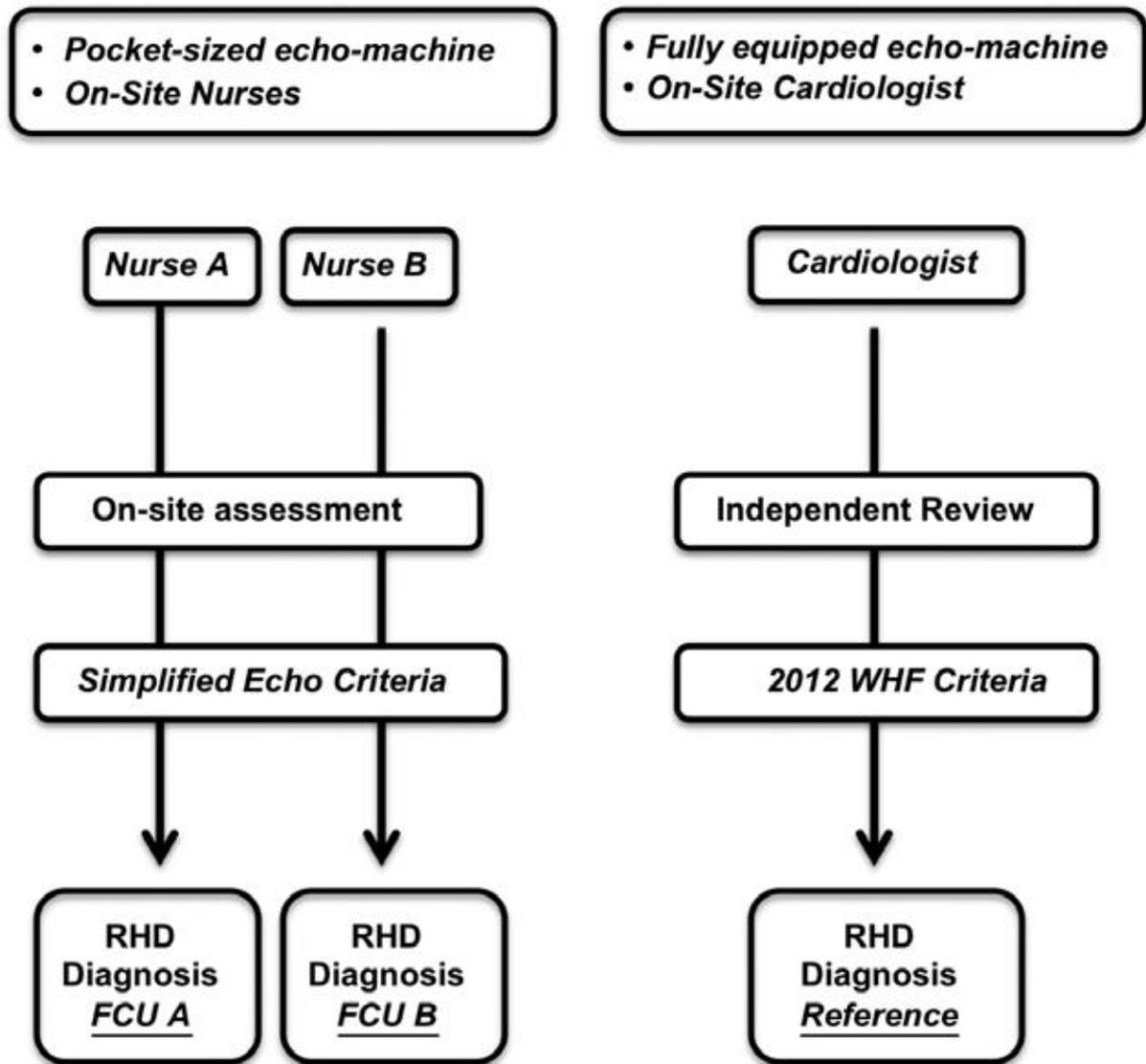
Figure 2.4. Methods of study n°2.

2.3.6. Outcomes measures

Part 1. The sensitivity and specificity of various echocardiography criteria were assessed individually and in combination. Equal importance was given to sensitivity and to specificity in order to test a method that would be applicable in remote and deprived regions with no need for further diagnostic testing.

The different echocardiographic criteria tested in part 1 were: (i) any mitral regurgitation (MR); (ii) MR jet length ≥ 1.5 cm; (iii) MR jet length ≥ 2.0 cm; (iv) morphological changes of the mitral valve defined as any irregular/focal thickening of the mitral leaflet, chordal thickening, restricted leaflet motion, excessive leaflet

motion or flail; (v) any aortic regurgitation (AR); (vi) MR jet length ≥2.0 cm or any AR.

Part 2. The ability to detect RHD (borderline and/or definite RHD) was evaluated by comparing FCU (on-site diagnosis by nurses performing FCU by pocket-echocardiography) to the reference approach.

2.3.7. Bias

The underlying prevalence of RHD may impact on the case detection rates, with possibly more false positives in low-prevalence areas where mitral regurgitation is likely to be physiological. Also the severity of heart valve disease may influence the ability to accurately detect RHD by FCU.

2.3.8. Statistical methods

Participant characteristics were described as median [IQR], mean [SD] or proportions, as appropriate. Categorical variables were compared using chi-square test. Sensitivity and specificity were calculated for the detection of any RHD (including borderline and definite RHD *as per* WHF criteria), with 95% CI. Confidence intervals for sensitivity and specificity were computed using the log-odds scale. Additional sensitivity analysis was performed for definite RHD cases. A predefined analysis was performed for part 1 of the study, including: (i) sample size calculations based on the hypothesis that the FCU approach would yield a sensitivity of 80% with 95%CI of 70-90% if 61 definite RHD and 61 controls were included in the study; (ii) the sensitivity and specificity to detect RHD for both nurses, with predefined cut-off values of 70%, in order to prospectively implement a simplified algorithm in part 2. To evaluate agreement between investigators, we used kappa coefficient with 95% CI or percentage of agreement, as appropriate. Perceived differences in image quality (qualified as poor, moderate and good) by the two non-expert users according to the readings of the PhD candidate were compared between the two users using Bowker's test of symmetry. All data were analysed with the use of Statistical Analysis System software (version 9.3).

2.3.9. Ethics

Participants were enrolled after parental written consent. Ethical clearance was granted from the Committee for the Protection of Persons of Overseas Territories and from the French Institute of Medical Research and Health.

2.4. Study 3: Symptomatic Rheumatic Heart Disease: estimated prevalence, incidence, characteristics and outcomes in New Caledonia

2.4.1. Aims

The main objective was to describe the characteristics of patients admitted to hospital for or with RHD, to estimate prevalence and incidence of RHD, and to assess outcomes in those who presented with newly diagnosed (or incident) RHD. The secondary objective was to identify factors associated with poor outcomes defined by a composite cardiovascular endpoint.

2.4.2. Study design

Retrospective hospital-based cohort with systematic review of hospital charts and cross-sectional follow-up to assess outcomes.

2.4.3. Participants

Hospital records of all individuals with a primary or secondary ICD 10 separation diagnosis of ARF or RHD from January 1st 2005 to December 31st 2012 were examined. Patients admitted with RHD in 2013 were prospectively enrolled. Patients who fulfilled WHF criteria for definite RHD were included in the study.[53] A subset of patients with newly diagnosed RHD between 2005 and 2013 with quantification of heart valve disease was considered for the analysis of outcomes.[66]

2.4.5. Data collection and outcomes

Data collected at the time of diagnosis

For each participant, the following data were retrospectively collected: demographics (age, sex), ethnicity, month and year of diagnosis, family history of RHD, ARF at presentation, valve disease on first echocardiogram and its severity,[67] NYHA class, LVEF on echocardiogram, pulmonary hypertension on echocardiogram (defined as pulmonary artery systolic pressure > 35 mmHg), presence of supraventricular arrhythmias (defined as paroxysmal or permanent atrial fibrillation, atrial flutter or atrial tachycardia). Mild heart valve disease included mild single left-sided valve disease and mild multiple heart valve disease (e.g., mild mitral regurgitation and mild aortic regurgitation). Heart valve disease was considered moderate if one of the left sided valves presented with moderate mitral regurgitation, mitral stenosis or aortic regurgitation. One single severe left-sided regurgitative/stenotic valve lesion was considered severe heart valve disease.[67]

Follow-up

Patients were invited to attend a specialist clinic from March 2013 to December 2013. If patients could not attend, a questionnaire was filled over the telephone either with the patient or the general practitioner, and the latest medical reports were collected.

Data on treatment included use of secondary prophylaxis (benzathine penicillin G injections or oral treatment), at any time from diagnosis and at the time of interview (i.e., on-going secondary prophylaxis). The National Register of Secondary Prophylaxis held by the ASS-NC was consulted when data was missing on the hospital chart. The population being captive, all major events (see below) such as heart failure, stroke or embolism would lead to admission to CHT. Vital status and cause of death were checked in the national mortality register (DASS) in March 2014 for patients lost to follow-up between March and December 2013. Use of cardiac interventions through the EVASAN office (in charge of overseas referrals) was also checked in March 2014 for patients lost to follow-up.

Outcomes and factors associated with events

Major cardiovascular events (MACE), based on information available in the hospital chart or in outpatients' clinic letters, included: heart failure (defined by NYHA class

III or IV), peripheral embolism, stroke, heart valve intervention, and cardiovascular death. Heart valve interventions included percutaneous mitral valvuloplasty and open-heart valve surgery. Additional adverse events were collected: severe haemorrhage (defined as leading to death, intra-cranial bleeding, bleeding associated with haemoglobin drop of ≥2g/dL or need for transfusion of at least 2 red-cell packs), infective endocarditis (defined as possible or definite infective endocarditis according to modified Duke criteria)[68], heart valve thrombosis (in patients with a mechanical valve), cardiogenic shock, and pregnancy-related complications (defined as maternal or foetal complications, including heart failure, need for surgery, termination of pregnancy, pre-term birth, and low-birth weight).

The analysis focused on patients with newly diagnosed RHD who presented with no MACE at the time of diagnosis.

A team of two research nurses collected all the data. A third party (the PhD candidate) arbitrated in case of disagreement.

2.4.6. Bias

Given the retrospective nature of this work there are a certain number unavoidable bias. Only patients admitted to a tertiary centre were included, with potential referral bias of most severe cases during a 9-year period. This is also true for the prevalence estimates; patients with RHD not seeking assistance to the hospital between 2005 and 2013 could not be included. The reason for reporting this prevalence estimate is to allow comparison of hospital and population-based data in the New Caledonian population.

Missing data have contributed to diminishing the sample size. Restricting the study population to patients with strict echocardiographic criteria reduced further our sample size and may introduce a bias. The analysis focused on patients admitted with uncomplicated RHD at the time of diagnosis, which underestimates the burden of the disease, but allows the identification of factors associated with the advent of adverse outcomes. Missing data precluded the inclusion of secondary prophylaxis in the main Cox proportional hazard analysis, with however the possibility to perform sensitivity analysis. Secondary prophylaxis could not be treated as a time-dependent variable given the difficulties in estimating adherence to treatment in spite of multiple sources

of data collection. Diagnosis of ARF was at the discretion of the physician, and did not necessarily fulfil modified Jones'[69] or Australasian criteria.[64]

2.4.7. Statistical methods

The incidence (person-years) of newly diagnosed RHD and of ARF is presented with Poisson 95% CI. The prevalence of RHD was also computed for 2013. The New Caledonian Bureau of Statistics population estimates published in 2014 were used for population denominators for the total, Melanesian and class-age populations.

The results are reported as median and interquartile range (IQR) or as numbers and percentages. Categorical variables were compared using chi-square test or Fisher's exact test, and continuous variables using Student t-test. Only patients with no MACE at hospital admission were further eligible for the analysis on incident MACE. The incidence of cardiovascular events was calculated per 1,000 person-years. Factors associated with MACE were analysed using a Cox proportional hazard model. Time to event was calculated as time from diagnosis to first event or last follow-up. Hazard Ratios (HR) for the Cox model were calculated accordingly with their 95% confidence intervals (CI). Sensitivity analysis was performed in regards to secondary prophylaxis. Significance was defined as P-values less than 0.05. All data were verified and analysed with the use of Statistical Analysis System software (version 9.3).

2.4.8. Ethics

Patients were asked to give oral consent to be enrolled in the study at time of follow-up interview. Ethical clearance was provided accordingly by the IRB Ethical Review Committee of the Institut National de la Santé et de la Recherche Médicale (French Institute of Health and Medical Research), Paris, France who waived written consent.

3. Results

3.1. Study 1. Part 1. Lessons from the first nationwide echocardiography-based screening programme for Rheumatic Heart Disease

A public health campaign targeting schoolchildren in New Caledonia

3.1.1. Abstract

Background. The World Health Organization recommends active surveillance of Rheumatic Heart Disease (RHD) in endemic regions. Echocardiography has emerged as an early diagnostic tool. This is the first nationwide echocardiographic screening campaign for RHD in schoolchildren.

Methods. A screening programme based on systematic use of ultrasounds to detect RHD was undertaken (2008-2011) by the government of New Caledonia. Children with suspected abnormalities were referred to cardiology clinics where final diagnosis was made. Were analyzed factors associated with the presence of RHD, and methods of the survey were assessed.

Results. Among the 18,621 children targeted by the programme (82.1% of the population born 1998-2001), 17,287 (92.8%) were finally screened, 1,619 (9.4%) were referred for a second opinion on non-portable equipment, and 418/1,619 (25.8%) did not attend the clinic. Out of the 17,287 schoolchildren screened, 157 were actually diagnosed with RHD (overall prevalence of 9.5 per 1,000 [95% CI 8.1-11.1]), with higher prevalence among older children (aged ≥ 11 years) (p=0.04), Oceanic populations (p<0.0001), and remote locations (p<0.0001). The majority of children (353/418, 84.4% cases) with lesions at school who were lost to diagnosis within the referral system were suspected of RHD and were at high risk according to their demographic characteristics.

Conclusions. A nationwide program of echocardiography-based screening for RHD provides valuable data for future policy planning. Although feasible, the methods

carry a number of limitations, including a two-step diagnostic procedure leaving large numbers undiagnosed.

3.1.2. Introduction

Rheumatic Heart Disease still yields high prevalence rates in the Pacific and in Australia among indigenous populations.[22, 28, 70] In contrast, the condition has been nearly eradicated in other French overseas islands over two decades ago by means of classic comprehensive prevention programmes.[71]

One of the recommended strategies by the World Health Organization includes active surveillance in order to detect the disease in its early course and start secondary prophylaxis by penicillin, the only treatment proven to prevent progression of the disease.[35] The use of ultrasounds has been shown to be of particular interest to increase case-detection, considering also silent RHD lesions.[19, 47, 48, 72] The advent of new technological capacities that could reduce the burden of disease has increased the interest of the international community for this neglected condition.[73] However, before ultrasounds may become an attractive tool for active surveillance, several issues need to be addressed.[55, 74] To date, all studies have focused on samples driven from the population, as part of specific research programmes,[19, 47-50, 72] and finally none has addressed the epidemiological perspective by targeting an entire population. A first nationwide active surveillance program based on the echocardiographic diagnosis of RHD targeting schoolchildren had been launched in New Caledonia, conducted under the auspices of the ASS-NC in the attempt to control the burden of the disease

This is a unique opportunity to assess the methods and results of the first survey of the kind. The advantages and limitations of this strategy are explored here.

3.1.3. Methods

These have been described in detail in Section 2.1. In summary, the ASS-NC undertook a nationwide screening yearly campaign targeting 4th graders in all primary schools. The diagnosis was based on echocardiographic features of RHD according to predefined criteria agreed amongst the local Cardiology community.

3.1.4. Results

Completeness of the active surveillance program

Among the 18,621 children listed in the active surveillance program, the majority (17,697; 95%) were born between 1998 and 2002 and represented approximately 82.1% of the overall New Caledonian population born 1998-2002.

Out of the 18,621 targeted by programme, 858 (4.6%) were absent the day of screening, and 376 (2.0%) provided no parental consent. Among the 17,287 children finally screened, 1,619 (9.4%) were referred for a second opinion on non-portable equipment, and 418/1,619 (25.8%) did not attend the clinic.
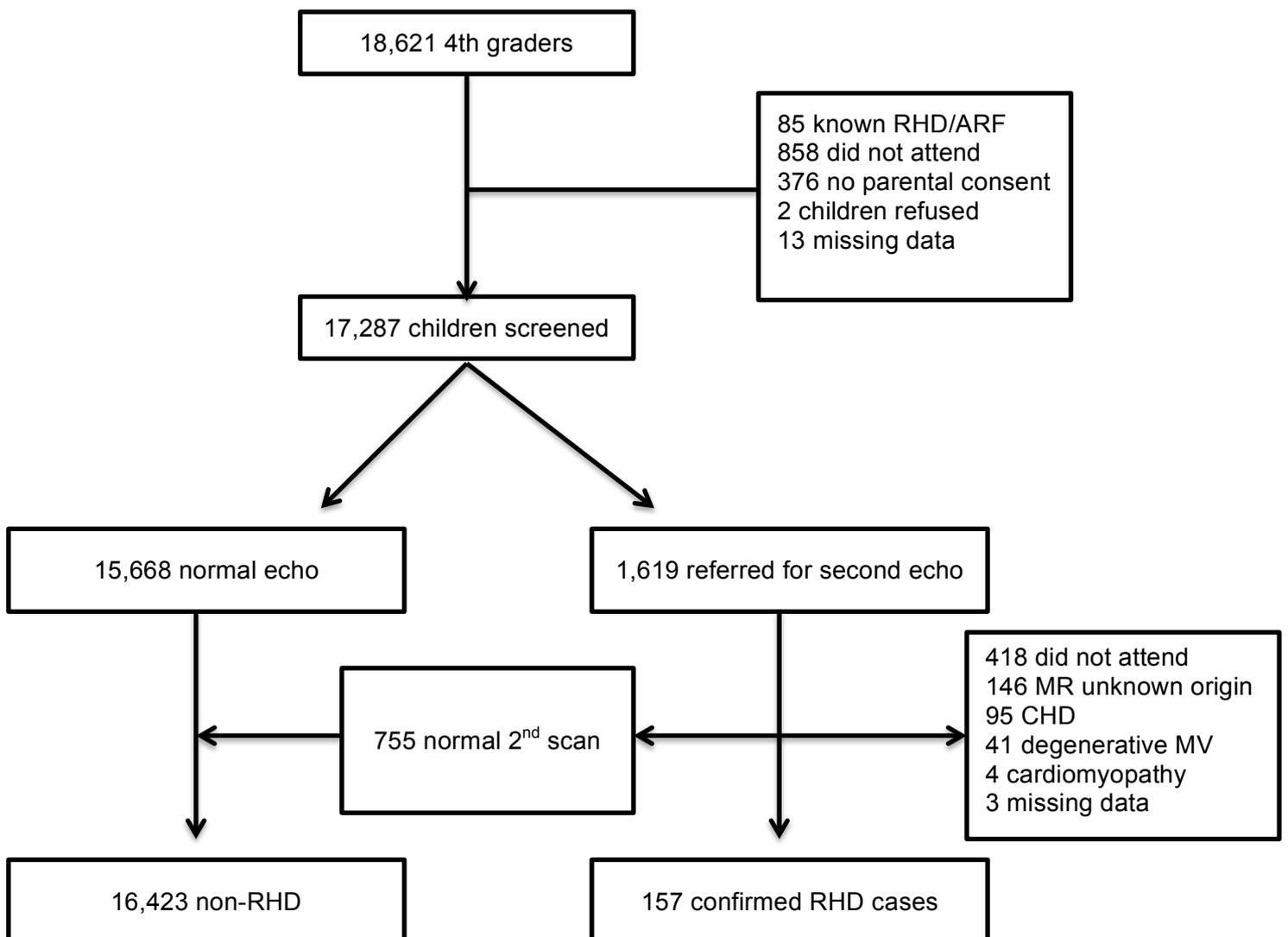
Figure 3.1. Completeness of the screening programme.

RHD Prevalence and factors associated with features of RHD

One hundred and fifty-seven children were finally diagnosed with asymptomatic RHD following this two-step echocardiographic approach (i.e., presented no history of ARF or previously known RHD) giving an overall prevalence of 9.5 per 1,000 [95% CI 8.1-11.1]. Stratified according to the year of screening, the prevalence of RHD was significantly higher in: older children (aged $\geq$11 years) (p=0.04), Oceanic populations (p<0.0001) and remote locations (Northern and Loyalty Islands Provinces) (p<0.0001).

