

## The Cayetano Cough Monitor: A Method for Investigating Spread of Infection in Tuberculosis

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5 Infection in Tuberculosis  
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† *in memoriam* Luz Caviedes who passed away in November 2012

## ABSTRACT

*Background:* Cough is a key symptom of tuberculosis (TB) as well as the main cause of transmission. However, cough frequency (number of coughs per hour) in patients with TB has been poorly studied. The main aim of this study is to describe cough patterns before and after TB treatment and to determine baseline factors that affect cough frequency in these patients. Secondly, we will evaluate the correlation between cough frequency and TB microbiological resolution.

*Methods:* This study will select participants with suspected TB from two tertiary hospitals in Lima, Peru. Participants will initially be evaluated through questionnaires, radiology, MODS broth TB-culture, auramine smear microscopy, and cough recordings. This cohort will be followed for the initial 60 days of anti-TB treatment, and throughout the study several microbiological samples as well as 24-hour cough event recordings will be collected. We will describe the variability of coughs and determine the association with baseline laboratory parameters of pulmonary TB. In addition, we will analyse the reduction in cough frequency in predicting TB cure, adjusted for potential confounders.

*Discussion:* This will be the first published peer-reviewed study cough frequency in TB patients since the 1960s. The data could be used to develop new technologies to predict TB outcomes during treatment. Understanding the variation of cough frequency during treatment will help clinicians and policy-makers take better decisions regarding isolation and airborne precautions in patients with TB.

### Strengths and limitations of this study

- Our study has the limitation that recordings have been processed through a semi-automated algorithm. To decrease time constraints our long-time goal is to create a fully automated processing system. We anticipate that experience gained with semi-automated analysis will aid us in developing future algorithms
- A strength of this project is that its results will reflect actual cough frequency in pulmonary tuberculosis by utilising 24-hour recordings in the patients' normal-day settings (traffic, dogs barking, etc.). We expect that this will generate a novel method of evaluating cough in TB that can be used in real-world scenarios.
- The algorithm employed in this project has been validated specifically for patients with pulmonary tuberculosis, which enables us to use this algorithm in our patients.

## INTRODUCTION

Tuberculosis (TB) is an infectious disease, and was responsible for 9.0 million new cases and 1.5 million deaths in 2013.[1] TB is transmitted in the air[2 ,3] and cough is the most important cause of transmission.[4] Cough in people with pulmonary TB disease arises as a result of the inflammatory response to mycobacterial pulmonary infection. A reduction in cough is assumed to result in decreased spread of infection. Despite its crucial role in TB transmission, a recent literature review[5] reported that cough frequency during TB therapy has not been studied since work carried out by Loudon in the 1960s.[6 ,7] Thus, longitudinal cough frequency studies in TB are needed.

Loudon described cough frequency in eight-hour overnight periods for nine weeks. All sounds with amplitude and frequency consistent with possible cough events were recorded and then manually reviewed.[7 ,8] His findings show a two-fold reduction in the first two weeks of treatment, from a mean of 13.6 to 4.75 coughs/hour.[7] *Mycobacterium TB* colony forming units (CFU) also reduced significantly, from  $10^6$  at baseline  $10^3$  two weeks later.[9 ,10] This evidence led to the idea that drug-susceptible TB patients become sufficiently non-infective by the second week of treatment that they no longer posed a risk to others. This and other evidence led to the often-used policy that two weeks was the necessary duration of respiratory isolation for newly diagnosed patients commenced on appropriate treatment. Current evidence[11] and guidelines affirm this position;[12 ,13] however, this two week policy has been criticised.[14 ,15] Our group has shown that drug-susceptible TB patients remain sputum culture positive for longer.[16] Most

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3 importantly, the assumption that TB patients are no longer coughing at two  
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5 weeks has never been corroborated.  
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10 The 2015 CHEST guidelines state that acoustic parameters are the best  
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12 parameter to evaluate the frequency of cough.[17] In order to ensure accurate  
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14 measurement, it is important to use a standardised method such as  
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16 automated cough counting with a validated algorithm. Despite the recently  
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18 growing literature on this topic, these methods are principally being used in  
19  
20 the field of non-infectious chronic disease.[18-23] Whilst algorithms for cough-  
21  
22 counting have been validated[24-28] our research protocol appears to be the  
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24 first to do so specifically in patients with pulmonary TB.[29 ,30]  
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29 To address this knowledge gap, we have developed the Cayetano Cough  
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31 Monitor (CayeCoM) and here describe a protocol for it to be used to study  
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33 cough frequency in patients with pulmonary TB.  
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## 37 38 **METHODS**

### 39 40 **Study objectives**

41  
42 The primary objective of this study is to describe cough frequency patterns in  
43  
44 adults with pulmonary TB before and after treatment initiation.  
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48 The second objective of this study is to determine baseline characteristics that  
49  
50 correlate with cough frequency, such as patient demographics, radiological  
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52 findings, presence of multi drug-resistant TB (MDR-TB), and HIV status.  
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55 The third objective of this study is to test for an association between cough  
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57 frequency and microbiological resolution of TB disease.  
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## Study design

This prospective cohort study will follow adult patients with pulmonary TB through their treatment period in Lima, Peru.

Subjects with a confirmed or suspected diagnosis of active pulmonary TB will be referred to our study team. After written informed consent, we will record coughs prior to initiation of TB treatment. Subjects will provide us with early-morning sputum samples that will be tested for active pulmonary TB disease by testing at least one sputum sample using the microscopic-observation drug-susceptibility (MODS) broth culture assay[31-33] and auramine smear microscopy, which assessed the bacillary load.

Patients in whom the pulmonary TB diagnosis is confirmed by MODS will receive treatment delivered by the National TB Programme as per standard practice.[34] Figure 1 summarises the data to be collected at baseline and during the 60 days of follow-up.

## Study sites

Peru has one of the highest TB incidence rates in the Americas.[35] More than one-third of the incident TB cases in the Andean region are from Peru. With respect to rates of MDR-TB and extensively drug resistant (XDR) TB, Peru ranks first in all of the Americas. However, underreporting in the region may contribute to Peru's overrepresentation, as shown in the latest Pan American Health Organization (PAHO) report.[35]

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5 Within Peru, Lima and its metropolitan area account for most cases of MDR-  
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7 TB and XDR-TB.[36] Thus, we will recruit patients from two hospitals: Hospital  
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9 Nacional Dos de Mayo, located in the historic centre of Lima; and Hospital  
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11 Nacional Daniel Alcides Carrión, located in Callao and which belongs to  
12  
13 Lima's metropolitan area.  
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18 Our main site, Hospital Nacional Dos de Mayo (HNDM), is a 650-bed teaching  
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20 and public national tertiary referral hospital run by the Peruvian Ministry of  
21  
22 Health (MINSA). It provides services to the poor population from the  
23  
24 surrounding inner city area. HNDM is the only hospital in Peru with a negative  
25  
26 pressure ward available for TB patients. Our secondary site is another tertiary  
27  
28 referral hospital run by MINSA, Hospital Nacional Daniel Alcides Carrión. This  
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30 462-bed teaching health facility lies in the Callao region.  
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### 36 **Study population**

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38 The infectious disease and pulmonary physicians will refer subjects to the  
39  
40 research team. Criteria for referral are suspicion of active pulmonary TB or a  
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42 confirmed case of active pulmonary TB who has not yet started treatment.  
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44 Active pulmonary TB is defined by a positive MODS culture result. Subjects  
45  
46 will be excluded if they were less than 18 years of age, pregnant, had started  
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48 a new treatment regimen for TB within the last 30 days, or are unable or  
49  
50 unwilling to provide informed consent. If a patient changes treatment regimen,  
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52 for example due to treatment failure or to an adverse drug reaction, this would  
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3 also be considered as a new regimen. Pregnancy is defined by a positive  
4 result on serum or urine beta human chorionic gonadotropin ( $\beta$ -hCG) assay.  
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### 9 10 **Outcomes and case definitions**

11 The primary outcomes for this study are cough frequency and microbiological  
12 data from serial sputum samples. Cough frequency is defined as the number  
13 of cough episodes, or cough epochs, within a time period. Cough epochs are  
14 defined as cough events that are within a two-second period frame.[30]  
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22 Regarding microbiological data, participants will be entered into the study if  
23 they have a positive culture result. Treatment regimens will be adjusted as  
24 needed by the treating team based on the results of the MODS drug-  
25 susceptibility testing from their sputum. Our study team will not be involved in  
26 the treatment regimen selection.  
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36 Sputum smear conversion is defined as three consecutive smear-negative  
37 results, collected at least 8 hours apart after initial smear positivity at  
38 diagnosis.[37] Culture conversion is defined as two consecutive negative  
39 culture results, taken at least 30 days apart. This last definition is the one  
40 used in the Ministry of Health (MINSA)[34] and is recommended by the World  
41 Health Organization (WHO).[38] The date of conversion will be considered as  
42 the date of the first negative sputum smear or culture contributing to  
43 conversion.  
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3 Secondary outcomes include weight, temperature, and radiological  
4 characteristics. When possible, radiological interpretation data from chest  
5 films and thoracic computed tomography (CT) scans will be obtained. Chest  
6 X-ray films (CXR) provide a high negative predictive value for the presence of  
7 active TB[39] but CT scans provide higher sensitivity for the detection of  
8 lymphadenopathy, early bronchogenic spread, and to evaluate cavitation and  
9 disease activity.[40]  
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### 20 21 **Sample size**

