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## The Pan African Pulmonary Hypertension Cohort (PAPUCO): implementing a contemporary registry on pulmonary hypertension in Africa

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3 **THE PAN AFRICAN PULMONARY HYPERTENSION**  
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9 **CONTEMPORARY REGISTRY ON PULMONARY**  
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11 **HYPERTENSION IN AFRICA**  
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### Running Title

The Pan African Pulmonary Hypertension Cohort (PAPUCO)

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## ABSTRACT

### Introduction

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure. Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared to developed countries due to the high prevalence of risk factors in the region.

### Methods and Analysis

A multinational multicentre registry-type cohort study was established and tailored to resource-constraint settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa. PH will be diagnosed by specialist cardiologists using Echocardiography (RVSP>35 mmHg, absence of pulmonary stenosis and acute right heart failure) usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, electrocardiogram and chest x-ray changes in keeping with PH as per guidelines. Additional investigations such as CT-scan, ventilation/perfusion scan or right heart catheterisation will be performed at the discretion of the treating physician. Functional tests include 6-minute walk test and Karnofsky Performance Score. The WHO classification system for PH will be applied to describe the different aetiologies of PH. Several sub-studies have been implemented within the registry to investigate specific types of PH and their outcome at up to 24 months. Data will be analysed by an independent institution following a data analyse plan.

## Ethics and Dissemination

All local Ethics Committees of the participating centres approved the protocol. The data will be disseminated through peer-reviewed journals, at national and international conferences and public events at local care providers.

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## ARTICLE SUMMARY

### Article focus

- In this manuscript we aim to provide an overview of pulmonary hypertension in Africa and the epidemiology of risk factors prevalent in the region.
- We aim to answer the question why Africa needs a registry for pulmonary hypertension.
- We describe how we implemented the registry in scarce resources settings.

### Key messages

- Risk factors for pulmonary hypertension are highly endemic in Africa.
- The incidence of pulmonary hypertension is expected to be higher in Africa compared to developed countries.
- A diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings without access to right heart catheterisation has been developed.
- 12 centres are participating in the Pan African Pulmonary hypertension Cohort (PAPUCO) study and more than 250 patients have been recruited so far.

### Strengths and limitations of this study

- The PAPUCO study is the first multinational registry on pulmonary hypertension in Africa.
- PAPUCO centres have different levels of medical infrastructure and not all patients underwent the same rigorous work-up.



## INTRODUCTION

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure (RHF).[1] The epidemiology of PH in Africa and the distribution of its multitude of aetiologies has not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region.[2-5] Many known risk factors for PH are hyperendemic in this part of the world, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary haemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary disease, PH and, often, to RHF with premature death. Also a lack of specialist paediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH.[6] Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH.[6-8] However, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive RHF.[4,9] Thus, within the registry we expect the entire spectrum of aetiologies of PH. In this manuscript, we aim to provide an overview of PH in Africa and the epidemiology of risk factors prevalent in the region, and answer the question why Africa needs a registry for PH just as much as most other parts of the world and how we implemented it in the setting of scarce resources.

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5 **Preliminary evidence of a significant burden of pulmonary hypertension and its risk**  
6 **factors in Africa**  
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10 In recent years, there has been increasing awareness of the clinical significance of PH and cor  
11 pulmonale in Africa. This applies equally to the recognition of the importance of PH and  
12 RHF as both a primary diagnosis and as a poor prognostic marker for those primarily affected  
13 by left-sided heart failure. Data on the precursors and risk factors of those conditions are  
14 limited to few reports. The largest study on PH/RHF in Africa has been conducted within *the*  
15 *Heart of Soweto Study* in South Africa; 2505 patients presented with *de novo* heart failure  
16 between 2006-2008.[5] Of those 697 (28%) were diagnosed with PH/RHF. PH/RHF was the  
17 primary diagnosis in 50% of those patients. The majority presented with dyspnoea and a  
18 mean right ventricular systolic pressure (RVSP) above 50 mmHg. Left heart disease (31%),  
19 chronic lung disease due to Chronic Obstructive Pulmonary Disease (COPD) and  
20 tuberculosis (26%), and PH (20%) due to HIV (HIV-PH), CHD, or idiopathic PH were the  
21 most common causes of PH. Sani et al. described the prevalence of PH in patients with RHD  
22 at a tertiary centre in Nigeria.[10] Of 1312 Echocardiography (ECHO) studies 10% had  
23 evidence of RHD; secondary PH was present in 80% of patients with RHD. The same centre  
24 reported on 53 patients with PH on ECHO among 80 patients admitted with heart failure with  
25 hypertensive heart disease (25%), peripartum cardiomyopathy (25%), dilated  
26 cardiomyopathy (17%), and RHD (13%) being the most common causes of PH.[11] A study  
27 from Uganda showed a prevalence of PH in patients with newly diagnosed RHD (n=309) of  
28 33%.[12] A smaller survey from Lagos, Nigeria investigated the prevalence of cardiovascular  
29 disease in an HIV-positive cohort and found one patient of 100 patients to have HIV-PH.[13]  
30 An ECHO study on 102 HIV-patients presenting with cardiac symptoms in Tanzania  
31 revealed PH in 13%.[14] PH with a RVSP>30 mmHg was present in 4% of long-term  
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3 survivors in a Zimbabwe cohort of vertically acquired HIV infection.[15] Haemolytic  
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5 anaemia is a known risk factor for PH; a screening study of patients with sickle-cell disease  
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7 (SCD) in Nigeria showed a PH prevalence of 25%;[16] a study from Egypt indicates that  
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9 patients with  $\beta$ -Thalassaemia are at risk of PH.[17] Another study from Egypt found a PH  
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11 prevalence of 9% in patients seropositive for schistosomal antibodies. Ahmed et al. from  
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13 Sudan described 14 consecutive cases of PH with previously treated pulmonary TB and  
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15 conclude that PH can even occur after resolution of TB, most like due to persistent lung  
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17 destruction.[18] This data suggests that left heart disease, chronic lung disease, RHD, HIV,  
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19 schistosomiasis and SCD might be the most common underlying diseases to cause PH within  
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21 the spectrum of aetiologies of PH that we will find within the Pan African Pulmonary  
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23 hypertension Cohort (PAPUCO)  
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## 30 **RATIONAL AND OBJECTIVES**

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32 Worldwide, PH has received great increase in awareness at the beginning of the 21<sup>st</sup> century  
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34 (Figure 1), but less than one per cent (0.7%) of the publications are from Africa. It is  
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36 expected that PH is more prevalent in Africa compared to developed countries, but little  
37  
38 information is available about African patients with PH. Exposure to risk factors, human  
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40 genetic variation, different socio-economic backgrounds, lifestyles, co-morbidities, nutrition  
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42 and disparities in access to health services makes the African population unique, but  
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44 heterogeneous at the same time. Therefore, most research data and clinical guidelines from  
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46 high-income countries cannot be translated into the African context. It is within the context  
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48 described above that the Pan African Pulmonary hypertension Cohort (PAPUCO), a Pan  
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50 Africa registry-type cohort study, was established (Figure 2).  
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54 Scientific and clinical research has been fundamental in improving human health.[19] In fact,  
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56 research has demonstrated to be an excellent vehicle to implement new technologies and to  
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3 facilitate training for its use, and to develop new systems and establish the services around it -  
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5 jointly leading to technical improvement, sharpening of skills and capacity development.

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7 Besides the main objectives of the PAPUCO registry to define and understand PH in Africa  
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9 (Box 1), this multinational and multicentre research project therefore aims to also develop  
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11 sustainable clinical and research capacity across the African continent as well as raising  
12  
13 awareness for PH and its risk factors.  
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19 **Box 1: PAPUCO objectives**

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21 *Primary objective*

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23 • To describe disease presentation, disease severity and aetiologies of PH, comorbidities, the  
24 diagnostic and therapeutic management, and natural course of PH in Africa

25 *Secondary objectives*

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27 • To describe the overall 6-month survival rate  
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29 • To describe the 24-month survival rate in patients with HIV-PH  
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31 • To compare 6-month survival rates between different groups of PH  
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33 • To determine the predictors of mortality across the different groups.

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35 Abbreviations: PH, pulmonary hypertension; HIV, human immunodeficiency virus  
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38 The prevalence of PH in Africa varies geographically, according to underlying risk factors  
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40 and diseases and the diagnosis of PH is most likely often missed, not only during early stages  
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42 due to the subtle nature of presentation of PH, but also at more advanced stage of disease due  
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44 to lack of awareness by primary care doctors and low index of suspicion, limited access to  
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46 ECHO services and tertiary care. However, it is crucial to diagnose PH in Africa early and  
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48 reliably to ensure better care for these patients (Box 2).  
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53 **Box 2: The significance of PH in Africa: Why we need to diagnose?**

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55 • The right to know  
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57 • Prognostic implications  
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- Access to tertiary care: heart failure management, anticoagulation, home oxygen, COPD management, access to PH-specific drugs (Sildenafil)
- Access to cardiothoracic surgery: valve repair/replacement, correction of congenital heart disease, heart transplantation
- Access to social and disability grants
- To raise awareness of PH and its risk factors

Abbreviations: PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease

## METHODS AND ANALYSIS

### Study design and setting

The Pan African Pulmonary hypertension Cohort (PAPUCO) research group was established in 2011 with the aim to implement a registry-type cohort study on pulmonary hypertension in Africa according to STROBE guidelines. The registry aims to recruit consecutive patients 1) with newly diagnosed PH based clinical and ECHO criteria, 2) are able or likely to return for 6-month follow-up, 3) are at least 18 years old (except for paediatric centres in Mozambique and Nigeria), and 4) consented in writing to participate in the registry. Centre eligibility include 1) availability of ECHO and training in assessing right heart function, 2) experience in diagnosing PH according to WHO classification, 3) experience in clinical management of patients with right heart failure, and 4) resources to review patients at 6-month follow-up. Participating centres will be invited to join the registry at African cardiac meetings and conferences.

### Definition of pulmonary hypertension, diagnostic algorithm and data points

As shown in Box 3, PH is defined as documented elevated RVSP > 35 mmHg on trans-thoracic ECHO in the absence of pulmonary stenosis and acute right heart failure; usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, and possibly electrocardiogram (ECG) and chest x-ray (CXR) changes in keeping with PH as per guidelines.[20] Right heart catheterisation is optional. The WHO

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3 classification system for PH will be applied to describe the different aetiologies of PH. Once  
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5 definitive assessment and treatment has been applied, the following specific data will be  
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7 documented for each individual: a) all major cardiovascular diagnoses according ICD 10  
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9 coding, and b) up to five non-cardiovascular diagnoses according ICD 10 coding.[21] Figure  
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11 3 shows the diagnostic algorithm to diagnose PH in resource-constraint settings without  
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13 access to right heart catheterisation that has been developed following the guidelines for the  
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15 diagnosis of PH of the European Society of Cardiology and European Respiratory  
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17 Society.[20] Key information collected will include information on demographic profile,  
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19 socio-economic background, medical history, co-morbidities, cardiac risk factors, and  
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21 environmental exposures. The clinical aspects of the assessment include symptoms scoring, a  
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23 full clinical examination, physical and clinical status; functional tests include WHO  
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25 functional class (WHO FC), 6-minute walk test (6MWT) and Karnofsky Performance Score.  
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27 Technical procedures include ECHO, CXR, and 12-lead ECG. Further investigations are at  
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29 the discretion of the treating physician and typically include lung function tests,  
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31 ventilation/perfusion lung scans, and high resolution computed tomography and computed  
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33 tomography pulmonary angiography, and right heart catheterization, if available (Figure 3).  
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35 Data on heart failure treatment and co-medication, hospitalization and death, and 6-month  
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37 outcome will also be collected.  
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46 **Box 3: Evidence to diagnose PH in resource-constraint settings**

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- Symptoms: SOB, fatigue, cough, chest pain, palpitations
  - Clinical exam: raised JVP, peripheral oedema, ascites, loud p2, systolic murmur, central cyanosis
  - ECG: sinus tachycardia, p-pulmonale, right axis deviation, right bundle branch block, RVH
  - CXR: cardiomegaly, pleural effusion, prominent pulmonary arteries
  - ECHO: dilated right atrium and ventricle, interventricular septal flattening, RVSP>35 mmHg, TAPSE<15 mm

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Abbreviations: SOB, shortness of breath; JVP, jugular vein pressure; ECG, electrocardiogram; RVH, right ventricular hypertrophy; CXR, chest X-ray; ECHO, Echocardiography; RVSP, right ventricular

systolic pressure; TAPSE, tricuspid annular plane systolic excursion

## *Echocardiography*

### Echocardiography in adults

ECHO modalities applied included M-mode, two dimensional (2D) and Doppler studies.

ECHO will be done with 3 to 5 MHz sector transducer. Complete 2D ECHO examination

will be performed according to the recommendations of the American Society of ECHO

(ASE).[22] M-mode ECHO will be derived from 2D images. The M-mode cursor on the 2D

scan will move to specific areas of the heart to obtain measurements according to the

recommendation of the committee on M-mode standardization of the ASE. Doppler indices

of left ventricular (LV) diastolic filling will be obtained. Complete Doppler study will be

done according to the recommendations of the ASE. From the M-mode measurements,

indices of LV function will be derived. These include shortening fraction, ejection fraction

(EF), and LV mass, cardiac output and relative wall thickness. ECHO examinations include

(a) valvular assessment, (b) left atrial size, (c) left ventricular size and function, (d) a semi

quantitative estimate of the severity of valvular regurgitation, (e) size and function of the

right atrium and ventricle and (f) evidence of pulmonary hypertension. Doppler will be used

to examine the valves on suspicion of any valvular lesion. ECHO findings associated with PH

includes dilated pulmonary artery and dilation and hypertrophy of the right ventricle (RV),

diastolic flattening of the interventricular septum and Doppler evidence of PH.[23] Doppler

ECHO estimates pulmonary artery systolic pressure (PASP). By measuring the maximum

velocity of the tricuspid regurgitant jet ( $v$ ), the transtricuspid pressure gradient will be

calculated using the modified Bernoulli equation ( $4v^2$ ).[24] The PASP is approximated by

adding the transtricuspid gradient to the right atrial pressure (RAP) as applied in the formula

$[PASP=4v^2+RAP]$ . The PASP is equivalent to RVSP in the absence of pulmonary outflow

obstruction. In our study, the systolic regurgitant tricuspid flow will be assessed in the

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3 parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views to  
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5 determine the highest velocity, which reflects PASP/RVSP.[25] PH is defined as *mild* if  
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7 RVSP was 36-50 mmHg, *moderate* if RVSP was 51-60 mmHg and *severe* if RVSP was >60  
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9 mmHg.[26] In addition, we further assessed right ventricular function by measuring the  
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11 systolic displacement of the lateral portion of the tricuspid annular plane excursion (TAPSE)  
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13 on the M-mode tracing under the 2D-echo guidance.[27] Peak mitral early diastolic velocity  
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15 (E in m/s), the E-wave deceleration time (DCT in ms) and the velocity at atrial contraction (A  
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17 in m/s) are measured using pulsed-wave Doppler. Left ventricular filling pressure classes  
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19 were defined in accordance with the ASE 2009 guidelines.[28] In patients with heart failure  
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21 and reduced ejection fraction (HFrEF) raised LV filling pressure is defined as  $E/A \geq 2$  if in  
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23 sinus rhythm or  $DCT < 150$  ms if in atrial fibrillation (AF); normal LV filling pressure is  
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25 defined as  $E/A < 1$  in patients in sinus rhythm or  $DCT \geq 200$  ms for those in AF; patients  
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27 between these limits will be classified as undetermined. In heart failure and preserved  
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29 ejection fraction (HFpEF), LV filling pressure is classified as follows: raised LV filling  
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31 pressure if left atrium is dilated and normal LV filling pressure if left atrium has normal size.  
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### 39 Echocardiography in infants and children

40 Translating the definitions of PH in adults to children, especially to infants, is controversial.  
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42 Within the paediatric cardiology community experts suggest that the ratio of the PASP to the  
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44 systemic systolic blood pressure  $> 0.4$  should be the diagnostic criterion.[29] The fact that the  
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46 threshold of pulmonary vascular resistance (PVR) increase has not been included in the  
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48 abovementioned definition is another limitation to its use in children or infants, since  
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50 paediatric PH is mainly caused by left-to-right shunt congenital heart disease; and if PVR  
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52 shows no significant increase in such cases, the patient may be considered only as a dynamic  
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54 PH case led by increased pulmonary blood flow, rather than pulmonary vascular disease.  
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3 Paediatric guidelines suggest that PAP >25 mmHg and PVR>3 Wood units remain in the  
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5 definition of PH.[30] In our cohort of children with congenital heart malformations we not  
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7 only used tricuspid and pulmonary regurgitation envelopes, but also the flow across the  
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9 ventricular septal defect or persistent ducts arteriosus to measure the gradient between the  
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11 two circulations and therefore estimate the pulmonary pressure. Indirect signs of PH such as  
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13 dilatation of the RV, RV-hypertrophy and dilatation of the main pulmonary artery were  
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15 added to Doppler data to confirm the diagnosis.  
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### 20 21 *Accuracy of Echocardiography in the diagnosis of PH*