	RHD N=157	Non-RHD N=16,423	Prevalence per 1,000	Univariate p	Multivariate p
Year of screening, n (%)					
2008	39 (24.84)	3959 (24.11	9.8 [6.9- 13.3]		
2009	33 (21.02)	4238 (25.81)	7.7 [5.3- 10.8]		
2010	44 (28.03)	4192 (25.53)	10.4 [7.6- 13.9]		
2011	41 (26.11)	4034 (24.56)	10.1 [7.2- 13.6]		
Age, mean (SD)	9.86 (0.76)	9.76 (0.70)		0.07	
Age class*				0.04	0.04
≤ 9 years	40 (25.64)	5703 (34.93)	7 [5- 9.5]		
10 years	93 (59.62)	8771 (53.72)	10.5 [8.5- 12.8]		
≥11 years	23 (14.74)	1854 (11.35)	12.3 [7.8- 18.3]		
Sex, n (%)				0.18	0.12
Female	86 (54.78)	8113 (49.40)	10.5 [8.4- 12.9]		
Male	71 (45.22)	8310 (50.60)	8.5 [6.6- 10.7]		
Province, n (%)					
Loyalty Islands	23 (14.65)	1678 (10.22)	13.5 [8.6- 20.2]	<0.0001	<0.0001
Northern Province	66 (42.04)	3105 (18.91)	20.8 [16.1- 26.4]		
Southern Province	68 (43.31)	11640 (70.88)	5.8 [4.5- 7.4]		
Location, n (%)					
Noumea	32 (20.38)	6451 (39.28)	4.9 [3.4- 7]	<0.0001	
Suburbs of Noumea	27 (17.20)	4025 (24.51)	6.7 [4.4- 9.7]		
Outside greater Noumea	98 (62.42)	5947 (36.21)	16.2 [13.2- 19.7]		
Ethnicity†, n (%)					
Caucasian or Asian	11 (7.01)	5609 (34.17)	2 [1- 3.5]	<0.0001	<0.0001
Melanesian	137 (87.26)	9243 (56.31)	14.6 [12.3- 17.2]		
Polynesian	9 (5.73)	1553 (9.46)	5.8 [2.6- 10.9]		

Table 3.1. Factors associated with asymptomatic RHD.

The 418 children who were suspected of cardiac lesions at school and who did not attend the 2nd echocardiography were significantly older (p=0.02), more often male (p=0.008), from the Northern Province (p<0.001), and predominantly Melanesian (p<0.0001) when compared to the 1,201 children seen at the cardiology clinic. The rate of attendance to the clinic improved over time (p<0.001). Among the large numbers of children (25.8%) with lesions at school who were lost to diagnosis within the referral system, the majority (353/418, 84.4% cases) were suspected of RHD and were at high risk according to their demographic characteristics.

3.1.5. Discussion

I report here the results of a unique program that has aimed at mass echo-screening for RHD; the majority (82.1%) of the children in a specific age group being captured by the school-based survey between 2008 and 2011. The analysis of a nationwide program provides valuable data in the planning of future healthcare policies regarding RHD. The survey presents a number of advantages and limitations. The population at risk of RHD is defined by ethnicity, place of residence, and age group. Although feasible, there are several limitations inherent to the methods used. Pitfalls in the completeness of the active surveillance campaigns are mainly the consequence of a two-step diagnostic transversal approach since a significant proportion of children (25%) with suspected lesions at school are finally lost to follow-up with no definite diagnosis or treatment.

The prevalence of RHD varied greatly across the different ethnic groups. Oceanic (i.e., Melanesian and Polynesian), especially Melanesian, children were at higher risk of RHD when compared to non-Oceanic children. Also, the prevalence was independently higher in the Northern and Loyalty Islands Provinces, two remote regions with less access to specialized care. Targeting population at risk may avoid consuming a vast amount of resources that could be otherwise used to strengthen the RHD control programme.

The programme missed children at risk for RHD: absentees (no systematic second visits were scheduled), those out of school, but, most importantly, those who did not attend the cardiology clinic for a second confirmatory echocardiogram. A two-step approach to diagnose RHD has been used in many studies, inviting children suspected at school to attend a cardiology clinic using non-portable sophisticated equipment.[19, 48, 50] Although ideal from an imaging perspective, a fourth of the children with suspected abnormalities did not attend the free of charge cardiology clinic. These children are at high risk of RHD based on their age, ethnicity and geographic location. On the other hand, the majority of children referred for a second scan did not have RHD. These facts highlight the two main limitations of a two-step approach: children at higher risk of RHD may not attend the confirmation scan and miss the opportunity of early medical treatment; whilst the cardiology clinics' capacity is overwhelmed by a majority of healthy children. Studies exploring more simple and affordable ways to accurately diagnose RHD on site are most needed to render echocardiographic screening affordable and feasible in poorly resourced settings.[75, 76]

These results open new perspectives in public health RHD research. Indeed, several issues need to be explored before the most appropriate methods for active surveillance are identified. Surveys tailored to the local epidemiology that prioritize populations at risk, serial screening throughout childhood, simpler ways of conducting echo-screening (e.g., one step approach with on site diagnosis), and cost-effectiveness need to be addressed before transposing such programs to resource-deprived settings.

3.1.6. Conclusions

The first nationwide program of echocardiography-based screening for RHD in schoolchildren provides valuable data for future planning of healthcare policies. Although feasible, such methodology carries a number of limitations that need to be highlighted: a complex diagnostic approach leaves up to one fourth of suspected cases undiagnosed. These results suggest that screening restricted to high-risk populations (indigenous populations living in remote areas and overcrowded living conditions) should also be explored. Simplified approaches, and cost-effectiveness need to be addressed before transposing such programs to resource-deprived settings.

3.2. Study 1. Part 2. Outcomes of asymptomatic echocardiography-screened rheumatic heart disease

3.2.1. Abstract

Objective – To assess the outcomes of Rheumatic Heart Disease (RHD) diagnosed by means of echocardiography-based screening.

Methods – A cohort of children with and with no RHD was driven from a systematic echocardiography-based nationwide surveillance among 4th grade (age 9-10 years) schoolchildren in New Caledonia (2008–2011).

Results - Out of 17,633 children screened, 157 were detected with findings of RHD. Among them, 114 consented children (76.5%) were enrolled (RHD-group), and were compared to 227 randomly selected healthy classmates (non-RHD group). After a median follow-up period of 2.58 years [1.31-3.63], incidence of ARF was similar in RHD and non-RHD groups (p=0.23): 10.28/1000/year and 3.31/1000/year, respectively. By echocardiography, 90 children in the RHD group (78.9%) still presented with RHD at follow-up, compared to 31 (13.7%) in the non-RHD group (p<0.0001). Only 12 children (10.5%) experienced progression of RHD over time, mild single valve disease lesions remaining unchanged in the majority of cases (61 out of 73, 83.6%). Overcrowded living conditions were independently associated with persistent RHD on echocardiography (OR 8.27 95% CI (1.67-41.08), p<0.01). Benzathine penicillin G was given in 88.6% of children in the RHD-group.

Conclusions – Children screened positive for RHD by echocardiography have mostly mild but irreversible heart valve disease under secondary prophylaxis. These findings also suggest that a single screening point in childhood may prove insufficient in high-risk populations.

3.2.2. Introduction

Echocardiography-based screening may present an attractive method for RHD control, ultrasounds being more sensitive to detect very mild valve lesions.[19]

However, the natural history of echocardiography-detected RHD has never been established and the need for secondary prophylaxis still remains debated.[77, 78] There are therefore several unanswered questions in the field, as the outcomes of children screened for RHD, the need for secondary prophylaxis, and the target age-range. I assessed here the outcomes through a cohort study of children with and without RHD who took part in the first large RHD echocardiography-based surveillance program.

3.2.3. Methods

These have been described in detail in Section 2.2. Briefly, I conducted the follow-up of a cohort of children with findings of RHD and matched controls. The aim of the study was to assess the outcomes of children detected by echocardiography as having RHD (RHD group), compared to those without RHD (non-RHD group). In addition, factors associated with persistence or progression of disease were identified.

Participants
Among the 17,633 children screened, 157 were diagnosed with RHD (i.e., presented no history of ARF or previously known RHD). One hundred fourteen out of 157 (72.6%) consented to be finally enrolled in the specific follow-up program, including secondary prophylaxis by oral or injectable penicillin. Among the children with no RHD on echocardiogram between 2008 and 2011, 227 classmates were randomly selected matched according to ethnicity (and classroom).

3.2.4. Results

<u>*Characteristics according to the initial diagnosis*</u>
One hundred and fourteen children with RHD diagnosed by echocardiography and 227 previously healthy children participated in the study. The mean age (SD) at the time of screening was 9.9±0.7 in the RHD group, and 10.0±0.7 in the normal baseline echocardiography group (non-RHD group), with a sex ratio (M/F) of 0.9 in the RHD group and of 1.0 in the non-RHD group.
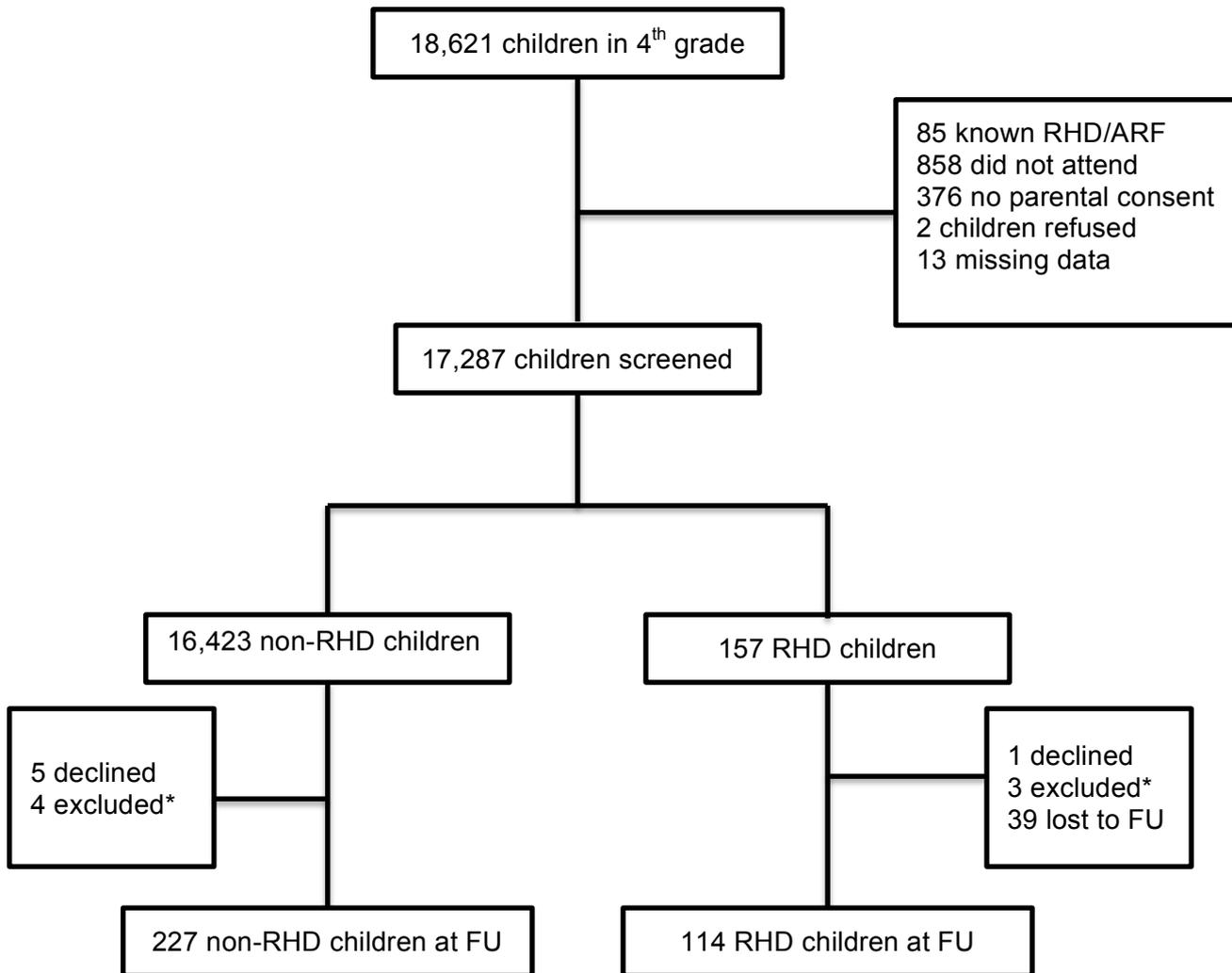
Figure 3.2. Flow chart of the cohort study on outcomes in asymptomatic echocardiography-screened RHD.*Other diagnosis after serial echocardiography (CHD).

Among the 114 children with a positive screening for RHD, the baseline echocardiogram showed mitral regurgitation in 107 cases (93.9%), aortic regurgitation in 34 cases (29.8%), and mitral stenosis in 6 cases (5.2%). Multiple left-sided valve involvement was present in 30 (26.3%) cases. Available in 60 cases, median baseline left ventricular ejection fraction was 65% IQR (61-70.5). Physiological mitral regurgitation was present in 16 out of 227 (7.1%) children with normal findings on the echocardiogram at school.

Characteristics	RHD N=114	Non-RHD N=227
Number of years to FU, median (IQR)	2.2 (1.5-3.6)	2.6 (1.3-3.6)
Year of screening, n (%)		
2008	29 (25.4)	54 (23.8)
2009	24 (21.0)	54 (23.8)
2010	32 (28.1)	53 (23.3)
2011	29 (25.4)	66 (29.1)
Age*, mean (SD)	9.9 (0.7)	10.0 (0.7)
Male, n (%)	54 (47.4)	115 (50.7)
Province, n (%)		
Loyalty Islands	16 (14.0)	31 (13.7)
Northern Province	46 (40.3)	115 (50.7)
Southern Province	52 (45.6)	81 (35.7)
Ethnicity, n (%)		
Oceanic†	97 (85.1)	185 (81.5)
Caucasian	4 (3.5)	4 (1.8)
Other	13 (11.4)	38 (16.7)
Number of siblings by mother, n (%)		
≤ 2	26 (22.8)	48 (21.2)
3-5	66 (57.9)	140 (61.9)
≥ 6	22 (19.3)	38 (16.8)
Maternal employment, n (%)		
No formal occupation	55 (48.2)	109 (48.0)
Receives salary	58 (50.9)	107 (47.1)
Unknown	1 (0.9)	11 (4.8)
Maternal education, n (%)		
Primary school	51 (44.7)	119 (52.4)
Secondary school	48 (42.1)	88 (38.8)
High education‡	7 (6.1)	10 (4.4)
Unknown	8 (7.0)	10 (4.4)
Housing, n (%)		
Concrete	71 (62.3)	127 (55.9)
Partly concrete§	32 (28.1)	76 (33.5)
Non-concrete	10 (8.9)	22 (9.7)
Unknown	1 (0.9)	2 (0.9)
Lived ≥1 year out of the household, n (%)	35 (30.7)	63 (27.7)
Usual mode of transport: private car, n (%)	78 (68.4)	137 (60.3)

Table 3.2. Characteristics of children at baseline. *Age at the time of screening. †Includes
Melanesians and Polynesians. ‡Defined as a University/College degree. §Defined as having
a concrete floor but with traditional walls and/or roofs (wood and palm trees)

Outcomes of children with RHD

The incidence of ARF was of 10.28/1,000 person-years after a median follow-up
period of 2.58 years [1.31-3.63]. One child (0.9%) suffered from heart failure during

the follow-up period. No heart valve interventions were carried out during the study period.

Twenty-four children (21.0%) in the RHD group presented with an audible pathological murmur at follow-up. Eleven out of these 24 children (45.8%) had valve disease grade ≥2/4 on the follow-up scan.

One hundred and one children out of 114 cases (88.6%) received benzathine penicillin G. The periodicity of penicillin injections over the follow-up period is described in Figure 3.3. Six (5.3%) were offered oral secondary prophylaxis and 7 (6.3%) received no antibiotics.
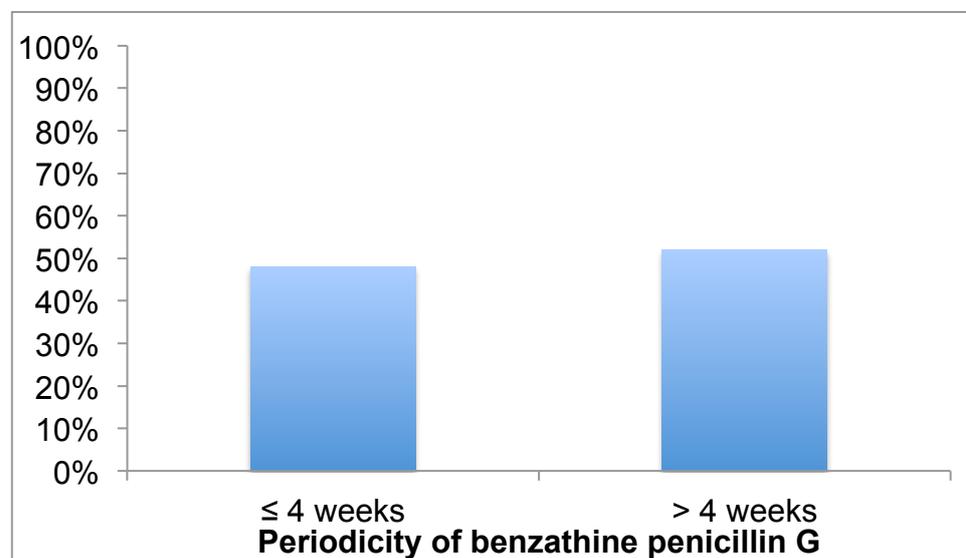
Figure 3.3. Periodicity of benzathine penicillin injections in children with RHD.

Among the 114 initial cases, 41 (36.0%) presented with a definite diagnosis of RHD at follow-up; 49 (43.0%) had features consistent with borderline RHD; and 24 (21.1%) had normal findings according to the WHF criteria.[53]
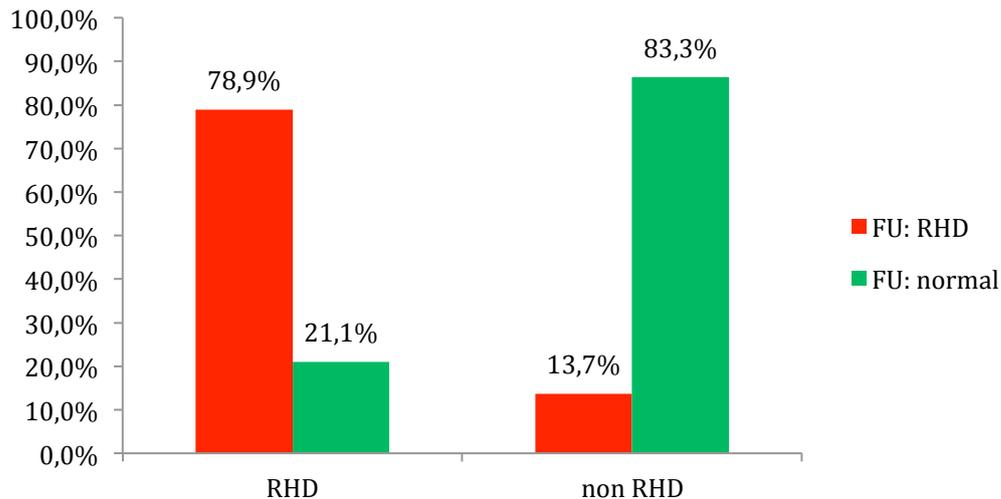
Figure 3.4. Echocardiographic diagnosis at follow-up. FU, follow-up.

Among the 24 out of 114 RHD cases who did not fulfil the WHF criteria for RHD on the FU scan, 19 presented with mild mitral regurgitation (i.e., grade 1/4), 2 with a combination of mild mitral regurgitation and mild aortic regurgitation, 1 with mild aortic regurgitation, and 2 children had no aortic or mitral regurgitation. Thus, among the 114 children with RHD, 112 (98.2%) were deemed to have significant left-sided regurgitation on the follow-up echocardiogram regardless WHF criteria.

Neither hospital admission nor deaths were reported among the children lost to follow-up between January 1st 2008 and August 1st 2013.

Factors associated with the persistence of RHD among the group of children with RHD were identified. Univariate analysis of the persistence of RHD (either definite or borderline RHD) is presented in Table 3.3. On multivariate analysis, stratified according the year of screening, the number of people per bedroom remained the only significant factor associated with persistence of RHD: number of people per bedroom < 3 *vs.* ≥ 3, OR 8.27 95% CI (1.67-41.08), p<0.01. The association remained significant when children with borderline RHD were excluded from the analysis: number of people per bedroom < 3 *vs.* ≥ 3, OR 7.70 95% CI (1.28-46.45), p=0.03. There was no significant association between persistence of RHD and compliance to secondary prophylaxis (p=0.78).

	Persistent RHD N=90	Normal echo N=24	Univariate P – value	Multivariate OR (95% CI)	Multivariate P - value
Year of screening, n (%)					
2008	24 (26.7)	5 (20.8)			
2009	14 (15.6)	10 (41.7)			
2010	28 (31.1)	4 (16.7)			
2011	24 (26.7)	5 (20.8)			
Age*, mean (SD)	10.0 (0.7)	9.7 (0.9)	0.2		
Male, n (%)	45 (50.0)	9 (37.5)	0.3		
Ethnicity, n (%)			0.9		
Oceaniac† *vs.* European or Asian	76 (84.4)	21 (87.5)			
Number of siblings by mother, n (%)			0.2		
≤ 2	22 (24.4)	4 (16.7)			
3-5	49 (54.4)	17 (70.8)			
≥ 6	19 (21.1)	3 (12.5)			
Maternal employment, n (%)			0.4		
No formal occupation	45 (50.6)	10 (41.7)			
Receives salary	44 (49.4)	14 (58.3)			
Maternal education, n (%)			0.048	1.97(0.69-5.64)	0.20
Primary school	38 (46.3)	13 (54.2)			
Secondary school	41 (50.0)	7 (29.2			
High education‡	3 (3.7)	4 (16.7)			
Housing, n (%)			0.9		
Concrete	56 (62.9)	15 (62.5)			
In part concrete§	8 (9.0)	2 (8.3)			
Non-concrete	25 (28.1)	7 (29.2)			
Lived ≥1 year out of the household, n (%)	29 (32.2)	6 (25.0)	0.2		
Usual mode of transport: private car, n (%)	63 (70.0)	15 (62.5)	0.4		
Number of people per bedroom, n (%) ≥3	32 (35.6)	2 (8.3)	0.003	8.27(1.67-41.08)	<0.01
Penicillin injections§§, n (%)			0.78		
≤ 4 weeks	38 (42.2)	12 (50.0)			
> 4 weeks	44 (91.1)	11 (45.8)			

Table 3.3. Factors associated with the presistence of RHD. *Age at the time of screening. †Includes Melanesians and Polynesians. ‡Defined as a Univerity/College degree.*

The severity of valve disease in the RHD group at baseline and at follow-up is depicted in Table 3.4. Overall, 102 out of 114 children (89.5%) had unchanged severity of valve disease, whilst 12 (10.5%) experienced progression of their valve disease and none improved significantly. Six children (5.2%) presented with new valve lesions. Mild single valve disease lesions remained unchanged in the majority of cases (61 out of 73 cases, 83.6%). There was no significant association between outcomes in terms of valve disease severity and the number of people per bedroom <3 vs. $\geq$ 3 (Fischer exact test, p=1); or the periodicity of penicillin injections (6 weekly injections or less vs. no injections or every periodicity over 6 weeks, Fischer exact test, p=0.08).