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23 In a pilot study we estimated that the frequency of cough in TB patients before  
24 receiving treatment is approximately 327 coughs during a 24-hour period with  
25 a standard deviation of approximately 50. A sample size of 97 patients would  
26 enable us to detect a conservative decrease of the mean number of coughs in  
27 the 24-hour period of at least 45 coughs after two weeks of treatment, with a  
28 5% Type I error probability and 80% power.  
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38 Under the hypothesis that TB patients before treatment experience a high  
39 cough frequency, we hypothesise that after two weeks of anti-TB treatment,  
40 there will be a clinical response accompanied by a significant reduction in  
41 cough frequency. Response is defined as at least a two-fold reduction in  
42 cough frequency. Response is defined as at least a two-fold reduction in  
43 cough frequency, which was previously shown to occur within the first 2  
44 weeks of treatment.[7] For power calculations, it is assumed that all subjects  
45 will eventually respond to treatment, according to our definition of response,  
46 and that once cough frequency has reduced in an individual it will not rise  
47 again. We assume that after the two weeks of treatment approximately 10%  
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3 of patients would maintain a high frequency of cough. Thus, a sample size of  
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5 97 patients will allow us to detect an odds ratio of at least 3.2 for the risk of  
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7 patients not responding to TB treatment in two weeks of therapy, under a 95%  
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9 significance and 80% power.  
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### 11 12 13 14 **Study organisation**

15 The Asociación Benéfica (A.B.) PRISMA and Universidad Peruana Cayetano  
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17 Heredia in Lima, Peru will provide local administrative oversight. Overseas,  
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19 oversight will be conducted by Johns Hopkins University in Baltimore,  
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21 Maryland, USA.  
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25 In Lima, the Pampas office of A.B. PRISMA will provide operations and  
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27 logistic support for fieldwork. An additional collaborating signal processing  
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29 team will be based locally in the Universidad Nacional de Ingeniería, Lima,  
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31 Peru, as well as at Tufts University, Massachusetts, USA.  
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35 Our collaborating biostatisticians are based at Tufts University, Tulane  
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37 University, and Universidad Peruana Cayetano Heredia, Lima, Peru. All  
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39 investigators are involved in protocol design and technical support and will  
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41 remain involved in the on-going analyses.  
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### 44 45 46 **Personnel, training and logistics**

47 Nurses have been trained by study staff to obtain sputum samples in a best-  
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49 practice fashion based on previous work,[41 ,42] and to operate and  
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51 troubleshoot all recorder devices, memory cards, and battery packs. Written  
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53 informed consent is required by all participants. At the time of enrolment  
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55 subjects will follow the procedures outlined in Figure 1.  
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5 Subjects with active pulmonary TB will be followed throughout their TB  
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7 treatment. After the identification of active pulmonary TB and based on  
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9 convenience basis, subjects who consent will undergo CXR and a non-  
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11 contrast thoracic CT scan.  
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16 The first day of a new TB treatment regimen is defined as "Day 0". An initial  
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18 questionnaire will be completed on that day (Supplementary 1). This  
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20 questionnaire is similar to the one that was employed in a previous study.[43]  
21  
22 Baseline cough frequency will be obtained by performing an audio recording  
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24 of the patients before they obtain their microbiological results, which is usually  
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26 a few days prior to treatment initiation. Hence, subjects will be recorded from  
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28 at least one day prior to treatment and throughout their first two weeks of  
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30 treatment. They will be subsequently recorded for 24 hours on or around days  
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32 21, 30 and 60 of treatment, although up to two days date deviation for  
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34 Sundays and public holidays will be allowed.  
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41 Recordings will start at 09:00 hours and will be as continuous as possible.  
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43 Occasionally incomplete recordings could be obtained due to malfunction of  
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45 equipment or patient non-compliance. On the recording days clinical data will  
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47 be gathered, including: weight, temperature, sputum samples for smear and  
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49 MODS results. The number of days to culture positivity on the MODS assays  
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51 will be recorded in order to assess the microbiological burden in the patients'  
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53 samples.  
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### Audio recording

Design of the audio recording equipment, the CayeCoM device, builds on previous chronic cough ambulatory audio recordings.[25 ,44 ,45] The CayeCoM device is a Marantz PMD 620 professional handheld recorder, using an Audio-Technica AT899 sub-mini microphone with an AT8537 microphone power module. The microphone will be attached at the patient's lapel as shown in Figure 2. The recorder is adapted to work with an external lithium battery supply (Enix Energies 800040) to enable continuous 24-hour recordings. The audio is recorded onto a SanDisk SDHC 8 GB card, at a sample rate of 48 kHz, encoding 64 kbps in mono in MP3 format. The audio equipment is kept inside a basic pack connected to a lapel microphone. Batteries and SD cards will be exchanged daily by the study nurses. In pilot research, subjects tolerated the audio equipment well, wearing them 24 hours a day and taking them off only to bathe.

### Processing of audio recordings

The recorded signals will be analysed after all patient recordings are completed. For cough analysis, software developed by our group and previously described in detail will be used.[29 ,30] This semi-automated approach has an initial automated step that removes the large majority of possible events. Thus on average, review time is reduced by nearly two orders of magnitude compared to a fully manual review in which the entire recording is reviewed.

## Microbiology

The microbiological tests will be carried out in a Biosafety Containment Level 3 research laboratory situated within Universidad Peruana Cayetano Heredia in Lima, Peru. The sputum samples will be digested and decontaminated by the standard NaOH-N-acetyl cysteine method.[46] For smear microscopy, an aliquot of 100 µl is stained with Auramine O and examined with x400 magnification. Results are determined as negative, paucibacillary (1-19 acid fast bacilli [AFB] visualized in 40 fields), 1+ (20-199 AFB visualized in 40 fields), 2+ (5-50 AFB per field) and 3+ (>50 AFB per field). Culture and MODS susceptibility testing will be performed with the remaining samples, according to standard protocols.[31-33]

## Radiology

Radiological information will be gathered, when possible, on a convenience basis. Priority will be given to CT scans, since they have been shown to be more sensitive. Films will be read by a local radiologist and a US board-certified radiologist blinded to the patient's demographics and outcomes. They will provide an interpretation that is standardised as per our study protocol to describe radiological findings including cavitation, consolidation, lymphadenopathy, and effusions (Supplementary 2). Cavitations will be further described by size, location, presence or absence of an air-fluid level, and cavity wall thickness based on prior work that shows the relevance of these findings to pulmonary TB.[47-49]

## Statistical methodology and analysis



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3 All questionnaire data will be double-digitised from paper forms using Visual  
4 FoxPro 9 Service Pack 2 (Microsoft Corp. Redmond, Washington, USA) and  
5  
6 microbiological data will be double entered using Microsoft Access 2010  
7  
8 (Microsoft Corp. Redmond, Washington, USA). These two data sets will be  
9  
10 cross-compared for validity and errors. From these data, descriptive statistics  
11  
12 will be tabulated and graphed.  
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18 Cough analysis processing results will be stored as Matlab (Mathworks, Inc,  
19  
20 Natick MA) files containing information regarding each event and its  
21  
22 timestamp. Algorithmically detected coughs will be annotated in the files. After  
23  
24 manual review, isolated cough events will be grouped into cough epochs, or  
25  
26 bursts of closely spaced individual coughs within 2 seconds, following  
27  
28 published work on cough evaluation.[50] We have previously published a  
29  
30 review and discussion of these various metrics (including number of individual  
31  
32 coughs, number of cough bouts or epochs, and number of 1-sec periods  
33  
34 containing cough).[30]  
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41 For the first study objective of describing cough frequency, cough epochs will  
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43 be plotted throughout the day, and cough frequency will be summarized as  
44  
45 the frequency of cough epochs per hour. To address the second study  
46  
47 objective, characterising correlated of cough frequency, we will use  
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49 generalised estimating equations (GEE) based Poisson or negative binomial  
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51 regression with baseline microbiologic status, and trigonometric (sine/cosine)  
52  
53 terms to model circadian periodicity, as the independent variables. In addition,  
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55 a multiple logistic regression in a longitudinal generalized linear model (GLM)  
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3 framework analysis will evaluate a function of sputum bacillary load and with  
4  
5 cough frequency that we propose as a potential predictor of TB  
6  
7 transmissibility. In all cases we will correct for outliers, and nested models will  
8  
9 be compared using the likelihood ratio test.  
10

11 To test the association between cough frequency and microbiological  
12 resolution of TB disease associated with the third aim of this study, time-to-  
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14 event survival analyses where the outcomes of interest are sputum smear  
15  
16 conversion, and culture conversion, as defined above, and the primary  
17  
18 predictors of interest are cough frequency at baseline, during treatment, and  
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20 time to two-fold reduction in cough frequency. In addition, secondary analyses  
21  
22 of weight, temperature, and radiological characteristics, will be conducted  
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24 using generalized linear models and GEE logistic regression as appropriate.  
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### 34 **Ethical considerations**