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23 Diagnosing PH is challenging when relying on bedside tests. RHC is the gold standard to  
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25 diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear  
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27 excessive risks and be impractical in any cost-constrained environment. Also RHC is only  
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29 available at very few centres in Africa. A viable device to diagnose PH in Africa needs to be  
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31 widely available, accurate, safe, and cost-effective. ECHO has become increasingly available  
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33 in Africa and reliably allows the measurements to describe functional and morphologic  
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35 features of PH and to indirectly measure the pressures in the pulmonary artery; hence, to  
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37 diagnose PH. Nonetheless, the exact measurements of the mean and systolic pulmonary  
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39 artery are not possible, the PASP remains estimate, and the use of ECHO to diagnose PH  
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41 questionable.[31,32] A number of possible explanations for this “inaccuracy” merit attention:  
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43 1) conditions for a reproducible calculation of PAPS/RVSP include the presence of sufficient  
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45 TR to produce a Doppler envelope and appropriate gain adjustments. An “undergained”  
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47 spectral signal will tend to result in underestimated PAPS whereas an “overgained” spectral  
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49 signal might overestimate the measurements; 2) careful adjustment of the transducer position  
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51 and the use of colour flow Doppler are critical in order to reduce the Doppler angle and to  
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53 obtain the maximal regurgitant flow velocity and severe TR will cause a laminar flow which  
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3 invalidates the Bernoulli equation; 3) volume status and systemic blood pressure are other  
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5 factors that potentially influence the measurement of PAPS; and 4) the highest value of RAP  
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7 in the ASE guidelines is 15 mmHg, but RAP measured by RHC can exceed 15 mmHg. In  
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9 spite of all these shortcomings, several studies have been published in the literature  
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11 demonstrating good sensitivity and specificity of ECHO versus RHC.[33-35] In the  
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13 REVEAL registry, there was a good correlation in PASP between ECHO and RHC at  
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15 baseline, even if repeated ECHO measurements alone were not sufficient to monitor changes  
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17 in PASP or progression of PH.[36] In the first systematic review and meta-analysis  
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19 addressing the diagnostic accuracy of ECHO in PH by Janda and colleagues, the authors  
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21 concluded that the correlation of PASP by ECHO compared to PASP by RHC was good with  
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23 a summary correlation coefficient of 0.70 (95% CI 0.67 to 0.73).[37] Also, the authors  
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25 showed that the diagnostic accuracy of ECHO in PH was also acceptable with a summary  
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27 sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85),  
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29 respectively. Additional, Damy and colleagues demonstrated in their recent work that PAPS  
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31 when measured in “good ECHO hands” is a strong predictor of mortality.[38] Last but not  
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33 the least, easily obtainable ECHO parameters like E/A ratio, DCT, LA size can reliably  
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35 distinguish between PH due to lung disease and PH due to left heart disease, allowing for  
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37 rapid triage of patients with need for RHC. In summary, ECHO is far beyond a good  
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39 modality to confirm both the presence and aetiology of PH in the majority of suspected cases  
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41 when performed and interpreted by the requisite expertise under incorporation of all  
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43 information obtained during a detailed ECHO assessment. ECHO will always provide  
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45 incremental information in PH that cannot be obtained using RHC, whether in developed or  
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47 developing countries.  
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## 56 **Data cleaning process and statistical analysis**

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3 All study data will be collected on electronic case report forms and stored on a dedicated  
4  
5 secure central database. Cases will be reviewed by at least two investigators (FT, AD, KS,  
6  
7 AOM) for completeness and data validated. Query reports will be sent to the sites and  
8  
9 resolved by the site investigators. If consensus on the WHO classification of PH cannot be  
10  
11 reached, a third investigator's opinion will be requested. Data will then be verified and  
12  
13 transferred to SPSS Statistics 17.0 for all analyses by an independent team at Preventative  
14  
15 Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Normally distributed  
16  
17 continuous data will be presented as mean  $\pm$  standard deviation and non-Gaussian distributed  
18  
19 variables as median plus interquartile range. Categorical data will be presented as percentages  
20  
21 with 95% confidence intervals (CI) where appropriate. For patient group comparisons, we  
22  
23 will use Chi Square ( $\chi^2$ ) analysis with calculation of odds ratios (OR) and 95% CI (where  
24  
25 appropriate) for discrete variables and Students t-test and analysis of variance for normally  
26  
27 distributed continuous variables. Multiple logistic regression analyses (entry model) will be  
28  
29 performed on age, sex and baseline risk factors to derive adjusted ORs for the risk of  
30  
31 presenting with PH/RHF overall, chronic lung disease and PH WHO Group 1. Significance  
32  
33 will be accepted at the two-sided level of 0.05. ECG analysis will be will be subject to  
34  
35 blinded coding according to published Minnesota criteria to determine any pathological  
36  
37 abnormalities.[39]  
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#### 45 **PAPUCO sub-studies**

46  
47 Several sub-studies have been established within the PAPUCO registry. The ECHO sub-  
48  
49 study aims to describe in detail the ECHO characteristics of right ventricular function in PH.  
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51 The HIV-PH sub-study aims to describe the phenotype of HIV-PH in Africa. The congenital  
52  
53 heart disease and rheumatic heart disease sub-studies aim to describe the contribution of  
54  
55 congenital heard disease and rheumatic heart disease to PH in Africa. In addition, serum will  
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3 be collected at selected centres for studies on biomarker profile. The HIV.INFLAME sub-  
4  
5 study aims to examine the role of inflammatory markers and oxidative stress on the  
6  
7 development of HIV-PH. We hypothesizing that HIV-positive patients with PH have a pro-  
8  
9 inflammatory state and raised markers of oxidative stress compared to healthy HIV-positive  
10  
11 controls and that increased markers of inflammation and oxidative stress and decreased  
12  
13 antioxidant capacity are predictors of outcome and indicators of disease severity.  
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### 16 17 18 **Ethics and dissemination**

19  
20 All PAPUCO centres require ethical approval from their local ethics committee review board.  
21  
22 Written inform consent must be obtain from every patient participating in the registry.  
23  
24 Study results will be disseminated in peer-reviewed journals. The first publication will  
25  
26 include baseline and 6-month follow-up data from all centres. Sub-study publications on the  
27  
28 HIV-cohort with 24-month follow-up and the cohort of patients with PH due to left heart  
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30 disease will be published after recruitment and follow-up has been completed. Laboratory-  
31  
32 based research will be published after work is completed.  
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### 39 **The online data collection platform**

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41 A tailor-made databases has developed by *integerafrica research and development* to fulfil  
42  
43 the study requirements. Open-source technology was used to develop the web-based system  
44  
45 that allows investigators to collect, store, analyse, report on and exports clinical research data.  
46  
47 The interface is simple and user friendly and leads the user through the data entry process. It  
48  
49 anonymises personal patient data: data is stored as electronic case report forms on a secure,  
50  
51 encrypted and backed-up server. It provides hierarchic permissions and validation at the point  
52  
53 of data entry. Multimedia data formats, i.e. scans of ECGs, CXRs, and ECHO images can be  
54  
55 uploaded on the platform, allowing storage of complete clinical records and data together.  
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Tools for education, training, and communication are installed within the web-portal. Frequently Asked Questions serve as a guide on how to the use of the platform. After secure login, documents such as paper case report forms, informed consent forms, study information sheets and patient education sheets on PH are available for download. All data can be exported in various formats for further analysis. The platform has been developed to cater for mobile Internet connectivity available in most parts of Africa and a unique research platform far beyond a simple web-based database.

### Recruitment process

Twelve centres have received ethics approval and are currently actively recruiting; additional six countries are showing interest in joining the registry (Figure 2). All centres are government-run public health care institutions with different medical infrastructure profiles and all but one are cardiac centres within tertiary care hospitals (Table 1); one centre is an infectious diseases referral clinic in South Africa. At total of 254 patients have been recruited until December 2013 (Figure 5).

Table 1: Medical infrastructure at PAPUCO centres - diagnostic equipment and medical services

Centre	ECG	CXR	ECHO	RHC	CS	HRCT	CTPA	LFT	V/Q	Lab
CM01	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
CM02	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>					X <sup>1</sup>
CM03	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>							X <sup>1</sup>
MZ01	X	X	X							X
MZ02	X	X	X			X		X		X
NG01	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>		X <sup>1</sup>		X <sup>1</sup>
NG02	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
NG03	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>

NG04	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>							X <sup>1</sup>
NG05	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
SA01	X	X	X	X	X	X	X	X	X	X
SA02	X	X	X			X	X			X

Abbreviations: CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG01, Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; NG04, Department of Medicine, University of Uyo Teaching Hospital, Uyo, Nigeria; NG05, Federal Medical Centre, Umuahia, Nigeria; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg, South Africa and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa. ECG, electrocardiogram; CXR, chest X-ray; ECHO, Echocardiography; RHC, right heart catheterisation; CS, cardiac surgery; HRCT, high resolution computed tomography; CTPA, computed tomography pulmonary angiography; LFT, lung function tests; V/Q, ventilation/perfusion lung scan; Lab, laboratory facility for haematology, chemistry, and microbiology; X, equipment/service available at the centre and free-of-charge for the patients; X<sup>1</sup>, patients have to cover the costs for the service (out of pocket payments).

## LIMITATIONS

The PAPUCO registry is an example of a functioning registry in low-resource settings.

Limited resources should therefore not be seen as a limitation, but rather as a development opportunity. PAPUCO centres have different levels of medical infrastructure and not all patients will undergo the same rigorous work-up in all centres - especially when compared to developed countries. Therefore, the clinical skills of the treating physician are often more important (and valuable!) than an additional diagnostic test in order to pin down the aetiology of PH in a patient. Moreover, patients often have to pay out of their pocket for diagnostic tests and therefore accessibility to tests is limited due to the financial means of the patient.

Although we aim for consecutive patient enrolment at each centre, we understand that this is often not feasible due to high patient volume and workload of doctors.

## SUMMARY

1  
2  
3 PAPUCO is a contemporary registry on PH in Africa using high international standards to  
4  
5 diagnose PH. It will provide new insight on PH in Africa and ultimately improve diagnosis  
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7 and care of patients. PAPUCO is already a showcase for registry activities in Africa and a  
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9 vehicle to capacity generation and sustainable development in the health care sector. It  
10  
11 interconnects health centres far beyond pulmonary hypertension.  
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## 14 15 16 **LEGENDS OF FIGURES**

17  
18 Figure 1: Number of publications on pulmonary hypertension per annum since 1970 (grey  
19  
20 bars) with moving average (blue line). Title search terms in PubMed were "pulmonary  
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22 hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension";  
23  
24 results are displayed annually between 1970 and 2013.  
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29 Figure 2: The PAPUCO map displays countries currently participating in the PAPUCO  
30  
31 registry (number of centres per country in brackets).  
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36 Figure 3: Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint  
37  
38 settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB,  
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40 tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease;  
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42 LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus;  
43  
44 US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed  
45  
46 tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed  
47  
48 tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan  
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54 Figure 4: Diagnosing pulmonary hypertension using transthoracic 2D-Doppler  
55  
56 Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right  
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3 ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-  
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5 wave Doppler across the TV in the 4-chamber view showing severe TR, despite the  
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7 deceivingly less impressive color-flow jet seen across the valve; C: M-Mode measurement of  
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9 TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right  
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11 ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left  
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13 atrium; TV: tricuspid valve; TR: tricuspid regurgitation.  
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19 Figure 5: PAPUCO registry - monthly enrolment until December 2013. Number of patients  
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21 recruited per month since the launch of the registry in May 2011.  
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31 Research in Africa of the University of Cape Town provided institutional support. The  
32  
33 electronic research platform was developed by *integerafrica research and development*.  
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## 38 **CONTRIBUTORS**

39  
40 KS, AOM, FT were responsible for the initial idea, literature review, and study design and  
41  
42 planning. All authors have contributed to the setup of the PAPUCO registry and have  
43  
44 contributed to various aspects of the study design with input relating to their specific  
45  
46 expertise in the field. FT, AD, AOM, LB, MUS, KMK, OSO, AM, PU, ASI, AD, KS have  
47  
48 developed the study protocol, FT and KS wrote the study protocol, FT developed the  
49  
50 database, FT, AD, AOM, KS cleaned the database, LB trained the doctors in  
51  
52 Echocardiography of the heart and developed the Echo protocol, AD trained doctors in  
53  
54 Cameroon, OSO trained doctors in Nigeria, SS developed the statistical analysis plan. FT,  
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AD, AOM, MUS, KMK, OSO, IM, AM, PU, KT, RB, AD, KS were substantially involved in data acquisition. All authors read and approved the final manuscript.

### COMPETING INTEREST

We declare no competing interest.

### ETHICS APPROVAL

All centres received ethics approval from their local ethics committees.

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### REFERENCES

- 1 Simonneau G, Gatzoulis MA, Adatia I, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;**62**:D34–41.  
doi:10.1016/j.jacc.2013.10.029
- 2 Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. *Eur Heart J* 2013;**34**:3538–46.  
doi:10.1093/eurheartj/eh388
- 3 Sliwa K, Carrington MJ, Becker A, *et al.* Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J* 2012;**33**:866–74.  
doi:10.1093/eurheartj/ehr398
- 4 Sliwa K, Wilkinson D, Hansen C, *et al.* Spectrum of heart disease and risk factors in a

- 1  
2  
3 black urban population in South Africa (the Heart of Soweto Study): a cohort study.  
4  
5 *Lancet* 2008;**371**:915–22. doi:10.1016/S0140-6736(08)60417-1  
6  
7  
8  
9 5 Stewart S, Mocumbi AO, Carrington MJ, *et al.* A not-so-rare form of heart failure in  
10 urban black Africans: pathways to right heart failure in the Heart of Soweto Study  
11 cohort. *Eur J Heart Fail* 2011;**13**:1070–7. doi:10.1093/eurjhf/hfr108  
12  
13  
14  
15  
16 6 Mocumbi AO, Lameira E, Yaksh A, *et al.* Challenges on the management of congenital  
17 heart disease in developing countries. *Int J Cardiol* 2011;**148**:285–8.  
18 doi:10.1016/j.ijcard.2009.11.006  
19  
20  
21  
22  
23  
24 7 Sliwa K, Mocumbi AO. Forgotten cardiovascular diseases in Africa. *Clin Res Cardiol*  
25 2010;**99**:65–74. doi:10.1007/s00392-009-0094-1  
26  
27  
28  
29 8 Sliwa K, Carrington M, Mayosi BM, *et al.* Incidence and characteristics of newly  
30 diagnosed rheumatic heart disease in urban African adults: insights from the heart of  
31 Soweto study. *Eur Heart J* 2010;**31**:719–27. doi:10.1093/eurheartj/ehp530  
32  
33  
34  
35  
36  
37 9 Stewart S, Wilkinson D, Hansen C, *et al.* Predominance of heart failure in the Heart of  
38 Soweto Study cohort: emerging challenges for urban African communities. *Circulation*  
39 2008;**118**:2360–7. doi:10.1161/CIRCULATIONAHA.108.786244  
40  
41  
42  
43  
44  
45 10 Sani MU, Karaye KM, Borodo MM. Prevalence and pattern of rheumatic heart disease  
46 in the Nigerian savannah: an echocardiographic study. *Cardiovasc J Afr* 2007;**18**:295–9.  
47  
48  
49  
50 11 Karaye KM, Saidu H, Bala MS, *et al.* Prevalence, clinical characteristics and outcome of  
51 pulmonary hypertension among admitted heart failure patients. *Ann Afr Med*  
52 2013;**12**:197–204. doi:10.4103/1596-3519.122685  
53  
54  
55  
56  
57 12 Okello E, Wanzhu Z, Musoke C, *et al.* Cardiovascular complications in newly  
58  
59  
60

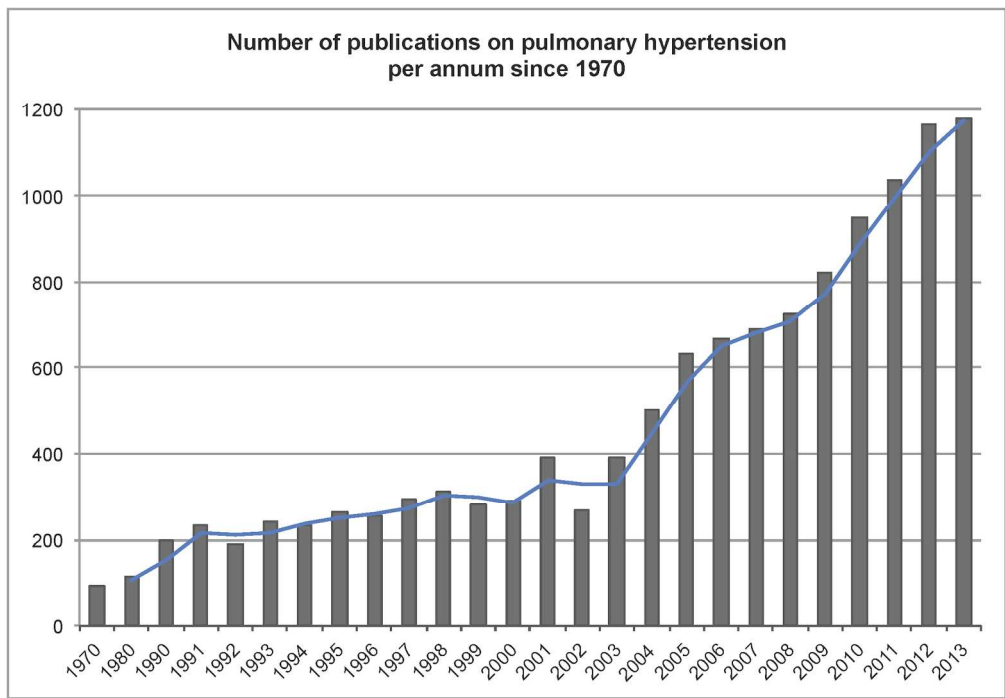
- 1  
2  
3 diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda. *Cardiovasc J*  
4  
5 *Afr* 2013;**24**:80–5. doi:10.5830/CVJA-2013-004  
6  
7
- 8  
9 13 Olusegun-Joseph DA, Ajuluchukwu JNA, Okany CC, *et al.* Echocardiographic patterns  
10  
11 in treatment-naïve HIV-positive patients in Lagos, south-west Nigeria. *Cardiovasc J Afr*  
12  
13 2012;**23**:e1–6. doi:10.5830/CVJA-2012-048  
14
- 15  
16 14 Chillo P, Bakari M, Lwakatare J. Echocardiographic diagnoses in HIV-infected patients  
17  
18 presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam,  
19  
20 Tanzania. *Cardiovasc J Afr* 2012;**23**:90–7. doi:10.5830/CVJA-2011-060  
21  
22
- 23  
24 15 Miller RF, Kaski JP, Hakim J, *et al.* Cardiac disease in adolescents with delayed  
25  
26 diagnosis of vertically acquired HIV infection. *Clin Infect Dis* 2013;**56**:576–82.  
27  
28 doi:10.1093/cid/cis911  
29
- 30  
31 16 Aliyu ZY, Gordeuk V, Sachdev V, *et al.* Prevalence and risk factors for pulmonary  
32  
33 artery systolic hypertension among sickle cell disease patients in Nigeria. *Am J Hematol*  
34  
35 2008;**83**:485–90. doi:10.1002/ajh.21162  
36  
37
- 38  
39 17 Mokhtar GM, Tantawy AAG, Adly AAM, *et al.* Clinicopathological and radiological  
40  
41 study of Egyptian  $\beta$ -thalassemia intermedia and  $\beta$ -thalassemia major patients: relation to  
42  
43 complications and response to therapy. *Hemoglobin* 2011;**35**:382–405.  
44  
45 doi:10.3109/03630269.2011.598985  
46  
47
- 48  
49 18 Ahmed AEH, Ibrahim AS, Elshafie SM. Pulmonary hypertension in patients with  
50  
51 treated pulmonary tuberculosis: analysis of 14 consecutive cases. *Clin Med Insights Circ*  
52  
53 *Respir Pulm Med* 2011;**5**:1–5. doi:10.4137/CCRPM.S6437  
54  
55
- 56  
57 19 WHO. World Health Organization: The World Health Report 2013: Research for  
58  
59  
60