	At baseline N=114	At follow-up N=114
Mitral regurgitation, n (%)	107 (93.9)	111 (97.4)
Physiological MR	7 (6.1)	44 (38.6)
Grade 1	79 (69.3)	58 (50.9)
Grade 2	18 (15.8)	6 (5.2)
Grade 3	3 (2.6)	1 (0.9)
Grade 4	0	1 (0.9)
Aortic regurgitation, n (%)	34 (29.8)	38 (33.3)
Physiological AR	7 (6.1)	18 (15.8)
Grade 1	23 (20.2)	17 (14.9)
Grade 2	3 (2.6)	2 (1.8)
Grade 3	1 (0.9)	1 (0.9)
Grade 4	0	0
Mitral stenosis, n (%)	6 (5.2)	7 (6.1)
Mild	5 (4.4)	4 (3.5)
Moderate	1 (0.9)	2 (1.8)
Severe	0	1 (0.9)
Multiple valve disease	30 (26.3)	37 (32.7)

Table 3.4. Echocardiographic features of heart valve disease

Outcomes of children with no RHD at the time of screening

There was no significant difference in terms of incidence of ARF between the RHD and the non-RHD groups. The incidence of ARF was of 10.28/1,000 person-years and 3.31/1,000 person-years in RHD and non-RHD groups (p=0.23), respectively. Three children (1.3%) in the non-RHD group presented with a murmur at follow-up. There were no complications, nor hospital admissions or death, in the non-RHD group.

Among the 227 children with normal baseline echocardiograms, 2 (0.9%) presented with a definite diagnosis of RHD, 29 (12.8%) had features of borderline RHD, and 189 (83.3%) presented normal findings at follow-up.[53]

After stratification for the year of screening, children with an initial diagnosis of RHD had an increased risk [RR 5.60 (3.98-7.87), (p<0.0001)] to have an abnormal echocardiogram at follow-up (either definite or borderline RHD), compared to children with a normal baseline echocardiogram.

3.2.5. Discussion

This is, to the best of my knowledge, the largest cohort of children diagnosed with RHD and with no RHD by means of school-based echocardiography screening to this date. The majority of valve lesions, albeit mild, persist under secondary prophylaxis. Overcrowded living conditions were associated with the persistence of the disease. Children at risk of RHD with normal baseline echocardiograms when aged 9-10 years yield considerable risk of developing ARF or RHD later in adolescence.

Most children with RHD (78.1%) presented with persistent disease according to the currently recommended criteria under secondary prophylaxis.[53] These findings are in good agreement with smaller series, where RHD persisted in approximately 67-75% of cases. [50, 57, 58] Of note, left-sided valve disease, often mild and unchanged in severity, remained present in the vast majority of RHD children in our study. The apparent discrepancies in our results as regards to presence of RHD *versus* valve disease quantification may be explained by the fact that the WHF criteria are stringent in terms of pathological regurgitation. A complete continuous Doppler envelope of mitral regurgitation jet is necessary to validate the WHF criteria.[53] But mitral regurgitation is classically posteriorly directed in RHD and a complete envelope may

be difficult to obtain, especially when valve disease is mild, as was the case in this study.

The number of people per bedroom was associated with the persistence of RHD on echocardiogram. Promiscuity increases the risk to GAS exposure, thereby leading to recurrent or chronic ARF attacks.[79] These findings highlight the importance of taking into account risk factors for ARF when facing mild valve lesions that may be of rheumatic origin. Living conditions may become part of the decision-making process regarding secondary prophylaxis, especially in the setting of borderline RHD lesions in asymptomatic children.[80]

Only one child out of 157 presented with a serious complication (heart failure that resolved under medical therapy). There were no interventions or deaths in our cohort, suggesting the benign course of echo-screened RHD. These results should be taken with caution given the relatively short follow-up period (2 years) whilst it usually takes decades before presenting with advanced disease.[16, 81]

Approximately half the RHD children received secondary prophylaxis as currently recommended by the latest regional guidelines.[64] As in other countries, there is still place for improvement, especially in the setting of universal healthcare coverage as provided in New Caledonia.[81-83] There was no significant association between the compliance to secondary prophylaxis and outcomes in terms of persistence of RHD or severity of valve disease, likely due to the study design. Data on the natural history of subclinical RHD are lacking and some experts in the field have questioned the need for secondary prophylaxis, especially in those diagnosed as borderline RHD.[77] Since the landmark study that suggested echo-based screening as a possible option for disease-control,[19] other groups have found that ultrasound-led diagnosis may be of interest, with higher sensitivity and specificity than auscultation.[21] To the best of my knowledge, three prospective studies assessing the prognostic significance of subclinical RHD are currently on going.[48, 84, 85] It may however take several years before data are available to establish guidelines in the field. In the meanwhile, these findings suggest that, based on the precautionary principle, secondary prophylaxis should be offered to these children given that their valve lesions remained stable under such (albeit imperfect) treatment.

This study supports the need for another screening point later in childhood. Children with no RHD at age 9-10 years are at risk of developing ARF later in adolescence.

Age matters in terms of cumulative incidence of ARF and of the prevalence of RHD.[21, 28, 52] Acute rheumatic fever incidence was similar in RHD and non-RHD groups. The annual incidence in this cohort is similar to figures reported in other regions.[28, 86] In addition to high ARF incidence, a significant proportion of children with normal echocardiograms at school presented 2 years later with either definite RHD (0.9%) or borderline RHD (12.8%). Repeat screening may be an option to increase case-detection rates in those with mild disease that may benefit the most from secondary prophylaxis.

Strengths and limitations

In addition to what has been outlined in the Methods section 2.2.6, this study may have lacked power to assess clinical outcomes (i.e., ARF attacks). The study was neither designed nor powered to assess the impact of secondary prophylaxis on echocardiography-screened, often mild and subclinical, RHD.

3.2.6. Conclusions

Rheumatic heart disease diagnosed by echocardiography-based screening is often mild but nevertheless an irreversible condition in schoolchildren under secondary prophylaxis. Overcrowding appears to be the strongest predictor of the persistence of the disease. Serial assessment throughout childhood may be of interest. Further studies are warranted to assess the need for secondary prophylaxis in subclinical RHD.

3.3. Study 2. Screening for Rheumatic Heart Disease: Evaluation of a Focused Cardiac Ultrasound Approach

3.3.1. Abstract

Objective – To compare FCU to a reference approach for RHD screening.

Methods and Results – Prospective comparison of FCU to a reference approach for RHD screening in a school children population. FCU included (i) the use of a pocket-

sized echocardiography machine, (ii) non-expert staff (two nurses with specific training), and (iii) a simplified set of echocardiographic criteria. The reference approach used standardized echocardiographic examination, reviewed by an expert cardiologist, according to 2012 WHF criteria. Among the six different echocardiographic criteria first tested in a preliminary phase (Part 1), mitral regurgitation jet length ≥2cm or any aortic regurgitation was considered best suited to be FCU criteria. Of the 1,217 subjects enrolled (mean 9.6±1 years, 49.6% male), 49 (4%) were diagnosed with RHD by the reference approach (Part 2). The sensitivity of FCU for the detection of RHD was 83.7% (95% CI 73.3-94.0) for nurse A and 77.6% (95% CI 65.9-89.2) for nurse B. FCU yielded a specificity of 90.9% (95% CI 89.3-92.6) and 92.0% (95% CI 90.4-93.5) according to users. Percentage of agreement among nurses was 91.4%. When restricted to definite RHD only, the performance of the FCU approach was better. Focused cardiac ultrasound yielded a sensitivity of 93.3% (95% CI 64.7-99.1) and 86.7% (95% CI 59.5-96.7) according to nurses A and B, respectively; the percentage of agreement between nurses was then 91.8%.

Conclusions – Focused cardiac ultrasound by non-experts using pocket-devices appears feasible and yields acceptable sensitivity and specificity for RHD detection when compared to the state-of-the-art approach, thereby opening new perspectives for mass screening for RHD in low-resource settings.

3.3.2. Introduction

The WHO had recommended active surveillance of RHD in the past. There are however no guidelines as how screening should be undertaken. The WHF has provided guidelines to optimize echocardiographic RHD diagnosis.[53, 56] There are certain issues that may prevent implementation of active surveillance by echocardiography in regions where RHD prevalence is highest.[19, 48, 72] Concerns include the cost of comprehensive portable equipment, the complexity of echocardiographic criteria, and the need for highly trained health workers in countries where access to specialist care remains limited. All these factors represent significant barriers to mass screening in low-income countries.[29] Echocardiography may however

emerge as the method of choice for active surveillance in highly endemic regions in this rapidly moving field.[46]

Study n°2 prospectively assessed a new approach for RHD screening based on FCU combining the use of a pocket-size echo system, performed by nurses after a standardized training program, and using a simplified diagnostic algorithm.

3.3.3. Methods

Methods have been detailed in Section 2.3. Briefly, the study comprises two parts. We first tested the most appropriate simplified set of echocardiographic criteria for RHD to be used for FCU among 189 selected children with and without RHD in March 2013 (Part 1 of the study). These children had previously participated in the yearly echo-screening campaigns conducted in New Caledonia since 2008 (then aged 9-10 years). We then prospectively evaluated the feasibility and performance of a FCU approach among a population of school children (4th graders aged 9-10 years in Nouméa, the capital city, and its suburbs) from April to August 2013 (Part 2).

3.3.4. Results

Evaluation of the optimal simplified set of echocardiographic criteria for FCU approach – Part 1

One hundred and eighty-nine children were enrolled in this preliminary study. Mean age was 12.2 years (SD 2.0) and 84 (44.4%) were male. One hundred and six (56.1%) children had findings of RHD (63 definite and 43 borderline RHD), whereas 83 (43.9%) had normal echocardiograms.

The breakdown of echocardiographic findings according to WHF criteria is presented in Table 3.5.

Sensitivity and specificity of the six criteria interpreted by the nurses, when compared to the reference approach, are reported on Table 3.6 and Figure 3.5. Overall, there was an important heterogeneity with sensitivity varying from 26.4 (95% CI 18.9-35.6) to 97.2 (95% CI 91.7-99.1), specificity from 13.5 (95% CI 7.6-20.9) to 91.6 (95% CI 64.3-83.4), with also a wide range for inter-observer agreement (kappa varying from 0.09 to 0.57).

Reference echocardiographic findings	RHD N=106 (%)	No RHD N=83 (%)	All, N=189 (%)
Definite RHD	63 (59.4)	0	63 (33.3)
Borderline RHD	43 (40.6)	0	43 (22.8)
MR	101 (95.3)	51 (61.4)	152 (80.4)
Physiological MR	21 (19.8)	46 (55.4)	67 (35.4)
MR grade 1	73 (68.9)	5 (6.0)	78 (41.3)
MR grade 2	1 (9.4)	0	1 (0.5)
MR grade ≥3	6 (5.7)	0	6 (3.2)
AR	36 (34.0)	10 (12.0)	46 (24.3)
Physiological AR	13 (12.3)	9 (10.8)	22 (11.6)
AR grade 1	17 (16.0)	1 (1.2)	18 (9.5)
AR grade 2	5 (4.7)	0	5 (2.6)
AR grade ≥3	1 (0.9)	0	1 (0.5)
Mitral stenosis (mean gradient≥4mmHg)	6 (5.7)	0	6 (3.2)
MR :			
Seen in 2 views	98 (92.5)	39 (47.0)	137 (72.5)
Jet length≥2cm	80 (75.5)	9 (10.8)	89 (47.1)
Vmax≥3m/s	86 (92.0)	15 (18.1)	101 (53.4)
Pan-systolic	58 (54.7)	0	58 (30.7)
AR :			
Seen in 2 views	32 (30.2)	9 (10.8)	41 (21.7)
Jet length≥1cm	32 (30.2)	8 (9.6)	40 (21.2)
Vmax≥3m/s	25 (23.6)	5 (6.0)	30 (15.9)
Pan-diastolic	20 (18.9)	0	20 (10.6)
Morphological changes of the MV			
AML thicknening≥3mm	45 (42.5)	0	45 (23.8)
Restricted leaflet motion	93 (87.7)	1 (1.2)	94 (49.7)
Chordal thickening	90 (84.9)	0	90 (47.6)
Excessive leaflet motion	1 (0.9)	0	1 (0.5)
Flail	2 (1.9)	0	2 (1.1)
Morphological changes of the AV:			
Coaptation defect	3 (2.8)	0	3 (1.6)
Restricted leaflet motion	2 (1.9)	0	2 (1.1)
Prolapse	4 (3.8)	0	4 (2.1)
Irregular or focal thickening	12 (11.3)	2 (2.4)	14 (7.4)

Table 3.5. Echocardiographic findings - Part 1.

Criteria tested	Sensitivity nurse A	Sensitivity nurse B	Specificity nurse A	Specificity nurse B	kappa
MR	87.7 (80-92.7)	97.2 (91.7-99.1)	55.4 (44.6-59.9)	13.5 (7.6-20.9)	0.27 (0.14-0.40)
MR ≥ 1.5 cm	81.1 (72.5-87.5)	84 (75.8-89.8)	69.9 (59.2-69.1)	57.8 (47.0-61.6)	0.47 (0.35-0.60)
MR ≥ 2.0 cm	67 (57.5-75.3)	83.1 (73.5-71.9)	66 (56.5-74.4)	74.7 (64.3-71.1)	0.51 (0.39-0.63)
Morphological changes of the MV	61.3 (51.7-70.1)	54.7 (45.2-63.9)	57.8 (47-61.6)	74.7 (64.3-71.1)	0.09 (-0.05-0.23)
AR	33 (24.7-42.5)	26.4 (18.9-35.6)	89.2 (80.5-68.1)	91.6 (64.3-83.4)	0.57 (0.43-0.71)
MR ≥ 2.0 cm or AR	76.4 (67.4-83.5)	70.7 (61.4-78.6)	73.5 (63.0-70.7)	69.9 (59.2-69.1)	0.48 (0.35-0.60)

Table 3.6. Sensistivity and specificity of all critieria tested in Part 1.

Among the six criteria tested, the combined criteria of MR jet length≥2.0cm or any aortic regurgitation (regardless the length) appeared to achieve the best combination of sensitivity and specificity. Compared to the reference approach, sensitivity of the combined criteria to detect any RHD was 76.4% (95% CI 67.4-83.5) and 70.7% (95%CI 61.4-78.6) for nurses A and B, respectively. The specificity to detect any RHD was of 73.5% (95%CI 63.0-70.7) and 69.9% (95%CI 59.2-69.1) according to nurses A and B, respectively.
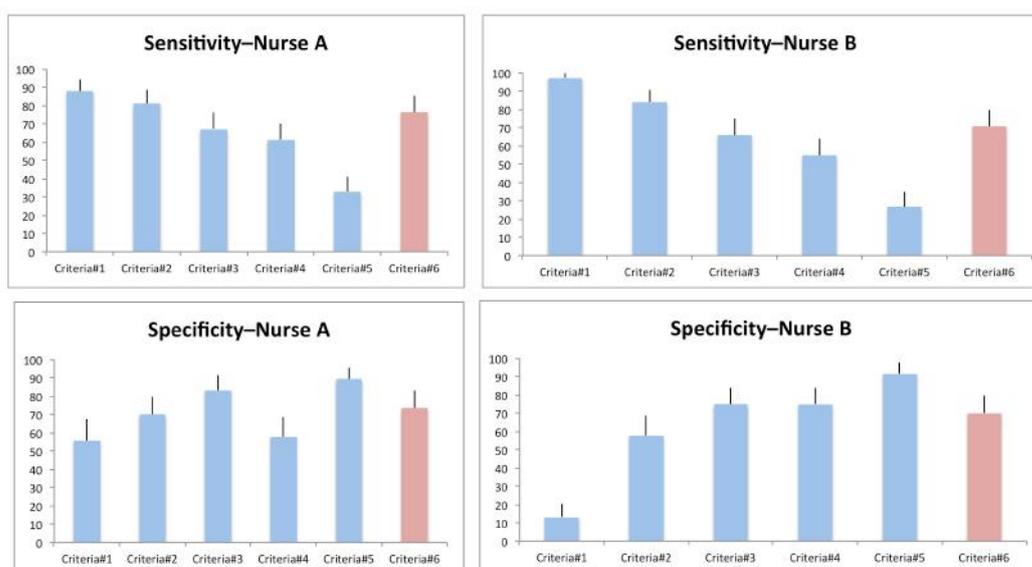
Figure 3.5. Sensitivity and specificity of all criteria tested in Part 1.

The agreement between nurses was moderate for the detection of all RHD cases when using the combined criteria (kappa value of 0.48, 95% CI 0.35-0.60).
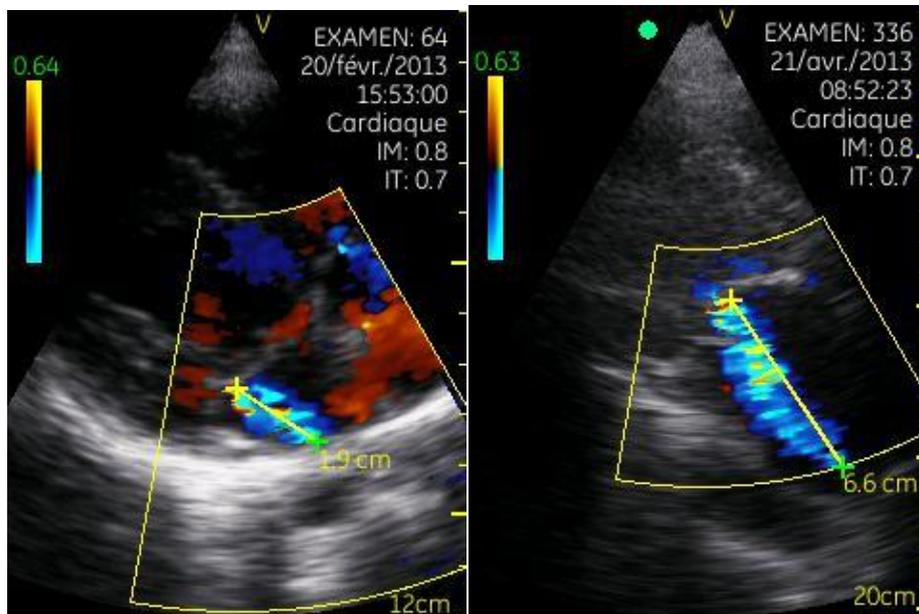
Figure 3.6. Echocardiograms by FCU. Right panel: MR jet length<2cm. Left pannel: MR jet length≥2cm.

Assessment of image quality and on-site diagnosis – Part 1

Image quality of the FCU recordings was evaluated as good in 68 (36.8%) and 79 (42.7%), fair in 109 (58.9%) and 104 (56.2%), and poor in 8 (4.3%) and 2 (1.1%) cases, for nurses A and B, respectively (missing data in 4 cases), without significant difference between the two nurses (P=0.07).