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36 Ethical approval has been obtained from the ethics committees at A.B.  
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38 PRISMA in Lima, Peru, the Universidad Peruana Cayetano Heredia in Lima,  
39  
40 Peru, and Johns Hopkins University, in Baltimore, USA. Written informed  
41  
42 consent will be obtained from all participants. Test results will be delivered by  
43  
44 telephone call or at subsequent visits at which time a team physician or nurse  
45  
46 will be able to explain the results to the study participants. TB treatment  
47  
48 remains the responsibility of the medical staff in charge and the national TB  
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50 Programme.  
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### 55 **Discussion**

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57 We will determine cough frequency before and during anti-TB treatment using  
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3 the CayeCoM device. We will identify baseline predictors of cough frequency  
4 during TB treatment and evaluate the correlation between change in cough  
5 frequency and microbiological resolution.  
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11 The medical literature currently lacks information about cough frequency in  
12 TB. As recently noted by Turner and Bothamley,[5] cough frequency in  
13 patients undergoing TB treatment has only been studied once, almost half a  
14 century ago.[6 ,7] This previous study has the limitation of only being  
15 conducted within an 8-hour period, overnight, and thus there is no information  
16 on daytime coughing or the effect of the diurnal rhythm on cough. A similar  
17 study[51] demonstrated that the severity of cough and pathological chest x-  
18 ray findings were associated with higher levels of TB transmission. However,  
19 their study did not measure cough frequency but instead focused on a  
20 subjective characteristic: cough severity. It should be noted that to assess  
21 cough frequency one must utilise objective acoustic parameters, since self-  
22 reported cough is unreliable.[17] As reported in abstract form, the objective  
23 acoustic Leicester Cough Monitor (LCM) has been used to evaluate 24-hour  
24 cough recordings in patients with pulmonary TB before starting treatment,  
25 showing that cough frequency is reduced at night.[52] This further justifies re-  
26 evaluation of Loudon's overnight study.  
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48 Our project has several strengths and limitations. An important strength is the  
49 generation of 24-hour cough recordings, which will provide lengthy recordings,  
50 will enable evaluation of cough patterns at different times of day, and also has  
51 the benefit of being recorded during a normal day in real-world settings where  
52 we expect our device to be used in the future. Normal day recordings are filled  
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3 with noise, which is a challenge for analysis of cough recordings, considering  
4 that traffic and environmental noise (such as dogs barking, music, and  
5 television) may generate noises similar to cough. To diminish this effect we  
6 have incorporated a time-varying estimate of the noise background as well as  
7 a data quality control. Having a semi-automated algorithm is a limitation, since  
8 it requires time and human input, but also a strength since the human ear is  
9 the gold standard for determining the characteristic sound of cough. Similar to  
10 Loudon's proposal,[8] our algorithm will help to screen and reduce the length  
11 of the recordings to ~5% of their original length, without affecting sensitivity  
12 and improving specificity.[30] Fully automated processing remains a long-term  
13 goal for our group, and we anticipate that experience gained with semi-  
14 automated analysis will aid us in developing future algorithms.

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32 CayeCoM has been validated for 24-hour recordings,[30] whereas  
33 PulmoTrack (PulmoTrack-CC, KarmelSonix, Haifa, Israel) was validated for  
34 25 minutes[27] and the Hull Automatic Cough Counter for 1-hour  
35 recordings.[25] Other systems have also validated their algorithms for 24-hour  
36 recordings, such as the LCM,[26 ,53] VitaloJAK,[28] and the LifeShirt  
37 System.[24] However, in contrast to our study, none of these algorithms have  
38 been validated in the setting of pulmonary TB nor within real-life settings (e.g.  
39 traffic). We expect that this project will generate a novel method of evaluating  
40 cough in TB that can be used in real-world scenarios, potentially where  
41 laboratory investigations are unavailable.

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Cough frequency should provide additional information regarding the

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3 evolution of the patients' medical condition. If a correlation with bacteriological  
4 treatment response is demonstrated, this has the possibility to contribute to  
5 patient management without relying on a laboratory in adult patients with  
6 pulmonary TB. However, we should be careful when monitoring TB patients  
7 since many might worsen their biomarkers after an initial positive response to  
8 therapy. It could assist with decisions regarding the need for on-going  
9 respiratory isolation of patients, treatment duration, and identification of  
10 patients with treatment failure who may need modification of their treatment  
11 regimens. The device also has the potential to be used remotely, as in  
12 telemedicine. This is potentially important in a country such as Peru, where  
13 the majority of doctors live in the capital, leaving most of the country without a  
14 physician in their region.

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**Conflicts of interest:**

All authors declare that they have no conflict of interest in relation to this work.

**Ethics approval:**

Ethical approval has been obtained from the ethics committees at A.B. PRISMA in Lima, Peru, the Universidad Peruana Cayetano Heredia in Lima, Peru, and Johns Hopkins University, in Baltimore, USA.

**Contributors:**

All authors were involved in the study design and writing of the manuscript, and all reviewed the final manuscript before submission. MAB and JWL directly contributed to study design and are responsible for supervision of data gathering. AP, BHT, JWL, MZ and GL will be responsible for data management and statistical analysis for this project.

**Data Sharing Statement:**

No unpublished data are available. We aim to publish and disseminate our results, once the project is complete. We also expect to create and maintain an online repository for TB cough sounds as well as the statistical analysis employed.

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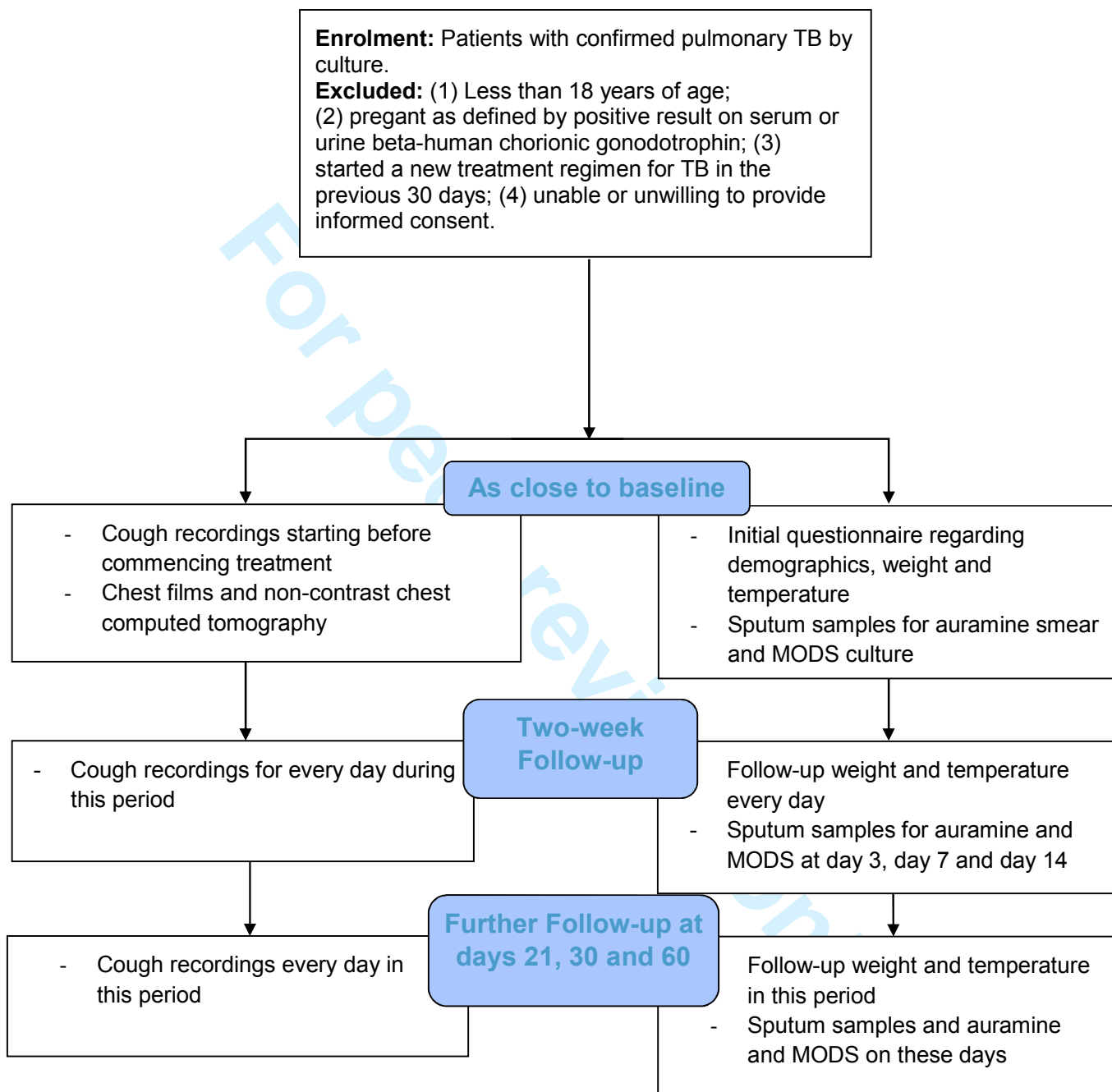
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Figure 1 – Flow Diagram for CayeCoM Study