- 1  
2  
3 Universal Health Coverage. *Euro Surveill* 2013;**18**:20559.  
4  
5  
6 20 Galiè N, Hoeper MM, Humbert M, *et al*. Guidelines for the diagnosis and treatment of  
7  
8 pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary  
9  
10 Hypertension of the European Society of Cardiology (ESC) and the European  
11  
12 Respiratory Society (ERS), endorsed by the International Society of Heart and Lung  
13  
14 Transplantation (ISHLT). *Eur. Heart J.* 2009;**30**:2493–537.  
15  
16 doi:10.1093/eurheartj/ehp297  
17  
18  
19  
20 21 WHO. WHO | International Classification of Diseases (ICD). *WHO* 1994.  
22  
23  
24 22 Henry WL, DeMaria A, Gramiak R, *et al*. Report of the American Society of  
25  
26 Echocardiography Committee on Nomenclature and Standards in Two-dimensional  
27  
28 Echocardiography. *Circulation* 1980;**62**:212–7.  
29  
30  
31 23 Jaffe CC, Weltin G. Echocardiography of the right side of the heart. *Cardiol Clin*  
32  
33 1992;**10**:41–57.  
34  
35  
36 24 Sciomer S, Magri D, Badagliacca R. Non-invasive assessment of pulmonary  
37  
38 hypertension: Doppler-echocardiography. *Pulm Pharmacol Ther* 2007;**20**:135–40.  
39  
40 doi:10.1016/j.pupt.2006.03.008  
41  
42  
43  
44 25 Quiñones MA, Otto CM, Stoddard M, *et al*. Recommendations for quantification of  
45  
46 Doppler echocardiography: a report from the Doppler Quantification Task Force of the  
47  
48 Nomenclature and Standards Committee of the American Society of Echocardiography.  
49  
50 *J Am Soc Echocardiogr.* 2002;**15**:167–84.  
51  
52  
53  
54 26 Schachna L, Wigley FM, Chang B, *et al*. Age and risk of pulmonary arterial  
55  
56 hypertension in scleroderma. *Chest* 2003;**124**:2098–104.  
57  
58  
59  
60

- 1  
2  
3 27 Forfia PR, Fisher MR, Mathai SC, *et al.* Tricuspid annular displacement predicts  
4 survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006;**174**:1034–41.  
5  
6 doi:10.1164/rccm.200604-547OC  
7  
8  
9  
10 28 Nagueh SF, Appleton CP, Gillebert TC, *et al.* Recommendations for the evaluation of  
11 left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*  
12 2009;**10**:165–93. doi:10.1093/ejehocard/jep007  
13  
14  
15  
16  
17  
18 29 Barst RJ, Ertel SI, Beghetti M, *et al.* Pulmonary arterial hypertension: a comparison  
19 between children and adults. *Eur Respir J* 2011;**37**:665–77.  
20  
21 doi:10.1183/09031936.00056110  
22  
23  
24  
25  
26 30 Ivy DD, Abman SH, Barst RJ, *et al.* Pediatric Pulmonary Hypertension. *J Am Coll*  
27 *Cardiol* 2013;**62**:D117–26. doi:10.1016/j.jacc.2013.10.028  
28  
29  
30  
31 31 Penning S, Robinson KD, Major CA, *et al.* A comparison of echocardiography and  
32 pulmonary artery catheterization for evaluation of pulmonary artery pressures in  
33 pregnant patients with suspected pulmonary hypertension. *Am J Obstet Gynecol*  
34 2001;**184**:1568–70.  
35  
36  
37  
38  
39  
40  
41 32 Fisher MR, Forfia PR, Chamera E, *et al.* Accuracy of Doppler echocardiography in the  
42 hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*  
43 2009;**179**:615–21. doi:10.1164/rccm.200811-1691OC  
44  
45  
46  
47  
48  
49 33 Lanzarini L, Fontana A, Campana C, *et al.* Two simple echo-Doppler measurements can  
50 accurately identify pulmonary hypertension in the large majority of patients with chronic  
51 heart failure. *J Heart Lung Transplant* 2005;**24**:745–54.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 34 Laaban JP, Diebold B, Zelinski R, *et al.* Noninvasive estimation of systolic pulmonary  
4 artery pressure using Doppler echocardiography in patients with chronic obstructive  
5 pulmonary disease. *Chest* 1989;**96**:1258–62.  
6  
7  
8  
9  
10  
11 35 Matsuyama W, Ohkubo R, Michizono K, *et al.* Usefulness of transcutaneous Doppler  
12 jugular venous echo to predict pulmonary hypertension in COPD patients. *Eur Respir J*  
13 2001;**17**:1128–31.  
14  
15  
16  
17  
18 36 Farber HW, Foreman AJ, Miller DP, *et al.* REVEAL Registry: correlation of right heart  
19 catheterization and echocardiography in patients with pulmonary arterial hypertension.  
20  
21  
22 *Congest Heart Fail* 2011;**17**:56–64. doi:10.1111/j.1751-7133.2010.00202.x  
23  
24  
25  
26 37 Janda S, Shahidi N, Gin K, *et al.* Diagnostic accuracy of echocardiography for  
27 pulmonary hypertension: a systematic review and meta-analysis. *Heart* 2011;**97**:612–22.  
28  
29  
30  
31  
32  
33  
34 38 Damy T, Goode KM, Kallvikbacka-Bennett A, *et al.* Determinants and prognostic value  
35 of pulmonary arterial pressure in patients with chronic heart failure. *Eur Heart J*  
36 2010;**31**:2280–90. doi:10.1093/eurheartj/ehq245  
37  
38  
39  
40  
41 39 Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic  
42 findings: standards and procedures for measurement and classification. Boston  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
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Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension"; results are displayed annually between 1970 and 2013.  
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Review only

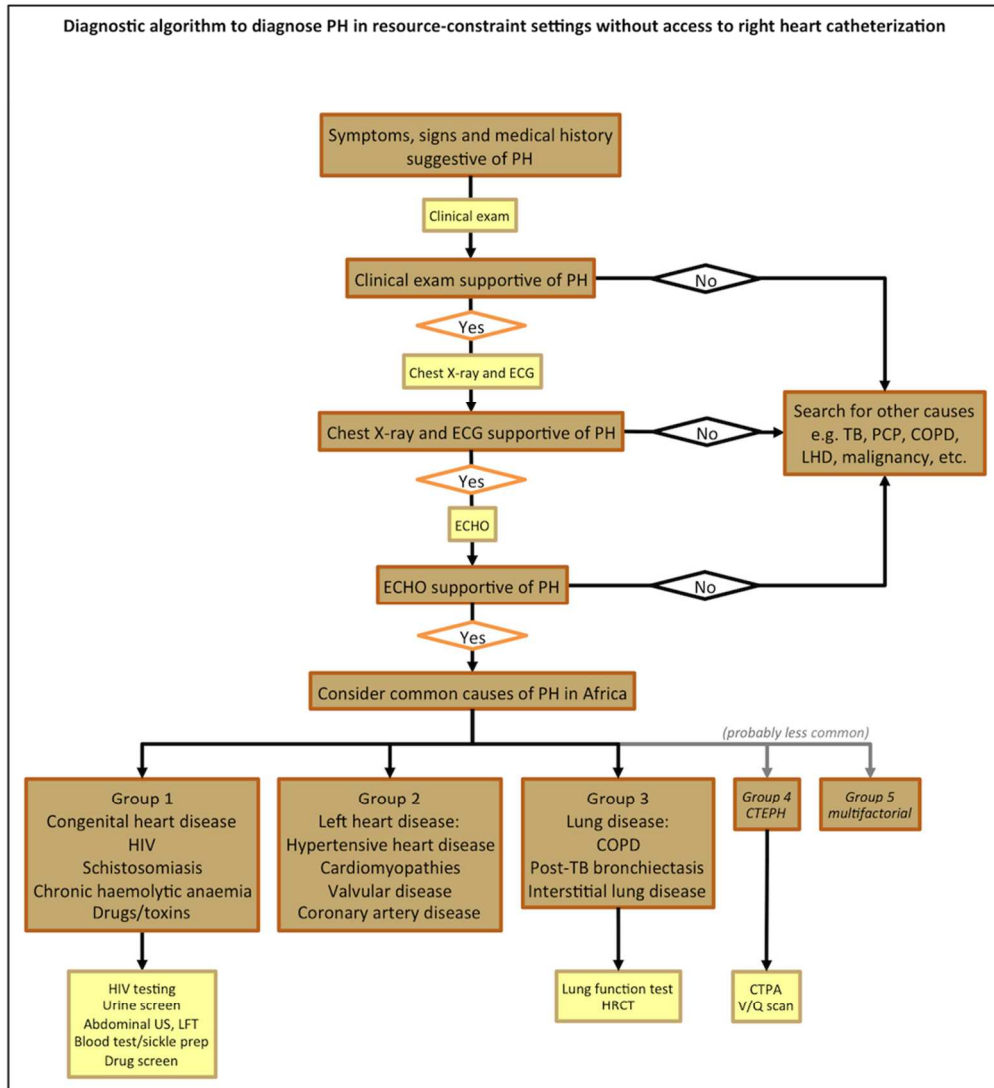
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### PAPUCO Map

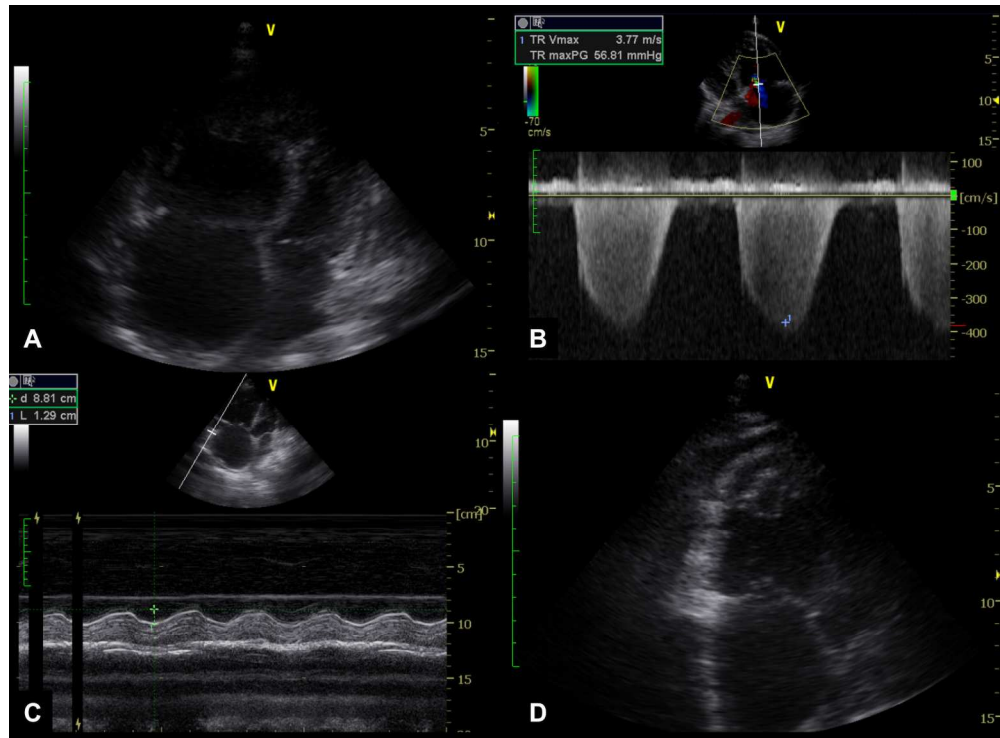


The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).  
90x99mm (300 x 300 DPI)





Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus; US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan  
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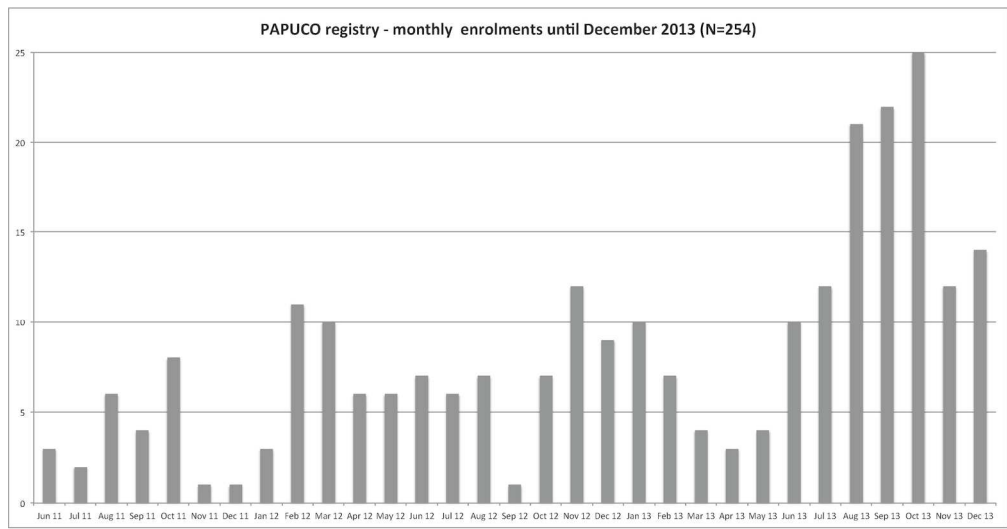


Diagnosing pulmonary hypertension using transthoracic 2D-Doppler Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-wave Doppler across the TV in the 4-chamber view showing severe TR, despite the deceptively less impressive color-flow jet seen across the valve; C: M-Mode measurement of TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left atrium; TV: tricuspid valve; TR: tricuspid regurgitation.

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PAPUCO registry - monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.  
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# BMJ Open

## RATIONALE AND DESIGN OF THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA



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# **RATIONALE AND DESIGN OF THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA**

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### Running Title

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## ABSTRACT

### Introduction

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure. Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared to developed countries due to the high prevalence of risk factors in the region.

### Methods and Analysis

A multinational multicentre registry-type cohort study was established and tailored to resource-constraint settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa. PH will be diagnosed by specialist cardiologists using Echocardiography (RVSP>35 mmHg, absence of pulmonary stenosis and acute right heart failure) usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, electrocardiogram and chest x-ray changes in keeping with PH as per guidelines (ESC/ERS guidelines). Additional investigations such as CT-scan, ventilation/perfusion scan or right heart catheterisation will be performed at the discretion of the treating physician. Functional tests include 6-minute walk test and Karnofsky Performance Score. The WHO classification system for PH will be applied to describe the different aetiologies of PH. Several sub-studies have been implemented within the registry to investigate specific types of PH and their outcome at up to 24 months. Data will be analysed by an independent institution following a data analyse plan.

## Ethics and Dissemination

All local Ethics Committees of the participating centres approved the protocol. The data will be disseminated through peer-reviewed journals, at national and international conferences and public events at local care providers.

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## ARTICLE SUMMARY

### Article focus

- In this manuscript we aim to provide an overview of pulmonary hypertension in Africa and the epidemiology of risk factors prevalent in the region.
- We aim to answer the question why Africa needs a registry for pulmonary hypertension.
- We describe how we implemented the registry in scarce resources settings.

### Key messages

- Risk factors for pulmonary hypertension are highly endemic in Africa.
- The incidence of pulmonary hypertension is expected to be higher in Africa compared to developed countries.
- A diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings without access to right heart catheterisation has been developed.
- 12 centres are participating in the Pan African Pulmonary hypertension Cohort (PAPUCO) study and more than 250 patients have been recruited so far.

### Strengths and limitations of this study

- The PAPUCO study is the first multinational registry on pulmonary hypertension in Africa.
- PAPUCO centres have different levels of medical infrastructure and not all patients underwent the same rigorous work-up.

## INTRODUCTION

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure (RHF).[1] The epidemiology of PH in Africa and the distribution of its multitude of aetiologies has not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region.[2-5] Many known risk factors for PH are hyperendemic in this part of the world, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary haemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary disease, PH and, often, to RHF with premature death. Also a lack of specialist paediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH.[6] Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH.[6-8] However, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive RHF.[4,9] Thus, within the registry we expect the entire spectrum of aetiologies of PH. In this manuscript, we aim to provide an overview of PH in Africa and the epidemiology of risk factors prevalent in the region, and answer the question why Africa needs a registry for PH just as much as most other parts of the world and how we implemented it in the setting of scarce resources.