When an experienced cardiologist reviewed FCU recorded by nurses in the field, the sensitivity and specificity of the diagnoses made by the nurses were not statistically significantly different from the corresponding values obtained from the experienced cardiologist. Mean scanning time per FCU scan was 5.9 min (1.7) for nurse A and 7.0 min (1.9) for nurse B.
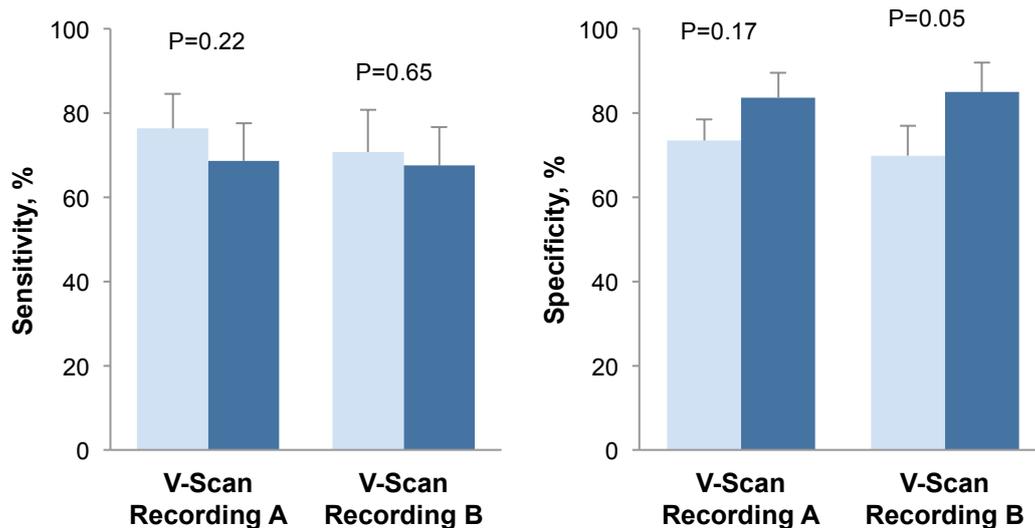
Figure 3.7. Inter-reader variability of FCU examinations (acquired by the nurses). *Light blue: nurse's on site interpretation, dark blue: cardiologist's interpretation after review of the nurses' recordings. A, stands for "nurse A"; B for "Nurse B".*

Focused cardiac ultrasound in the population – Part 2

Among the 1,217 children included at school (mean age 9.6±0.5 years; 603 male, 49.6%), 49 (4.0%) were diagnosed with findings of RHD according to the reference approach, including 15 definite and 34 borderline RHD cases.

The sensitivity of FCU to detect any RHD cases was 83.7% (95% CI 70.7-91.6) for nurse A and 77.6% (95% CI 63.9-87.1) for nurse B. Focused cardiac ultrasound yielded a specificity of 90.9% (95% CI 89.1-92.4) and 92.0% (95% CI 90.3-93.4) according to nurses A and B, respectively. The percentage of agreement between nurses was 91.4%.

When restricted to definite RHD, the performance of the FCU approach was better. Focused cardiac ultrasound yielded a sensitivity of 93.3% (95% CI 64.7-99.1) and 86.7% (95% CI 59.5-96.7) according to nurses A and B, respectively. The percentage of agreement between nurses was 91.8%. All RHD valve lesions detected in schools were graded as mild with no case of mitral stenosis.
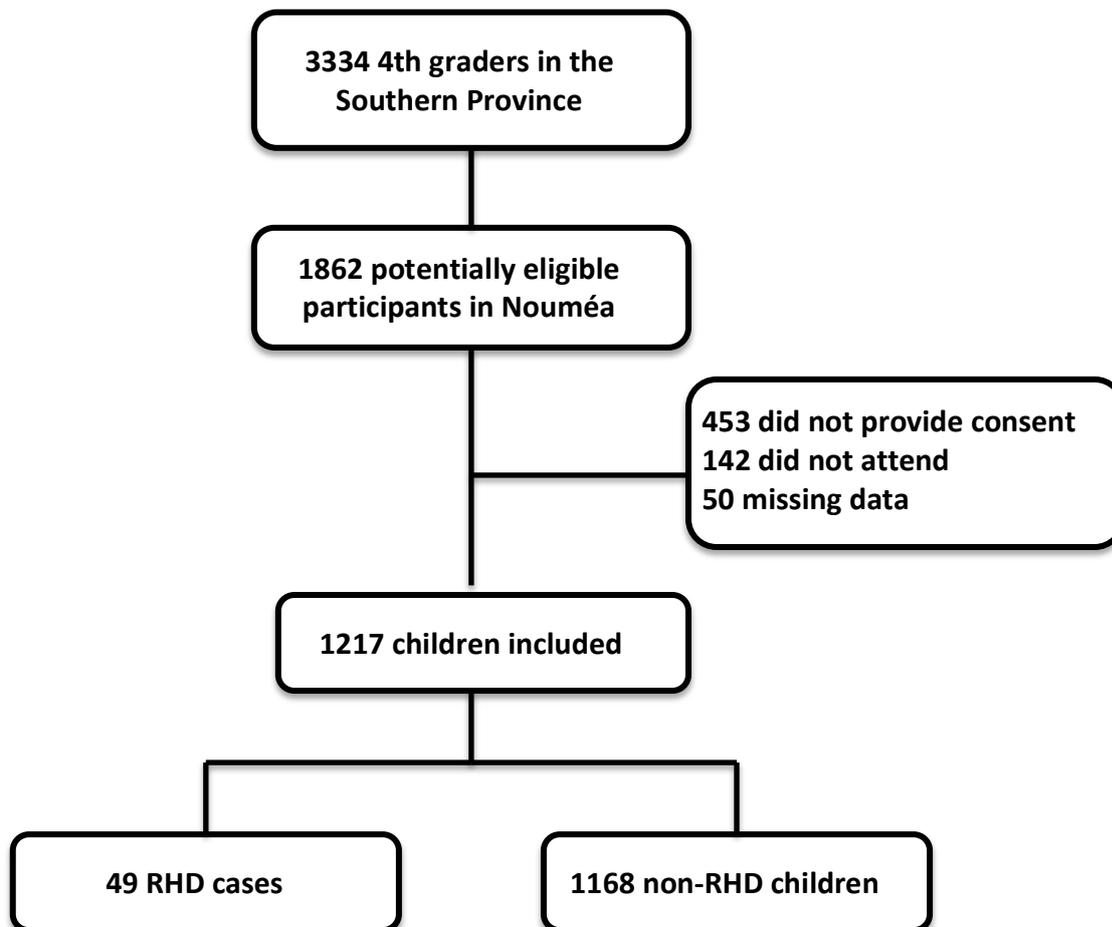
Figure 3.8. Flow chart of the school-based study - Part 2.

Combined criteria	*Nurse A*	*Nurse B*
Sensitivity of Any RHD (definite and borderline), *N=49*	83.7 (70.7-91.6)	77.6 (63.9-87.1)
Sensitivity of Definite RHD only, *N=15*	93.3 (64.7-99.1)	86.7 (59.5-96.7)
Specificity N=1168	90.9 (89.1-92.4)	92.0 (90.3-93.4)
Combined criteria	Kappa	Concordance
Any RHD (definite and borderline), *N=1217*	0.57 (0.50-0.65)	91.4%
Definite RHD only, *N=1183*	0.53 (0.44-0.61)	91.8%

Table 3.7. Performance of FCU approach in schoolchildren.

3.3.5. Discussion

This study is the first evaluation of a FCU approach for RHD screening by non-experts with pocket devices using simple echocardiographic criteria. Such an approach may be potentially applicable in many poorly resourced settings. After establishing an optimal simplified diagnostic algorithm for non-experts, the approach was tested in the field. These findings suggest that this approach, although imperfect, yields acceptable sensitivity and specificity (~80%) to detect RHD within minutes with no further readings when compared to the state-of-the-art approach.[53]

Overall, this study tested a combination of three factors: (i) the adequacy of the pocket- echo machine in detecting RHD; (ii) the proficiency of the nurses after brief training; and (iii) the performance of simplified criteria combining MR jet ≥2.0cm or any AR (regardless of jet length). This global strategy incorporates affordable equipment by non-experienced users with the aim to be translated into public health policies with widespread applicability.

Image quality of the pocket-echocardiograms was good or fair in the majority (~90%) of cases by two operators, as in other settings including adults with larger body habitus.[87, 88] Beaton and colleagues have recently shown that pocket-echo (V-scan, GE®) was highly sensitive and specific (>90%) to diagnose RHD in a set of previously screened schoolchildren when operated by an experienced cardiologist with off-line interpretation by another experienced cardiologist on a dedicated software.[75] Their findings are of the outmost importance since they demonstrate the technical capabilities of pocket-echo for RHD screening. However, the extent to which their methods could be translated into public health policies, in the light of a scarcity of specialized health workers in many low-income countries, remains questionable.[29] Not surprisingly, the performance of pocket-echo in this study was lower, even when an experienced reader interpreted the nurses' echocardiograms, suggesting that operators' skills in acquiring the images may impact on the performance of a FCU strategy.

The choice to test non-experienced users was deliberate since it would be the most likely scenario in low-income countries. Sensitivity and specificity of the FCU approach were higher in Part 2 than in Part 1. Proficiency may have improved following additional tailored training between the two parts of the study, which would suggest the impact of longer training schemes on the accuracy of a FCU approach by non-experts. Several studies have tested FCU by non-experts with variable results. This may be due to high expectancies of FCU and to different training schemes.[89, 90] Echocardiography requires skilled users in image acquisition and during interpretation. Galderesi and colleagues showed that trainees yield lower performance when compared to experienced cardiologists, in spite of 15 hours of lectures and approximately 150 supervised echocardiograms for the purpose of FCU with a V-scan.[91] The training scheme was based on a previous experience in neighbouring Fiji with a total of approximately 60 hours of training (combining lectures and supervised hands-on sessions).[92] Consistently, these results are similar to this pilot study that assessed the feasibility of echo-screening by nurses using standard non portable equipment.[92] As outlined by the American Society of Echocardiography and the European Society of Cardiology, standardization of training programs and proficiency are of outmost need before the widespread use of pocket-echo for FCU, especially for screening purposes by non-experts.[93, 94] In the absence of such standardization, varying results may be obtained according to the skills and motivation of different health workers. There may be room for improvement in the proficiency of RHD screening by non-experts, possibly through the experience acquired in the field.[65]

Lastly, simplified echocardiographic criteria were used for the diagnosis of RHD on-site. Diagnostic criteria directly impact on the case-detection rates, which may partly explain the performance of the FCU strategy in the detection of RHD.[95] The increasing interest in exploring echocardiographic detection of silent or subclinical RHD has led to the publication of standardized echocardiographic criteria.[19, 47, 48, 53, 72] In the lack of a gold standard for RHD diagnosis, the WHF criteria are of the outmost importance as a surrogate marker of the disease. Although based on the best level of evidence, the WHF criteria require experienced operators and readers since it includes the use of continuous Doppler and the analysis of morphological changes of the mitral and aortic valves.[53] Morphological criteria appear to be of additional value in experienced hands with high-end equipment.[95] However, preliminary data suggest that more simple criteria may carry acceptable sensitivity and specificity when it

comes to RHD detection.[76, 96] This prospective evaluation demonstrates that complex diagnostic criteria is not applicable to pocket-echo, such as the analysis of morphological changes of the mitral valve, in line with a previous report.[75]

Studies have so far systematically used a two-step diagnostic approach using high quality non-portable equipment and qualified cardiologists.[19, 47-50, 72, 96] Although imperfect, the methods of this study explore ways of providing a diagnosis on site with no need for further testing or readings. Remoteness is a major barrier to healthcare delivery, especially in rural areas in developing countries. Therefore, a rapid diagnosis in school or in the community (without the need for further testing in hospital) seems most appropriate in the planning of active surveillance for RHD.

In addition, the performance of this FCU approach improves in the detection of definite RHD, with a sensitivity of almost 90%. Definite RHD requires secondary prophylaxis by penicillin for at least 10 years whilst borderline RHD should be offered regular follow-up.[56] Indeed, some authors question the pathogenicity of borderline RHD although significantly more prevalent among children at risk of RHD.[96, 97] High sensitivity for the detection of definite RHD is therefore crucial for the management of screened populations, whereas the interest of screening borderline RHD remains unclear.

Further studies are needed in order to validate this strategy before being translated into public health policies. Cost-effectiveness analysis should however consider simplified strategies for active surveillance as the one described in this work.

3.3.6. Conclusions

Focused cardiac ultrasound with pocket-sized devices, operated by non-experts, through simple echocardiographic criteria, appears feasible and yields acceptable sensitivity and specificity for RHD detection when compared to the state-of-art approach. Focused cardiac ultrasound has the potential to provide a diagnosis on-site within minutes. However, echocardiography-based screening cannot be advocated for at this stage, and further evaluation is needed before implementation in countries where RHD remains endemic.

3.4. Study 3. Symptomatic Rheumatic Heart Disease: estimated prevalence, characteristics and outcomes in New Caledonia

3.4.1. Abstract

Objectives. We aimed at assessing the prevalence, incidence, outcomes and influencing factors of RHD in the contemporary era.

Methods. Hospital-based cohort of patients admitted with RHD according to WHF echocardiographic criteria were enrolled (2005-2013). The incidence of major cardiovascular events (MACE) including heart failure, peripheral embolism, stroke, heart valve intervention, and cardiovascular death was calculated, and their determinants identified.

Results. Among the 1,142 patients identified, 831 validated WHF criteria for definite RHD. The estimated prevalence of definite RHD in New Caledonia was 2.80 per 1,000 inhabitants (95% CI 2.60 –3.00) in 2013. Among Indigenous Melanesians the prevalence was 4.93 per 1,000 (95% CI 4.50-5.35). The annual incidence of RHD by WHF criteria was 2.08 per 10,000 person-years (95% CI 1.89-2.27) overall; and 3.68 per 10,000 person-years (95% CI 3.28-4.08) in Indigenous Melanesians. A subset of 396 patients had newly diagnosed RHD and quantification of left-sided valve disease; 43.9% were male with median age 18 years [IQR 10-40]. 127 (32.1%) patients presented with mild, 131 (33.1%) with moderate, and 138 (34.8%) with severe heart valve disease. 205 (51.8%) had features of ARF. 106 (26.8%) presented with at least one major cardiovascular event. Among the remaining 290 patients, after a median follow-up period of 4.08 (95% CI 1.84-6.84) years, 7 patients (2.4%) died and 62 (21.4%) had a first MACE. The annual incidence of first MACE and of heart failure was 59.05‰ (per 1,000) (95% CI 44.35-73.75), and 29.06‰ (95% CI19.29-38.82), respectively. The severity of RHD at diagnosis (moderate *vs.* mild HR 3.39 (0.95 – 12.12); severe *vs.* mild RHD HR 10.81 (3.11 – 37.62), p<0.001), and ongoing secondary prophylaxis at follow-up (HR 0.27 (0.12-0.63), p=0.01) were the two most influential factors associated with MACE.

Conclusions. Rheumatic heart disease remains endemic in New Caledonia, especially among Indigenous Melanesians. Newly diagnosed RHD is associated with poor outcomes, mainly in patients with moderate or severe valve disease and no secondary prophylaxis.

3.4.2. Introduction

The burden of RHD is still a major challenge in the developing world with approximately 15-20 million people affected and 345,000 deaths per year worldwide.[2, 5] The most recent available epidemiological data are mainly issued by echocardiography-based screening studies. This is somehow questionable given that the natural history of subclinical RHD still needs to be fully assessed. Hospital data may be valuable, especially when the catchment area comprises the entire region or country. In the case of this thesis both population-based and hospital-based data were available, providing a comprehensive picture of the epidemiology of RHD in New Caledonia. Multiple sources of data may validate, or not, the model incorporating symptomatic and asymptomatic RHD (Figure 1.4).

In addition, there is limited contemporary data on the characteristics of patients with newly diagnosed RHD.[16] Only a handful of clinical studies assessed predictors of outcomes in ARF and RHD either present a highly selected population,[8] or date back to the 1950's when access to interventions was extremely limited.[42] The two contemporary hospital-based registers have so far described characteristics of patients with no or limited (up to 30 months) follow-up.[16, 81]

In this section of the thesis are presented the results of a hospital-based cohort study.[98] The objective was twofold: to estimate prevalence and incident figures of RHD in New Caledonia; and to describe the characteristics and outcomes of patients with newly diagnosed RHD according to standardized and pre-specified diagnostic criteria. Another secondary objective was to assess factors associated with outcomes, focusing on patients with no major cardiovascular events at entry.

3.4.3. Methods

The methods of this study have been detailed in Section 2.4. of this thesis.

Briefly, potential participants were retrospectively identified through primary or secondary ICD 10 separation diagnosis of ARF or RHD of hospital admissions at CHT from January 1st 2005 to December 31st 2012. Patients were also prospectively identified in 2013. Patients were considered as suffering of definite RHD if they fulfilled the WHF criteria for "definite" RHD[53].

Specific attention was taken in the description of patients with newly diagnosed RHD (or incident RHD) for whom quantification of heart valve disease[67] was available. Factors associated with outcomes were analysed in this subset of patients.

3.4.4. Results

Estimated prevalence and incidence of RHD in New Caledonia

A total of 1,142 patients were identified. Among the 1,142 patients, 831 presented with WHF criteria for definite RHD, including 78 deaths between 2005 and 2013 (Figure 3.9). The overall prevalence of RHD was 3.14 per 1,000 (95% CI 2.93-3.35). The estimated prevalence of RHD by WHF criteria in 2013 was of 2.80 per 1,000 inhabitants (95% CI 2.60–3.00). The prevalence was higher in Indigenous Melanesians: 4.93 per 1,000 (95% CI 4.50-5.35). In children aged 9 and 10 years, the estimated prevalence rates were 1.43 (95% CI 0.29-2.57) and 1.59 (95% CI 0.41-2.77) per 1,000, respectively.
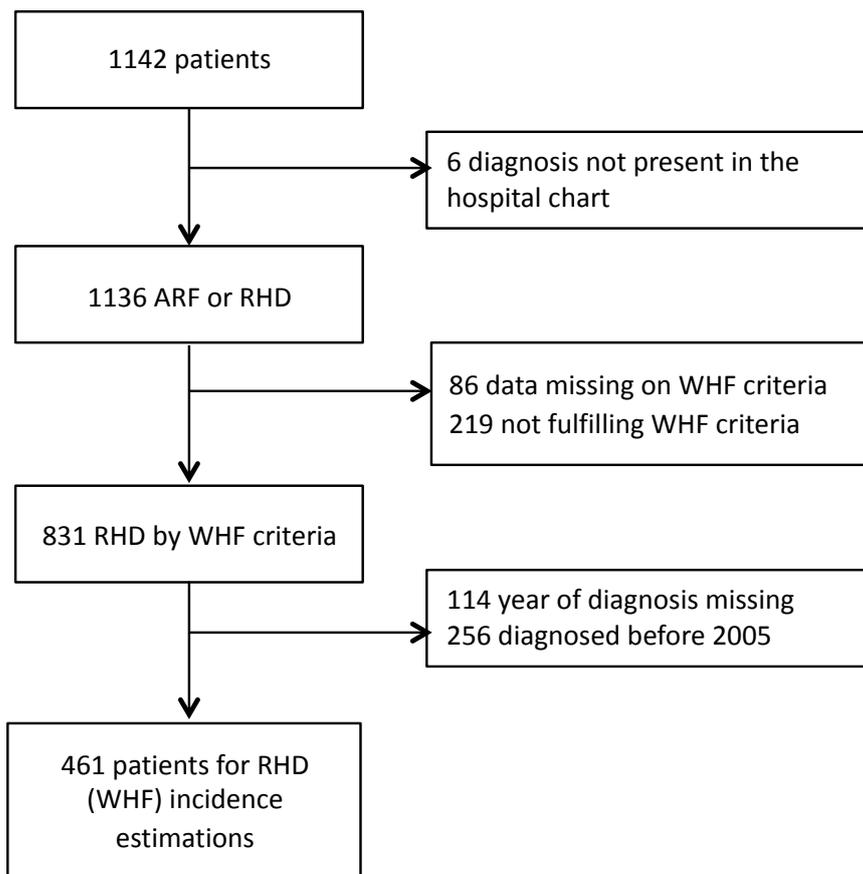
Figure. 3.9. Flow chart of the hospital-based cohort.

The annual incidence of RHD by WHF criteria was 2.08 per 10,000 person-years (95% CI 1.89-2.27) during the study period. The annual incidence of RHD over the study period is represented in Figure 3.10. The annual incidence of RHD revealed by ARF was overall 1.03 per 10,000 person- years, and 5.01 per 10,000 person-years in those under 15 years of age. The annual RHD incidence according to class-age and to the clinical presentation (with or no ARF) is depicted in Table 3.8.
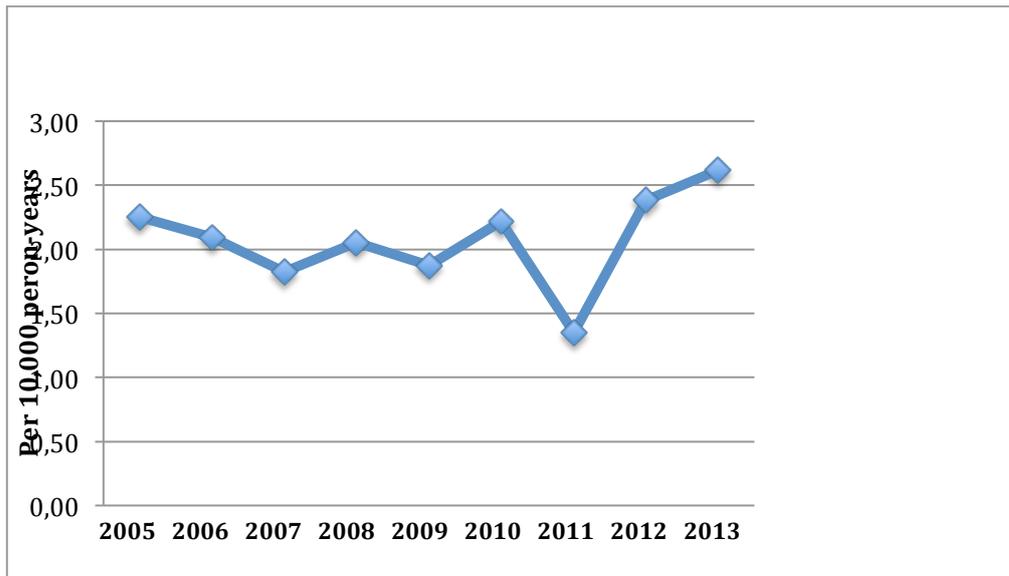
Figure 3.10. Annual incidence of RHD by WHF criteria.