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Figure 2 – Picture of the Cayetano Cough Monitor (CayeCoM)



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Código del paciente: \_\_\_\_\_  
 Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

Entrevistador: \_\_\_\_\_

### **Cuestionario Inicial Para Todos Los Participantes:**

#### Datos Demográficos:

1. Edad: \_\_\_\_\_
2. Sexo: \_\_\_\_\_

#### Antecedentes:

3. ¿Cuántas personas normalmente duermen en casa?: \_\_\_\_\_ Personas
4. ¿Cuántas habitaciones hay en su hogar? (sin contar baño, pasadizo, cocina, depósito, garaje): \_\_\_\_\_ habitaciones.
5. ¿Cuál es el ingreso mensual de la vivienda? S/. \_\_\_\_\_
6. ¿Cuánto gasta su familia en alimentación cada semana? S/. \_\_\_\_\_
7. ¿Cuántas personas en su vivienda comen de esos alimentos que compran semanalmente? \_\_\_\_\_ Personas
8. ¿Cuántas veces en el último mes usted se ha acostado con bastante hambre porque no había comida en casa? \_\_\_\_\_ días

#### Historia de Tuberculosis:

La tuberculosis es una enfermedad que se trata con varios antibióticos a la vez, y cuyo tratamiento dura varios meses.

9. ¿Ha sido diagnosticado con TBC anteriormente?
  - a. Si
  - b. No → *Pase a la pregunta 15*
  - c. NS

10. ¿Cuántas veces? \_\_\_\_\_

11. Si recibió tratamiento para la TBC, ¿dónde recibió la mayor parte del tratamiento?
  - a. NA
  - b. Mismo distrito
  - c. Otro distrito
  - d. Otra ciudad
  - e. Otro país

12. Si recibió tratamiento para la TBC ¿por cuántos meses en total lo tomó? \_\_\_\_\_

13. Si recibió tratamiento previo, en que esquema estaba (lo más recién): -  
 \_\_\_\_\_

14. Si recibió tratamiento para la TBC ¿cumplió con el tratamiento previo?
  - a. NA
  - b. Si
  - c. No → \_\_\_\_\_
  - d. NS

#### Factores de Riesgo

15. ¿Ha compartido un cuarto con alguien que haya tenido TBC comprobada?
  - a. Si, y esta persona también tenía una tos persistente
  - b. Si, pero esta persona concurrente no tenía una tos persistente
  - c. No → *Pase a la pregunta 18*
  - d. NS

16. ¿Dónde compartió este ambiente con alguien infectado con TBC?
  - a. NA
  - b. Trabajo
  - c. Casa
  - d. Hospital
  - e. Otro: \_\_\_\_\_

17. ¿Por cuántos días compartió este ambiente con la persona con TBC comprobada? \_\_\_\_\_

18. Aparte de usted, ¿alguien más en casa esta actualmente recibiendo medicinas para la TBC?
  - a. Si → Quien: \_\_\_\_\_
  - b. No
  - c. NS

#### Creencias y Conocimiento de la Enfermedad

19. ¿Dónde escuchó de la TBC por primera vez?
  - a. Familia
  - b. Amigos
  - c. Colegio
  - d. Puesto de Salud
  - e. TV
  - f. Radio
  - g. NS

20. ¿Puede alguien con TBC y tos infectar a sus familiares?
  - a. Si
  - b. No
  - c. NS

Cuestionario Inicial Para Todos Los Participantes

1

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

Código del paciente: \_\_\_\_\_

Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

21. ¿Qué tan contagiosa cree que es la TBC?

- a. Nada
- b. Poquito
- c. Mucho
- d. Bastante
- e. Lo mas

22. ¿Qué tan seria cree que es la TBC?

- a. Nada
- b. Poquito
- c. Mucho
- d. Bastante
- e. Lo mas

23. En general, ¿qué puede hacer uno por si mismo para protegerse de contraer la TBC? [Marcar el factor más importante, no sugerir repuestas].

- a. Vacunarse
- b. Comer
- c. Dormir bien, descansar
- d. Vivir una vida ordenada
- e. Mantenerse alejado de la gente con TBC
- f. Educarse
- g. Otro: \_\_\_\_\_
- h. NS

¿Cuales son los síntomas de la TBC?

[Marcar los factores, no sugerir repuestas].

24. Tos mencionada

Si  No 

25. Hemoptysis mencionada

Si  No 

26. Fiebre mencionada

Si  No 

27. Baja de peso mencionada

Si  No 

28. Fatiga, decaimiento mencionada

Si  No 

29. Palidez, un cierto semblante mencionada

Si  No 

30. ¿Qué debe hacer una persona con TBC para mejorarse? [Marcar el factor más importante, no sugerir repuestas].

- a. Tomar sus medicinas, asistir a controles
- b. Comer mas, comer mejor
- c. Descansar
- d. Tener fe
- e. Abrigarse
- f. Otro: \_\_\_\_\_
- g. NS

31. ¿Cómo puede hacer una persona con TBC para no contagiar la TBC a otros? [Marcar el factor más importante, no sugerir repuestas].

- a. Cubrirse la boca al toser
- b. Quedarse en casa, mantenerse alejado
- c. Seguir el tratamiento
- d. Separar cubiertos
- e. Otro: \_\_\_\_\_
- f. NS

32. ¿Se puede curar la TBC?

- a. Siempre
- b. Normalmente sí
- c. A veces
- d. Raramente
- e. Nunca

**Direcciones:** Marque una X sobre la línea la posición que escoges.

Ejemplo: -----□-----

33. Con que frecuencia esta tosiendo hoy, en un promedio de 24 horas?

**Direcciones:** Marque una X, en el cuadrado, todas las alternativas que corresponden.Ejemplo: 

34. Que indicadores utilizó para escoger a que posición poner sus X?

- Los números: 1, 2, 3, 4, 5
- Las palabras: nunca, poquito, mucho, casi siempre

- Las figuras: 

Cuestionario Inicial Para Todos Los Participantes

2

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

Código del paciente: \_\_\_\_\_

Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

**Direcciones:** Marque con X la alternativa que corresponde.Ejemplo: 

35. ¿Comparado con hace tres días, tiene más frecuencia de tos el día de hoy?

- a.  Tosiendo ahora menos  
 b.  Tosiendo ahora igual  
 c.  Tosiendo ahora más

37. Si tiene tos, ¿a que hora en el día tiene más frecuencia: *mañana, tarde o noche*?

- a.  Mañana  
 b.  Tarde  
 c.  Noche

36. El día de hoy, ¿ha tenido *solo tos, tos con flema o solo flema*?

- a.  Solo tos  
 b.  Tos con flema  
 c.  Solo flema

38. Qué tan frecuentemente tose?

- a.  Cada pocos segundos  
 b.  Cada pocos minutos  
 c.  Cada pocas horas  
 d.  No tose

**Direcciones:** Marque el numero de días en total que tiene los siguientes síntomas desde que se enfermó. Marque 0 si ningún día.

39. ¿Cuántos días usted ha tenido los siguientes síntomas?

- a. Tos seca \_\_\_\_\_  
 b. Tos con flema \_\_\_\_\_  
 c. Tos con sangre \_\_\_\_\_  
 d. Fiebre \_\_\_\_\_  
 e. Falta de aire \_\_\_\_\_  
 f. Perdida de peso \_\_\_\_\_  
 g. Cansancio o decaimiento \_\_\_\_\_  
 h. Sudor nocturno \_\_\_\_\_  
 i. Falta de apetito \_\_\_\_\_

**Direcciones:** Responde a la pregunta en el lugar indicado.

40. Actualmente, ¿como se siente? (0 = mal, 10 = bien): \_\_\_\_\_

41. Cuando tiene tos, ¿cuántas toses tiene por hora? \_\_\_\_\_

42. Preguntas sobre VIH

	Manifiesto del paciente	Historia clínica
a. Usted ha sido diagnosticado por VIH?	_____	_____
b. Fecha de Diagnostico:	_____	_____
c. Ultima Carga Viral:	_____	_____
d. Fecha de ultima Carga Viral:	_____	_____
e. Ultimo resultado CD4:	_____	_____
f. Fecha de Ultimo resultado CD4:	_____	_____
g. Tiempo tomanda TARGA (años)	_____	_____

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

### **Radiologic Interpretation Data Form**

Date of read: \_\_\_\_\_

Radiologist Name: \_\_\_\_\_

Radiologist Signature: \_\_\_\_\_

Patient code: \_\_\_\_\_

Patient gender:  male  female

Patient age: \_\_\_\_\_

#### **1. Type of film:**

AP  PA  Lateral from R  Lateral from L  Thoracic CT  
without contrast  Other: \_\_\_\_\_