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5 **Preliminary evidence of a significant burden of pulmonary hypertension and its risk**  
6 **factors in Africa**  
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10 In recent years, there has been increasing awareness of the clinical significance of PH and cor  
11 pulmonale in Africa. This applies equally to the recognition of the importance of PH and  
12 RHF as both a primary diagnosis and as a poor prognostic marker for those primarily affected  
13 by left-sided heart failure. Data on the precursors and risk factors of those conditions are  
14 limited to few reports. The largest study on PH/RHF in Africa has been conducted within *the*  
15 *Heart of Soweto Study* in South Africa; 2505 patients presented with *de novo* heart failure  
16 between 2006-2008.[5] Of those 697 (28%) were diagnosed with PH/RHF. PH/RHF was the  
17 primary diagnosis in 50% of those patients. The majority presented with dyspnoea and a  
18 mean right ventricular systolic pressure (RVSP) above 50 mmHg. Left heart disease (31%),  
19 chronic lung disease due to Chronic Obstructive Pulmonary Disease (COPD) and  
20 tuberculosis (26%), and pulmonary arterial hypertension (PAH) (20%) due to HIV (HIV-  
21 PAH), CHD, or idiopathic PAH were the most common causes of PH. Sani et al. described  
22 the prevalence of PH in patients with RHD at a tertiary centre in Nigeria.[10] Of 1312  
23 Echocardiography (ECHO) studies 10% had evidence of RHD; secondary PH was present in  
24 80% of patients with RHD. The same centre reported on 53 patients with PH on ECHO  
25 among 80 patients admitted with heart failure with hypertensive heart disease (25%),  
26 peripartum cardiomyopathy (25%), dilated cardiomyopathy (17%), and RHD (13%) being  
27 the most common causes of PH.[11] A study from Uganda showed a prevalence of PH in  
28 patients with newly diagnosed RHD (n=309) of 33%.[12] A smaller survey from Lagos,  
29 Nigeria investigated the prevalence of cardiovascular disease in an HIV-positive cohort and  
30 found one patient of 100 patients to have HIV-PAH.[13] An ECHO study on 102 HIV-  
31 patients presenting with cardiac symptoms in Tanzania revealed PH in 13%.[14] PH with a  
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3 RVSP>30 mmHg was present in 4% of long-term survivors in a Zimbabwe cohort of  
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5 vertically acquired HIV infection.[15] Haemolytic anaemia is a known risk factor for PH; a  
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7 screening study of patients with sickle-cell disease (SCD) in Nigeria showed a PH prevalence  
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9 of 25%;[16] a study from Egypt indicates that patients with  $\beta$ -Thalassaemia are at risk of  
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11 PH.[17] Another study from Egypt found a PH prevalence of 9% in patients seropositive for  
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13 schistosomal antibodies. Ahmed et al. from Sudan described 14 consecutive cases of PH with  
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15 previously treated pulmonary TB and conclude that PH can even occur after resolution of TB,  
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17 most like due to persistent lung destruction.[18] This data suggests that left heart disease,  
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19 chronic lung disease, RHD, HIV, schistosomiasis and SCD might be the most common  
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21 underlying diseases to cause PH within the spectrum of aetiologies of PH that we will find  
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23 within the Pan African Pulmonary hypertension Cohort (PAPUCO)  
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## 30 **RATIONALE AND OBJECTIVES**

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32 Worldwide, PH has received great increase in awareness at the beginning of the 21<sup>st</sup> century,  
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34 but less than one per cent of the publications are from Africa (Figure 1). It is expected that  
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36 PH is more prevalent in Africa compared to developed countries, but little information is  
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38 available about African patients with PH. Exposure to risk factors, human genetic variation,  
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40 different socio-economic backgrounds, lifestyles, co-morbidities, nutrition and disparities in  
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42 access to health services makes the African population unique, but heterogeneous at the same  
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44 time. Therefore, most research data and clinical guidelines from high-income countries  
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46 cannot be translated into the African context. It is within the context described above that the  
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48 Pan African Pulmonary hypertension Cohort (PAPUCO), a Pan Africa registry-type cohort  
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50 study, was established (Figure 2).  
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54 Scientific and clinical research has been fundamental in improving human health.[19] In fact,  
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56 research has demonstrated to be an excellent vehicle to implement new technologies and to  
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3 facilitate training for its use, and to develop new systems and establish the services around it -  
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5 jointly leading to technical improvement, sharpening of skills and capacity  
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7 development[20,21]. Besides the main objectives of the PAPUCO registry to define and  
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9 understand PH in Africa (Box 1), this multinational and multicentre research project therefore  
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11 aims to also develop sustainable clinical and research capacity across the African continent as  
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13 well as raising awareness for PH and its risk factors.  
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19 Box 1: PAPUCO objectives

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21 *Primary objective*

- To describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa

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25 *Secondary objectives*

- To describe the overall 6-month survival rate
- To describe the 24-month survival rate in patients with HIV-PAH
- To compare 6-month survival rates between different groups of PH
- To determine the predictors of mortality across the different groups.

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33 Abbreviations: PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; HIV, human  
34 immunodeficiency virus  
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38 The prevalence of PH in Africa varies geographically, according to underlying risk factors  
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40 and diseases and the diagnosis of PH is most likely often missed, not only during early stages  
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42 due to the subtle nature of presentation of PH, but also at more advanced stage of disease due  
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44 to lack of awareness by primary care doctors and low index of suspicion, limited access to  
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46 ECHO services and tertiary care. However, it is crucial to diagnose PH in Africa early and  
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48 reliably to ensure better care for these patients (Box 2).  
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54 Box 2: The significance of PH in Africa: Why we need to diagnose?

- The right to know

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- Prognostic implications
- Access to tertiary care: heart failure management, anticoagulation, home oxygen, COPD management, access to PH-specific drugs (Sildenafil)
- Access to cardiothoracic surgery: valve repair/replacement, correction of congenital heart disease, heart transplantation
- Access to social and disability grants
- To raise awareness of PH and its risk factors

Abbreviations: PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease

## METHODS AND ANALYSIS

### Study design and setting

The Pan African Pulmonary hypertension Cohort (PAPUCO) research group was established in 2011 with the aim to implement a registry-type cohort study on pulmonary hypertension in Africa. The registry aims to recruit consecutive patients 1) with newly diagnosed PH based clinical and ECHO criteria, 2) are able or likely to return for 6-month follow-up, 3) are at least 18 years old (except for paediatric centres in Mozambique and Nigeria), and 4) consented in writing to participate in the registry. Centre eligibility include 1) availability of ECHO and training in assessing right heart function, 2) experience in diagnosing PH according to WHO classification, 3) experience in clinical management of patients with right heart failure, and 4) resources to review patients at 6-month follow-up. Participating centres will be invited to join the registry at African cardiac meetings and conferences.

### Definition of pulmonary hypertension, diagnostic algorithm and data points

As shown in Box 3, PH is defined as documented elevated RVSP>35 mmHg on trans-thoracic ECHO in the absence of pulmonary stenosis and acute right heart failure; usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, and possibly electrocardiogram (ECG) and chest x-ray (CXR) changes in keeping with PH as per European Society of Cardiology and European Respiratory Society



(ESC/ERS) guidelines on pulmonary hypertension.[5,22] Right heart catheterisation is optional. The updated WHO classification system for PH (Dana Point 2008) will be applied to describe the different aetiologies of PH[22,23]. Once definitive assessment and treatment has been applied, the following specific data will be documented for each individual: a) all major cardiovascular diagnoses according ICD 10 coding, and b) up to five non-cardiovascular diagnoses according ICD 10 coding.[24] Figure 3 shows the diagnostic algorithm to diagnose PH in resource-constraint settings without access to right heart catheterisation that has been developed following the ESC/ERS guidelines for the diagnosis of PH.[22] Key information collected will include information on demographic profile, socio-economic background, medical history, co-morbidities, cardiac risk factors, and environmental exposures. The clinical aspects of the assessment include symptoms scoring, a full clinical examination, physical and clinical status; functional tests include WHO functional class (WHO FC), 6-minute walk test (6MWT) and Karnofsky Performance Score. Technical procedures include ECHO, CXR, and 12-lead ECG. Further investigations are at the discretion of the treating physician and typically include lung function tests, ventilation/perfusion lung scans, and high resolution computed tomography and computed tomography pulmonary angiography, and right heart catheterization, if available (Figure 3). Data on heart failure treatment and co-medication, hospitalization and death, and 6-month outcome will also be collected.

Box 3: Evidence to diagnose PH in resource-constraint settings

- Symptoms: SOB, fatigue, cough, chest pain, palpitations
- Clinical exam: raised JVP, peripheral oedema, ascites, loud p2, systolic murmur, central cyanosis
- ECG: sinus tachycardia, p-pulmonale, right axis deviation, right bundle branch block, RVH
- CXR: cardiomegaly, pleural effusion, prominent pulmonary arteries
- ECHO: dilated right atrium and ventricle, interventricular septal flattening, RVSP>35 mmHg, TAPSE<15 mm

Abbreviations: SOB, shortness of breath; JVP, jugular vein pressure; ECG, electrocardiogram; RVH, right ventricular hypertrophy; CXR, chest X-ray; ECHO, Echocardiography; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion

### *Echocardiography*

#### Echocardiography in adults

ECHO modalities applied included M-mode, two dimensional (2D) and Doppler studies.

ECHO will be done with 3 to 5 MHz sector transducer. Complete 2D ECHO examination will be performed according to the recommendations of the American Society of ECHO (ASE).[25] M-mode ECHO will be derived from 2D images. The M-mode cursor on the 2D scan will move to specific areas of the heart to obtain measurements according to the recommendation of the committee on M-mode standardization of the ASE. Doppler indices of left ventricular (LV) diastolic filling will be obtained. Complete Doppler study will be done according to the recommendations of the ASE. From the M-mode measurements, indices of LV function will be derived. These include shortening fraction, ejection fraction (EF), and LV mass, cardiac output and relative wall thickness. ECHO examinations include (a) valvular assessment, (b) left atrial size, (c) left ventricular size and function, (d) a semi quantitative estimate of the severity of valvular regurgitation, (e) size and function of the right atrium and ventricle and (f) evidence of pulmonary hypertension. Doppler will be used to examine the valves on suspicion of any valvular lesion. ECHO findings associated with PH includes dilated pulmonary artery and dilation and hypertrophy of the right ventricle (RV), diastolic flattening of the interventricular septum and Doppler evidence of PH.[26] Doppler ECHO estimates pulmonary artery systolic pressure (PASP). By measuring the maximum velocity of the tricuspid regurgitant jet ( $v$ ), the transtricuspid pressure gradient will be calculated using the modified Bernoulli equation ( $4v^2$ ).[27] The PASP is approximated by adding the transtricuspid gradient to the right atrial pressure (RAP) as applied in the formula  $[PASP=4v^2+RAP]$ . The PASP is equivalent to RVSP in the absence of pulmonary outflow

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3 obstruction. The RAP is estimated by the respiratory variation size of the vena cava inferior  
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5 in M-mode.[28] In our study, the systolic regurgitant tricuspid flow will be assessed in the  
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7 parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views to  
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9 determine the highest velocity, which reflects PASP/RVSP.[29] PH is defined as *mild* if  
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11 RVSP was 36-50 mmHg, *moderate* if RVSP was 51-60 mmHg and *severe* if RVSP was >60  
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13 mmHg.[30] In addition, we further assessed right ventricular function by measuring the  
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15 systolic displacement of the lateral portion of the tricuspid annular plane excursion (TAPSE)  
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17 on the M-mode tracing under the 2D-echo guidance.[31] Peak mitral early diastolic velocity  
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19 (E in m/s), the E-wave deceleration time (DCT in ms) and the velocity at atrial contraction (A  
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21 in m/s) are measured using pulsed-wave Doppler. Left ventricular filling pressure classes  
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23 were defined in accordance with the ASE 2009 guidelines.[32] In patients with heart failure  
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25 and reduced ejection fraction (HFrEF) raised LV filling pressure is defined as E/A  $\geq 2$  if in  
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27 sinus rhythm or DCT <150 ms if in atrial fibrillation (AF); normal LV filling pressure is  
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29 defined as E/A <1 in patients in sinus rhythm or DCT  $\geq 200$  ms for those in AF; patients  
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31 between these limits will be classified as undetermined. In heart failure and preserved  
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33 ejection fraction (HFpEF), LV filling pressure is classified as follows: raised LV filling  
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35 pressure if left atrium is dilated and normal LV filling pressure if left atrium has normal size.  
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#### 43 Echocardiography in infants and children

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45 Translating the definitions of PH in adults to children, especially to infants, is controversial.  
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47 Within the paediatric cardiology community experts suggest that the ratio of the PASP to the  
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49 systemic systolic blood pressure >0.4 should be the diagnostic criterion.[33] The fact that the  
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51 threshold of pulmonary vascular resistance (PVR) increase has not been included in the  
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53 abovementioned definition is another limitation to its use in children or infants, since  
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55 paediatric PH is mainly caused by left-to-right shunt congenital heart disease; and if PVR  
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3 shows no significant increase in such cases, the patient may be considered only as a dynamic  
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5 PH case led by increased pulmonary blood flow, rather than pulmonary vascular disease.  
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8 Paediatric guidelines suggest that  $mPAP > 25$  mmHg and  $PVR > 3$  Wood units remain in the  
9  
10 definition of PAH.[34] In our cohort of children with congenital heart malformations we not  
11  
12 only used tricuspid and pulmonary regurgitation envelopes, but also the flow across the  
13  
14 ventricular septal defect or persistent ducts arteriosus to measure the gradient between the  
15  
16 two circulations and therefore estimate the pulmonary pressure. Indirect signs of PH such as  
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18 dilatation of the RV, RV-hypertrophy and dilatation of the main pulmonary artery were  
19  
20 added to Doppler data to confirm the diagnosis.  
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### 23 24 25 *Accuracy of Echocardiography in the diagnosis of PH*

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27 Diagnosing PH is challenging when relying on bedside tests. RHC is the gold standard to  
28  
29 diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear  
30  
31 excessive risks and be impractical in any cost-constrained environment. Also RHC is only  
32  
33 available at very few centres in Africa. A viable device to diagnose PH in Africa needs to be  
34  
35 widely available, accurate, safe, and cost-effective. ECHO has become increasingly available  
36  
37 in Africa and reliably allows the measurements to describe functional and morphologic  
38  
39 features of PH and to indirectly measure the pressures in the pulmonary artery; hence, to  
40  
41 diagnose PH. Nonetheless, the exact measurements of the mean and systolic pulmonary  
42  
43 artery are not possible, the PASP remains estimate, and the use of ECHO to diagnose PH  
44  
45 questionable.[35,36] A number of possible explanations for this “inaccuracy” merit attention:  
46  
47 1) conditions for a reproducible calculation of PASP/RVSP include the presence of sufficient  
48  
49 TR to produce a Doppler envelope and appropriate gain adjustments. An “undergained”  
50  
51 spectral signal will tend to result in underestimated PASP whereas an “overgained” spectral  
52  
53 signal might overestimate the measurements; 2) careful adjustment of the transducer position  
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3 and the use of colour flow Doppler are critical in order to reduce the Doppler angle and to  
4  
5 obtain the maximal regurgitant flow velocity and severe TR will cause a laminar flow which  
6  
7 invalidates the Bernoulli equation; 3) volume status and systemic blood pressure are other  
8  
9 factors that potentially influence the measurement of PASP; and 4) the highest value of RAP  
10  
11 in the ASE guidelines is 15 mmHg, but RAP measured by RHC can exceed 15 mmHg. In  
12  
13 spite of all these shortcomings, several studies have been published in the literature  
14  
15 demonstrating good sensitivity and specificity of ECHO versus RHC.[37-39] In the  
16  
17 REVEAL registry, there was a good correlation in PASP between ECHO and RHC at  
18  
19 baseline, even if repeated ECHO measurements alone were not sufficient to monitor changes  
20  
21 in PASP or progression of PH.[40] In the first systematic review and meta-analysis  
22  
23 addressing the diagnostic accuracy of ECHO in PH by Janda and colleagues, the authors  
24  
25 concluded that the correlation of PASP by ECHO compared to PASP by RHC was good with  
26  
27 a summary correlation coefficient of 0.70 (95% CI 0.67 to 0.73).[41] Also, the authors  
28  
29 showed that the diagnostic accuracy of ECHO in PH was also acceptable with a summary  
30  
31 sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85),  
32  
33 respectively. Additionally, Dany and colleagues demonstrated in their recent work that PASP  
34  
35 when measured in “good ECHO hands” is a strong predictor of mortality.[42] Last but not  
36  
37 the least, easily obtainable ECHO parameters like E/A ratio, DCT, LA size can reliably  
38  
39 distinguish between PH due to lung disease and PH due to left heart disease, allowing for  
40  
41 rapid triage of patients with need for RHC. In summary, ECHO is far beyond a good  
42  
43 modality to confirm both the presence and aetiology of PH in the majority of suspected cases  
44  
45 when performed and interpreted by the requisite expertise under incorporation of all  
46  
47 information obtained during a detailed ECHO assessment. ECHO will always provide  
48  
49 incremental information in PH that cannot be obtained using RHC, whether in developed or  
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51 developing countries.  
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### Data cleaning process and statistical analysis

All study data will be collected on electronic case report forms and stored on a dedicated secure central database. Cases will be reviewed by at least two investigators (FT, AD, KS, AOM) for completeness and data validated. Query reports will be sent to the sites and resolved by the site investigators. If consensus on the WHO classification of PH cannot be reached, a third investigator's opinion will be requested. Data will then be verified and transferred to SPSS Statistics 17.0 for all analyses by an independent team at Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Normally distributed continuous data will be presented as mean  $\pm$  standard deviation and non-Gaussian distributed variables as median plus interquartile range. Categorical data will be presented as percentages with 95% confidence intervals (CI) where appropriate. For patient group comparisons, we will use Chi Square ( $\chi^2$ ) analysis with calculation of odds ratios (OR) and 95% CI (where appropriate) for discrete variables and Students t-test and analysis of variance for normally distributed continuous variables. Multiple logistic regression analyses (entry model) will be performed on age, sex and baseline risk factors to derive adjusted ORs for the risk of presenting with PH/RHF overall, chronic lung disease and PH WHO Group 1. Significance will be accepted at the two-sided level of 0.05. ECG analysis will be subject to blinded coding according to published Minnesota criteria to determine any pathological abnormalities.[43] We aim to adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for this type of study wherever possible.[44]

### PAPUCO sub-studies

Several sub-studies have been established within the PAPUCO registry. The ECHO sub-study aims to describe in detail the ECHO characteristics of right ventricular function in PH.

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3 The HIV-PAH sub-study aims to describe the phenotype of HIV-PAH in Africa. The  
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5 congenital heart disease and rheumatic heart disease sub-studies aim to describe the  
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7 contribution of congenital heart disease and rheumatic heart disease to PH in Africa. In  
8  
9 addition, serum will be collected at selected centres for studies on biomarker profile. The  
10  
11 HIV.INFLAME sub-study aims to examine the role of inflammatory markers and oxidative  
12  
13 stress on the development of HIV-PAH. We hypothesizing that HIV-positive patients with  
14  
15 PH have a pro-inflammatory state and raised markers of oxidative stress compared to healthy  
16  
17 HIV-positive controls and that increased markers of inflammation and oxidative stress and  
18  
19 decreased antioxidant capacity are predictors of outcome and indicators of disease severity.  
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### 25 **Ethics and dissemination**

26  
27 All PAPUCO centres require ethical approval from their local ethics committee review board.  
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29 Written informed consent must be obtain from every patient participating in the registry.  
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31 Study results will be disseminated in peer-reviewed journals. The first publication will  
32  
33 include baseline and 6-month follow-up data from all centres. Sub-study publications on the  
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35 HIV-cohort with 24-month follow-up and the cohort of patients with PH due to left heart  
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37 disease will be published after recruitment and follow-up has been completed. Laboratory-  
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39 based research will be published after work is completed.  
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### 45 **The online data collection platform**

46  
47 A tailor-made databases has developed by *integerafrica research and development* to fulfil  
48  
49 the study requirements. Open-source technology was used to develop the web-based system  
50  
51 that allows investigators to collect, store, analyse, report on and exports clinical research data.  
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53 The interface is simple and user friendly and leads the user through the data entry process. It  
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55 anonymises personal patient data: data is stored as electronic case report forms on a secure,  
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encrypted and backed-up server. It provides hierarchic permissions and validation at the point of data entry. Multimedia data formats, i.e. scans of ECGs, CXRs, and ECHO images can be uploaded on the platform, allowing storage of complete clinical records and data together.