Population	Annual incidence of RHD by WHF criteria per 10,000 person years (95% CI)	Annual incidence of RHD revealed by ARF per 10,000 person years (95% CI)	Annual incidence of RHD with no ARF per 10,000 person years (95% CI)
Age <15 years	5.01 (4.27-5.74)	3.97 (3.31-4.62)	1.04 (0.71-1.38)
Age 15-24 years	1.67 (1.24-2.10)	0.92 (0.60-1.24)	0.75 (0.46-1.04)
Age 25-39 years	1.83 (1.46-2.20)	0.64 (0.42-0.86)	1.19 (0.89-1.49)
Age ≥40 years	1.55 (1.29-1.82)	0.25 (0.14-0.36)	1.30 (1.06-1.55)

Table 3.8. The annual RHD incidence according to age

Eighty-four children were diagnosed with symptomatic RHD and were 9-10 years old between 2008 and 2011. Table 3.9 compares hospital-based and population-based prevalence estimates in children aged 9-10 years.

Year	Asymptomatic subclinical RHD prevalence per 1,000 [95% CI]	Symptomatic RHD prevalence per 1,000 [95% CI]
2008	9.3 [6.3- 13.2]	1.97 [1.15-3.16]
2009	6.5 [4.1- 9.6]	1.74 [0.97-2.87]
2010	10.3 [7.4- 14.1]	3.13 (2.07-4.56)
2011	9.9 [6.9- 13.7]	2.90 [1.88-4.28]

Table 3.9. Annual prevalence of rheumatic heart disease in children aged 9-10 years by means of two data sources: systematic echocardiography-based screening for asymptomatic subclinical RHD, and hospital cohort for symptomatic RHD.

Characteristics of patients with newly diagnosed RHD according to WHF criteria and valve disease quantification

Among the 461 patients with newly diagnosed RHD, 396 patients had formal quantitation of heart valve disease. 174 (43.9%) were male with a median age of 18 years (IQR 10-40). 274 (71.9%) were indigenous Melanesians, 85 (22.3%) were Polynesians, and 22 (5.8%) were of other ethnicity. 205 (51.8%) presented with ARF. Based on standardized echocardiograms, 127 (32.1%) patients had mild heart valve disease, 131 (33.1%) had moderate valve disease, and 138 (34.8%) had severe heart valve disease at the time of diagnosis. Mitral regurgitation was the most frequent heart valve disease, followed by aortic regurgitation and mitral stenosis. Multiple valve disease was present in 56.3% of cases. Moderate or severe tricuspid regurgitation was present in 4.5% of patients. 32 (8.1%) patients had permanent or paroxysmal atrial fibrillation. 37 (9.3%) patients had left ventricular ejection fraction under 60%.

Among the 396 patients included, 106 (26.8%) presented with MACE at entry. There were 83/106 patients admitted with heart failure, among which: 12 leading to urgent valve intervention (i.e., within 30 days); 5 with concomitant stroke; and one with concomitant stroke and urgent intervention. In addition, 12/106 patients were admitted with stroke; 10/106 underwent urgent intervention; and one was admitted with stroke and underwent intervention.

Characteristics at diagnosis	All N=396
Age, median (IQR)	18 (10-40)
Male, n (%)	174 (43.9)
Ethnicity*	
-Indigenous Melanesians	274 (71.9)
-Polynesians	85 (22.3)
-Other	22 (5.8)
Presentation with ARF	205 (51.8)
Family history of RHD or ARF**	114 (60.6)
Supra ventricular arrhythmias***	32 (8.1)
Initial left-sided valve disease on echocardiogram	
Mitral regurgitation, n (%)	
Nil	69 (17.4)
Grade 1/4	162 (40.9)
Grade 2/4	110 (27.8)
Grade ≥ 3/4	55 (13.9)
Mitral stenosis, n (%)	
Nil	265 (66.9)
Mild	42 (10.6)
Moderate	30 (7.6)
Severe	59 (14.9)
Aortic regurgitation, n (%)	
Nil	201 (50.8)
Grade 1/4	109 (27.5)
Grade 2/4	53 (13.4)
Grade ≥3/4	33 (8.)
Aortic stenosis, n (%)	
Nil	370 (93.4)
Mild	10 (2.5)
Moderate	9 (2.3)
Severe	1 (0.5)
Multiple left-sided valve disease, n (%)	223 (56.3)
Overall severity of RHD§	
-Mild	127 (32.1)
-Moderate	131 (33.1)
-Severe	138 (34.8)
Moderate or severe TR§§, n (%)	17 (4.5)
LVEF<60%, n (%)	37 (9.3)

Table 3.10. Characteristics of patients with newly diagnosed RHD. *Missing data in*

*15 cases. **Up to 2nd degree relatives; missing data in 208 cases. ***Defined as*

paroxysmal or persistent atrial fibrillation, flutter or atrial tachycardia. §Defined as

mild RHD if single or multiple left sided valve disease graded as mild; moderate RHD

defined as at least mitral or aortic moderate valve disease (regurgitation or stenosis);

severe RHD defined as at least mitral or aortic severe valve disease (regurgitation or

stenosis). §§Missing data in 22 cases.

Outcomes and their determinants in patients with no major cardiovascular events at entry

Patients with no MACE at presentation (N=290) were eligible for further analysis. Median age was 13 (IQR 10-31) years, 131 (45.2%) were male, and 185 (63.8%) presented with ARF. Patients with ARF were younger (p<0.01), had more often a family history of ARF (p=0.01), less atrial arrhythmias (p<0.01), and had different heart valve disease pattern (p<0.01) when compared to those with no ARF (Table 3.11).

The 290 patients were followed up for median 4.08 (95% CI 1.84-6.84) years. Overall, there were 62 MACE; the annual incidence of MACE was 59.05‰ (95% CI 44.35-73.75); and median follow-up period to MACE was 10.49 (95% CI 2.04-35.03) months. Taken individually, the annual incidence of heart failure (34 patients) was 29.06‰ (95% CI 19.29-38.82). The annual incidence of stroke was 7.26‰ (95% CI 2.52-12.01). The survival rate was 97.89% (CI 95% 95.97-99.64) at 4 years, and 96.21% (CI 95% 89.95-98.60) at 8 years after diagnosis. During the study period, 7 patients (2.4%) died of whom 4 from cardiovascular death (i.e., incidence of RHD-attributable mortality of 3.16 ‰ (95% CI 0.06-6.26) per year). Causes of cardiovascular death included: heart failure (N=2), stroke (N=1), and infective endocarditis (N=1). Other events were noted during the study period: atrial fibrillation in 7 (2.4%), infective endocarditis in 8 (2.8%) patients, cardiogenic shock in 2 (0.70%), major hemorrhage in 8 (2.8%) patients. Among the 59 women in childbearing age (i.e., 15-45 years of age), 9 (15.2%) developed complications during subsequent pregnancies.

Characteristics at diagnosis	No ARF N=105	ARF at presentation N=185	All N=290	P
Age, median (IQR)	31 (15-47)	11 (9-15)	13 (10-31)	<0.001
Male, n (%)	43 (40.9)	88 (47.6)	131 (45.2)	0.3
Ethnicity, n (%)				
-Indigenous Melanesians	73 (70.9)	127 (71.7)	200 (69.0)	0.12
-Polynesians	20 (19.4)	43 (24.3)	63 (21.7)	
-Other	10 (9.7)	8 (4.5)	18 (6.2)	
Family history of RHD or ARF, n (%)	39 (56.5)	52 (76.5)	91 (66.4)	0.01
Supra ventricular arrhythmias	7 (6.7)	0 (0.0)	7 (2.4)	<0.001
Initial left-sided valve disease on echocardiogram				
Mitral regurgitation, n (%)				0.06
Nil	21 (20.0)	17 (9.2)	38 (13.1)	
Grade 1/4	44 (41.9)	91 (49.2)	135 (46.6)	
Grade 2/4	28 (26.7)	58 (31.3)	86 (29.7)	
Grade ≥ 3/4	12 (11.4)	19 (10.3)	31 (10.7)	
-Mitral stenosis, n (%)				<0.001
Nil	16 (15.2)	161 (87.0)	177 (61.0)	
Mild	14 (13.3)	15 (8.1)	29 (10.0)	
Moderate	59 (56.2)	6 (3.2)	65 (22.4)	
Severe	16 (15.2)	3 (1.6)	19 (6.6)	
Aortic regurgitation, n (%)				<0.001
Nil	51 (48.6)	102 (55.1)	153 (52.8)	
Grade 1/4	23 (21.9)	69 (37.3)	92 (31.7)	
Grade 2/4	23 (21.9)	8 (4.3)	31 (10.7)	
Grade ≥3/4	8 (7.6)	6 (3.2)	14 (4.8)	
Aortic stenosis, n (%)				0.004
Nil	94 (89.5)	182 (98.4)	276 (95.2)	
Mild	5 (4.7)	1 (0.5)	6 (2.0)	
Moderate	4 (3.8)	2 (1.1)	6 (2.0)	
Severe	2 (1.9)	0 (0.0)	2 (0.7)	
Multiple left-sided valve disease, n (%)	70 (66.7)	81 (43.8)	151 (52.0)	<0.001
Overall severity of RHD				
-Mild	27 (25.7)	97 (52.4)	124 (42.8)	<0.001
-Moderate	44 (41.9)	61 (33.0)	105 (36.2)	
-Severe	34 (32.4)	27 (14.6)	61 (21.0)	
Moderate or severe TR, n (%)	2 (2.0)	2 (1.1)	4 (1.4)	0.35
LVEF<60%, n (%)	7 (6.7)	2 (1.1)	9 (3.1)	0.01
PASP>35 mmHg, n (%)	13 (12.4)	8 (4.3)	21 (7.2)	0.01

Table 3.11. Characteristics according to ARF status.

Events	Incidence per 1 000 persons year (95% CI)
MACE	59.05 (44.35-73.75)
Death	4.74 (0.95-8.54)
Cardiovascular death	3.16 (0.06-6.26)
Heart Failure	29.06 (19.29-38.82)
Stroke	7.26 (2.52-12.01)
Non-neurologic embolism	1.59 (0-3.78)
Heart valve interventions	36.47 (25.17-47.77)

Table 3.12. Incidence rates for MACE.

Secondary prophylaxis was prescribed at least at one point in time during follow-up in 235 (81.0%) patients. Continuation of secondary prophylaxis was reported in 159 out of 227 (70.0%) patients (missing data in 63 cases). The use of secondary prophylaxis at time of interview varied according to age (7.5% in patients aged>40 years; 94.7% in patients aged 5-20 years old).

In addition to patients (24/396) in need for urgent heart valve interventions within 30 days of diagnosis, 40 patients (13.8%) underwent either percutaneous or surgical procedures during the study period. The annual incidence of heart valve interventions was 36.47‰ (95% CI 25.17-47.77). Fifty-nine heart valve interventions were undertaken in these 40 (13.8%) patients, including 7 (2.4%) percutaneous mitral valvuloplasty; 5 (1.7%) mitral valve repair; 23 (7.9%) mitral valve replacement; 18 (6.2%) aortic valve replacement.

Factors included in the univariate analysis are described in Table 3.13.

Characteristics significantly associated with MACE on multivariate analysis were: the severity of heart valve disease at diagnosis (moderate *vs.* mild HR 3.36 (95% CI 1.10 – 10.34); severe *vs.* mild RHD 10.54 (95% CI 3.50 – 31.75), p<0.001), ARF at diagnosis (HR 0.46 (95% CI 0.24-0.89), p=0.02), and older age (21-40 *vs.* 5-20 years old, HR 2.88 (95% CI 1.34-6.22); over 40 *vs.* 5-20 years old, HR 5.15 (95% CI 2.44-10.88), p<0.01).

Factor	Univariate HR (95% CI)	Univariate P value
Mild RHD	1	<0.001
Moderate RHD	8.1 (2.8-23.3)	
Severe RHD	24.9 (8.8-70.8)	
ARF *vs.* no ARF	0.17 (0.09-0.30)	<0.001
Sex (male)	0.8 (0.5-1.3)	0.34
Melanesian	0.6 (0.4-1.1)	0.09
Age group		
5-20 yrs	1	<0.001
21-40 yrs	6.1 (2.9-12.41)	
>40 yrs	15.2 (8.0-28.8)	
On-going secondary prophylaxis at FU	0.13 (0.07-0.23)	<0.001

Table 3.13. Univariate analysis of factors associated with MACE.
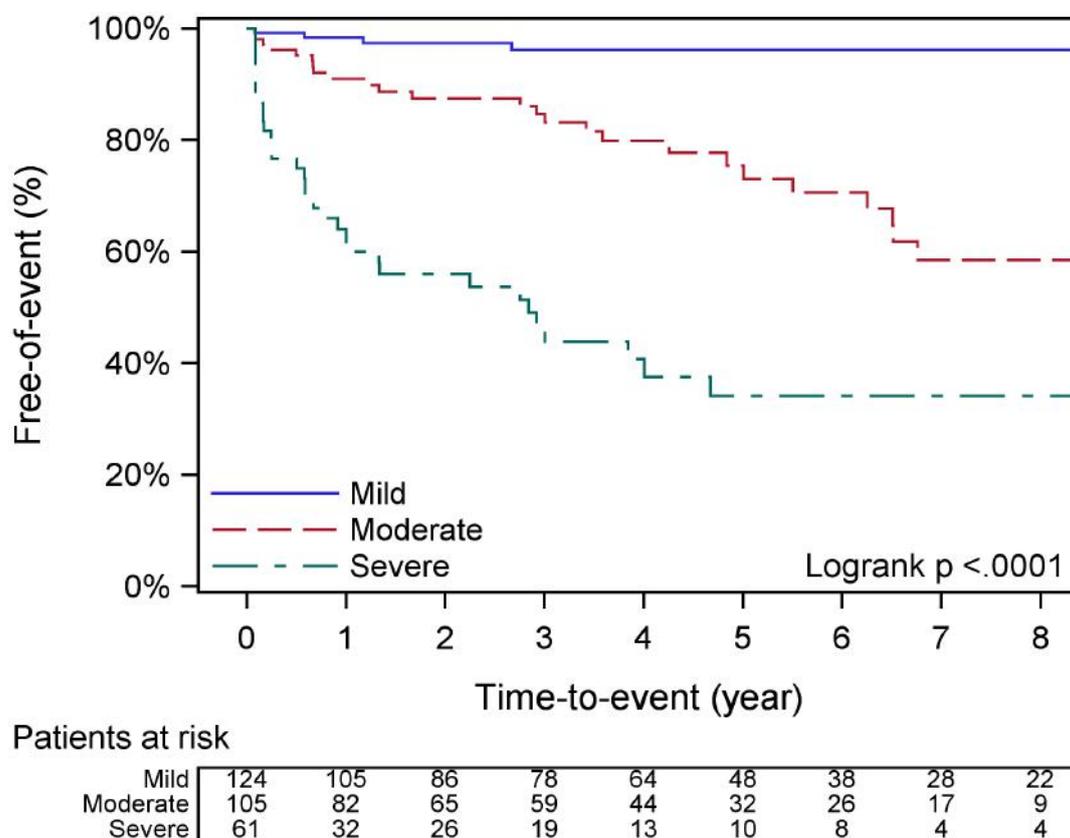
Figure 3.11. Kaplan Meier survival free of MACE according to VHD severity.

Factor	Multivariate HR (95% CI)	Multivariate P value
Mild RHD	1	<0.001
Moderate RHD	3.36 (1.10 – 10.34)	
Severe RHD	10.54 (3.50 – 31.75)	
ARF *vs.* no ARF	0.46 (0.24-0.89)	0.02
Sex (male)	0.81 (0.48 - 1.36)	0.43
Melanesian	0.66 (0.37-1.18)	0.16
Age group		
5-20 yrs	1	<0.001
21-40 yrs	2.88 (1.34-6.22)	
>40 yrs	5.15 (2.44-10.88)	

Table 3.14. Multivariate analysis of factors associated with MACE.

After sensitivity analysis including secondary prophylaxis at the time of interview (63 patients with missing information), two factors remained associated with outcomes: the severity of heart valve disease at diagnosis (moderate *vs.* mild HR 3.22 (0.90 – 11.49); severe *vs.* mild RHD HR 11.07 (3.21 – 38.22), p<0.001), and on-going secondary prophylaxis at the time of interview (HR 0.33 (0.14-0.79), p=0.013).

Factor	Multivariate HR (95% CI)	Multivariate P value
Mild RHD	1	<0.001
Moderate RHD	3.22 (0.90 – 11.49)	
Severe RHD	11.07 (3.21 – 38.22)	
ARF *vs.* no ARF	0.54 (0.25-1.14)	0.10
Sex (male)	0.82 (0.47 - 1.45)	0.50
Melanesian	1.07 (0.54-2.13)	0.84
Age group		
5-20 yrs	1	0.31
21-40 yrs	1.97 (0.79-4.92)	
>40 yrs	2.10 (0.72-6.10)	
On-going secondary prophylaxis at follow-up.	0.33 (0.14-0.79)	0.013

Table 3.15. Sensitivity analysis of factors associated with MACE.

3.4.5. Discussion

This study contributes to the current knowledge of RHD in two ways, by providing: epidemiological figures in New Caledonia; and data on outcomes. In addition to population-based figures driven by echocardiography screening in schoolchildren, this study confirms that RHD and ARF remain a significant health care issue in the Pacific, especially among Indigenous Melanesians. Unlike other studies, the incidence of RHD does not increase with age in this cohort. These findings may be explained by the overrepresentation of patients diagnosed during an ARF attack (half our patients presented with ARF) when compared to other settings. Nonetheless, a significant proportion of patients (~25%) are still diagnosed at the onset of complications and/or at a stage when heart valve interventions are urgently needed. The severity of heart valve disease was evenly distributed at presentation with one third having mild heart valve disease, one third moderate, and the remaining third severe heart valve disease. Approximately 20% needed heart valve intervention during the study period (median follow-up ~4 years). Survival rates were as high as 96% at median follow-up 4 years. The annual incidence of complications and RHD-related mortality is high even in young patients who are initially admitted with uncomplicated RHD (~59‰ per year). Factors associated with outcomes include: the severity of heart valve disease at diagnosis and continuation of secondary prophylaxis. Our results suggest that early diagnosis and secondary prophylaxis is cornerstone to reducing the burden of RHD.

Rheumatic heart disease remains prevalent in New Caledonia based on hospital figures of well-characterised patterns of disease. The prevalence is higher among Indigenous Melanesians, in keeping with the results of study n°1. The hospital-based prevalence estimates in children aged 9-10 years were approximately threefold lower than figures driven from the echocardiography-based survey (~3 versus 10 per 1,000). These results are in keeping with the recently advanced model incorporating asymptomatic and symptomatic RHD.[54] Indeed, a significant number of subclinical RHD may never lead to symptomatic disease and a large proportion of patients with RHD and a murmur may not present cardiovascular events.

Interestingly, ARF diagnosis appeared to be a major component in the detection of RHD. These results are encouraging since ARF diagnosis provides the opportunity to introduce secondary prophylaxis early and prevent complications.

Although RHD still remains present in New Caledonia, the incidence of RHD and ARF is much lower than in other settings. Sliwa and colleagues reported figures as high as 235 per 10,000 person-years in South Africa in 2006-2007.[16] Similarly the incidence of ARF is of approximately 200 per 100,000 person-years in Northern Australia.[28] Hospital-based figures are subject to debate given the selection bias it implies. Sliwa and colleagues also estimated their figures from a hospital register. Also more stringent case definitions in this work (WHF criteria) may have led to more conservative figures. In the report by Lawrence, notification data was the major source with no verification of the accuracy of diagnosis.[28] Although methods differed, the major differences between New Caledonia on the one hand, and South Africa and Australia on the other, suggest that these are truly related to the burden of the disease. Unlike reported in South-Africa,[16] the incidence of RHD decreased with age, suggesting that ARF detection drives RHD diagnosis in New Caledonia. Indeed, it has been recommended that every child with ARF to be admitted to CHT in order to ensure appropriate testing and treatment. The magnitude of the problem related to RHD is not as high in New Caledonia as in other underprivileged and remote regions.

Our study population is young and mainly indigenous, in keeping with population-based studies in the region.[28, 98, 99] The characteristics of our population are overall consistent with the two other RHD hospital-based registers published to this date.[16, 81] Half our patients had ARF, as in other upper-middle income settings.[81] A history of ARF is more often reported in wealthier settings,[81] suggesting the impact of health-care services in the ability to diagnose the condition.[100] The heart valve disease pattern is slightly different from that described in the heart of Soweto study,[16] with a higher proportion of mild mitral and aortic regurgitation in our study, likely due to the inclusion of children and adolescents with ARF. Patients presenting with ARF were younger, with milder heart valve disease, less left ventricular impairment and pulmonary hypertension when compared to those with no ARF.