2. Date of film: Day: \_\_\_\_\_ Month: \_\_\_\_\_ Year: \_\_\_\_\_

3. Rotation: \_\_\_\_\_

4. Adequacy of inhalation: \_\_\_\_\_

	<b>Site</b>	<b>a. Consolidation?</b>	<b>b. Cavitation?</b>	<b>c. Pneumatocele?</b>	<b>d. Atelectasis?</b>
5	Right upper lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
6	- anterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
7	- apical	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
8	- posterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
9	Right middle lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
10	Right lower lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
11	- superior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
12	- basal	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
13	Left upper lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
14	- anterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
15	- apical	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
16	- posterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
17	Lingula	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
18	Left lower lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
19	- superior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
20	- basal	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no

21. Pleural effusion?  yes  no  
left?  small  medium  large  
right?  small  medium  large



La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

22. Miliary spread?  yes  no

23. Pneumothorax?  yes  no

where and size: \_\_\_\_\_

24. Lymphadenopathy:  yes  no

which lymph nodes groups

hilar  mediastinal

25. Pericardial effusion?  yes  no

left?  small  medium  large

26. Bronchiectasis?  yes  no

where: \_\_\_\_\_

27. Fibrosis?  yes  no

where: \_\_\_\_\_

any retractions, deviations? \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

28. Mediastinal thickening?  yes  no

29. Any tree-in-bud pattern? Where? \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

30. Cavitation: For each cavity, please describe:

Cavity # 1:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  think  thick smooth nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 2:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  think  thick smooth nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity #3:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 4:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 5:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

More cavities?  yes: please use another sheet to describe  no

Other findings such as fractures, cardiac abnormalities, exudative / fibrotic densities, bronchogenic spread, mass-like lesions (calcified vs. non-calcified), please describe:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

31. Normal film?  yes  no

# BMJ Open

## A protocol for studying cough frequency in people with pulmonary tuberculosis

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Date Submitted by the Author:	04-Jan-2016
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<b>Primary Subject Heading</b>:	Global health
Secondary Subject Heading:	Respiratory medicine, Infectious diseases, Global health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Cough, Monitoring

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3 **Title:** A protocol for studying cough frequency in people with pulmonary  
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† *in memoriam* Luz Caviedes who passed away in November 2012

## ABSTRACT

*Introduction:* Cough is a key symptom of tuberculosis (TB) as well as the main cause of transmission. However, a recent literature review (Turner et al. 2015, J Infect Dis) found that cough frequency (number of coughs per hour) in patients with TB has only been studied once, by Loudon in 1969 (Loudon et al. 1969, Am Rev Respire Dis). The main aim of this study is to describe cough patterns before and after TB treatment and to determine baseline factors that affect cough frequency in these patients. Secondly, we will evaluate the correlation between cough frequency and TB microbiological resolution.

*Methods:* This study will select participants with culture confirmed TB from two tertiary hospitals in Lima, Peru. Based on Loudon's results, we estimated that a sample size of 107 patients was sufficient to detect clinically significant changes in cough frequency. Participants will initially be evaluated through questionnaires, radiology, MODS broth TB-culture, auramine smear microscopy, and cough recordings. This cohort will be followed for the initial 60 days of anti-TB treatment, and throughout the study several microbiological samples as well as 24-hour cough event recordings will be collected. We will describe the variability of coughs and determine the association with baseline laboratory parameters of pulmonary TB. In addition, we will analyse the reduction in cough frequency in predicting TB cure, adjusted for potential confounders.

*Ethics and dissemination:* Ethical approval has been obtained from the ethics committees at A.B. PRISMA in Lima, Peru, the Universidad Peruana Cayetano Heredia in Lima, Peru, and Johns Hopkins University, in Baltimore, USA. We aim to publish and disseminate our findings in peer-reviewed journals. We also expect to create and maintain an online repository for TB cough sounds as well as the statistical analysis employed.



### Strengths and limitations of this study

- The algorithm employed in this project has been validated specifically for patients with pulmonary tuberculosis, which enables us to use this algorithm in our patients.
- A strength of this project is that its results will reflect actual cough frequency in pulmonary tuberculosis by utilising 24-hour recordings in the patients' normal-day settings (traffic, dogs barking, etc.). We expect that this will generate a novel method of evaluating cough in TB that can be used in real-world scenarios.
- Our study has the limitation that recordings have been processed through a semi-automated algorithm. To decrease time constraints our long-time goal is to create a fully automated processing system. We anticipate that experience gained with semi-automated analysis will aid us in developing future algorithms.

## INTRODUCTION

Tuberculosis (TB) is an infectious disease, and was responsible for 9.6 million new cases and 1.5 million deaths in 2014.[1] TB is transmitted in the air[2 ,3] and cough is the most important cause of transmission.[4] Cough in people with pulmonary TB disease arises as a result of the inflammatory response to mycobacterial pulmonary infection. A reduction in cough is assumed to represent adequate response to treatment, and to result in decreased risk of spread of infection. Despite its crucial role in TB transmission, a recent literature review[5] reported that cough frequency during TB therapy has not been studied since work carried out by Loudon in the 1960s.[6 ,7] Thus, longitudinal cough frequency studies in TB are needed.

Loudon described cough frequency in eight-hour overnight periods for nine weeks. All sounds with amplitude and frequency consistent with possible cough events were recorded and then manually reviewed.[8] His findings show a two-fold reduction in the first two weeks of treatment, from a mean of 13.6 to 4.75 coughs/hour.[7] *Mycobacterium TB* colony forming units (CFU) also reduced significantly, from  $10^6$  at baseline to  $10^3$  two weeks later.[9 ,10] This evidence led to the idea that drug-susceptible TB patients become sufficiently non-infective by the second week of treatment that they no longer posed a risk to others. This and other evidence led to the often-used policy that two weeks was the necessary duration of respiratory isolation for newly diagnosed patients commenced on appropriate treatment. Current evidence[11] and guidelines affirm this position;[12 ,13] however, this two week policy has been criticised.[14 ,15] Our group has shown that drug-

1  
2  
3 susceptible TB patients remain sputum culture positive for longer.[16 ,17]  
4  
5 Most importantly, the assumption that TB patients are no longer coughing at  
6  
7 two weeks has never been corroborated.  
8  
9

10  
11  
12 The 2015 CHEST guidelines state that acoustic parameters are the best  
13  
14 parameter to evaluate the frequency of cough.[18] In order to ensure accurate  
15  
16 measurement, it is important to use a standardised method such as  
17  
18 automated cough counting with a validated algorithm. Despite the recently  
19  
20 growing literature on this topic, these methods are principally being used in  
21  
22 the field of non-infectious chronic disease.[19-24] Whilst algorithms for cough-  
23  
24 counting have been validated[25-29] our research protocol appears to be the  
25  
26 first to do so specifically in patients with pulmonary TB.[30 ,31]  
27  
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29

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32 To address this knowledge gap, we have developed the Cayetano Cough  
33  
34 Monitor (CayeCoM) and here describe a protocol for it to be used to study  
35  
36 cough frequency in patients with pulmonary TB.  
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## 40 **METHODS**

### 41 **Study objectives**

42  
43 The primary objective of this study is to describe cough frequency patterns in  
44  
45 adults with pulmonary TB before and after treatment initiation.  
46  
47

48  
49 The second objective of this study is to determine baseline characteristics that  
50  
51 correlate with cough frequency, such as patient demographics, radiological  
52  
53 findings, presence of multi drug-resistant TB (MDR-TB), and HIV status.  
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57 The third objective of this study is to test for an association between changes  
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3 in cough frequency and microbiological resolution of TB disease during  
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5 therapy.  
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### 8 9 **Study design**

10 This prospective cohort study will follow adult patients with pulmonary TB  
11  
12 through their treatment period in Lima, Peru.  
13  
14

15  
16  
17  
18 Subjects with a confirmed or suspected diagnosis of active pulmonary TB will  
19  
20 be referred to our study team. After obtaining written informed consent, we will  
21  
22 record coughs prior to initiation of TB treatment. Subjects will provide us with  
23  
24 early-morning sputum samples that will be tested for active pulmonary TB  
25  
26 disease by testing at least one sputum sample using the microscopic-  
27  
28 observation drug-susceptibility (MODS) broth culture assay[32-34] and  
29  
30 auramine smear microscopy, to assess the bacillary load.  
31  
32  
33

34  
35  
36 Patients in whom the pulmonary TB diagnosis is confirmed by MODS will  
37  
38 receive treatment delivered by the National TB Programme as per standard  
39  
40 practice.[35] Figure 1 summarises the data to be collected at baseline and  
41  
42 during the 60 days of follow-up.  
43  
44  
45

### 46 47 **Study sites**

48  
49 Peru has one of the highest TB incidence rates in the Americas.[36] More  
50  
51 than one-third of the incident TB cases in the Andean region are from Peru.  
52  
53 With respect to rates of MDR-TB and extensively drug resistant (XDR) TB,  
54  
55 Peru ranks first in all of the Americas. However, underreporting in the region  
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3 may contribute to Peru's overrepresentation, as shown in the latest Pan  
4  
5 American Health Organisation (PAHO) report.[36]  
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10 Within Peru, Lima and its metropolitan area account for most cases of MDR-  
11  
12 TB and XDR-TB.[37] Thus, we will recruit patients from two hospitals: Hospital  
13  
14 Nacional Dos de Mayo, located in the historic centre of Lima; and Hospital  
15  
16 Nacional Daniel Alcides Carrión, located in Callao and which belongs to  
17  
18 Lima's metropolitan area.  
19