Tools for education, training, and communication are installed within the web-portal.

Frequently Asked Questions serve as a guide on how to the use of the platform. After secure login, documents such as paper case report forms, informed consent forms, study information sheets and patient education sheets on PH are available for download. All data can be exported in various formats for further analysis. The platform has been developed to cater for mobile Internet connectivity available in most parts of Africa and a unique research platform far beyond a simple web-based database.

### Recruitment process

Twelve centres have received ethics approval and are currently actively recruiting; additional six countries are showing interest in joining the registry (Figure 2). All centres are government-run public health care institutions with different medical infrastructure profiles and all but one are cardiac centres within tertiary care hospitals (Table 1); one centre is an infectious diseases referral clinic in South Africa. At total of 254 patients have been recruited until December 2013 (Figure 5).

Table 1: Medical infrastructure at PAPUCO centres - diagnostic equipment and medical services

Centre	ECG	CXR	ECHO	RHC	CS	HRCT	CTPA	LFT	V/Q	Lab
CM01	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
CM02	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>					X <sup>1</sup>
CM03	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>							X <sup>1</sup>
MZ01	X	X	X							X
MZ02	X	X	X			X		X		X



NG01	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>		X <sup>1</sup>		X <sup>1</sup>
NG02	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
NG03	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
NG04	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>							X <sup>1</sup>
NG05	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
SA01	X	X	X	X	X	X	X	X	X	X
SA02	X	X	X			X	X			X

Abbreviations: CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG01, Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; NG04, Department of Medicine, University of Uyo Teaching Hospital, Uyo, Nigeria; NG05, Federal Medical Centre, Umuahia, Nigeria; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg, South Africa and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa. ECG, electrocardiogram; CXR, chest X-ray; ECHO, Echocardiography; RHC, right heart catheterisation; CS, cardiac surgery; HRCT, high resolution computed tomography; CTPA, computed tomography pulmonary angiography; LFT, lung function tests; V/Q, ventilation/perfusion lung scan; Lab, laboratory facility for haematology, chemistry, and microbiology; X, equipment/service available at the centre and free-of-charge for the patients; X<sup>1</sup>, patients have to cover the costs for the service (out of pocket payments).

## LIMITATIONS

The PAPUCO registry is an example of a functioning registry in low-resource settings.

Limited resources should therefore not be seen as a limitation, but rather as a development opportunity. PAPUCO centres have different levels of medical infrastructure and not all patients will undergo the same rigorous work-up in all centres - especially when compared to developed countries. Therefore, the clinical skills of the treating physician are often more important (and valuable!) than an additional diagnostic test in order to pin down the aetiology of PH in a patient. Moreover, patients often have to pay out of their pocket for diagnostic tests and therefore accessibility to tests is limited due to the financial means of the patient. Although we aim for consecutive patient enrolment at each centre, we understand that this is often not feasible due to high patient volume and workload of doctors.

**SUMMARY**

PAPUCO is a contemporary registry on PH in Africa using high international standards to diagnose PH. It will provide new insight on PH in Africa and ultimately improve diagnosis and care of patients. PAPUCO is already a showcase for registry activities in Africa and a vehicle to capacity generation and sustainable development in the health care sector. It interconnects health centres far beyond pulmonary hypertension.

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## CONTRIBUTORS

KS, AOM, FT were responsible for the initial idea, literature review, and study design and planning. All authors have contributed to the setup of the PAPUCO registry and have contributed to various aspects of the study design with input relating to their specific expertise in the field. FT, AD, AOM, LB, MUS, KMK, OSO, AM, PU, ASI, AD, KS have developed the study protocol, FT and KS wrote the study protocol, FT developed the database, FT, AD, AOM, KS cleaned the database, LB trained the doctors in Echocardiography of the heart and developed the Echo protocol, AD trained doctors in Cameroon, OSO trained doctors in Nigeria, SS developed the statistical analysis plan. FT, AD, AOM, MUS, KMK, OSO, IM, AM, PU, KT, RB, AD, KS were substantially involved in data acquisition. All authors read and approved the final manuscript.

## COMPETING INTEREST

We declare no competing interest.

## ETHICS APPROVAL

All centres received ethics approval from their local ethics committees.

## FUNDING

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## LEGENDS OF FIGURES

Figure 1: Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Less than one per cent (0.7%) of the publications were from Africa (not displayed). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension" and Africa and African country names; results are displayed annually between 1970 and 2013.

Figure 2: The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).

Figure 3: Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus; US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan

Figure 4: Diagnosing pulmonary hypertension using transthoracic 2D-Doppler Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-

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2  
3 wave Doppler across the TV in the 4-chamber view showing severe TR, despite the  
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5 deceptively less impressive color-flow jet seen across the valve; C: M-Mode measurement of  
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7 TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right  
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9 ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left  
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11 atrium; TV: tricuspid valve; TR: tricuspid regurgitation.  
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16 Figure 5: PAPUCO registry - monthly enrolment until December 2013. Number of patients  
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18 recruited per month since the launch of the registry in May 2011.  
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## REFERENCES

- 1 Simonneau G, Gatzoulis MA, Adatia I, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;**62**:D34–41. doi:10.1016/j.jacc.2013.10.029
- 2 Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. *Eur Heart J* 2013;**34**:3538–46. doi:10.1093/eurheartj/eh388
- 3 Sliwa K, Carrington MJ, Becker A, *et al.* Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J* 2012;**33**:866–74. doi:10.1093/eurheartj/ehr398
- 4 Sliwa K, Wilkinson D, Hansen C, *et al.* Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet* 2008;**371**:915–22. doi:10.1016/S0140-6736(08)60417-1
- 5 Stewart S, Mocumbi AO, Carrington MJ, *et al.* A not-so-rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort. *Eur J Heart Fail* 2011;**13**:1070–7. doi:10.1093/eurjhf/hfr108
- 6 Mocumbi AO, Lameira E, Yaksh A, *et al.* Challenges on the management of congenital heart disease in developing countries. *Int J Cardiol* 2011;**148**:285–8. doi:10.1016/j.ijcard.2009.11.006
- 7 Sliwa K, Mocumbi AO. Forgotten cardiovascular diseases in Africa. *Clin Res Cardiol* 2010;**99**:65–74. doi:10.1007/s00392-009-0094-1
- 8 Sliwa K, Carrington M, Mayosi BM, *et al.* Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. *Eur Heart J* 2010;**31**:719–27. doi:10.1093/eurheartj/ehp530
- 9 Stewart S, Wilkinson D, Hansen C, *et al.* Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. *Circulation* 2008;**118**:2360–7. doi:10.1161/CIRCULATIONAHA.108.786244
- 10 Sani MU, Karaye KM, Borodo MM. Prevalence and pattern of rheumatic heart disease in the Nigerian savannah: an echocardiographic study. *Cardiovasc J Afr* 2007;**18**:295–9.
- 11 Karaye KM, Saidu H, Bala MS, *et al.* Prevalence, clinical characteristics and outcome of pulmonary hypertension among admitted heart failure patients. *Ann Afr Med* 2013;**12**:197–204. doi:10.4103/1596-3519.122685
- 12 Okello E, Wanzhu Z, Musoke C, *et al.* Cardiovascular complications in newly diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda. *Cardiovasc J Afr* 2013;**24**:80–5. doi:10.5830/CVJA-2013-004
- 13 Olusegun-Joseph DA, Ajuluchukwu JNA, Okany CC, *et al.* Echocardiographic patterns

- 1  
2  
3 in treatment-naïve HIV-positive patients in Lagos, south-west Nigeria. *Cardiovasc J Afr*  
4 2012;**23**:e1–6. doi:10.5830/CVJA-2012-048  
5  
6 14 Chillo P, Bakari M, Lwakatare J. Echocardiographic diagnoses in HIV-infected patients  
7 presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam,  
8 Tanzania. *Cardiovasc J Afr* 2012;**23**:90–7. doi:10.5830/CVJA-2011-060  
9  
10 15 Miller RF, Kaski JP, Hakim J, *et al.* Cardiac disease in adolescents with delayed  
11 diagnosis of vertically acquired HIV infection. *Clin Infect Dis* 2013;**56**:576–82.  
12 doi:10.1093/cid/cis911  
13  
14 16 Aliyu ZY, Gordeuk V, Sachdev V, *et al.* Prevalence and risk factors for pulmonary  
15 artery systolic hypertension among sickle cell disease patients in Nigeria. *Am J Hematol*  
16 2008;**83**:485–90. doi:10.1002/ajh.21162  
17  
18 17 Mokhtar GM, Tantawy AAG, Adly AAM, *et al.* Clinicopathological and radiological  
19 study of Egyptian  $\beta$ -thalassemia intermedia and  $\beta$ -thalassemia major patients: relation to  
20 complications and response to therapy. *Hemoglobin* 2011;**35**:382–405.  
21 doi:10.3109/03630269.2011.598985  
22  
23 18 Ahmed AEH, Ibrahim AS, Elshafie SM. Pulmonary hypertension in patients with  
24 treated pulmonary tuberculosis: analysis of 14 consecutive cases. *Clin Med Insights Circ*  
25 *Respir Pulm Med* 2011;**5**:1–5. doi:10.4137/CCRPM.S6437  
26  
27 19 WHO. World Health Organization: The World Health Report 2013: Research for  
28 Universal Health Coverage. *Euro Surveill* 2013;**18**:20559.  
29  
30 20 Chu KM, Jayaraman S, Kyamanywa P, *et al.* Building research capacity in Africa:  
31 equity and global health collaborations. *PLoS Med* 2014;**11**:e1001612.  
32  
33 21 Noormahomed EV, Mocumbi AO, Preziosi M, *et al.* Strengthening research capacity  
34 through the medical education partnership initiative: the Mozambique experience. *Hum*  
35 *Resour Health* 2013;**11**:62. doi:10.1186/1478-4491-11-62  
36  
37 22 Galiè N, Hoepfer MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of  
38 pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary  
39 Hypertension of the European Society of Cardiology (ESC) and the European  
40 Respiratory Society (ERS), endorsed by the International Society of Heart and Lung  
41 Transplantation (ISHLT). *Eur. Heart J.* 2009;**30**:2493–537.  
42 doi:10.1093/eurheartj/ehp297  
43  
44 23 Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of  
45 pulmonary hypertension. *J Am Coll Cardiol* 2009;**54**:S43–54.  
46 doi:10.1016/j.jacc.2009.04.012  
47  
48 24 WHO. WHO | International Classification of Diseases (ICD). *WHO* 1994.  
49  
50 25 Henry WL, DeMaria A, Gramiak R, *et al.* Report of the American Society of  
51 Echocardiography Committee on Nomenclature and Standards in Two-dimensional  
52 Echocardiography. *Circulation* 1980;**62**:212–7.  
53  
54 26 Jaffe CC, Weltin G. Echocardiography of the right side of the heart. *Cardiol Clin*  
55  
56  
57  
58  
59  
60

- 1  
2  
3 1992;**10**:41–57.  
4  
5 27 Sciomer S, Magri D, Badagliacca R. Non-invasive assessment of pulmonary  
6 hypertension: Doppler-echocardiography. *Pulm Pharmacol Ther* 2007;**20**:135–40.  
7 doi:10.1016/j.pupt.2006.03.008  
8  
9 28 Beigel R, Cercek B, Luo H, *et al*. Noninvasive evaluation of right atrial pressure. *J Am*  
10 *Soc Echocardiogr* 2013;**26**:1033–42. doi:10.1016/j.echo.2013.06.004  
11  
12 29 Quiñones MA, Otto CM, Stoddard M, *et al*. Recommendations for quantification of  
13 Doppler echocardiography: a report from the Doppler Quantification Task Force of the  
14 Nomenclature and Standards Committee of the American Society of Echocardiography.  
15 *J Am Soc Echocardiogr*. 2002;**15**:167–84.  
16  
17 30 Schachna L, Wigley FM, Chang B, *et al*. Age and risk of pulmonary arterial  
18 hypertension in scleroderma. *Chest* 2003;**124**:2098–104.  
19  
20 31 Forfia PR, Fisher MR, Mathai SC, *et al*. Tricuspid annular displacement predicts  
21 survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006;**174**:1034–41.  
22 doi:10.1164/rccm.200604-547OC  
23  
24 32 Nagueh SF, Appleton CP, Gillebert TC, *et al*. Recommendations for the evaluation of  
25 left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*  
26 2009;**10**:165–93. doi:10.1093/ejehocard/jep007  
27  
28 33 Barst RJ, Ertel SI, Beghetti M, *et al*. Pulmonary arterial hypertension: a comparison  
29 between children and adults. *Eur Respir J* 2011;**37**:665–77.  
30 doi:10.1183/09031936.00056110  
31  
32 34 Ivy DD, Abman SH, Barst RJ, *et al*. Pediatric Pulmonary Hypertension. *J Am Coll*  
33 *Cardiol* 2013;**62**:D117–26. doi:10.1016/j.jacc.2013.10.028  
34  
35 35 Penning S, Robinson KD, Major CA, *et al*. A comparison of echocardiography and  
36 pulmonary artery catheterization for evaluation of pulmonary artery pressures in  
37 pregnant patients with suspected pulmonary hypertension. *Am J Obstet Gynecol*  
38 2001;**184**:1568–70.  
39  
40 36 Fisher MR, Forfia PR, Chamera E, *et al*. Accuracy of Doppler echocardiography in the  
41 hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*  
42 2009;**179**:615–21. doi:10.1164/rccm.200811-1691OC  
43  
44 37 Lanzarini L, Fontana A, Campana C, *et al*. Two simple echo-Doppler measurements can  
45 accurately identify pulmonary hypertension in the large majority of patients with chronic  
46 heart failure. *J Heart Lung Transplant* 2005;**24**:745–54.  
47 doi:10.1016/j.healun.2004.03.026  
48  
49 38 Laaban JP, Diebold B, Zelinski R, *et al*. Noninvasive estimation of systolic pulmonary  
50 artery pressure using Doppler echocardiography in patients with chronic obstructive  
51 pulmonary disease. *Chest* 1989;**96**:1258–62.  
52  
53 39 Matsuyama W, Ohkubo R, Michizono K, *et al*. Usefulness of transcutaneous Doppler  
54 jugular venous echo to predict pulmonary hypertension in COPD patients. *Eur Respir J*  
55  
56  
57  
58  
59  
60



1  
2  
3 2001;**17**:1128–31.  
4

- 5 40 Farber HW, Foreman AJ, Miller DP, *et al*. REVEAL Registry: correlation of right heart  
6 catheterization and echocardiography in patients with pulmonary arterial hypertension.  
7 *Congest Heart Fail* 2011;**17**:56–64. doi:10.1111/j.1751-7133.2010.00202.x  
8
- 9 41 Janda S, Shahidi N, Gin K, *et al*. Diagnostic accuracy of echocardiography for  
10 pulmonary hypertension: a systematic review and meta-analysis. *Heart* 2011;**97**:612–22.  
11 doi:10.1136/hrt.2010.212084  
12
- 13 42 Damy T, Goode KM, Kallvikbacka-Bennett A, *et al*. Determinants and prognostic value  
14 of pulmonary arterial pressure in patients with chronic heart failure. *Eur Heart J*  
15 2010;**31**:2280–90. doi:10.1093/eurheartj/ehq245  
16
- 17 43 Prineas RJ, Crow RS, Blackburn H. *The Minnesota code manual of*  
18 *electrocardiographic findings: standards and procedures for measurement and*  
19 *classification*. Boston Massachusetts : : John Wright 1982.  
20
- 21 44 Elm von E, Altman DG, Egger M, *et al*. Strengthening the Reporting of Observational  
22 Studies in Epidemiology (STROBE) statement: guidelines for reporting observational  
23 studies. *BMJ* 2007;**335**:806–8. doi:10.1136/bmj.39335.541782.AD  
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**RATIONALE AND DESIGN OF THE PAN AFRICAN  
PULMONARY HYPERTENSION COHORT (PAPUCO)  
STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY  
ON PULMONARY HYPERTENSION IN AFRICA**

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7  
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## ABSTRACT

### Introduction

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure. Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared to developed countries due to the high prevalence of risk factors in the region.

### Methods and Analysis

A multinational multicentre registry-type cohort study was established and tailored to resource-constraint settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa. PH will be diagnosed by specialist cardiologists using Echocardiography (RVSP>35 mmHg, absence of pulmonary stenosis and acute right heart failure) usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, electrocardiogram and chest x-ray changes in keeping with PH as per guidelines ([ESC/ERS guidelines](#)). Additional investigations such as CT-scan, ventilation/perfusion scan or right heart catheterisation will be performed at the discretion of the treating physician. Functional tests include 6-minute walk test and Karnofsky Performance Score. The WHO classification system for PH will be applied to describe the different aetiologies of PH. Several sub-studies have been implemented within the registry to investigate specific types of PH and their outcome at up to 24 months. Data will be analysed by an independent institution following a data analyse plan.

## Ethics and Dissemination

All local Ethics Committees of the participating centres approved the protocol. The data will be disseminated through peer-reviewed journals, at national and international conferences and public events at local care providers.

For peer review only

## ARTICLE SUMMARY

### Article focus

- In this manuscript we aim to provide an overview of pulmonary hypertension in Africa and the epidemiology of risk factors prevalent in the region.
- We aim to answer the question why Africa needs a registry for pulmonary hypertension.
- We describe how we implemented the registry in scarce resources settings.

### Key messages

- Risk factors for pulmonary hypertension are highly endemic in Africa.
- The incidence of pulmonary hypertension is expected to be higher in Africa compared to developed countries.
- A diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings without access to right heart catheterisation has been developed.
- 12 centres are participating in the Pan African Pulmonary hypertension Cohort (PAPUCO) study and more than 250 patients have been recruited so far.

### Strengths and limitations of this study

- The PAPUCO study is the first multinational registry on pulmonary hypertension in Africa.
- PAPUCO centres have different levels of medical infrastructure and not all patients underwent the same rigorous work-up.

## INTRODUCTION

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure (RHF).[1] The epidemiology of PH in Africa and the distribution of its multitude of aetiologies has not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region.[2-5] Many known risk factors for PH are hyperendemic in this part of the world, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary haemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary disease, PH and, often, to RHF with premature death. Also a lack of specialist paediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH.[6] Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH.[6-8] However, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive RHF.[4,9] Thus, within the registry we expect the entire spectrum of aetiologies of PH. In this manuscript, we aim to provide an overview of PH in Africa and the epidemiology of risk factors prevalent in the region, and answer the question why Africa needs a registry for PH just as much as most other parts of the world and how we implemented it in the setting of scarce resources.