Late diagnosis remains however a reality in many cases, revealed by the onset of complications in young and middle-aged adults. Almost one third present with major cardiovascular complications including: heart failure, stroke, non-neurological

embolism, or cardiovascular death. Furthermore, the incidence of heart failure was high in patients admitted with initially uncomplicated RHD (~30‰ per year), followed by stroke. Other complications included atrial fibrillation and haemorrhagic events. Maternal morbidity was also notable, in keeping with previous reports.[101, 102] Patients were at considerable risk of developing infective endocarditis, as suggested in a previous report focusing on Oceanic populations.[103]

When restricted to patients with uncomplicated RHD at entry, we report mortality rates of 2.4% at median 4 years follow-up. Lawrence and colleagues recently reported crude all cause mortality rates of 3.9% at 5 years.[28] Our results are therefore consistent with those from neighbouring Australia. However, mortality rates from New Caledonia and Australia, two high-income countries where patients have access to treatment, may not be transposable to resource poor settings, and should not lead to underestimating the global burden of the disease.[2]

Patients with uncomplicated RHD remain at high risk of heart failure, thromboembolic events, and infective endocarditis. When combining all major cardiovascular events, the annual incidence is high (~59‰), considering the young age of our population.

One fifth of our study population needed heart valve interventions during the study period. Of note, over one third of patients had severe valve disease and heart valve interventions may have been underused, as previously described in other settings.[104] The New Caledonian social security provides free of charge access to medical treatment and interventions. Invasive procedures may be carried out urgently with use of air-transport to the closest surgical centre (Sydney, Australia). Heart valve interventions are however not accessible in many countries where RHD remains endemic, especially in low-income countries.[31, 105, 106]

Approximately 55% of the patients with newly diagnosed RHD were under secondary prophylaxis at follow-up. All these patients had been diagnosed with RHD less than ten years before follow-up.[64] One fourth of these patients were however 40 years old or more in whom secondary prophylaxis was usually stopped. The majority of children and adolescents were on secondary prophylaxis at the time of interview. However, as in other hospital- or population-based registers, there is room for improvement in terms of adherence to guidelines.[81, 83, 100]

Two factors were associated with poor outcomes. The severity of valve disease at diagnosis is understandably associated with adverse events, such as heart failure[28] or need of heart valve interventions.[16] Continuation of secondary prophylaxis was associated with better outcomes. Patients diagnosed with RHD during an ARF attack presented better outcomes but this was not confirmed when adjusting for secondary prophylaxis. These results therefore stress the importance of early diagnosis, when heart valve disease is still mild, which bears excellent prognosis. Identifying children with ARF is an opportunity to limit the burden of disease. Our results may also suggest that screening for these mild but definite lesions in children under 20 years could be of interest in order to avoid disease progression and future complications.[19, 95] As stressed in the Mosi-o-Tunya call, there is urgent need to build ARF/RHD registers in endemic regions to detect the condition early and implement secondary prophylaxis.[107]

3.4.6. Conclusions

Rheumatic heart disease and ARF remain prevalent and incident in New Caledonia, especially among Indigenous Melanesians. However, the burden of the disease seems less than in other parts of the world. Newly diagnosed RHD is often revealed by ARF and/or by complications. Mortality is low but morbidity remains high, especially when heart valve disease is moderate or severe and in the absence of secondary prophylaxis. These results add to the limited data on the burden of RHD and should warrant early diagnosis when heart valve disease is still mild to introduce and continue secondary prophylaxis.

4. Summary and conclusions

This thesis incorporated three linked studies to explore critical questions regarding the burden of asymptomatic and symptomatic rheumatic heart disease (RHD). This summary chapter lists the unique contributions made by these studies, presents implications for both policy and practice, and makes recommendations for future research.

4.1. Principal findings

The primary purpose of the thesis was to determine the outcomes of asymptomatic and symptomatic RHD. More specifically, this thesis provides epidemiological data on RHD by quantifying incidence and prevalence of the condition based on population and hospital-based cohorts. The work encapsulated in this thesis explored issues in the field of echocardiography-based screening for subclinical RHD in terms of feasibility and outcomes. Finally, outcomes of newly diagnosed symptomatic RHD and factors associated with poor outcomes could be identified.

There are five principal findings from this series of studies. Firstly, the studies presented in this thesis contribute to the data on the global burden of the disease by providing accurate case definitions. The prevalence estimates derived from a hospital-based cohort and from a nationwide school-based screening programme support the pyramid model of RHD epidemiology. Indeed, asymptomatic RHD is at least threefold more prevalent, and constitutes the base of the pyramid, with only a minority of cases being seen in hospital, often at the onset of symptoms, either acute rheumatic fever or when cardiovascular events occur. The figures driven from these two independent studies suggest that, although RHD still remains prevalent in New Caledonia, the burden is less than among other indigenous populations (e.g., neighbouring Australia) or in deprived regions (sub-Saharan Africa).

Populations at risk of RHD were identified through a nationwide screening programme. The translation of methods of echocardiography-based screening used for research purposes into public health policies demonstrated to bear significant limitations in terms of completeness. These results suggest that surveys should focus on populations at risk only and that more simple ways to detect RHD are warranted.

Outcomes of children with asymptomatic RHD detected by echocardiography are variable although the majority of valve lesions persist with little clinical implications. Promiscuity is associated with the persistence of the condition. Rheumatic heart disease being a dynamic condition, a significant proportion of children at high risk of RHD with normal baseline echocardiograms may present with acute rheumatic fever or borderline lesions at 2 years of follow-up. These results suggest that a single screening point in the lifetime of children at risk may be insufficient for disease control.

Having demonstrated that disease persists in most cases of asymptomatic echocardiography-detected RHD, more simple methods for RHD detection were explored. Focused cardiac ultrasound (FCU) performed and interpreted by nurses after a short training scheme using pocket-echocardiographic machines and simplified criteria appears to yield acceptable sensitivity and specificity for RHD detection. This method performs better (sensitivity ~90%) when focusing on definite RHD according to World Heart Federation criteria.

Finally, outcomes of symptomatic RHD are depicted in a population with reliable surgical and mortality registers. A significant proportion of patients present at the onset of complications and/or at a stage when heart valve interventions are urgently needed. This is worrisome given the access to primary care in the country. The survival rate was of ~96% at 8 years in those with uncomplicated RHD at presentation. However, the incidence of major cardiovascular events was as high as 59‰ annually in a young population. Factors associated with poor outcomes in the subset of patients with uncomplicated RHD at presentation were the severity of heart valve disease and discontinuation of secondary prophylaxis.

4.2. Implications for policy and practice

The findings of this thesis may have important policy and clinical implications. Methods previously used in research for echocardiography-based screening cannot be translated into public health policies, due to implementation issues, especially at larger scales. A single screening point in the lifetime of children at risk is insufficient to prevent RHD given the dynamic nature of the disease. Targeting populations at risk is warranted.

The natural history of asymptomatic RHD detected by systematic echocardiography is variable although the majority of these mild valve lesions persist over time. Considering factors as promiscuity may help in guiding treatment by identifying patients with non-reversible RHD.

Focused cardiac ultrasound by non-experts using pocket-echocardiographic machines may be an alternate method for RHD screening. Although imperfect in terms of RHD detection, FCU may be easier to implement than WHF recommended methods.

The persistence of symptomatic RHD in New Caledonia highlights the fact that this remains a public health issue among the indigenous population. A significant proportion of patients present at the onset of complications and/or with moderate to severe heart valve disease. These results prompt further action for RHD control and supports the initiatives taken by the Agence Sanitaire et Sociale de Nouvelle Calédonie to detect the condition at its early stages.

Outcomes of patients with newly diagnosed uncomplicated RHD demonstrate that mortality data is insufficient to quantitate the burden of disease. The condition bears high risk for complications but acceptable mortality rates in settings where patients have access to treatment. Further effort should be put into the continuation and adherence to secondary prophylaxis. Patients at risk of major cardiovascular events may benefit from closer follow-up and early interventions.

4.3. Implications for future research

These findings should promote research in the field of echocardiography-based RHD screening not only in terms of imaging methods but also in public health implementation including cost-effectiveness of systematic screening.

Although asymptomatic RHD mostly persists over time, longer follow-up periods may be needed to fully address the significance of subclinical asymptomatic RHD and the need for secondary prophylaxis in borderline RHD.

Focused cardiac ultrasound has gained interest from other groups in the RHD field and larger scale studies would enable to validate, or not, this method in a variety of settings with different underlying RHD phenotypes and variable skilled healthcare workers.

Longitudinal data are needed in New Caledonia in order to test the efficacy of public health policies including systematic screening of schoolchildren in terms of RHD prevalence and its outcomes.

In conclusion, the findings of this thesis have addressed key questions regarding the outcomes of asymptomatic and symptomatic RHD. These results may set the scene for further comprehensive studies of asymptomatic and symptomatic RHD while providing key datasets to affect and influence policy.

5. Résumé de la thèse en langue française

5.1. Introduction

La cardiopathie rhumatismale (CR) demeure la première cause de cardiopathie acquise chez les enfants et les jeunes adultes à travers le Monde en raison de sa prévalence encore élevée dans les pays en voie de développement et parmi les populations aborigènes de certains pays développés.

La CR est la séquelle de l'atteinte cardiaque du rhumatisme articulaire aigu (RAA), syndrome auto-immun post-infectieux. Il s'agit classiquement d'une angine à Streptocoque du groupe A qui induit chez l'hôte une réaction immunitaire inappropriée. Le RAA peut affecter différents organes avec une présentation clinique variable, la cardite survenant dans 2/3 des cas. La CR résulte le plus souvent d'accès répétés de RAA. Le dépistage précoce de la maladie est une stratégie attractive permettant de traiter par antibioprophylaxie les enfants avant l'aggravation des lésions valvulaires. Dans ce contexte, l'échocardiographie apparaît comme un outil de dépistage performant pour la détection précoce des lésions valvulaires rhumatismales. Le concept de CR « infraclinique » est d'abord apparu chez des patients atteints de RAA, pour s'étendre aux populations à risque (c'est-à-dire résidant en zone d'endémie). Malgré le nombre croissant d'études démontrant l'intérêt de l'échographie cardiaque dans le dépistage précoce, certaines questions demeurent en suspends. La valeur pronostique de ces lésions valvulaires minimes reste à démontrer. Aussi est-il question des méthodes de dépistage, car celles utilisées dans le cadre de la recherche nécessitent des appareils onéreux et une expertise technique.

Les travaux que consitutent cette thèse s'efforcent de répondre à certaines de ces questions, en décrivant le pronostic de la CR symptomatique, et asymptomatique dépistée par échographie, ainsi que des méthodes simplifiées de dépistage échocardiographique. Trois études originales ont été menées dans le cadre de cette thèse et sont présentées ici. La version complète est disponible en langue anglaise.

5.2. Matériels et Méthodes

5.2.1. Données sociodémographiques, économiques et sanitaires en Nouvelle Calédonie

La Nouvelle-Calédonie archipel de l'océan Pacifique Sud, est Pays d'Outre Mer français. Sa population se chiffre à 268 767 habitants.[108] La répartition de la population calédonienne par communauté d'appartenance est : mélanésienne pour 40%, européenne pour 29%, wallisienne ou futurienne pour 9%, métisse pour 8%, et autre pour 7% de la population. Il s'agit d'un pays à revenus élevé, avec un produit intérieur brut (PIB) par habitant de 26 654 euros (33ème au rang mondial). Il existe des disparités ethniques dans la répartition des richesses. Les provinces Nord et des Îles Loyauté, qui comptent une population majoritairement mélanésienne, ont un revenu médian 2 à 2,5 fois moindre par rapport à la Province Sud où réside une majorité d'européens.

La densité médicale en Nouvelle-Calédonie est de 223 médecins pour 100 000 habitants. Il existe une disparité importante entre le Nord et le Sud avec une densité médicale de 274/ 100 000 dans le Sud contre 96/ 100 000 dans le nord et 80 / 100 000 dans les îles Loyauté.

Le Centre Hospitalier Territorial de Nouvelle Calédonie (CHT) est le seul centre teriaire de l'archipel pourvoyeur de soins spécialisés dans le pays. Les patients sont évacués soit vers la Métropole, soit vers l'Australie pour les interventions valvulaires. L'accès aux soins de proximité est assuré par des centres médico-sociaux dans chacune des communes.

L'Agence Saniatire et Sociale de Nouvelle Calédonie (ASS-NC) coordonne les politiques de prévention des maladies non transmissibles. L'ASS-NC a mis en place une vaste campagne de dépistage de la CR par l'échographie cardiaque systématique ciblant tous les enfants scolarisés en classe de CM1 (âge attendu 9-10 ans) en 2008 et tient un registre d'antibioprophylaxie secondaire à l'échelle nationale. Il existe en outre un Département des Evacuations Sanitaires (EVASAN) dont la mission est, entre autres, de prendre en charge toute évacuation pour des interventions valvulaires cardiaques. En outre, un registre de mortalité nationale est tenu par le Département des Affaires Sanitaires et Sociales (DASS).

5.2.2. Materiel et Méthodes de l'étude n°1: évaluation des campagnes de dépistage écho-guidées et devenir des enfants sans et avec Cardiopathie Rhumatismale infraclinique

Campagnes de dépistage écho-guidées en Nouvelle Calédonie

Des campagnes annuelles de dépistage systématique visent tous les enfants scolarisés en classe de CM1 en Nouvelle Calédonie. Elles ont été mises en place en 2008 après une étude pilote menée en 2007. Après avoir obtenu l'autorisation des institutions de tutelle, une information est menée auprès des enfants et de leurs parents. Tous les enfants ayant une autorisation parentale participent au dépistage. Celui-ci se déroule en deux temps. Une première échographie (échographe portable VIVID I) réalisée par un médecin à l'école statue sur la normalité ou la suspicion de pathologie. Le diagnostic n'est porté que sur un deuxième examen réalisé sur un échographe non portatif par l'un des cardiologues participant au programme. Les critères diagnostiques ont été préalablement établis par le groupe de travail et sont proches de ceux de l'Organisation Mondiale pour la Santé (OMS) et de ceux publiés en 2012 par la Fédération Mondiale du Cœur (World Heart Federation, WHF).

Tous les enfants diagnostiqués comme porteurs de CR ont été inclus dans le registre d'antibioprophylaxie et ont été pris en charge à 100% par le système de sécurité sociale néo-calédonienne.

Objectifs

Les objectifs de cette étude sont triples :
- d'évaluer la première campagne de dépistage écho-guidée de la CR à l'échelle nationale
- d'estimer la prévalence de la CR dans la population ciblée par les campagnes de dépistage
- de suivre une cohorte d'enfants sans et avec CR

Méthodologie de l'étude de cohorte

Etude de cohorte rétrospective issue des campagnes de dépistage de 2008 à 2011 inclus. Suivi réalisé en 2012.

Critères d'inclusion : tous les cas de CR étaient eligibles. Les non-cas de CR ont été choisis de façon aléatoire, appariés aux cas de CR selon l'ethnie et par classe d'école. Deux non-cas ont été tirés au sort par cas.

Critères d'exclusion : diagnostic alternatif lors d'examens de suivi (cardiopathie congénitale).

Données collectées : charactéristiques socio-démographiques ; valvulopathie et sa sévérité initiales ; données échographiques et cliniques au suivi.

Protocoles d'échographie

L'échographie initiale a été menée sur un appareil portable (VIVID I, GE®) selon un protocole et des critères diagnostiques prédéfinis. Les images initiales n'ont pas été systématiquement sauvegardées.

L'échographie de suivi a été réalisée sur le même appareil, soit au siège de l'ASS-NC, soit dans les centres de soins de proximité. L'acquisition des images a suivi un protocole prédéfini et le diagnostic porté lors de la relecture des examens anonymisés (sans connaître le statut cas/non-cas) par la doctorante selon les critères de la WHF.

Reccueil des données au suivi

Outre des données socio-démographiques et économiques supplémentaires, la présence d'un souffle pathologique (avant l'échographie), la survenue d'événements cliniques (épisode de RAA ou complications), le recours à l'antibioprophylaxie et ses modalités ont été colligées. Le registre de mortalité et le service des admissions du CHT ont été consultés pour les perdus de vue.

Biais de l'étude

Cette étude comporte un certain nombre de biais en partie liés à son caractère rétrospectif. Premièrement les critères diagnostiques, quoique similaires, ont changé au cours de l'étude. S'agissant d'un programme de dépistage à large échelle, les examens n'avaient pas été systématiquement sauvegardés et une réatribution du diagnostic n'a donc pas pu être conduite.

5.2.3. Materiel et Méthodes de l'étude n°2: évaluation d'une méthode simplifiée de dépistage écho-guidé de la Cardiopathie Rhumatismale

Définitions

Echographie de référence : échographie réalisée par un cardiologue et diagnostic porté par un expert (doctorante) après relecture en aveugle des échographies en utilisant les critères de la WHF.

Méthode simplifiée : échoscopie réalisée et interprétée par un(e) infirmier(ère) naïf en échographie en utilisant un algorithme simplifié à l'aide d'échographes de poche, après une formation courte.

Objectifs

L'étude comporte deux parties avec des objectifs différents :

Partie n°1 : identifier les critères diagnostiques simplifiés pour le diagnostic de CR en les comparant aux critères de référence de la WHF dans une population sélectionnée.

Partie n°2 : tester la performance de ces critères diagnostiques à l'aide d'échographes de poche par des non-experts en situation de dépistage à l'école au sein d'une population à prévalence plus basse que lors de la Partie n°1.

Méthodologie de l'étude. Il s'agit d'une étude prospective conduite en deux parties.

Participants

Partie n°1 : des enfants issus des années précédentes des campagnes de dépistage, sans et avec CR, ont été sollicités afin de participer à cette phase pilote en février et mars 2013.

Partie n°2 : des enfants participant au dépsitage scolaire annuel de la CR conduite par l'ASS-NC à Nouméa se sont vus proposer de participer à l'étude entre avril et juillet 2013.

Protocole d'échographie

Chaque participant a eu 3 échographies par 3 opérateurs différents (un cardiologue ; deux par des infirmières) dans un ordre aléatoire, chaque opérateur étant en aveugle par rapport aux données du participant et aux résultats des autres opérateurs.

L'échographie de référence a été menée suivant un protocole d'acquisition d'images prédéfini à l'aide d'un échographie portable VIVID I (GE®).

L'échoscopie comportait le même protocole d'acquisition des images, le diagnostic étant porté à la fin de l'acquisition des images sur les mesures faites par l'infirmier (ère) sur un échographe de poche Vscan (GE®).

Les critères testés lors de la 1ère partie de l'étude étaient: (i) la présence d'un jet d'insuffisance mitrale (IM) ; (ii) la présence d'un jet d'insuffisance aortique (IA) ; (iii) la reconnaissance d'anomalies morphologiques (cf. critères WHF Méthodes) ; (iv) la présence d'un jet d'IM de longueur ≥2cm ; (v) la présence d'un jet d'IM de longueur ≥1,5cm ; la combinaison d'un jet d'IM ≥2cm et d'une IAo.

Formation à l'échoscopie

La formation a comporté 3 jours de cours théoriques suivis de 30 heures de stage avec un ratio instructeur/apprenant de 1 pour 2. Les objectifs pédagogiques ont porté sur: la reconnaissance des structures cardiaques ; l'acquisition des coupes parasternale grand et petit axe, apicale 4, 3 et 2 cavités et l'utilisation du Doppler couleur ; la reconnaissance d'anomalies morphologiques mitrale et aortique évocatrices de CR ; la reconnaissance des jets d'IM et d'IAo; la mesure de la longueur de jets d'IM et d'IAo. La formation a été complétée par la relecture et la réinterprétation de 50 des examens réalisés lors de la première partie. Un stage supplémentaire d'acquisition des images de 12 heures a également été mis en place. Cette formation complémentaire était sous la forme du tutorat de 1 :1.

5.2.4. Materiel et Méthodes de l'étude n°3: estimation de la prévalence, de l'incidence et pronostic de la Cardiopathie Rhumatismale symptomatique

Objectifs : Estimer la prévalence et l'incidence de la CR symptomatique en Nouvelle Calédonie ; décrire les caractéristiques et le pronostic des patients hospitalisés pour CR et identifier des facteurs associés à la survenue d'événement(s) sous la forme d'un critère composite (insuffisance cardiaque, accident vasculaire cérébral, embolie périphérique, intervention valvulaire, décès cardiovasculaire).

Méthodologie : Etude rétrospective de cohorte hospitalière.

<u>Participants</u> : Les participants potentiels ont été identifiés via le Dapartement d'informatique médicale du CHT à l'aide de codes diagnostiques de RAA et de CR de 2005 à 2012. Les patients admis en 2013 ont été inclus prospectivement.

<u>Critères d'inclusion</u> : validation des critères échographiques de la WHF pour le diagnostic de CR certaine.

Une étude ancillaire porte sur le groupe de patients nouvellement diagnostiqués de CR et sans complication à l'admission afin d'identifier les facteurs associés à la survenue d'événements.

Un suivi centralisé a été mené entre mars et décembre 2013. Le registre de mortalité de la DASS et le bureau des EVASAN ont été consultés pour les patients perdus de vue.

<u>Données recueillies</u>

Les données socio-démographiques, les caractériques de la valvulopathie et sa quantification, la présence d'une poussée de RAA et la survenue de complications ont été recuillies au moment du diagnostic. Les événements indésirables suivants ont été colligés lors du suivi : insuffisance cardiaque définie par un stade NYHA III ou IV, l'embolie périphérique, l'accident vasculaire cérébral, l'intervention valvulaire, le décès cardiovasculaire. Les traitements dont le recours à l'antibioprophylaxie ont également été colligés. Le registre national d'antibioprophylaxie tenu par l'ASS-NC a été conuslté en cas de donnée manquante.