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22  
23 Our main site, Hospital Nacional Dos de Mayo (HNDM), is a 650-bed teaching  
24  
25 and public national tertiary referral hospital run by the Peruvian Ministry of  
26  
27 Health (MINSa). It provides services to the poor population from the  
28  
29 surrounding inner city area. HNDM is the only hospital in Peru with a negative  
30  
31 pressure ward available for TB patients. Our secondary site is another tertiary  
32  
33 referral hospital run by MINSa, Hospital Nacional Daniel Alcides Carrión. This  
34  
35 462-bed teaching health facility lies in the Callao region.  
36  
37

### 38 39 40 **Study population**

41  
42 The infectious disease and pulmonary physicians will refer subjects to the  
43  
44 research team. Criteria for referral are suspicion of active pulmonary TB or a  
45  
46 confirmed case of active pulmonary TB who has not yet started treatment.  
47  
48

49 Active pulmonary TB is defined by a positive MODS culture result. Subjects  
50  
51 will be excluded if they were less than 18 years of age, pregnant, have started  
52  
53 a new treatment regimen for TB within the last 7 days, or are unable or  
54  
55 unwilling to provide informed consent. If a patient changes treatment regimen,  
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3 for example due to treatment failure or to an adverse drug reaction, this would  
4  
5 also be considered as a new regimen. Pregnancy is defined by a positive  
6  
7 result on serum or urine beta human chorionic gonadotropin ( $\beta$ -hCG) assay.  
8  
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### 10 11 12 **Outcomes and case definitions**

13  
14 The primary outcomes for this study are cough frequency and microbiological  
15  
16 data from serial sputum samples. Cough frequency is defined as the number  
17  
18 of cough episodes, or cough epochs, within a time period. Cough epochs are  
19  
20 defined as cough events that are within a two-second period frame.[31]  
21  
22

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25 Regarding microbiological data, participants will be entered into the study if  
26  
27 they have a positive culture result. Treatment regimens will be adjusted as  
28  
29 needed by the treating team based on the results of the MODS drug-  
30  
31 susceptibility testing from their sputum. Our study team will not be involved in  
32  
33 the treatment regimen selection.  
34  
35

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38 Sputum smear conversion is defined as three consecutive smear-negative  
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40 results, collected at least 8 hours apart after initial smear positivity at  
41  
42 diagnosis.[38] Culture conversion is defined as two consecutive negative  
43  
44 culture results, taken at least 30 days apart. This last definition is the one  
45  
46 used in the Ministry of Health (MINSAs)[35] and is recommended by the World  
47  
48 Health Organisation (WHO).[39] The date of conversion will be considered as  
49  
50 the date of the first negative sputum smear or culture contributing to  
51  
52 conversion.  
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3 Secondary outcomes include weight, temperature, and radiological  
4 characteristics. When possible, radiological interpretation data from chest  
5 films and thoracic computed tomography (CT) scans will be obtained. Chest  
6 X-ray films (CXR) provide a high negative predictive value for the presence of  
7 active TB[40] but CT scans provide higher sensitivity for the detection of  
8 lymphadenopathy, early bronchogenic spread, and to evaluate cavitation and  
9 disease activity.[41]  
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### 20 **Sample size**

21 In a pilot study we estimated that the frequency of cough in TB patients before  
22 receiving treatment is approximately 327 coughs during a 24-hour period with  
23 a standard deviation of approximately 50. A sample size of 97 patients would  
24 enable us to detect a conservative decrease of the mean number of coughs in  
25 the 24-hour period of at least 45 coughs after two weeks of treatment, with a  
26 5% Type I error probability and 80% power.  
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38 Under the hypothesis that TB patients before treatment experience a high  
39 cough frequency, we hypothesise that after two weeks of anti-TB treatment,  
40 there will be a clinical response accompanied by a significant reduction in  
41 cough frequency. Response is defined as at least a two-fold reduction in  
42 cough frequency. Response is defined as at least a two-fold reduction in  
43 cough frequency, which was previously shown to occur within the first 2  
44 weeks of treatment.[7] For power calculations, it is assumed that all subjects  
45 will eventually respond to treatment, according to our definition of response,  
46 and that once cough frequency has reduced in an individual it will not rise  
47 again. We assume that after the two weeks of treatment approximately 10%  
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3 of patients would maintain a high frequency of cough. Thus, a sample size of  
4  
5 97 patients will allow us to detect an odds ratio of at least 3.2 for the risk of  
6  
7 patients not responding to TB treatment in two weeks of therapy, under a 95%  
8  
9 significance and 80% power. An additional 10% of patients will be recruited, to  
10  
11 correct for patients who do not complete all of the study procedures. Thus, we  
12  
13 will aim to recruit a total of 107 patients.  
14  
15

### 16 17 18 **Study organisation** 19

20 The Asociación Benéfica (A.B.) PRISMA and Universidad Peruana Cayetano  
21  
22 Heredia in Lima, Peru will provide local administrative oversight. Overseas,  
23  
24 oversight will be conducted by Johns Hopkins University in Baltimore,  
25  
26 Maryland, USA.  
27  
28

29  
30 In Lima, the Pampas office of A.B. PRISMA will provide operations and  
31  
32 logistic support for fieldwork. An additional collaborating signal processing  
33  
34 team will be based locally in the Universidad Nacional de Ingeniería, Lima,  
35  
36 Peru, as well as at Tufts University, Massachusetts, USA.  
37  
38

39  
40 Our collaborating biostatisticians are based at Tufts University, Tulane  
41  
42 University, and Universidad Peruana Cayetano Heredia, Lima, Peru. All  
43  
44 investigators are involved in protocol design and technical support and will  
45  
46 remain involved in the ongoing analyses.  
47  
48

### 49 50 **Personnel, training and logistics** 51

52 Nurses have been trained by study staff to obtain sputum samples in a best-  
53  
54 practice fashion based on previous work,[42 ,43] and to operate and  
55  
56 troubleshoot all recorder devices, memory cards, and battery packs. We will  
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3 adhere to recommended infection prevention & control practices for TB to  
4 reduce bio-risk in healthcare professionals and patients.[44] Written informed  
5 consent is required prior to research participation. At the time of enrolment,  
6  
7 subjects will follow the procedures outlined in Figure 1.  
8  
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11  
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13  
14 Subjects with active pulmonary TB will be followed throughout their TB  
15 treatment. After the identification of active pulmonary TB and based on  
16 convenience basis, subjects who consent will undergo CXR and a non-  
17 contrast thoracic CT scan.  
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24  
25 The first day of a new TB treatment regimen is defined as “Day 0”. An initial  
26 questionnaire will be completed on that day (Supplementary File 1). It should  
27 be mentioned that we used a 5-level ordinal scale instead of 10 to make it  
28 simpler for our interviewees. We have found it easier in this setting for  
29 research participants to interpret 5-levels each with defining words (never,  
30 little, much, almost always, always) rather than 10. This questionnaire is  
31 similar to the one that was employed in a previous study.[45] Baseline cough  
32 frequency will be obtained by performing an audio recording of the patients  
33 before they obtain their microbiological results, which is usually a few days  
34 prior to treatment initiation. Hence, subjects will be recorded from at least one  
35 day prior to treatment and throughout their first two weeks of treatment. They  
36 will subsequently be recorded for 24 hours on or around days 21, 30 and 60  
37 of treatment, although up to two days date deviation for Sundays and public  
38 holidays will be allowed.  
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3 Recordings will start at 09:00 hours and will be as continuous as possible.  
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5 Occasionally incomplete recordings could be obtained due to malfunction of  
6  
7 equipment or patient non-compliance. On the recording days clinical data will  
8  
9 be gathered, including: weight, temperature, and sputum samples for smear  
10  
11 and MODS results. The number of days to culture positivity in the MODS  
12  
13 liquid culture assay will be recorded in order to assess the microbiological  
14  
15 burden in the patients' samples, based on prior work done with a similar  
16  
17 technique.[46]  
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### 25 **Audio recording**

26  
27 Design of the audio recording equipment, the CayeCoM device, builds on  
28  
29 previous chronic cough ambulatory audio recordings.[26 ,47 ,48] The  
30  
31 CayeCoM device is a Marantz PMD 620 professional handheld recorder,  
32  
33 using an Audio-Technica AT899 sub-mini microphone with an AT8537  
34  
35 microphone power module. The microphone will be attached at the patient's  
36  
37 lapel as shown in Figure 2. The recorder is adapted to work with an external  
38  
39 lithium battery supply (Enix Energies 800040) to enable continuous 24-hour  
40  
41 recordings. The audio is recorded onto a SanDisk SDHC 8 GB card, at a  
42  
43 sample rate of 48 kHz, encoding 64 kbps in mono in MP3 format. The audio  
44  
45 equipment is kept inside a basic pack connected to a lapel microphone.  
46  
47  
48 Batteries and SD cards will be exchanged daily by the study nurses. In pilot  
49  
50 research, subjects tolerated the audio equipment well, wearing them 24 hours  
51  
52 a day and taking them off only to bathe.  
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## Processing of audio recordings

The recorded signals will be analysed after all patient recordings are completed. For cough analysis, software developed by our group and previously described in detail will be used.[30 ,31] Thus we provide only a brief review here and refer interested readers to our previous publications.