## **Preliminary evidence of a significant burden of pulmonary hypertension and its risk factors in Africa**

In recent years, there has been increasing awareness of the clinical significance of PH and cor pulmonale in Africa. This applies equally to the recognition of the importance of PH and RHF as both a primary diagnosis and as a poor prognostic marker for those primarily affected by left-sided heart failure. Data on the precursors and risk factors of those conditions are limited to few reports. The largest study on PH/RHF in Africa has been conducted within *the Heart of Soweto Study* in South Africa; 2505 patients presented with *de novo* heart failure between 2006-2008.[5] Of those 697 (28%) were diagnosed with PH/RHF. PH/RHF was the primary diagnosis in 50% of those patients. The majority presented with dyspnoea and a mean right ventricular systolic pressure (RVSP) above 50 mmHg. Left heart disease (31%), chronic lung disease due to Chronic Obstructive Pulmonary Disease (COPD) and tuberculosis (26%), and pulmonary arterial hypertension (PAH) (20%) due to HIV (HIV-PAH), CHD, or idiopathic PAH were the most common causes of PH. Sani et al. described the prevalence of PH in patients with RHD at a tertiary centre in Nigeria.[10] Of 1312 Echocardiography (ECHO) studies 10% had evidence of RHD; secondary PH was present in 80% of patients with RHD. The same centre reported on 53 patients with PH on ECHO among 80 patients admitted with heart failure with hypertensive heart disease (25%), peripartum cardiomyopathy (25%), dilated cardiomyopathy (17%), and RHD (13%) being the most common causes of PH.[11] A study from Uganda showed a prevalence of PH in patients with newly diagnosed RHD (n=309) of 33%.[12] A smaller survey from Lagos, Nigeria investigated the prevalence of cardiovascular disease in an HIV-positive cohort and found one patient of 100 patients to have HIV-PAH.[13] An ECHO study on 102 HIV-patients presenting with cardiac symptoms in Tanzania revealed PH in 13%.[14] PH with a

RVSP>30 mmHg was present in 4% of long-term survivors in a Zimbabwe cohort of vertically acquired HIV infection.[15] Haemolytic anaemia is a known risk factor for PH; a screening study of patients with sickle-cell disease (SCD) in Nigeria showed a PH prevalence of 25%;[16] a study from Egypt indicates that patients with  $\beta$ -Thalassaemia are at risk of PH.[17] Another study from Egypt found a PH prevalence of 9% in patients seropositive for schistosomal antibodies. Ahmed et al. from Sudan described 14 consecutive cases of PH with previously treated pulmonary TB and conclude that PH can even occur after resolution of TB, most like due to persistent lung destruction.[18] This data suggests that left heart disease, chronic lung disease, RHD, HIV, schistosomiasis and SCD might be the most common underlying diseases to cause PH within the spectrum of aetiologies of PH that we will find within the Pan African Pulmonary hypertension Cohort (PAPUCO)

## RATIONAL AND OBJECTIVES

Worldwide, PH has received great increase in awareness at the beginning of the 21<sup>st</sup> century (~~Figure 1~~), but less than one per cent (~~0.7%~~) of the publications are from Africa (Figure 1). It is expected that PH is more prevalent in Africa compared to developed countries, but little information is available about African patients with PH. Exposure to risk factors, human genetic variation, different socio-economic backgrounds, lifestyles, co-morbidities, nutrition and disparities in access to health services makes the African population unique, but heterogeneous at the same time. Therefore, most research data and clinical guidelines from high-income countries cannot be translated into the African context. It is within the context described above that the Pan African Pulmonary hypertension Cohort (PAPUCO), a Pan Africa registry-type cohort study, was established (Figure 2).

Scientific and clinical research has been fundamental in improving human health.[19] In fact, research has demonstrated to be an excellent vehicle to implement new technologies and to

facilitate training for its use, and to develop new systems and establish the services around it - jointly leading to technical improvement, sharpening of skills and capacity development<sup>[20,21]</sup>. Besides the main objectives of the PAPUCO registry to define and understand PH in Africa (Box 1), this multinational and multicentre research project therefore aims to also develop sustainable clinical and research capacity across the African continent as well as raising awareness for PH and its risk factors.

#### Box 1: PAPUCO objectives

##### *Primary objective*

- To describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa

##### *Secondary objectives*

- To describe the overall 6-month survival rate
- To describe the 24-month survival rate in patients with HIV-PAH
- To compare 6-month survival rates between different groups of PH
- To determine the predictors of mortality across the different groups.

Abbreviations: PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus

The prevalence of PH in Africa varies geographically, according to underlying risk factors and diseases and the diagnosis of PH is most likely often missed, not only during early stages due to the subtle nature of presentation of PH, but also at more advanced stage of disease due to lack of awareness by primary care doctors and low index of suspicion, limited access to ECHO services and tertiary care. However, it is crucial to diagnose PH in Africa early and reliably to ensure better care for these patients (Box 2).

#### Box 2: The significance of PH in Africa: Why we need to diagnose?

- The right to know

- Prognostic implications
- Access to tertiary care: heart failure management, anticoagulation, home oxygen, COPD management, access to PH-specific drugs (Sildenafil)
- Access to cardiothoracic surgery: valve repair/replacement, correction of congenital heart disease, heart transplantation
- Access to social and disability grants
- To raise awareness of PH and its risk factors

Abbreviations: PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease

## METHODS AND ANALYSIS

### Study design and setting

The Pan African Pulmonary hypertension Cohort (PAPUCO) research group was established in 2011 with the aim to implement a registry-type cohort study on pulmonary hypertension in Africa ~~according to STROBE guidelines~~. The registry aims to recruit consecutive patients 1) with newly diagnosed PH based clinical and ECHO criteria, 2) are able or likely to return for 6-month follow-up, 3) are at least 18 years old (except for paediatric centres in Mozambique and Nigeria), and 4) consented in writing to participate in the registry. Centre eligibility include 1) availability of ECHO and training in assessing right heart function, 2) experience in diagnosing PH according to WHO classification, 3) experience in clinical management of patients with right heart failure, and 4) resources to review patients at 6-month follow-up. Participating centres will be invited to join the registry at African cardiac meetings and conferences.

### Definition of pulmonary hypertension, diagnostic algorithm and data points

As shown in Box 3, PH is defined as documented elevated RVSP > 35 mmHg on trans-thoracic ECHO in the absence of pulmonary stenosis and acute right heart failure; usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, and possibly electrocardiogram (ECG) and chest x-ray (CXR) changes in keeping

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3 with PH as per [European Society of Cardiology and European Respiratory Society](#)  
4 [\(ESC/ERS\) guidelines on pulmonary hypertension.](#)<sup>[5,22]</sup><sup>[20]</sup> Right heart catheterisation is  
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6 optional. The [updated](#) WHO classification system for PH ([Dana Point 2008](#)) will be applied  
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8 to describe the different aetiologies of PH<sup>[22,23]</sup>. Once definitive assessment and treatment  
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10 has been applied, the following specific data will be documented for each individual: a) all  
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12 major cardiovascular diagnoses according ICD 10 coding, and b) up to five non-  
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14 cardiovascular diagnoses according ICD 10 coding.<sup>[24]</sup><sup>[21]</sup> Figure 3 shows the diagnostic  
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16 algorithm to diagnose PH in resource-constraint settings without access to right heart  
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18 catheterisation that has been developed following the [ESC/ERS](#) guidelines for the diagnosis  
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20 of PH ~~of the European Society of Cardiology and European Respiratory Society.~~<sup>[22]</sup> Key  
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22 information collected will include information on demographic profile, socio-economic  
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24 background, medical history, co-morbidities, cardiac risk factors, and environmental  
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26 exposures. The clinical aspects of the assessment include symptoms scoring, a full clinical  
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28 examination, physical and clinical status; functional tests include WHO functional class  
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30 (WHO FC), 6-minute walk test (6MWT) and Karnofsky Performance Score. Technical  
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32 procedures include ECHO, CXR, and 12-lead ECG. Further investigations are at the  
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34 discretion of the treating physician and typically include lung function tests,  
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36 ventilation/perfusion lung scans, and high resolution computed tomography and computed  
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38 tomography pulmonary angiography, and right heart catheterization, if available (Figure 3).  
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40 Data on heart failure treatment and co-medication, hospitalization and death, and 6-month  
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42 outcome will also be collected.  
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52 Box 3: Evidence to diagnose PH in resource-constraint settings

- 54 • Symptoms: SOB, fatigue, cough, chest pain, palpitations
  - 55 • Clinical exam: raised JVP, peripheral oedema, ascites, loud p2, systolic murmur, central cyanosis
  - 56 • ECG: sinus tachycardia, p-pulmonale, right axis deviation, right bundle branch block, RVH
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- CXR: cardiomegaly, pleural effusion, prominent pulmonary arteries
- ECHO: dilated right atrium and ventricle, interventricular septal flattening, RVSP>35 mmHg, TAPSE<15 mm

Abbreviations: SOB, shortness of breath; JVP, jugular vein pressure; ECG, electrocardiogram; RVH, right ventricular hypertrophy; CXR, chest X-ray; ECHO, Echocardiography; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion

### ***Echocardiography***

#### Echocardiography in adults

ECHO modalities applied included M-mode, two dimensional (2D) and Doppler studies.

ECHO will be done with 3 to 5 MHz sector transducer. Complete 2D ECHO examination will be performed according to the recommendations of the American Society of ECHO

(ASE).<sup>[25][22]</sup> M-mode ECHO will be derived from 2D images. The M-mode cursor on the 2D scan will move to specific areas of the heart to obtain measurements according to the recommendation of the committee on M-mode standardization of the ASE. Doppler indices of left ventricular (LV) diastolic filling will be obtained. Complete Doppler study will be done according to the recommendations of the ASE. From the M-mode measurements, indices of LV function will be derived. These include shortening fraction, ejection fraction (EF), and LV mass, cardiac output and relative wall thickness. ECHO examinations include (a) valvular assessment, (b) left atrial size, (c) left ventricular size and function, (d) a semi quantitative estimate of the severity of valvular regurgitation, (e) size and function of the right atrium and ventricle and (f) evidence of pulmonary hypertension. Doppler will be used to examine the valves on suspicion of any valvular lesion. ECHO findings associated with PH includes dilated pulmonary artery and dilation and hypertrophy of the right ventricle (RV), diastolic flattening of the interventricular septum and Doppler evidence of PH.<sup>[26][23]</sup>

Doppler ECHO estimates pulmonary artery systolic pressure (PASP). By measuring the maximum velocity of the tricuspid regurgitant jet (v), the transtricuspid pressure gradient will be calculated using the modified Bernoulli equation ( $4v^2$ ).<sup>[27][24]</sup> The PASP is approximated

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3 by adding the transtricuspid gradient to the right atrial pressure (RAP) as applied in the  
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5 formula [PASP=4v<sup>2</sup>+RAP]. The PASP is equivalent to RVSP in the absence of pulmonary  
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7 outflow obstruction. The RAP is estimated by the respiratory variation size of the vena cava  
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9 inferior in M-mode.[28] In our study, the systolic regurgitant tricuspid flow will be assessed  
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11 in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber  
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13 views to determine the highest velocity, which reflects PASP/RVSP. [29][25] PH is defined  
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15 as *mild* if RVSP was 36-50 mmHg, *moderate* if RVSP was 51-60 mmHg and *severe* if RVSP  
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17 was >60 mmHg. [30][26] In addition, we further assessed right ventricular function by  
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19 measuring the systolic displacement of the lateral portion of the tricuspid annular plane  
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21 excursion (TAPSE) on the M-mode tracing under the 2D-echo guidance. [31][27] Peak mitral  
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23 early diastolic velocity (E in m/s), the E-wave deceleration time (DCT in ms) and the velocity  
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25 at atrial contraction (A in m/s) are measured using pulsed-wave Doppler. Left ventricular  
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27 filling pressure classes were defined in accordance with the ASE 2009 guidelines. [32][28] In  
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29 patients with heart failure and reduced ejection fraction (HFrEF) raised LV filling pressure is  
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31 defined as E/A  $\geq 2$  if in sinus rhythm or DCT <150 ms if in atrial fibrillation (AF); normal LV  
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33 filling pressure is defined as E/A <1 in patients in sinus rhythm or DCT  $\geq 200$  ms for those in  
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35 AF; patients between these limits will be classified as undetermined. In heart failure and  
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37 preserved ejection fraction (HFpEF), LV filling pressure is classified as follows: raised LV  
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39 filling pressure if left atrium is dilated and normal LV filling pressure if left atrium has  
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41 normal size.  
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#### 50 Echocardiography in infants and children

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52 Translating the definitions of PH in adults to children, especially to infants, is controversial.  
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54 Within the paediatric cardiology community experts suggest that the ratio of the PASP to the  
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56 systemic systolic blood pressure >0.4 should be the diagnostic criterion. [33][29] The fact that  
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3 the threshold of pulmonary vascular resistance (PVR) increase has not been included in the  
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5 abovementioned definition is another limitation to its use in children or infants, since  
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7 paediatric PH is mainly caused by left-to-right shunt congenital heart disease; and if PVR  
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9 shows no significant increase in such cases, the patient may be considered only as a dynamic  
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11 PH case led by increased pulmonary blood flow, rather than pulmonary vascular disease.  
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14 Paediatric guidelines suggest that  $mPAP > 25$  mmHg and  $PVR > 3$  Wood units remain in the  
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16 definition of PAH.<sup>[34][30]</sup> In our cohort of children with congenital heart malformations we  
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18 not only used tricuspid and pulmonary regurgitation envelopes, but also the flow across the  
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20 ventricular septal defect or persistent ducts arteriosus to measure the gradient between the  
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22 two circulations and therefore estimate the pulmonary pressure. Indirect signs of PH such as  
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24 dilatation of the RV, RV-hypertrophy and dilatation of the main pulmonary artery were  
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26 added to Doppler data to confirm the diagnosis.  
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### 32 *Accuracy of Echocardiography in the diagnosis of PH*

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34 Diagnosing PH is challenging when relying on bedside tests. RHC is the gold standard to  
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36 diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear  
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38 excessive risks and be impractical in any cost-constrained environment. Also RHC is only  
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40 available at very few centres in Africa. A viable device to diagnose PH in Africa needs to be  
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42 widely available, accurate, safe, and cost-effective. ECHO has become increasingly available  
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44 in Africa and reliably allows the measurements to describe functional and morphologic  
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46 features of PH and to indirectly measure the pressures in the pulmonary artery; hence, to  
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48 diagnose PH. Nonetheless, the exact measurements of the mean and systolic pulmonary  
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50 artery are not possible, the PASP remains estimate, and the use of ECHO to diagnose PH  
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52 questionable.<sup>[35,36][31,32]</sup> A number of possible explanations for this “inaccuracy” merit  
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54 attention: 1) conditions for a reproducible calculation of  $PA_{SPPS}/RVSP$  include the presence  
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3 of sufficient TR to produce a Doppler envelope and appropriate gain adjustments. An  
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5 “undergained” spectral signal will tend to result in underestimated PASPPS whereas an  
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7 “overgained” spectral signal might overestimate the measurements; 2) careful adjustment of  
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9 the transducer position and the use of colour flow Doppler are critical in order to reduce the  
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11 Doppler angle and to obtain the maximal regurgitant flow velocity and severe TR will cause a  
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13 laminar flow which invalidates the Bernoulli equation; 3) volume status and systemic blood  
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15 pressure are other factors that potentially influence the measurement of PASPPS; and 4) the  
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17 highest value of RAP in the ASE guidelines is 15 mmHg, but RAP measured by RHC can  
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19 exceed 15 mmHg. In spite of all these shortcomings, several studies have been published in  
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21 the literature demonstrating good sensitivity and specificity of ECHO versus RHC.<sup>[37-  
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23 39][33-35]</sup> In the REVEAL registry, there was a good correlation in PASP between ECHO  
24  
25 and RHC at baseline, even if repeated ECHO measurements alone were not sufficient to  
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27 monitor changes in PASP or progression of PH.<sup>[40][36]</sup> In the first systematic review and  
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29 meta-analysis addressing the diagnostic accuracy of ECHO in PH by Janda and colleagues,  
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31 the authors concluded that the correlation of PASP by ECHO compared to PASP by RHC  
32  
33 was good with a summary correlation coefficient of 0.70 (95% CI 0.67 to 0.73).<sup>[41][37]</sup>  
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35 Also, the authors showed that the diagnostic accuracy of ECHO in PH was also acceptable  
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37 with a summary sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to  
38  
39 85), respectively. Additionally, Damy and colleagues demonstrated in their recent work that  
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41 PASPPS when measured in “good ECHO hands” is a strong predictor of mortality.<sup>[42][38]</sup>  
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43 Last but not the least, easily obtainable ECHO parameters like E/A ratio, DCT, LA size can  
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45 reliably distinguish between PH due to lung disease and PH due to left heart disease,  
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47 allowing for rapid triage of patients with need for RHC. In summary, ECHO is far beyond a  
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49 good modality to confirm both the presence and aetiology of PH in the majority of suspected  
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51 cases when performed and interpreted by the requisite expertise under incorporation of all  
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3 information obtained during a detailed ECHO assessment. ECHO will always provide  
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5 incremental information in PH that cannot be obtained using RHC, whether in developed or  
6  
7 developing countries.  
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### 10 11 **Data cleaning process and statistical analysis**

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13 All study data will be collected on electronic case report forms and stored on a dedicated  
14  
15 secure central database. Cases will be reviewed by at least two investigators (FT, AD, KS,  
16  
17 AOM) for completeness and data validated. Query reports will be sent to the sites and  
18  
19 resolved by the site investigators. If consensus on the WHO classification of PH cannot be  
20  
21 reached, a third investigator's opinion will be requested. Data will then be verified and  
22  
23 transferred to SPSS Statistics 17.0 for all analyses by an independent team at Preventative  
24  
25 Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Normally distributed  
26  
27 continuous data will be presented as mean  $\pm$  standard deviation and non-Gaussian distributed  
28  
29 variables as median plus interquartile range. Categorical data will be presented as percentages  
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31 with 95% confidence intervals (CI) where appropriate. For patient group comparisons, we  
32  
33 will use Chi Square ( $\chi^2$ ) analysis with calculation of odds ratios (OR) and 95% CI (where  
34  
35 appropriate) for discrete variables and Students t-test and analysis of variance for normally  
36  
37 distributed continuous variables. Multiple logistic regression analyses (entry model) will be  
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39 performed on age, sex and baseline risk factors to derive adjusted ORs for the risk of  
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41 presenting with PH/RHF overall, chronic lung disease and PH WHO Group 1. Significance  
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43 will be accepted at the two-sided level of 0.05. ECG analysis will be will be subject to  
44  
45 blinded coding according to published Minnesota criteria to determine any pathological  
46  
47 abnormalities. [43][39] We aim to adhere to the Strengthening the Reporting of Observational  
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49 Studies in Epidemiology (STROBE) guidelines for this type of study wherever possible.[44]  
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### **PAPUCO sub-studies**

Several sub-studies have been established within the PAPUCO registry. The ECHO sub-study aims to describe in detail the ECHO characteristics of right ventricular function in PH. The HIV-P<sub>A</sub>H sub-study aims to describe the phenotype of HIV-P<sub>A</sub>H in Africa. The congenital heart disease and rheumatic heart disease sub-studies aim to describe the contribution of congenital heart disease and rheumatic heart disease to PH in Africa. In addition, serum will be collected at selected centres for studies on biomarker profile. The HIV.INFLAME sub-study aims to examine the role of inflammatory markers and oxidative stress on the development of HIV-P<sub>A</sub>H. We hypothesizing that HIV-positive patients with PH have a pro-inflammatory state and raised markers of oxidative stress compared to healthy HIV-positive controls and that increased markers of inflammation and oxidative stress and decreased antioxidant capacity are predictors of outcome and indicators of disease severity.