5.2.5. Méthodes statistiques pour l'ensemble des études

Les variables descriptives sont présentées avec leur moyenne ± dérivation standard (SD) ou médiane et intervalle interquartile. La comparaison des variables continues a été réalisée par le t-test de Student. Les variables discontinues ont été comparées par le test du Chi-2. Pour les étude n°1 et n°3 les prévalences ont été calculées avec un intervalle de confiance (IC) de 95% avec comme référentiel les données démographiques de l'ISEE; les données d'incidence sont expirmées par 10 0000 personnes années. Pour les analyses de facteurs prédisposant à la présence ou à la persistance de la CR des Odds Ratio et Hazard Ratio ont été calculés avec leurs IC de 95%. L'évaluation de la variabilité inter-observateur a été conduite par le test kappa ou le pourcentage de concordance pour l'étude n°2. Le risque de survenue

d'événements dans l'étude n°3 été a été analysé par la méthode de Kaplan Meier. Un modèle de Cox univarié puis multivarié a également été conduit, avec un analyse de sensibilité en raison de données manquantes. Toutes les analyses ont été ajustées sur l'âge et le sexe. Les patients suivis et perdus de vue ont été comparés via les tests de Mann-Whitney (pour les variables quantitatives non paramétriques), de Fisher (pour les variables quantitatives paramétriques), et le test du chi-deux de Pearson (pour les variables qualitatives). Un seuil $p < 0,05$ a été considéré comme significatif. Les logiciels SAS 9.3 et 9.4® ont été utilisés pour l'ensemble des analyses statistiques.

5.2.6. Considérations éthiques

Les autorisations des comités de protection des personnes de Bordeaux Outre-Mer ont été obtenues pour les 3 études. Le comité d'éthique du CHT a validé l'étude n°3. Les parents ou tuteurs des participants aux études n°1 et 2 ont donné leur consentement écrit. Les participants à l'étude n°3 ont été informés oralement de la réalisation de l'étude lors du suivi, le comité d'éthique dispensant d'un accord écrit pour cette étude observationnelle.

5.3. Résultats

5.3.1. Etude n°1: évaluation des campagnes de dépistage écho-guidées et devenir des enfants sans et avec CR infraclinique

Exhaustivité de la première campagne de dépistage écho-guidée de la CR à l'échelle nationale

Parmi les 18 621 enfants ciblés par les campagnes de dépistage entre 2008 et 2011, soit 82,1% de la population néocalédonienne née entre 1998 et 2002, 858 (4,6%) étaient absents le jour du dépistage. Parmi les 17 287 participant au dépistage, 1 619 (9,4%) ont été adressés pour une échographie de confirmation dont 418 (25,8%) ne se sont pas présentés.

Cent cinquante-sept enfants ont finalement été diagnostiqués comme porteurs de CR, soit une prevalence de 9,5 pour 1 000 (IC 95% 8,1-11,1). La prevalence était significativement plus élevée chez les enfants âgés de 11 ans ou plus (p=0,004), les

océaniens (p<0,0001) et ceux résidant dans les Provinces Nord et Iles Loyauté (p<0,0001).

Pronostic des lésions de CR asymptomatiques dépistées par échocardiographie

Parmi les 157 enfants dépistés entre 2008 et 2011, 114 ont participé à l'étude, conjointement à 227 non cas (soit des enfants ayant des échographies considérées normales lors du dépistage). L'âge moyen au moment du dépsitage était de 9,9±0,7 années dans le groupe CR et de 10,0±0,7 dans le groupe non-CR, avec un sexe-ratio (M/F) de 0,9 dans le groupe CR et de 1,0 dans le groupe non-CR. Les 114 enfants avec CR présentaient initialement les lésions valvulaires suivantes : insuffisance mitrale (IM) chez 107 (93,9%) cas, insuffisance aortique (IA) chez 34 (29,8%) cas, et sténose mitrale chez 6 (5,2%) cas. Une atteinte mitrale et aortique était présente chez 30 (26,3%) cas.

La durée médiane de suivi était de 2,58 années [IQR 1.31-3.63]. L'incidence annuelle de RAA était de 10,28 pour 1 000 chez les enfants ayant une CR dépistée par échographie. Un des enfants (0,9%) a présenté une complication clinique (insuffisance cardiaque) au cours du suivi. Aucune intervention valvulaire ni décès n'a été rapporté lors du suivi. Cent un (88,6%) enfants se sont vu prescrire une antibioprophylaxie secondaire par pénicilline injectable.

Parmi les 114 cas de CR, 41 (36,0%) avaient une CR certaine sur l'échographie de suivi, 49 (43,0%) avaient des lésions compatibles avec une CR limite, et 24 (21,1%) avaient une échographie dans les limites de la normale selon les critères WHF. Le facteur associé à la persistance de CR (certaine et limite) par analyse multivariée straitifée selon l'âge était le nombre de personnes par chambre (< 3 *vs.* ≥ 3, OR 8,27 IC 95% (1,67-41,08), p<0,01). Cette association demeurait significative lorsque les cas de CR limite étaient exclus de l'analyse (OR 7,70 IC 95% (1,28-46,45), p=0,03). Il n'y avait pas d'association significative entre la persistance des lésions et la compliance à l'antibioprophylaxie, définie comme une injection à intervalles inférieurs ou égaux à 4 semaines (p=0,78).

L'incidence annuelle de RAA chez les enfants non atteints de CR était de 3,31 pour 1000, ce qui n'était pas significativement différent des participants avec CR préalable (p=0,23). Parmi les 227 enfants avec échographie normale à l'état basal, 189 (89,3%) gardaient une échographie normale au suivi, 2 (0,9%) avaient une CR certaine et 29 (12,8%) avaient une CR limite.

5.3.2. Etude n°2 : évaluation d'une méthode simplifiée de dépistage écho-guidé de la Cardiopathie Rhumatismale

Partie n°1 : Identification de critères simplifiés pour l'échoscopie de dépsitage de la CR

En mars 2013, 189 participants ont été inclus dans cette phase préliminaire. L'âge moyen des participants était de 12,2 (0,2) ans et 84 (44,4%) étaient de sexe masculin. Cent six (56,1%) enfants avaient des lésions de CR (63 CR certaine, 43 CR limite) et 83 (43,9%) avaient une échographie normale.

La sensibilité et la spécificité des 6 critères testés par les infirmiers à l'aide de l'échographe de poche étaient variables en comparaison à la méthode de référence. Parmi les 6 critères testés, la présence d'un jet d'IM ≥2cm ou d'une IA quelle que soit la longueur avaient une sensibilité de 76.4% (IC 95% 67,4-83,5) et de 70.7% (IC 95% 61,4-78,6) pour chacun des infirmiers. La spécificité était de 73,5% (IC 95% 63.0-70.7) et de 69,9% (IC 95% 59,2-69,1) pour chaucn des infirmiers.

Partie n°2 : Evaluation de l'échoscopie utilisant le critère composite (IM ≥2cm ou IA) pour le dépistage de la CR en population scolaire

Le nombre de participants à cette deuxième phase a été de 1 217 (âge moyen 9,6 (0,5) années, 603 (49,6%) de sexe masculin). Un diagnostic de CR a été porté chez 49 (4,0%) des participants : 34 cas de CR limite, 15 cas de CR certaine. La sensibilité de l'échoscopie était de 83,7% (IC 95% 70,7-91,6) et de 77,6% (IC 95% 63,9-87,1) ; et la spécificté de 90,9% (IC 95% 89,1-92,4) et 92,0% (IC 95% 90,3-93,4) selon l'opérateur. La concordance des deux opérateurs était de 91,4%. Lorsque restreint aux cas de CR certaine, la sensibilité était de 93,3% (IC 95% 64,7-99,1) et 86.7% (IC 95% 59,5-96,7).

5.3.3. Etude n°3 : estimation de la prévalence, de l'incidence et du pronostic de la Cardiopathie Rhumatismale symptomatique

Epidémiologie de la CR symptomatique en Nouvelle Calédonie

De façon globale en Nouvelle Calédonie, la prévalence de la CR définie par les critères de CR certaine de la WHF était de 2,8 pour 1 000 (IC 95% 2,60-3,00) en 2013. Lorsque restreint à la population mélanésienne, la prévalence en 2013 était de 4,93 pour 1 000 (IC 95% 4,50-5,35). Celle-ci était de 1,43 (IC 95% 0,29-2,57) à 1,59 (IC 95% 0,412,77) pour 1 000 chez les enfants âgés de 9 et 10 ans, respectivemet. L'incidence annuelle moyenne de CR certaine était de 2,08 pour 10000 (IC 95% 1,89-2,27) personnes-années, sans variation au cours de la période de l'étude.

Pronostic de la CR symptomatique nouvellement diagnostiquée

Parmi les 461 patients admis au CHT avec CR ou RAA, 396 remplissaient les critères d'inclusion de l'étude évaluant le pronostique, à savoir : CR certaine incidente (2005-2013) selon les critères WHF avec quantification de la valvulopathie. 174 (43,9%) patients étaient de sexe masculin avec un âge médian de 18 (IQR 10-40) années. 274 (71,9%) étaient Mélanésiens, 85 (22,3%) Polynésiens et 22 (5,8%) d'autre communauté d'appartenance. 205 (51,8%) étaient admis pour RAA. Sur l'échographie diagnostique, 127 (32,1%) patients avaient une valvulopathie modérée, 131 (33,1%) moyenne et 138 (34,8%) sévère. Parmi les 396 patients inclus, 106 (26,8%) s'étaient présentés à l'occasion d'une complication correspondant soit à de l'insuffisance cardiaque (stade NYHA III ou IV), à une embolie périphérique, à un accident vasculaire cérébral, à la nécessité de recourir urgemment à une intervention valvulaire ou au décès cardiovasculaire. L'analyse visant à identifier des facteurs associés à la survenue d'événements sous la forme d'un critère composite a porté sur les 290 patients sans événement initial. Parmi ces 290 patients, l'âge médian était de 13 (IQR 10-31) années, 131 (45,2%) étaient de sexe masculin et 185 (63,8%) étaient diagnostiqués lors d'un accès de RAA. Ces 290 patents ont été suivis pendant une durée médiane de 4,08 (IC 95% 1,84-6,84) années. Il y a eu 62 événements pendant la durée de l'étude. Le taux de survie était de 97,89% (95% 95,97-99,4) à 4 ans et de 96,21% (95% IC 89,95-98,60) à 8 ans. L'incidence annuelle de l'événement composite était de 59,05‰ (IC 95% 44,35-73,75); avec une incidence annuelle

d'insuffisance cardiaque de 29,06‰ (IC 95% 19,29-38,82); d'accident vasculaire cerebral de 7,26‰ (IC 95% 2,52-12,01); et d'intervention valvulaire de 36,47‰ (IC 95% 25,17-47,77). Lors de l'analyse de sensibilité incluant les patients avec données sur l'antibioprpohylaxie secondaire, deux facteurs étaient associés à la survenue de l'événement composite: la sévérité de la valvulopathie sous-jacente à l'échographie initiale (valvulopathie moyenne *versus* modérée HR 3,22 (0,90 – 11,49); valvuloapthie severe *versus* modérée HR 11,07 (3,21 – 38,22), p<0.001); et l'antibioprophylaxie secondaire par pénicilline au moment du suivi (HR 0,33 (0,14-0,79), p=0,013).

5.4. Discussion

Les trois études présentées ici, disponibles dans leur intégralité dans la version anglaise de cette thèse, ont permis d'accroître les connaissances épidémiologiques de la CR en Nouvelle Calédonie. De façon plus large, elles ont eu comme objectif de répondre à certaines des questions dans le domaine dans le but de guider des politiques de santé publique futures dans les pays où la CR demeure endémique.

La première étude a démontré les difficultés à mettre en œuvre des campagnes de dépistage écho-guidées de la CR à l'échelle nationale. Une proportion importante de la population ciblée échappe au dépistage en milieu scolaire et un quart de ceux suspects de CR n'ont pas de diagnostic finalement posé, ne se présentant pas au rendez-vous de l'échographie de confirmation. Il paraît ainsi que la méthodologie utilisée dans les travaux de recherche n'est pas directement transposable en termes de santé publique. Aussi, seule une partie de la population calédonienne est à risque de CR. Cibler les enfants océaniens par des campagnes répétées avec un diagnostic posé à l'école permettrait d'optimiser l'efficacité de cette politique de santé publique.
Le suivi de la cohorte d'enfants sans et avec CR a permis d'apporter des informations pronostiques. La CR asymptomatique dépistée par l'échographie a un pronostic favorable à court terme, avec une persistance de lésions minimes dans la majorité des cas et peu d'événements cliniques. La promiscuité est un facteur associé à la persistance des lésions échographiques. En revanche, les enfants océaniens sans CR à l'âge de 9-10 ans ont un risque non négligeable de présenter soit un accès de RAA,

soit des lésions valvulaires échographiques à seulement 2 ans du dépistage négatif initial. Ces réusltats soulèvent des questions quant à l'âge de dépistage choisi en Nouvelle Calédonie et à l'intérêt éventuel de conduire des dépistages répétés au cours de l'adolescence au sein des populations à risque.

La deuxième étude est le prolongement de la première, visant à tester des méthodes de dépistage simplifié de la CR à l'aide de l'échoscopie cardiaque par des non-experts en utilisant des échographes de poche et un algorithme diagnostique adapté. Les résultats sont en faveur d'une sensibilité et d'une spécificité acceptables de cette méthode pour la détection de la CR asymptomatique. La sensibilité est meilleure, de l'ordre de 90%, lorsqu'on vise à dépister les enfants porteurs de CR certaine uniquement, seul cas de figure où l'antibioprophylaxie est recommandée. Quoiqu'imparfaits, ces résultats ouvrent la voie à d'autres études devant l'intérêt potentiel comme outils de dépistage de masse dans les pays en voie de développement où les ressources consacrées à la prévention de la CR sont limitées.

La troisième étude a permis d'asseoir les données épidémiologiques de la première. La CR demeure un fléau au sein de la population mélanésienne de Nouvelle Calédonie, sans diminution de l'incidence de 2005 à 2013. L'estimation de la prévalence à partir de cette cohorte hospitalière permet d'asseoir la continuité entre la CR asymptomatique dépistée par échographie et la CR symptomatique. Cette étude a permis en outre de décrire les caractéristiques des patients admis à l'hôpital avec une CR symptomatique. Quoiqu'encore endémique au sein de la population autochtone, la prévalance et l'incidence de la CR paraissent inférieures à celle rapportée en Australie ou en Afrique du Sud. Une proportion importante de nouveaux cas (~27%) se présente à l'occasion d'une complication alors que le système de soins de proximité donnerait en théorie la possibilité d'un diagnostic plus précoce. La mortalité à 8 ans parmi les patients avec une CR nouvellement diagnostiquée et sans complication initiale est basse mais l'incidence annuelle d'événements est élevée (~59‰) au sein de cette population jeune. La sévérité de la CR au diagnostic et l'antibioprophylaxie sont les deux facteurs associés à la survenue d'événements. Ces résultats sont en faveur de l'intérêt du diagnostic précoce, lorsque la valvulopathie est encore modérée, et de la poursuite du traitement antibiotique afin d'éviter les rechutes. Ceci plaide en faveur du dépistage systématique et de la mise en place de registres encadrant

l'administration d'antibioprophylaxie secondaire dans les pays où la CR demeure un problème de santé publique.

5.5. Conclusions

Les réulstats des trois études originales que constitue cette thèse apportent des résultats ayant un intérêt potentiel pour les actions de santé publique visant à contrôler le RAA et la CR en Nouvelle Calédonie et dans le Monde. Les méthodes issues des études à visée de recherche ne peuvent être transposées en campagnes de dépistage écho-guidées à l'échelle nationale. Le pronostic de la CR asymptomatique dépistée par échographie est bénin à moyen terme, quoique les lésions échographiques persistent dans la majorité des cas. La CR étant une maladie acquise, un dépistage ponctuel à un âge jeune (9-10 ans) ne permet pas de préjuger de l'absence de lésions à l'adolescence chez les populations à rsique. Une méthode de dépsitage par échoscopie à l'aide d'échographes de poche par des non-experts utilisant des critères diagnostiques adaptés pourrait avoir un intérêt dans les pays en voie de développement où la maladie demeure endémique. Enfin, les données épidémiologiques issues du dépistage échographique sont en accord avec celles de données hospitalières évaluant la CR symptomatique en Nouvelle Calédonie. Le diagnostic y est encore souvent porté à un stade tardif, révélé par des complications. La mortalité à 8 ans de la CR symptomatique sans complication initiale est basse mais la morbidité importante en Nouvelle Calédonie, pays où les patients ont accès aux interventions valvulaires.

6. References

1. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet* 2012; **379**(9819): 953-64.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-128.
3. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; **349**(9063): 1436-42.
4. Rheumatic Fever and Rheumatic Heart Disease (Technical Report Series, No 923). WHO technical report series; The Global Burden of Disease WHO 2004 Update. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html. (accessed August 1st 2015)
5. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis* 2005; **5**(11): 685-94.
6. Population Reference Bureau. http://www.prb.org/Publications/Datasheets/2008/2008wpds.aspx, (accessed August 1st 2015)
7. Diao M, Kane A, Ndiaye MB, et al. Pregnancy in women with heart disease in sub-Saharan Africa. *Archives of cardiovascular diseases* 2011; **104**(6-7): 370-4.
8. Gunther G, Asmera J, Parry E. Death from rheumatic heart disease in rural Ethiopia. *Lancet* 2006; **367**(9508): 391.
9. Kaplan MH, Bolande R, Rakita L, Blair J. Presence of Bound Immunoglobulins and Complement in the Myocardium in Acute Rheumatic Fever. Association with Cardiac Failure. *The New England journal of medicine* 1964; **271**: 637-45.
10. Kaplan MH, Svec KH. Immunologic Relation of Streptococcal and Tissue Antigens. Iii. Presence in Human Sera of Streptococcal Antibody Cross-Reactive with Heart Tissue. Association with Streptococcal Infection, Rheumatic Fever, and Glomerulonephritis. *J Exp Med* 1964; **119**: 651-66.
11. Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. *Lancet* 2005; **366**(9480): 155-68.
12. Sanyal SK, Thapar MK, Ahmed SH, Hooja V, Tewari P. The initial attack of acute rheumatic fever during childhood in North India; a prospective study of the clinical profile. *Circulation* 1974; **49**(1): 7-12.
13. Vardi P, Markiewicz W, Weiss Y, Levi J, Benderly A. Clinical-echocardiographic correlations in acute rheumatic fever. *Pediatrics* 1983; **71**(5): 830-4.
14. Vasan RS, Shrivastava S, Vijayakumar M, Narang R, Lister BC, Narula J. Echocardiographic evaluation of patients with acute rheumatic fever and rheumatic carditis. *Circulation* 1996; **94**(1): 73-82.
15. Figueroa FE, Fernandez MS, Valdes P, et al. Prospective comparison of clinical and echocardiographic diagnosis of rheumatic carditis: long term follow up of patients with subclinical disease. *Heart* 2001; **85**(4): 407-10.

16.   Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. *European heart journal* 2010; **31**(6): 719-27.

17.   Veasy LG. Time to take soundings in acute rheumatic fever. *Lancet* 2001; **357**(9273): 1994-5.

18.   Veasy LG, Wiedmeier SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. *The New England journal of medicine* 1987; **316**(8): 421-7.

19.   Marijon E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. *The New England journal of medicine* 2007; **357**(5): 470-6.

20.   Carapetis JR, Hardy M, Fakakovikaetau T, et al. Evaluation of a screening protocol using auscultation and portable echocardiography to detect asymptomatic rheumatic heart disease in Tongan schoolchildren. *Nat Clin Pract Cardiovasc Med* 2008; **5**(7): 411-7.

21.   Rothenbuhler M, O'Sullivan CJ, Stortecky S, et al. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. *The Lancet Global health* 2014; **2**(12): e717-26.

22.   Wilson N. Rheumatic heart disease in indigenous populations--New Zealand experience. *Heart, lung & circulation* 2010; **19**(5-6): 282-8.

23.   Parnaby MG, Carapetis JR. Rheumatic fever in indigenous Australian children. *Journal of paediatrics and child health* 2010; **46**(9): 527-33.

24.   Schaffer WL, Galloway JM, Roman MJ, et al. Prevalence and correlates of rheumatic heart disease in American Indians (the Strong Heart Study). *Am J Cardiol* 2003; **91**(11): 1379-82.

25.   Carapetis JR. Rheumatic heart disease in Asia. *Circulation* 2008; **118**(25): 2748-53.

26.   Nkgudi B, Robertson KA, Volmink J, Mayosi BM. Notification of rheumatic fever in South Africa -- evidence for underreporting by health care professionals and administrators. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 2006; **96**(3): 206-8.

27.   Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2163-96.

28.   Lawrence JG, Carapetis JR, Griffiths K, Edwards K, Condon JR. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. *Circulation* 2013; **128**(5): 492-501.

29.   Zuhlke L, Mirabel M, Marijon E. Congenital heart disease and rheumatic heart disease in Africa: recent advances and current priorities. *Heart* 2013; **99**(21): 1554-61.

30.   Grimaldi A, Ammirati E, Karam N, et al. Cardiac surgery for patients with heart failure due to structural heart disease in Uganda: access to surgery and outcomes. *Cardiovascular journal of Africa* 2014; **25**: 1-8.

31.   Mirabel M, Grimaldi A, Freers J, Jouven X, Marijon E. Access to cardiac surgery in sub-Saharan Africa. *Lancet* 2015; **385**(9968): 606.