Briefly, cough recordings will be analysed using a 2-step algorithm: first, event detection, followed by event classification into cough vs. non-cough.

Detection of acoustic events will be based on the signal energy proportional to the voltage-squared of the signal. An acoustic event will detect if the signal energy exhibited a rapid increase above a time-varying baseline estimate of ambient noise. The next stage of processing seeks to classify detected events. Here, the spectral features of each time frame in the acoustic event are characterised using Mel frequency cepstral coefficients and their derivatives. As described in detail elsewhere,[31] a training data set will be used to develop a classifier based on the sequential minimal optimisation (SMO) algorithm. Based on classifier outputs, each acoustic event will be marked as 'cough' or 'not-cough'.

Isolated cough events will be automatically combined into cough epochs, or bursts of closely spaced individual coughs, following previous research.[49] We will employ a definition of cough epochs, as defined in the 'Outcomes and case definitions' section above. Note that within the cough literature, a variety of metrics are available for describing cough, and there is no clear evidence as to which are most clinically meaningful. We have previously published a review and discussion of these various metrics (number of individual coughs,

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3 number of cough bouts or epochs, number of 1-sec periods containing cough,  
4  
5 etc.).[31]  
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8  
9 We will employ a semi-automated approach in which cough epochs that are  
10 automatically detected will then be manually reviewed to eliminate false  
11 positives. This is necessary as our recordings will be made in very noisy  
12 environments (outside clinical settings) and false detection rates for a fully  
13 automated system remain high. For this study, a simple graphical user  
14 interface will be constructed to allow nurses to review automatically detected  
15 epochs, enabling listening to each as often as needed, and then to either  
16 accept or reject the detected cough. Thus, the review of automatically  
17 detected coughs acts to eliminate algorithmic false positive coughs.  
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30 *Validation:* The approach described in the paragraphs above was previously  
31 validated using as gold standard a fully manual review of 60 files (15 subjects,  
32 4 randomly selected time periods per subject) in which two nurses listened to  
33 all files in their entirety.[31] Because nurses only manually marked the start of  
34 each cough, validation was compared on the basis of the epoch definition  
35 described above. The semi-automated approach described above gave  
36 75.5% sensitivity in detecting coughs (true positive rate of 6.8/hour) with an  
37 average false positive rate of 0.5/hour.[31] While the semi-automated  
38 approach does require time for human review, the initial automated step will  
39 remove the large majority of possible events. Thus on average, review time is  
40 reduced by nearly two orders of magnitude compared to a fully manual review  
41 in which the entire recording is reviewed. We will also maintain the privacy of  
42 subjects, as non-cough events, such as conversation, will never be reviewed  
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3 by the human ear.  
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### 7 **Microbiology**

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10 The microbiological tests will be carried out in a Biosafety Containment Level  
11  
12 3 research laboratory situated within Universidad Peruana Cayetano Heredia  
13  
14 in Lima, Peru. The sputum samples will be digested and decontaminated by  
15  
16 the standard NaOH-N-acetyl cysteine method.[50] For smear microscopy, an  
17  
18 aliquot of 100 µl is stained with Auramine O and examined with x400  
19  
20 magnification. Results are determined as negative, paucibacillary (1-19 acid  
21  
22 fast bacilli [AFB] visualized in 40 fields), 1+ (20-199 AFB visualized in 40  
23  
24 fields), 2+ (5-50 AFB per field) and 3+ (>50 AFB per field). Culture and MODS  
25  
26 susceptibility testing will be performed with the remaining samples, according  
27  
28 to standard protocols.[32-34]  
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### 34 **Radiology**

35  
36 Radiological information will be gathered, when possible, on a convenience  
37  
38 basis. Priority will be given to CT scans, since they have been shown to be  
39  
40 more sensitive. Films will be read by a local radiologist and a US board-  
41  
42 certified radiologist blinded to the patient's demographics and outcomes. They  
43  
44 will provide an interpretation that is standardised as per our study protocol to  
45  
46 describe radiological findings including cavitation, consolidation,  
47  
48 lymphadenopathy, and effusions (Supplementary File 2). Cavitations will be  
49  
50 further described by size, location, presence or absence of an air-fluid level,  
51  
52 and cavity wall thickness based on prior work that shows the relevance of  
53  
54 these findings to pulmonary TB.[51-53] We will also explore whether other  
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3 radiological findings are predictive of microbiological burden and cough  
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5 frequency.  
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### 9 10 **Statistical methodology and analysis**

11 All questionnaire data will be double digitised from paper forms using Visual  
12 FoxPro 9 Service Pack 2 (Microsoft Corp. Redmond, Washington, USA) and  
13 microbiological data will be double entered using Microsoft Access 2010  
14 (Microsoft Corp. Redmond, Washington, USA). These two data sets will be  
15 cross-compared for validity and errors. From these data, descriptive statistics  
16 will be tabulated and graphed.  
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27 Cough analysis processing results will be stored as Matlab (Mathworks, Inc,  
28 Natick MA) files containing information regarding each event and its  
29 timestamp. Algorithmically detected coughs will be annotated in the files. After  
30 manual review, isolated cough events will be grouped into cough epochs, or  
31 bursts of closely spaced individual coughs within 2 seconds, following  
32 published work on cough evaluation.[49] We have previously published a  
33 review and discussion of these various metrics (including number of individual  
34 coughs, number of cough bouts or epochs, and number of 1-sec periods  
35 containing cough).[31]  
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49 For the first study objective of describing cough frequency, cough epochs will  
50 be plotted throughout the day, and cough frequency will be summarised as  
51 the frequency of cough epochs per hour. Positively-skewed cough data may  
52 be log-transformed to facilitate data visualisation and analysis. To address the  
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3 second study objective, correlation of characteristics with cough frequency,  
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5 we will use generalised estimating equations (GEE) based Poisson or  
6  
7 negative binomial regression with baseline microbiologic status, and  
8  
9 trigonometric (sine/cosine) terms to model circadian periodicity, as the  
10  
11 independent variables. In addition, a multiple logistic regression in a  
12  
13 longitudinal generalised linear model (GLM) framework analysis will evaluate  
14  
15 a function of sputum bacillary load and with cough frequency that we propose  
16  
17 as a potential predictor of TB transmissibility. In all cases we will correct for  
18  
19 outliers, and nested models will be compared using the likelihood ratio test.  
20  
21 We will also consider variables such as gender, HIV status, drug resistance,  
22  
23 and previous history of TB, in our analysis, either by stratifying or by adjusting  
24  
25 for these variables in our models.  
26  
27

28  
29 To test the association between cough frequency and microbiological  
30  
31 resolution of TB disease associated with the third aim of this study, time-to-  
32  
33 event survival analyses where the outcomes of interest are sputum smear  
34  
35 conversion, and culture conversion, as defined above, and the primary  
36  
37 predictors of interest are cough frequency at baseline, during treatment, and  
38  
39 time to two-fold reduction in cough frequency. In addition, secondary analyses  
40  
41 of weight, temperature, and radiological characteristics, will be conducted  
42  
43 using generalised linear models and GEE logistic regression as appropriate.  
44  
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## 52 **Ethical considerations**

53  
54 Ethical approval has been obtained from the ethics committees at A.B.

55  
56 PRISMA in Lima, Peru, the Universidad Peruana Cayetano Heredia in Lima,  
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3 Peru, and Johns Hopkins University, in Baltimore, USA. Written informed  
4  
5 consent will be obtained from all participants. Test results will be delivered by  
6  
7 telephone or at subsequent visits at which time a team physician or nurse will  
8  
9 be able to explain the results to the study participants. TB treatment remains  
10  
11 the responsibility of the medical staff in charge and the National TB  
12  
13 Programme.  
14

## 15 16 17 **Discussion**

18  
19 We will determine cough frequency before and during anti-TB treatment using  
20  
21 the CayeCoM device. We will identify baseline predictors of cough frequency  
22  
23 during TB treatment and evaluate the correlation between change in cough  
24  
25 frequency and microbiological resolution.  
26  
27

28  
29  
30 The medical literature currently lacks information about cough frequency in  
31  
32 TB. As recently noted by Turner and Bothamley,[5] cough frequency in  
33  
34 patients undergoing TB treatment has only been studied once, almost half a  
35  
36 century ago.[6 ,7] This previous study has the limitation of only being  
37  
38 conducted within an 8-hour period, overnight, and thus there is no information  
39  
40 on daytime coughing or the effect of the diurnal rhythm on cough. A similar  
41  
42 study[54] demonstrated that the severity of cough and pathological chest x-  
43  
44 ray findings were associated with higher levels of TB transmission. However,  
45  
46 their study did not measure cough frequency but instead focused on a  
47  
48 subjective characteristic: cough severity. It should be noted that to assess  
49  
50 cough frequency one must utilise objective acoustic parameters, since self-  
51  
52 reported cough is unreliable.[18] As reported in abstract form, the objective  
53  
54 acoustic Leicester Cough Monitor (LCM) has been used to evaluate 24-hour  
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3 cough recordings in patients with pulmonary TB before starting treatment,  
4 showing that cough frequency is reduced at night.[55] This further justifies re-  
5 evaluation of Loudon's overnight study.  
6  
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9