### **Ethics and dissemination**

All PAPUCO centres require ethical approval from their local ethics committee review board. Written informed consent must be obtain from every patient participating in the registry. Study results will be disseminated in peer-reviewed journals. The first publication will include baseline and 6-month follow-up data from all centres. Sub-study publications on the HIV-cohort with 24-month follow-up and the cohort of patients with PH due to left heart disease will be published after recruitment and follow-up has been completed. Laboratory-based research will be published after work is completed.

### **The online data collection platform**

A tailor-made databases has developed by *integrafrica research and development* to fulfil the study requirements. Open-source technology was used to develop the web-based system

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3 that allows investigators to collect, store, analyse, report on and exports clinical research data.  
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5 The interface is simple and user friendly and leads the user through the data entry process. It  
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7 anonymises personal patient data: data is stored as electronic case report forms on a secure,  
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9 encrypted and backed-up server. It provides hierarchic permissions and validation at the point  
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11 of data entry. Multimedia data formats, i.e. scans of ECGs, CXRs, and ECHO images can be  
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13 uploaded on the platform, allowing storage of complete clinical records and data together.  
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15 Tools for education, training, and communication are installed within the web-portal.  
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17 Frequently Asked Questions serve as a guide on how to the use of the platform. After secure  
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19 login, documents such as paper case report forms, informed consent forms, study information  
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21 sheets and patient education sheets on PH are available for download. All data can be  
22  
23 exported in various formats for further analysis. The platform has been developed to cater for  
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25 mobile Internet connectivity available in most parts of Africa and a unique research platform  
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27 far beyond a simple web-based database.  
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### 34 **Recruitment process**

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36 Twelve centres have received ethics approval and are currently actively recruiting; additional  
37  
38 six countries are showing interest in joining the registry (Figure 2). All centres are  
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40 government-run public health care institutions with different medical infrastructure profiles  
41  
42 and all but one are cardiac centres within tertiary care hospitals (Table 1); one centre is an  
43  
44 infectious diseases referral clinic in South Africa. At total of 254 patients have been recruited  
45  
46 until December 2013 (Figure 5).  
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52 Table 1: Medical infrastructure at PAPUCO centres - diagnostic equipment and medical services

Centre	ECG	CXR	ECHO	RHC	CS	HRCT	CTPA	LFT	V/Q	Lab
CM01	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>

CM02	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>					X <sup>1</sup>
CM03	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>							X <sup>1</sup>
MZ01	X	X	X							X
MZ02	X	X	X			X		X		X
NG01	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>		X <sup>1</sup>		X <sup>1</sup>
NG02	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
NG03	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
NG04	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>							X <sup>1</sup>
NG05	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X <sup>1</sup>
SA01	X	X	X	X	X	X	X	X	X	X
SA02	X	X	X			X	X			X

Abbreviations: CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG01, Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; NG04, Department of Medicine, University of Uyo Teaching Hospital, Uyo, Nigeria; NG05, Federal Medical Centre, Umuahia, Nigeria; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg, South Africa and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa. ECG, electrocardiogram; CXR, chest X-ray; ECHO, Echocardiography; RHC, right heart catheterisation; CS, cardiac surgery; HRCT, high resolution computed tomography; CTPA, computed tomography pulmonary angiography; LFT, lung function tests; V/Q, ventilation/perfusion lung scan; Lab, laboratory facility for haematology, chemistry, and microbiology; X, equipment/service available at the centre and free-of-charge for the patients; X<sup>1</sup>, patients have to cover the costs for the service (out of pocket payments).

## LIMITATIONS

The PAPUCO registry is an example of a functioning registry in low-resource settings.

Limited resources should therefore not be seen as a limitation, but rather as a development opportunity. PAPUCO centres have different levels of medical infrastructure and not all patients will undergo the same rigorous work-up in all centres - especially when compared to developed countries. Therefore, the clinical skills of the treating physician are often more important (and valuable!) than an additional diagnostic test in order to pin down the aetiology of PH in a patient. Moreover, patients often have to pay out of their pocket for diagnostic

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3 tests and therefore accessibility to tests is limited due to the financial means of the patient.  
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5 Although we aim for consecutive patient enrolment at each centre, we understand that this is  
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7 often not feasible due to high patient volume and workload of doctors.  
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## 10 11 12 **SUMMARY**

13  
14 PAPUCO is a contemporary registry on PH in Africa using high international standards to  
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16 diagnose PH. It will provide new insight on PH in Africa and ultimately improve diagnosis  
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18 and care of patients. PAPUCO is already a showcase for registry activities in Africa and a  
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20 vehicle to capacity generation and sustainable development in the health care sector. It  
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22 interconnects health centres far beyond pulmonary hypertension.  
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## 27 28 **LEGENDS OF FIGURES**

29  
30 Figure 1: Number of publications on pulmonary hypertension per annum since 1970 (grey  
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32 bars) with moving average (blue line). Less than one per cent (0.7%) of the publications  
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34 where from Africa (not displayed). Title search terms in PubMed were "pulmonary  
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36 hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension" and  
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38 Africa and African country names; results are displayed annually between 1970 and 2013.  
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43 Figure 2: The PAPUCO map displays countries currently participating in the PAPUCO  
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45 registry (number of centres per country in brackets).  
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50 Figure 3: Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint  
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52 settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB,  
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54 tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease;  
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56 LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus;  
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3 US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed  
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5 tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed  
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7 tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan  
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11  
12 Figure 4: Diagnosing pulmonary hypertension using transthoracic 2D-Doppler

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14 Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right  
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16 ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-  
17  
18 wave Doppler across the TV in the 4-chamber view showing severe TR, despite the  
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20 deceptively less impressive color-flow jet seen across the valve; C: M-Mode measurement of  
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22 TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right  
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24 ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left  
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26 atrium; TV: tricuspid valve; TR: tricuspid regurgitation.  
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33 Figure 5: PAPUCO registry - monthly enrolment until December 2013. Number of patients  
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35 recruited per month since the launch of the registry in May 2011.  
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46  
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48  
49 by *integerafrica research and development*.  
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### 55 CONTRIBUTORS

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3 KS, AOM, FT were responsible for the initial idea, literature review, and study design and  
4  
5 planning. All authors have contributed to the setup of the PAPUCO registry and have  
6  
7 contributed to various aspects of the study design with input relating to their specific  
8  
9 expertise in the field. FT, AD, AOM, LB, MUS, KMK, OSO, AM, PU, ASI, AD, KS have  
10  
11 developed the study protocol, FT and KS wrote the study protocol, FT developed the  
12  
13 database, FT, AD, AOM, KS cleaned the database, LB trained the doctors in  
14  
15 Echocardiography of the heart and developed the Echo protocol, AD trained doctors in  
16  
17 Cameroon, OSO trained doctors in Nigeria, SS developed the statistical analysis plan. FT,  
18  
19 AD, AOM, MUS, KMK, OSO, IM, AM, PU, KT, RB, AD, KS were substantially involved in  
20  
21 data acquisition. All authors read and approved the final manuscript.  
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## 27 **COMPETING INTEREST**

28  
29 We declare no competing interest.  
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## 34 **ETHICS APPROVAL**

35  
36 All centres received ethics approval from their local ethic committees.  
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40

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## 48 **REFERENCES**

- 49  
50 [1 Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of](#)  
51 [pulmonary hypertension. \*J Am Coll Cardiol\* 2013;\*\*62\*\*:D34–41.](#)  
52 [doi:10.1016/j.jacc.2013.10.029](#)  
53  
54 [2 Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral](#)  
55 [therapy: a global perspective. \*Eur Heart J\* 2013;\*\*34\*\*:3538–46.](#)  
56 [doi:10.1093/eurheartj/eh388](#)  
57  
58  
59  
60



- 3 [Sliwa K, Carrington MJ, Becker A, et al. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. \*Eur Heart J\* 2012;\*\*33\*\*:866–74. doi:10.1093/eurheartj/ehr398](#)
- 4 [Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa \(the Heart of Soweto Study\): a cohort study. \*Lancet\* 2008;\*\*371\*\*:915–22. doi:10.1016/S0140-6736\(08\)60417-1](#)
- 5 [Stewart S, Mocumbi AO, Carrington MJ, et al. A not-so-rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort. \*Eur J Heart Fail\* 2011;\*\*13\*\*:1070–7. doi:10.1093/eurjhf/hfr108](#)
- 6 [Mocumbi AO, Lameira E, Yaksh A, et al. Challenges on the management of congenital heart disease in developing countries. \*Int J Cardiol\* 2011;\*\*148\*\*:285–8. doi:10.1016/j.ijcard.2009.11.006](#)
- 7 [Sliwa K, Mocumbi AO. Forgotten cardiovascular diseases in Africa. \*Clin Res Cardiol\* 2010;\*\*99\*\*:65–74. doi:10.1007/s00392-009-0094-1](#)
- 8 [Sliwa K, Carrington M, Mayosi BM, et al. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. \*Eur Heart J\* 2010;\*\*31\*\*:719–27. doi:10.1093/eurheartj/ehp530](#)
- 9 [Stewart S, Wilkinson D, Hansen C, et al. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. \*Circulation\* 2008;\*\*118\*\*:2360–7. doi:10.1161/CIRCULATIONAHA.108.786244](#)
- 10 [Sani MU, Karaye KM, Borodo MM. Prevalence and pattern of rheumatic heart disease in the Nigerian savannah: an echocardiographic study. \*Cardiovasc J Afr\* 2007;\*\*18\*\*:295–9.](#)
- 11 [Karaye KM, Saidu H, Bala MS, et al. Prevalence, clinical characteristics and outcome of pulmonary hypertension among admitted heart failure patients. \*Ann Afr Med\* 2013;\*\*12\*\*:197–204. doi:10.4103/1596-3519.122685](#)
- 12 [Okello E, Wanzhu Z, Musoke C, et al. Cardiovascular complications in newly diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda. \*Cardiovasc J Afr\* 2013;\*\*24\*\*:80–5. doi:10.5830/CVJA-2013-004](#)
- 13 [Olusegun-Joseph DA, Ajuluchukwu JNA, Okany CC, et al. Echocardiographic patterns in treatment-naïve HIV-positive patients in Lagos, south-west Nigeria. \*Cardiovasc J Afr\* 2012;\*\*23\*\*:e1–6. doi:10.5830/CVJA-2012-048](#)
- 14 [Chillo P, Bakari M, Lwakatara J. Echocardiographic diagnoses in HIV-infected patients presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam, Tanzania. \*Cardiovasc J Afr\* 2012;\*\*23\*\*:90–7. doi:10.5830/CVJA-2011-060](#)
- 15 [Miller RF, Kaski JP, Hakim J, et al. Cardiac disease in adolescents with delayed diagnosis of vertically acquired HIV infection. \*Clin Infect Dis\* 2013;\*\*56\*\*:576–82. doi:10.1093/cid/cis911](#)
- 16 [Aliyu ZY, Gordeuk V, Sachdev V, et al. Prevalence and risk factors for pulmonary](#)

- artery systolic hypertension among sickle cell disease patients in Nigeria. *Am J Hematol* 2008;**83**:485–90. doi:10.1002/ajh.21162
- 17 Mokhtar GM, Tantawy AAG, Adly AAM, *et al.* Clinicopathological and radiological study of Egyptian  $\beta$ -thalassemia intermedia and  $\beta$ -thalassemia major patients: relation to complications and response to therapy. *Hemoglobin* 2011;**35**:382–405. doi:10.3109/03630269.2011.598985
- 18 Ahmed AEH, Ibrahim AS, Elshafie SM. Pulmonary hypertension in patients with treated pulmonary tuberculosis: analysis of 14 consecutive cases. *Clin Med Insights Circ Respir Pulm Med* 2011;**5**:1–5. doi:10.4137/CCRPM.S6437
- 19 WHO. World Health Organization: The World Health Report 2013: Research for Universal Health Coverage. *Euro Surveill* 2013;**18**:20559.
- 20 Chu KM, Jayaraman S, Kyamanywa P, *et al.* Building research capacity in Africa: equity and global health collaborations. *PLoS Med* 2014;**11**:e1001612.
- 21 Noormahomed EV, Mocumbi AO, Preziosi M, *et al.* Strengthening research capacity through the medical education partnership initiative: the Mozambique experience. *Hum Resour Health* 2013;**11**:62. doi:10.1186/1478-4491-11-62
- 22 Galiè N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur. Heart J.* 2009;**30**:2493–537. doi:10.1093/eurheartj/ehp297
- 23 Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;**54**:S43–54. doi:10.1016/j.jacc.2009.04.012
- 24 WHO. WHO | International Classification of Diseases (ICD). WHO 1994.
- 25 Henry WL, DeMaria A, Gramiak R, *et al.* Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. *Circulation* 1980;**62**:212–7.
- 26 Jaffe CC, Weltin G. Echocardiography of the right side of the heart. *Cardiol Clin* 1992;**10**:41–57.
- 27 Sciomer S, Magri D, Badagliacca R. Non-invasive assessment of pulmonary hypertension: Doppler-echocardiography. *Pulm Pharmacol Ther* 2007;**20**:135–40. doi:10.1016/j.pupt.2006.03.008
- 28 Beigel R, Cercek B, Luo H, *et al.* Noninvasive evaluation of right atrial pressure. *J Am Soc Echocardiogr* 2013;**26**:1033–42. doi:10.1016/j.echo.2013.06.004
- 29 Quiñones MA, Otto CM, Stoddard M, *et al.* Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography.

- 1  
2  
3 [J Am Soc Echocardiogr. 2002;15:167–84.](#)
- 4  
5 30 [Schachna L, Wigley FM, Chang B, et al. Age and risk of pulmonary arterial](#)  
6 [hypertension in scleroderma. \*Chest\* 2003;124:2098–104.](#)
- 7  
8 31 [Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts](#)  
9 [survival in pulmonary hypertension. \*Am J Respir Crit Care Med\* 2006;174:1034–41.](#)  
10 [doi:10.1164/rccm.200604-547OC](#)
- 11  
12 32 [Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of](#)  
13 [left ventricular diastolic function by echocardiography. \*Eur J Echocardiogr\*](#)  
14 [2009;10:165–93. doi:10.1093/ejehocardi/jep007](#)
- 15  
16 33 [Barst RJ, Ertel SI, Beghetti M, et al. Pulmonary arterial hypertension: a comparison](#)  
17 [between children and adults. \*Eur Respir J\* 2011;37:665–77.](#)  
18 [doi:10.1183/09031936.00056110](#)
- 19  
20 34 [Ivy DD, Abman SH, Barst RJ, et al. Pediatric Pulmonary Hypertension. \*J Am Coll\*](#)  
21 [Cardiol](#) 2013;62:D117–26. doi:10.1016/j.jacc.2013.10.028
- 22  
23 35 [Penning S, Robinson KD, Major CA, et al. A comparison of echocardiography and](#)  
24 [pulmonary artery catheterization for evaluation of pulmonary artery pressures in](#)  
25 [pregnant patients with suspected pulmonary hypertension. \*Am J Obstet Gynecol\*](#)  
26 [2001;184:1568–70.](#)
- 27  
28 36 [Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the](#)  
29 [hemodynamic assessment of pulmonary hypertension. \*Am J Respir Crit Care Med\*](#)  
30 [2009;179:615–21. doi:10.1164/rccm.200811-1691OC](#)
- 31  
32 37 [Lanzarini L, Fontana A, Campana C, et al. Two simple echo-Doppler measurements can](#)  
33 [accurately identify pulmonary hypertension in the large majority of patients with chronic](#)  
34 [heart failure. \*J Heart Lung Transplant\* 2005;24:745–54.](#)  
35 [doi:10.1016/j.healun.2004.03.026](#)
- 36  
37 38 [Laaban JP, Diebold B, Zelinski R, et al. Noninvasive estimation of systolic pulmonary](#)  
38 [artery pressure using Doppler echocardiography in patients with chronic obstructive](#)  
39 [pulmonary disease. \*Chest\* 1989;96:1258–62.](#)
- 40  
41 39 [Matsuyama W, Ohkubo R, Michizono K, et al. Usefulness of transcutaneous Doppler](#)  
42 [jugular venous echo to predict pulmonary hypertension in COPD patients. \*Eur Respir J\*](#)  
43 [2001;17:1128–31.](#)
- 44  
45 40 [Farber HW, Foreman AJ, Miller DP, et al. REVEAL Registry: correlation of right heart](#)  
46 [catheterization and echocardiography in patients with pulmonary arterial hypertension.](#)  
47 [\*Congest Heart Fail\* 2011;17:56–64. doi:10.1111/j.1751-7133.2010.00202.x](#)
- 48  
49 41 [Janda S, Shahidi N, Gin K, et al. Diagnostic accuracy of echocardiography for](#)  
50 [pulmonary hypertension: a systematic review and meta-analysis. \*Heart\* 2011;97:612–22.](#)  
51 [doi:10.1136/hrt.2010.212084](#)
- 52  
53 42 [Damy T, Goode KM, Kallvikbacka-Bennett A, et al. Determinants and prognostic value](#)  
54 [of pulmonary arterial pressure in patients with chronic heart failure. \*Eur Heart J\*](#)  
55  
56  
57  
58  
59  
60