32.	Jaiyesimi F, Antia AU. Prognostic factors in childhood rheumatic disease. *Trop Geogr Med* 1981; **33**(1): 14-38.

33.	WHO programme for the prevention of rheumatic fever/rheumatic heart disease in 16 developing countries: report from Phase I (1986-90). WHO Cardiovascular Diseases Unit and principal investigators. *Bull World Health Organ* 1992; **70**(2): 213-8.

34.	Council of Europe, Committee of Ministers, Recommendation No. R (94) 11 on Screening as a Tool of Preventive Medicine (Oct. 10, 1994) http://www1.umn.edu/humanrts/instree/coerecr94-11.html. (accessed August 1st 2015)

35.	The WHO Global Programme for the Prevention of Rheumatic Fever and Rheumatic Heart Disease 1999; http://whqlibdoc.who.int/hq/2000/WHO_CVD_00.1.pdf. (accessed August 1st 2015)

36.	Strasser T, Dondog N, El Kholy A, et al. The community control of rheumatic fever and rheumatic heart disease: report of a WHO international cooperative project. *Bull World Health Organ* 1981; **59**(2): 285-94.

37.	Mathur KS, Wahal PK. Epidemiology of rheumatic heart disease--a study of 29,922 school children. *Indian Heart J* 1982; **34**(6): 367-71.

38.	al-Sekait MA, al-Sweliem AA, Tahir M. Rheumatic heart disease in schoolchildren in western district, Saudi Arabia. *J R Soc Health* 1990; **110**(1): 15-6, 9.

39.	Biancaniello T. Innocent murmurs. *Circulation* 2005; **111**(3): e20-2.

40.	Field MJ. Music of the heart. *Lancet* 2010; **376**(9758): 2074.

41.	Mahnke CB, Nowalk A, Hofkosh D, Zuberbuhler JR, Law YM. Comparison of two educational interventions on pediatric resident auscultation skills. *Pediatrics* 2004; **113**(5): 1331-5.

42.	Bland EF, Duckett Jones T. Rheumatic fever and rheumatic heart disease; a twenty year report on 1000 patients followed since childhood. *Circulation* 1951; **4**(6): 836-43.

43.	Meira ZM, Goulart EM, Colosimo EA, Mota CC. Long term follow up of rheumatic fever and predictors of severe rheumatic valvar disease in Brazilian children and adolescents. *Heart* 2005; **91**(8): 1019-22.

44.	Lanna CC, Tonelli E, Barros MV, Goulart EM, Mota CC. Subclinical rheumatic valvitis: a long-term follow-up. *Cardiology in the young* 2003; **13**(5): 431-8.

45.	Caldas AM, Terreri MT, Moises VA, et al. What is the true frequency of carditis in acute rheumatic fever? A prospective clinical and Doppler blind study of 56 children with up to 60 months of follow-up evaluation. *Pediatric cardiology* 2008; **29**(6): 1048-53.

46.	Marijon E, Tafflet M, Jouven X. Time to use ultrasound and not stethoscopes for rheumatic heart disease screening. *Nat Clin Pract Cardiovasc Med* 2008; **5**(7): E1-3.

47.	Paar JA, Berrios NM, Rose JD, et al. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. *Am J Cardiol* 2010; **105**(12): 1809-14.

48.	Beaton A, Okello E, Lwabi P, Mondo C, McCarter R, Sable C. Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren. *Circulation* 2012; **125**(25): 3127-32.

49.   Bhaya M, Panwar S, Beniwal R, Panwar RB. High prevalence of rheumatic heart disease detected by echocardiography in school children. *Echocardiography* 2010; **27**(4): 448-53.

50.   Saxena A, Ramakrishnan S, Roy A, et al. Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (Rheumatic Heart Echo Utilisation and Monitoring Actuarial Trends in Indian Children) study. *Heart* 2011; **97**(24): 2018-22.

51.   Webb R GT, Stirling J, Wilson N. Echocardiorgaphic findings in NZ children from a low-risk population for Acute Rheumatic Fever: implications for rheumatic heart disease screening. 62nd Annual Scientific Meeting Paediatric Society New Zealand. New Zealabd; 2010.

52.   Kane A, Mirabel M, Toure K, et al. Echocardiographic screening for rheumatic heart disease: age matters. *International journal of cardiology* 2013; **168**(2): 888-91.

53.   Remenyi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease--an evidence-based guideline. *Nature reviews Cardiology* 2012; **9**(5): 297-309.

54.   Zuhlke LJ, Steer AC. Estimates of the global burden of rheumatic heart disease. *Global heart* 2013; **8**(3): 189-95.

55.   Zuhlke L, Mayosi BM. Echocardiographic screening for subclinical rheumatic heart disease remains a research tool pending studies of impact on prognosis. *Current cardiology reports* 2013; **15**(3): 343.

56.   Remenyi B, Carapetis J, Wyber R, Taubert K, Mayosi BM, World Heart F. Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. *Nature reviews Cardiology* 2013; **10**(5): 284-92.

57.   Bhaya M, Beniwal R, Panwar S, Panwar RB. Two years of follow-up validates the echocardiographic criteria for the diagnosis and screening of rheumatic heart disease in asymptomatic populations. *Echocardiography* 2011; **28**(9): 929-33.

58.   Beaton A, Okello E, Aliku T, et al. Latent Rheumatic Heart Disease: Outcomes 2 Years After Echocardiographic Detection. *Pediatric cardiology* 2014.

59.   http://www.isee.nc/population/recensement/structure-de-la-population-et-evolutions. 2014 (accessed August 1st 2015)

60.   http://data.un.org/CountryProfile.aspx?crName=New Caledonia. (accessed August 1st 2015)

61.   http://www.isee.nc/revenu-conso/bcmpresent.html. (accessed November 1st 2013.

62.   DASS N-C. Situation sanitaire en Nouvelle-Calédonie, 2008. http://www.dass.gouv.nc/portal/page/portal/dass/librairie/fichiers/11140262.PDF. (accessed August 1st 2015)

63.   Baroux N, Rouchon B, Huon B, Germain A, Meunier JM, D'Ortenzio E. High prevalence of rheumatic heart disease in schoolchildren detected by echocardiography screening in New Caledonia. *Journal of paediatrics and child health* 2013; **49**(2): 109-14.

64.   RHDAustralia (ARF/RHD writing group), National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition). 2012.

http://www.rhdaustralia.org.au/sites/default/files/guideline_0.pdf (accessed August 1st 2015)

65.	Engelman D, Kado JH, Remenyi B, et al. Teaching focused echocardiography for rheumatic heart disease screening. *Annals of pediatric cardiology* 2015; **8**(2): 118-21.

66.	Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008; **118**(15): e523-661.

67.	Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006; **114**(5): e84-231.

68.	Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; **30**(4): 633-8.

69.	Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for the Diagnosis of Acute Rheumatic Fever in the Era of Doppler Echocardiography: A Scientific Statement From the American Heart Association. *Circulation* 2015.

70.	Fauchier T, Tafflet M, Filitoga G, et al. Acute Rheumatic Fever: A population-based study in Wallis, a South Pacific Island. *International journal of cardiology* 2014; **181C**: 30-1.

71.	Bach JF, Chalons S, Forier E, et al. 10-year educational programme aimed at rheumatic fever in two French Caribbean islands. *Lancet* 1996; **347**(9002): 644-8.

72.	Carapetis JR. Pediatric rheumatic heart disease in the developing world: echocardiographic versus clinical screening. *Nat Clin Pract Cardiovasc Med* 2008; **5**(2): 74-5.

73.	Maurice J. Rheumatic heart disease back in the limelight. *Lancet* 2013; **382**(9898): 1085-6.

74.	Roberts K, Colquhoun S, Steer A, Remenyi B, Carapetis J. Screening for rheumatic heart disease: current approaches and controversies. *Nature reviews Cardiology* 2013; **10**(1): 49-58.

75.	Beaton A, Aliku T, Okello E, et al. The utility of handheld echocardiography for early diagnosis of rheumatic heart disease. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2014; **27**(1): 42-9.

76.	Mirabel M, Celermajer DS, Ferreira B, et al. Screening for rheumatic heart disease: evaluation of a simplified echocardiography-based approach. *European heart journal cardiovascular Imaging* 2012; **13**(12): 1024-9.

77.   Roberts K, Colquhoun S, Steer A, Remenyi B, Carapetis J. Screening for rheumatic heart disease: current approaches and controversies. *Nature reviews Cardiology* 2013; **10**(1): 49-58.

78.   Grimaldi A, Ammirati E, Mirabel M, Marijon E. Challenges of using ultrasounds for subclinical rheumatic heart disease screening. *International journal of cardiology* 2013; **167**(6): 3061.

79.   Kaplan EL. T. Duckett Jones Memorial Lecture. Global assessment of rheumatic fever and rheumatic heart disease at the close of the century. Influences and dynamics of populations and pathogens: a failure to realize prevention? *Circulation* 1993; **88**(4 Pt 1): 1964-72.

80.   Sadiq M, Islam K, Abid R, et al. Prevalence of rheumatic heart disease in school children of urban Lahore. *Heart* 2009; **95**(5): 353-7.

81.   Zuhlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *European heart journal* 2014.

82.   Eissa S, Lee R, Binns P, Garstone G, McDonald M. Assessment of a register-based rheumatic heart disease secondary prevention program in an Australian Aboriginal community. *Aust N Z J Public Health* 2005; **29**(6): 521-5.

83.   Kearns TM, Schultz R, McDonald V, Andrews RM. Prophylactic penicillin by the full moon: a novel approach in Central Australia that may help to reduce the risk of rheumatic heart disease. *Rural Remote Health* 2010; **10**(3): 1464.

84.   Remond MG, Atkinson D, White A, et al. Rheumatic Fever Follow-Up Study (RhFFUS) protocol: a cohort study investigating the significance of minor echocardiographic abnormalities in Aboriginal Australian and Torres Strait Islander children. *BMC cardiovascular disorders* 2012; **12**: 111.

85.   Pilgrim T, Kalesan B, Karki P, et al. Protocol for a population-based study of rheumatic heart disease prevalence and cardiovascular outcomes among schoolchildren in Nepal. *BMJ Open* 2012; **2**(3).

86.   Tibazarwa KB, Volmink JA, Mayosi BM. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. *Heart* 2008; **94**(12): 1534-40.

87.   Liebo MJ, Israel RL, Lillie EO, Smith MR, Rubenson DS, Topol EJ. Is pocket mobile echocardiography the next-generation stethoscope? A cross-sectional comparison of rapidly acquired images with standard transthoracic echocardiography. *Annals of internal medicine* 2011; **155**(1): 33-8.

88.   Frederiksen CA, Juhl-Olsen P, Larsen UT, Nielsen DG, Eika B, Sloth E. New pocket echocardiography device is interchangeable with high-end portable system when performed by experienced examiners. *Acta Anaesthesiol Scand* 2010; **54**(10): 1217-23.

89.   Mjolstad OC, Andersen GN, Dalen H, et al. Feasibility and reliability of point-of-care pocket-size echocardiography performed by medical residents. *European heart journal cardiovascular Imaging* 2013; **14**(12): 1195-202.

90.   Panoulas VF, Daigeler AL, Malaweera AS, et al. Pocket-size hand-held cardiac ultrasound as an adjunct to clinical examination in the hands of medical students and junior doctors. *European heart journal cardiovascular Imaging* 2013; **14**(4): 323-30.

91.   Galderisi M, Santoro A, Versiero M, et al. Improved cardiovascular diagnostic accuracy by pocket size imaging device in non-cardiologic

outpatients: the NaUSiCa (Naples Ultrasound Stethoscope in Cardiology) study. *Cardiovascular ultrasound* 2010; **8**: 51.

92.   Colquhoun SM, Carapetis JR, Kado JH, et al. Pilot study of nurse-led rheumatic heart disease echocardiography screening in Fiji--a novel approach in a resource-poor setting. *Cardiology in the young* 2013; **23**(4): 546-52.

93.   Spencer KT, Kimura BJ, Korcarz CE, Pellikka PA, Rahko PS, Siegel RJ. Focused cardiac ultrasound: recommendations from the American Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2013; **26**(6): 567-81.

94.   Sicari R, Galderisi M, Voigt JU, et al. The use of pocket-size imaging devices: a position statement of the European Association of Echocardiography. *Eur J Echocardiogr* 2011; **12**(2): 85-7.

95.   Marijon E, Celermajer DS, Tafflet M, et al. Rheumatic heart disease screening by echocardiography: the inadequacy of World Health Organization criteria for optimizing the diagnosis of subclinical disease. *Circulation* 2009; **120**(8): 663-8.

96.   Roberts K, Maguire G, Brown A, et al. Echocardiographic Screening for Rheumatic Heart Disease in High and Low Risk Australian Children. *Circulation* 2014.

97.   Colquhoun SM. KJ, Remenyi B, .Wilson NJ, Carapetis JR, Steer AC. Echocardiographic screening in a resource poor setting: Borderline rheumatic heart disease could be a normal variant. *International Journal of Cardiology, in press* 2014.

98.   Mirabel M, Fauchier T, Bacquelin R, et al. Echocardiography screening to detect rheumatic heart disease: A cohort study of schoolchildren in French Pacific Islands. *International journal of cardiology* 2015; **188**: 89-95.

99.   Lennon D, Craig E. Re: Epidemiology of acute rheumatic fever in New Zealand 1996-2005 by Jaine R et al. 2008;44:564. *Journal of paediatrics and child health* 2009; **45**(12): 764.

100.   Remond MG, Severin KL, Hodder Y, et al. Variability in disease burden and management of rheumatic fever and rheumatic heart disease in two regions of tropical Australia. *Internal medicine journal* 2013; **43**(4): 386-93.

101.   North RA, Sadler L, Stewart AW, McCowan LM, Kerr AR, White HD. Long-term survival and valve-related complications in young women with cardiac valve replacements. *Circulation* 1999; **99**(20): 2669-76.

102.   Soma-Pillay P, MacDonald AP, Mathivha TM, Bakker JL, Mackintosh MO. Cardiac disease in pregnancy: a 4-year audit at Pretoria Academic Hospital. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 2008; **98**(7): 553-6.

103.   Mirabel M, Andre R, Barsoum P, et al. Ethnic disparities in the incidence of infective endocarditis in the Pacific. *International journal of cardiology* 2015; **186**: 43-4.

104.   Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *European heart journal* 2007; **28**(11): 1358-65.

105.   Mirabel M, Rattanavong S, Frichitthavong K, et al. Infective endocarditis in the Lao PDR: clinical characteristics and outcomes in a developing country. *International journal of cardiology* 2015; **180**: 270-3.

106.   Yankah C, Fynn-Thompson F, Antunes M, et al. Cardiac surgery capacity in sub-saharan Africa: quo vadis? *The Thoracic and cardiovascular surgeon* 2014; **62**(5): 393-401.

107.   Mayosi BM, Gamra H, Dangou JM, Kasonde J, nd All-Africa Workshop on Rheumatic F, Rheumatic Heart Disease p. Rheumatic heart disease in Africa: the Mosi-o-Tunya call to action. *The Lancet Global health* 2014; **2**(8): e438-9.

108.   http://www.isee.nc/population/recensement. (accessed August 1st 2015)

7. Appendices: Ethical, IRB and other institutions' approvals

Study n°1.

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

MINISTÈRE
DE L'ENSEIGNEMENT SUPÉRIEUR
ET DE LA RECHERCHE

**DIRECTION GENERALE POUR LA RECHERCHE
ET L'INNOVATION**

Comité consultatif sur le traitement de l'information
en matière de recherche dans le domaine de la santé

Dossier n° 12.421

Intitulé de la demande :   Cardiopathie rhumatismale de l'enfant : pronostic des lésions
infra-cliniques dépistées par l'échographie cardiaque en Nouvelle Calédonie.

Responsable scientifique : Mariana MIRABEL
Centre de Recherche Cardiovasculaire de Paris
INSERM U970
Hôpital Européen Georges Pompidou
56, rue Leblanc
75737 PARIS Cedex 15

Demandeur :   André SYROTA
INSERM
101, rue de Tolbiac
75654 PARIS Cedex 13

Dossier reçu le :   1.06.12

Dossier examiné le :   **5 juillet 2012**

Avis du Comité consultatif :

Avis favorable

Toutefois, la note d'information pour les enfants doit être remise à tous les enfants, sans limite d'âge. Il faut préciser pour la CNIL où seront conservées les fiches manuelles (dans le dossier enfant au niveau de l'ASSNC ?). Pour la saisie des données, il faut préférer un logiciel plus adapté qu'Excel, ce qui facilitera la saisie (logiciel gratuit Epidata, par exemple). Le terme « étude observationnelle transversale de cohorte » devrait être remplacé par « étude observationnelle de cohorte ».

Fait à Paris, le 11 juillet 2012

Jean-Louis Serre
Président du Comité consultatif

1, rue Descartes – 75231 Paris Cedex 05
http://www.recherche.gouv.fr

Instituts
thématiques **Inserm**

Institut national
de la santé et de la recherche médicale

Nos réf: CD/FC/2012-002
Dossier suivi par :
Christine DOSQUET -CEEI
@ : ceei@inserm.fr

Dr Mariana Mirabel
Centre de Recherche Cardiovasculaire
de Paris, Inserm U970
Hôpital Européen Georges Pompidou
56 rue Leblanc
75737 Paris CEDEX 15.

Paris, le 11 septembre 2012

Chère Madame,

Veuillez trouver ci-joint votre **avis n°12-073** pour votre projet intitulé :

**"Cardiopathie rhumatismale de l'enfant : pronostic des lésions
infra-cliniques dépistées par l'échographie cardiaque en Nouvelle
Calédonie",** examiné lors de la réunion du CEEI Du 11 septembre 2012.

Veuillez agréer, chére Madame, l'expression de mes salutations
distinguées.

Secrétaire du CEEI
Coulibaly Fatoumata

111

Study n°2.

Président : Professeur Emmanuel CUNY

Docteur Mariana MIRABEL
Centre de recherche cardiovasculaire de Paris
INSERM U970
Hôpital européen Georges Pompidou
56 rue Leblanc
75737 Paris cedex 15

Bordeaux, le 7 janvier 2013.

Réf. CPP : DC 2013/13
Vos réf. : demande d'avis consultatif

En date du 30 JANVIER 2013, conformément aux dispositions du Code de la Santé Publique, le CPP Sud-Ouest et Outre Mer III a examiné **la demande de conseil quant au cadre réglementaire** d'un projet de recherche intitulé :

"EVALUATION D'UNE METHODE SIMPLIFIEE POUR LE DEPISTAGE DE LA CARDIOPATHIE RHUMATISMALE EN NOUVELLE CALEDONIE."

La recherche a pour but de simplifier le programme de dépistage de la cardiopathie rhumatismale en milieu scolaire (CM1) en Nouvelle-Calédonie à l'aide de l'échographie V-scan GE commercialisé, comparé à l'échographie de référence Vivid i GE.

La recherche est basée sur un recueil de données d'imagerie cardiaque non irradiante issue d'une technique indolore et sans perte de chance pour les enfants inclus ; les données personnelles sont anonymisées.

La recherche est hors du champ des dispositions régissant la recherche biomédicale et les soins courants.

Pour le Comité et le Président
Le Secrétaire général
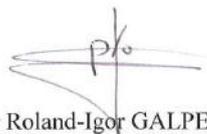
Dr Roland-Igor GALPERINE

CEEI - IRB

**Comité d'Evaluation Ethique
de l'Inserm**

Instituts
thématiques **Inserm**

Institut national
de la santé et de la recherche médicale

Nos réf: CD 13-005
Dossier suivi par :
Christine DOSQUET -CEEI
@ : ceei@inserm.fr

**Dr Mariana MIRABEL
Centre de Recherche Cardiovasculaire
de Paris, Inserm U970
Hôpital Européen Georges Pompidou
56 rue Leblanc,
75737 Paris CEDEX 15**

Paris, le 4 avril 2013

Chère Madame,

Veuillez trouver ci-joint votre **avis n°13- 092** pour votre projet intitulé :

**"Évaluation d'une méthode simplifiée pour le dépistage de la
Cardiopathie Rhumatismale en Nouvelle Calédonie ",**

examiné lors de la réunion du CEEI du 19 mars 2013.

Veuillez agréer, chère Madame, l'expression de mes salutations
distinguées.

Présidente du CEEI
Christine DOSQUET

Study n°3.

COMITÉ DE PROTECTION DES PERSONNES
SUD-OUEST ET OUTRE MER III

Président : Professeur Emmanuel CUNY

Docteur Mariana MIRABEL
INSERM U970
Hôpital Européen Georges Pompidou
56 rue Leblanc
75737 Paris cedex 15

Bordeaux, le 7 janvier 2013.

Réf. CPP : DC 2012/116
Vos réf. : demande d'avis consultatif

En date du 19 DECEMBRE 2012, conformément aux dispositions du Code de la Santé Publique, le CPP Sud-Ouest et Outre Mer III a examiné **la demande de conseil quant au cadre réglementaire** d'un projet de recherche intitulé :

"OBSERVATOIRE HOSPITALIER DE RHUMATISME ARTICULAIRE AIGU ET DE CARDIOPATHIE RHUMATISMALE."

La mise en place d'un observatoire hospitalier rétrospectif et prospectif dont l'objectif est l'estimation de la prévalence de la cardiopathie rhumatismale et la mesure de son impact en terme de morbi-mortalité est un projet qui se situe hors du champ des dispositions régissant la recherche biomédicale et les soins courants.

Pour le Comité et le Président
Le Secrétaire général

Dr Roland-Igor GALPERINE