2010;**31**:2280–90. doi:10.1093/eurheartj/ehq245

- 43 Prineas RJ, Crow RS, Blackburn H. *The Minnesota code manual of electrocardiographic findings: standards and procedures for measurement and classification*. Boston Massachusetts : : John Wright 1982.
- 44 Elm von E, Altman DG, Egger M, *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;**335**:806–8. doi:10.1136/bmj.39335.541782.AD
- 1—Simonneau G, Gatzoulis MA, Adatia I, *et al*. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;**62**:D34–41. doi:10.1016/j.jacc.2013.10.029
- 2—Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. *Eur Heart J* 2013;**34**:3538–46. doi:10.1093/eurheartj/ehz388
- 3—Sliwa K, Carrington MJ, Becker A, *et al*. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J* 2012;**33**:866–74. doi:10.1093/eurheartj/ehr398
- 4—Sliwa K, Wilkinson D, Hansen C, *et al*. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet* 2008;**371**:915–22. doi:10.1016/S0140-6736(08)60417-1
- 5—Stewart S, Mocumbi AO, Carrington MJ, *et al*. A not so rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort. *Eur J Heart Fail* 2011;**13**:1070–7. doi:10.1093/eurjhf/hfr108
- 6—Mocumbi AO, Lameira E, Yaksh A, *et al*. Challenges on the management of congenital heart disease in developing countries. *Int J Cardiol* 2011;**148**:285–8. doi:10.1016/j.ijcard.2009.11.006
- 7—Sliwa K, Mocumbi AO. Forgotten cardiovascular diseases in Africa. *Clin Res Cardiol* 2010;**99**:65–74. doi:10.1007/s00392-009-0094-1
- 8—Sliwa K, Carrington M, Mayosi BM, *et al*. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. *Eur Heart J* 2010;**31**:719–27. doi:10.1093/eurheartj/ehp530
- 9—Stewart S, Wilkinson D, Hansen C, *et al*. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. *Circulation* 2008;**118**:2360–7. doi:10.1161/CIRCULATIONAHA.108.786244
- 10—Sani MU, Karaye KM, Borodo MM. Prevalence and pattern of rheumatic heart disease in the Nigerian savannah: an echocardiographic study. *Cardiovasc J Afr* 2007;**18**:295–9.
- 11—Karaye KM, Saidu H, Bala MS, *et al*. Prevalence, clinical characteristics and outcome of pulmonary hypertension among admitted heart failure patients. *Ann Afr Med* 2013;**12**:197–204. doi:10.4103/1596-3519.122685

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59  
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- 12—Okello E, Wanzhu Z, Musoke C, *et al.* Cardiovascular complications in newly diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda. *Cardiovasc J Afr* 2013;**24**:80–5. doi:10.5830/CVJA-2013-004
- 13—Olusegun Joseph DA, Ajuluchukwu JNA, Okany CC, *et al.* Echocardiographic patterns in treatment naïve HIV positive patients in Lagos, south west Nigeria. *Cardiovasc J Afr* 2012;**23**:e1–6. doi:10.5830/CVJA-2012-048
- 14—Chillo P, Bakari M, Lwakatare J. Echocardiographic diagnoses in HIV infected patients presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam, Tanzania. *Cardiovasc J Afr* 2012;**23**:90–7. doi:10.5830/CVJA-2011-060
- 15—Miller RF, Kaski JP, Hakim J, *et al.* Cardiac disease in adolescents with delayed diagnosis of vertically acquired HIV infection. *Clin Infect Dis* 2013;**56**:576–82. doi:10.1093/cid/cis911
- 16—Aliyu ZY, Gordeuk V, Sachdev V, *et al.* Prevalence and risk factors for pulmonary artery systolic hypertension among sickle cell disease patients in Nigeria. *Am J Hematol* 2008;**83**:485–90. doi:10.1002/ajh.21162
- 17—Mokhtar GM, Tantawy AAG, Adly AAM, *et al.* Clinicopathological and radiological study of Egyptian  $\beta$ -thalassemia intermedia and  $\beta$ -thalassemia major patients: relation to complications and response to therapy. *Hemoglobin* 2011;**35**:382–405. doi:10.3109/03630269.2011.598985
- 18—Ahmed AEH, Ibrahim AS, Elshafie SM. Pulmonary hypertension in patients with treated pulmonary tuberculosis: analysis of 14 consecutive cases. *Clin Med Insights Circ Respir Pulm Med* 2011;**5**:1–5. doi:10.4137/CCRPM.S6437
- 19—WHO. World Health Organization: The World Health Report 2013: Research for Universal Health Coverage. *Euro Surveill* 2013;**18**:20559.
- 20—Galiè N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur. Heart J.* 2009;**30**:2493–537. doi:10.1093/eurheartj/ehp297
- 21—WHO. WHO | International Classification of Diseases (ICD). WHO 1994.
- 22—Henry WL, DeMaria A, Gramiak R, *et al.* Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. *Circulation* 1980;**62**:212–7.
- 23—Jaffe CC, Weltin G. Echocardiography of the right side of the heart. *Cardiol Clin* 1992;**10**:41–57.
- 24—Sciomer S, Magri D, Badagliacca R. Non-invasive assessment of pulmonary hypertension: Doppler echocardiography. *Pulm Pharmacol Ther* 2007;**20**:135–40. doi:10.1016/j.pupt.2006.03.008

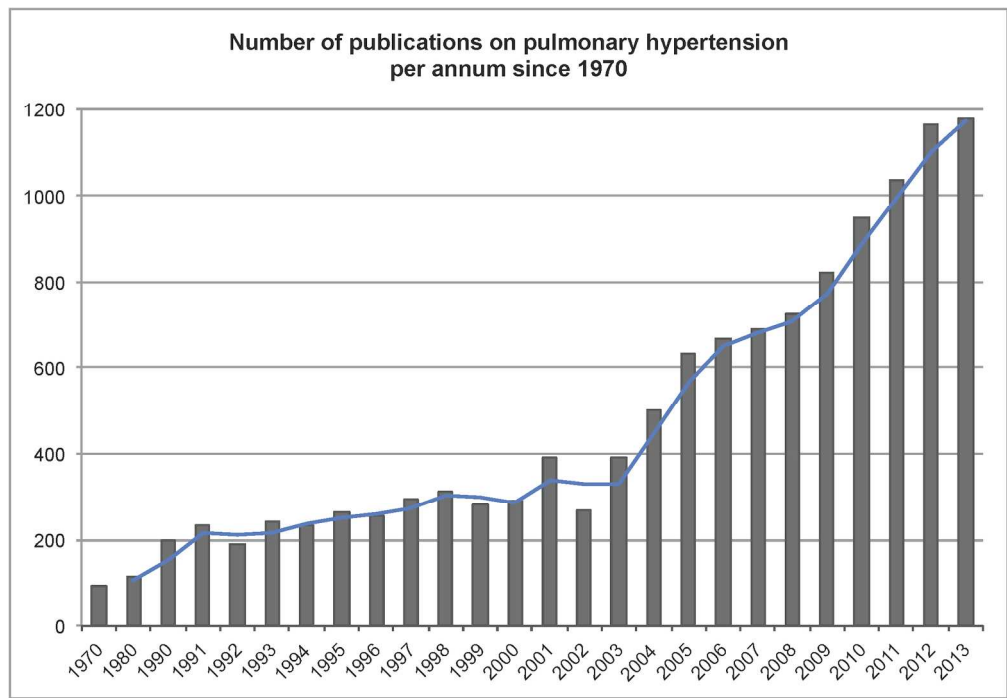
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- ~~25—Quiñones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;**15**:167–84.~~
- ~~26—Schachna L, Wigley FM, Chang B, et al. Age and risk of pulmonary arterial hypertension in scleroderma. *Chest* 2003;**124**:2098–104.~~
- ~~27—Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006;**174**:1034–41. doi:10.1164/rccm.200604-547OC~~
- ~~28—Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;**10**:165–93. doi:10.1093/ejechocard/jep007~~
- ~~29—Barst RJ, Ertel SI, Beghetti M, et al. Pulmonary arterial hypertension: a comparison between children and adults. *Eur Respir J* 2011;**37**:665–77. doi:10.1183/09031936.00056110~~
- ~~30—Ivy DD, Abman SH, Barst RJ, et al. Pediatric Pulmonary Hypertension. *J Am Coll Cardiol* 2013;**62**:D117–26. doi:10.1016/j.jacc.2013.10.028~~
- ~~31—Penning S, Robinson KD, Major CA, et al. A comparison of echocardiography and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. *Am J Obstet Gynecol* 2001;**184**:1568–70.~~
- ~~32—Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009;**179**:615–21. doi:10.1164/rccm.200811-1691OC~~
- ~~33—Lanzarini L, Fontana A, Campana C, et al. Two simple echo-Doppler measurements can accurately identify pulmonary hypertension in the large majority of patients with chronic heart failure. *J Heart Lung Transplant* 2005;**24**:745–54. doi:10.1016/j.healun.2004.03.026~~
- ~~34—Laaban JP, Diebold B, Zelinski R, et al. Noninvasive estimation of systolic pulmonary artery pressure using Doppler echocardiography in patients with chronic obstructive pulmonary disease. *Chest* 1989;**96**:1258–62.~~
- ~~35—Matsuyama W, Ohkubo R, Michizono K, et al. Usefulness of transthoracic Doppler jugular venous echo to predict pulmonary hypertension in COPD patients. *Eur Respir J* 2001;**17**:1128–31.~~
- ~~36—Farber HW, Foreman AJ, Miller DP, et al. REVEAL Registry: correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertension. *Congest Heart Fail* 2011;**17**:56–64. doi:10.1111/j.1751-7133.2010.00202.x~~
- ~~37—Janda S, Shahidi N, Gin K, et al. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart* 2011;**97**:612–22. doi:10.1136/hrt.2010.212084~~

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3 ~~38 Damy T, Goode KM, Kallvikbacka Bennett A, et al. Determinants and prognostic value~~  
4 ~~of pulmonary arterial pressure in patients with chronic heart failure. *Eur Heart J*~~  
5 ~~2010;**31**:2280–90. doi:10.1093/eurheartj/ehq245~~  
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7 ~~39 Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic~~  
8 ~~findings: standards and procedures for measurement and classification. Boston~~  
9 ~~Massachusetts: John Wright 1982.~~  
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Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Less than one per cent (0.7%) of the publications were from Africa (not displayed). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension" and Africa and African country names; results are displayed annually between 1970 and 2013.

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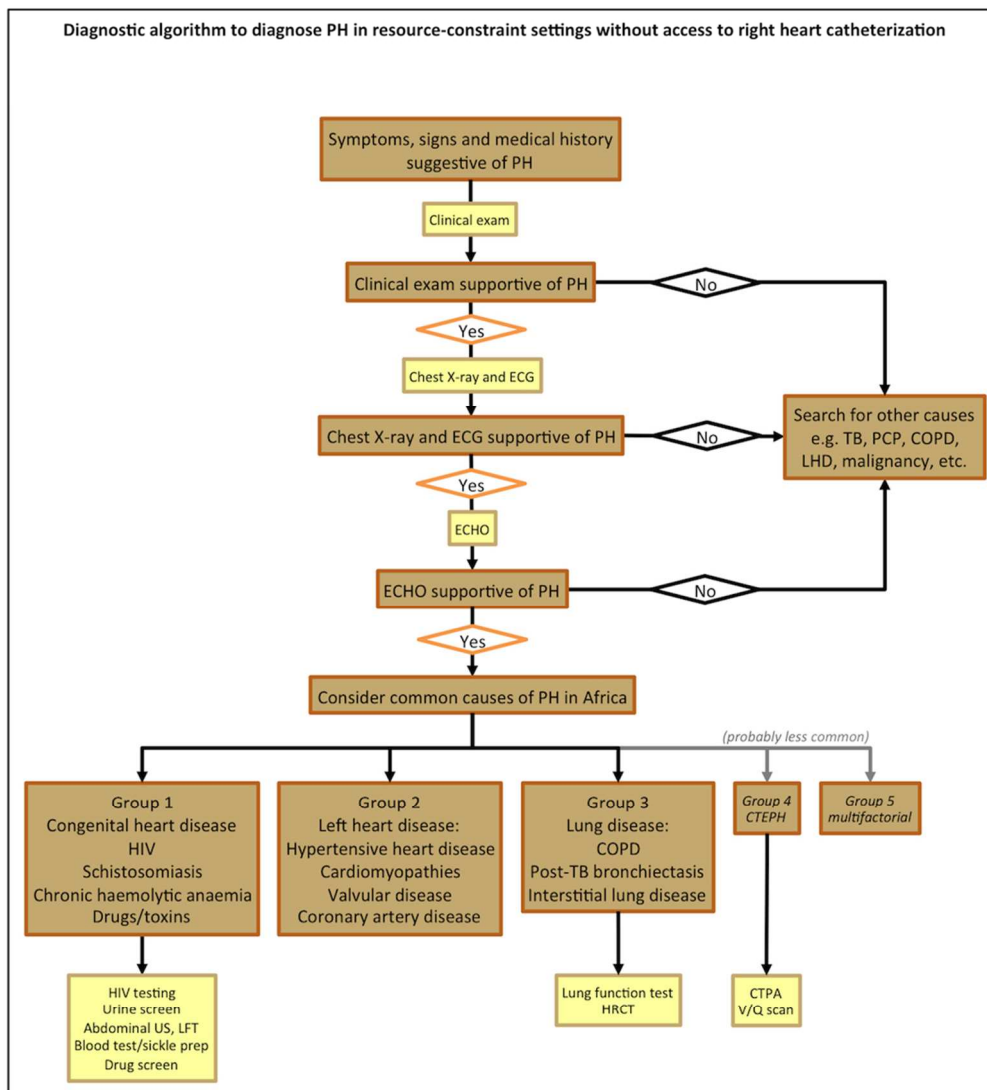


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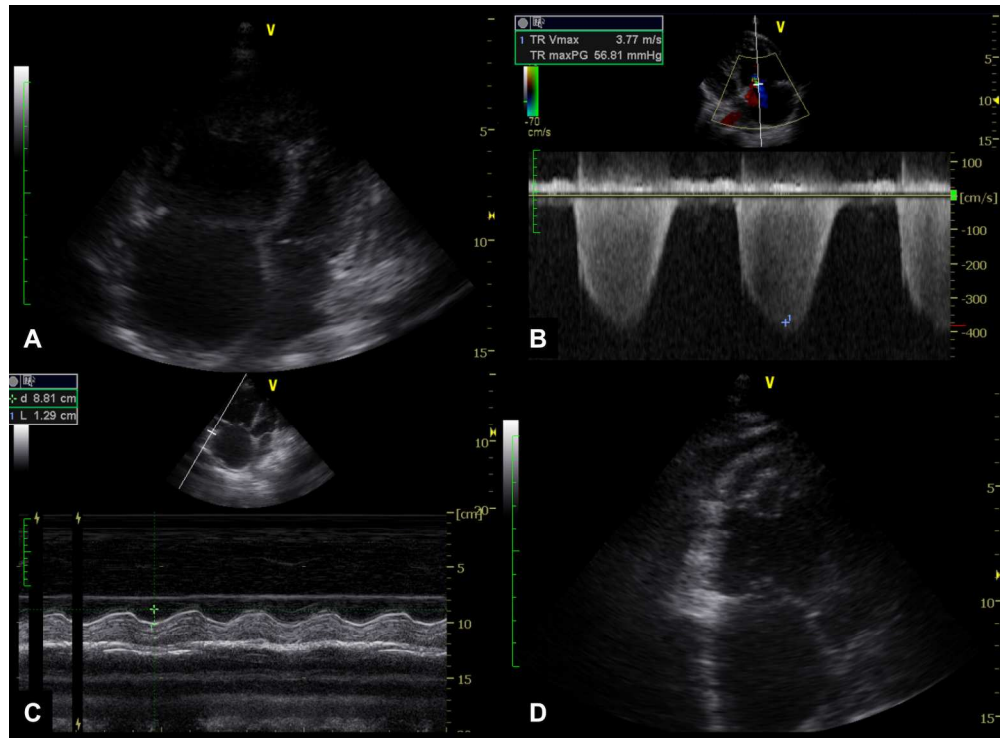
### PAPUCO Map



The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).  
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Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus; US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan  
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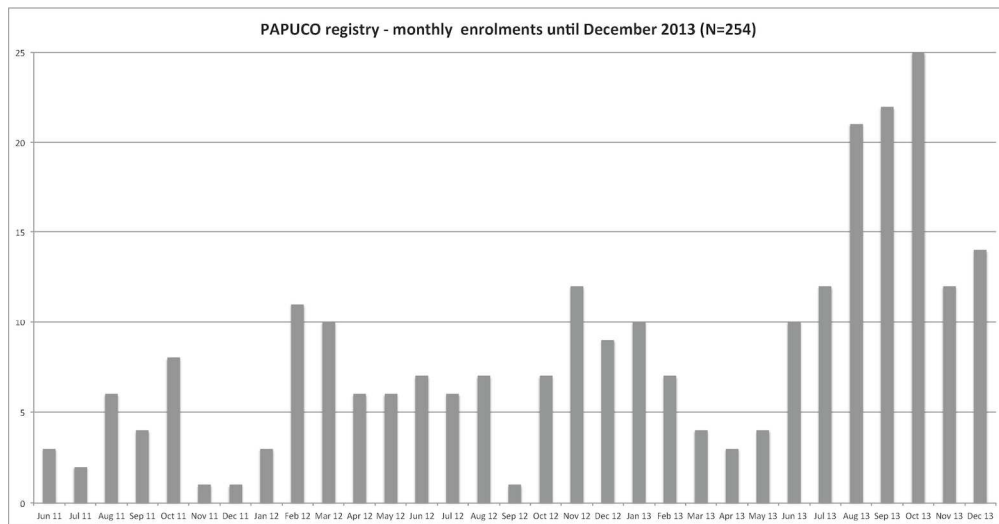


Diagnosing pulmonary hypertension using transthoracic 2D-Doppler Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-wave Doppler across the TV in the 4-chamber view showing severe TR, despite the deceptively less impressive color-flow jet seen across the valve; C: M-Mode measurement of TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left atrium; TV: tricuspid valve; TR: tricuspid regurgitation.

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PAPUCO registry - monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.  
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