10 Our project has several strengths and limitations. An important strength is the  
11 generation of 24-hour cough recordings, which will provide lengthy recordings,  
12 will enable evaluation of cough patterns at different times of day, and also has  
13 the benefit of being recorded during a normal day in real-world settings where  
14 we expect our device to be used in the future. Normal day recordings are  
15 confounded by background noise, which is a challenge for analysis of cough  
16 recordings, considering that traffic and environmental noise (such as dogs  
17 barking, music, and television) may generate noises similar to cough. To  
18 diminish this effect, we have incorporated a time-varying estimate of the noise  
19 background as well as a data quality control. Having a semi-automated  
20 algorithm is a limitation, since it requires time and human input, but also a  
21 strength since the human ear is the gold standard for determining the  
22 characteristic sound of cough. Similar to Loudon's proposal,[8] our algorithm  
23 will help to screen and reduce the length of the recordings to ~5% of their  
24 original length, without affecting sensitivity and improving specificity.[31] We  
25 aim to improve our sensitivity by fully automated processing remains a long-  
26 term goal for our group, and we anticipate that experience gained with semi-  
27 automated analysis will aid us in developing future algorithms. In addition, we  
28 are now developing second-generation devices where the validity is improved  
29 by employing accelerometers. This study is limited by restriction to only non-  
30 pregnant adults because this is the population for which the algorithm has  
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3 been validated. However, future research is planned to include these  
4  
5 important vulnerable populations.  
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7  
8 CayaCoM has been validated for 24-hour recordings,[31] whereas  
9  
10 PulmoTrack (PulmoTrack-CC, KarmelSonix, Haifa, Israel) was validated for  
11  
12 25 minutes[28] and the Hull Automatic Cough Counter for 1-hour  
13  
14 recordings.[26] Other systems have also validated their algorithms for 24-hour  
15  
16 recordings, such as the LCM,[27 ,56] VitaloJAK,[29] and the LifeShirt  
17  
18 System.[25] However, in contrast to our study, none of these algorithms have  
19  
20 been validated for pulmonary TB nor within real-life settings (e.g. traffic). We  
21  
22 expect that this project will generate a novel method to evaluate treatment  
23  
24 response. In future studies we intend to better assess infectiousness by  
25  
26 additionally quantifying TB in cough-generated aerosols.  
27  
28

29  
30 Cough frequency should provide additional information regarding the  
31  
32 evolution of the patients' medical condition. If a correlation with bacteriological  
33  
34 treatment response is demonstrated, then this would have the potential to  
35  
36 contribute to patient management without relying on a laboratory in adult  
37  
38 patients with pulmonary TB. However, it should be noted when monitoring TB  
39  
40 patients' response because some patients may have adverse treatment  
41  
42 outcomes despite an initial transient positive response to therapy. It could  
43  
44 assist with decisions regarding the need for on-going respiratory isolation of  
45  
46 patients, treatment duration, and identification of patients with treatment  
47  
48 failure who may need modification of their treatment regimens. The device  
49  
50 also has the potential to be used remotely, as in telemedicine. This is  
51  
52 potentially important in a country such as Peru, where the majority of doctors  
53  
54 live in the capital, leaving most of the country without a physician in their  
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3 region. Cough monitoring devices seem challenging; however, we believe that  
4  
5 this is the first step towards telemedicine in cough-TB. In Peru, many rural  
6  
7 areas do not have facilities for laboratory diagnosis, but have at least one  
8  
9 physician or healthcare professional. They may be trained in placing these  
10  
11 devices. We are also working on making devices smaller, cheaper, and easier  
12  
13 to use.  
14

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44  
45  
46  
47  
48

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1  
2  
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10

11  
12 **Conflicts of interest:**

13  
14 All authors declare that they have no conflict of interest in relation to this work.  
15

16  
17 **Ethics approval:**

18  
19 Ethical approval has been obtained from the ethics committees at A.B.

20  
21 PRISMA in Lima, Peru, the Universidad Peruana Cayetano Heredia in Lima,  
22  
23 Peru, and Johns Hopkins University, in Baltimore, USA.  
24  
25

26  
27 **Contributors:**

28  
29 All authors were involved in the study design and writing of the  
30  
31 manuscript, and all reviewed the final manuscript before submission. MAB  
32  
33 and JWL directly contributed to study design and are responsible for  
34  
35 supervision of data gathering. AP, BHT, JWL, MZ and GL will be responsible  
36  
37 for data management and statistical analysis for this project.  
38

39  
40 **Data Sharing Statement:**

41  
42 We aim to publish and disseminate our results, once the project is complete.  
43  
44 We also expect to create and maintain an online repository for TB cough  
45  
46 sounds as well as the statistical analysis employed.  
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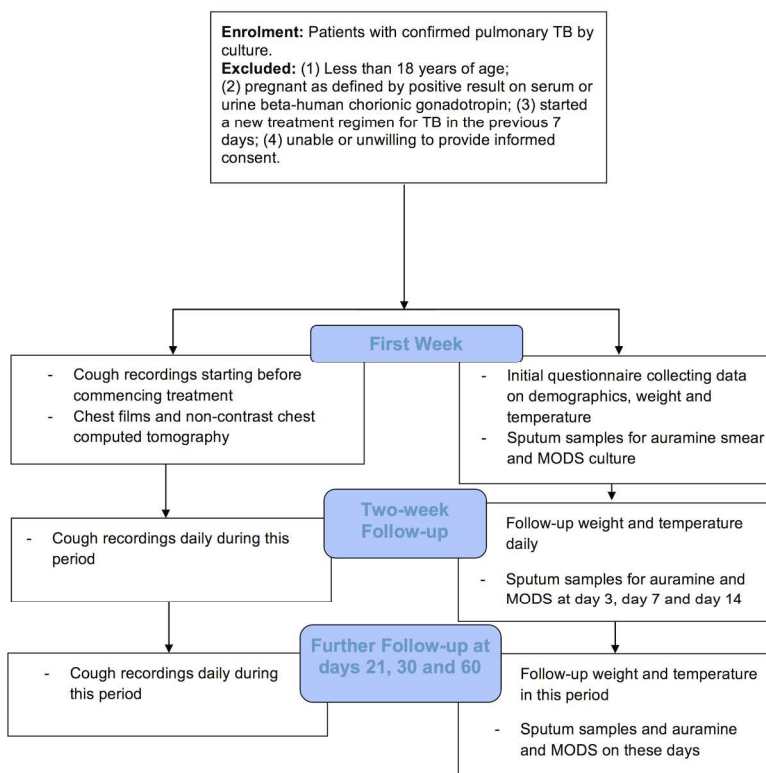


Figure 1 – Flow Diagram for CayeCoM Study  
 175x247mm (300 x 300 DPI)

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Figure 2 – Picture of the Cayetano Cough Monitor (CayeCoM)  
122x62mm (300 x 300 DPI)

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Código del paciente: \_\_\_\_\_

Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

Entrevistador: \_\_\_\_\_

**Cuestionario Inicial Para Todos Los Participantes:**

## Datos Demográficos:

1. Edad: \_\_\_\_\_

2. Sexo: \_\_\_\_\_

## Antecedentes:

3. ¿Cuántas personas normalmente duermen en casa?: \_\_\_\_\_ Personas

4. ¿Cuántas habitaciones hay en su hogar? (sin contar baño, pasadizo, cocina, depósito, garaje): \_\_\_\_\_ habitaciones.

5. ¿Cuál es el ingreso mensual de la vivienda? S/. \_\_\_\_\_

6. ¿Cuánto gasta su familia en alimentación cada semana? S/. \_\_\_\_\_

7. ¿Cuántas personas en su vivienda comen de esos alimentos que compran semanalmente? \_\_\_\_\_ Personas

8. ¿Cuántas veces en el ultimo mes usted se ha acostado con bastante hambre porque no había comida en casa? \_\_\_\_\_ días

## Historia de Tuberculosis:

La tuberculosis es una enfermedad que se trata con varios antibióticos a la vez, y cuyo tratamiento dura varios meses.

9. ¿Ha sido diagnosticado con TBC anteriormente?  
a. Si  
b. No → *Pase a la pregunta 15*  
c. NS

10. ¿Cuántas veces? \_\_\_\_\_

11. Si recibió tratamiento para la TBC, ¿dónde recibió la mayor parte del tratamiento?  
a. NA  
b. Mismo distrito  
c. Otro distrito  
d. Otra ciudad  
e. Otro país

12. Si recibió tratamiento para la TBC ¿por cuántos meses en total lo tomó? \_\_\_\_\_

13. Si recibió tratamiento previo, en que esquema estaba (lo mas recién): -  
\_\_\_\_\_14. Si recibió tratamiento para la TBC ¿cumplió con el tratamiento previo?  
a. NA  
b. Si  
c. No → \_\_\_\_\_  
d. NS

## Factores de Riesgo

15. ¿Ha compartido un cuarto con alguien que haya tenido TBC comprobada?  
a. Si, y esta persona también tenía una tos persistente  
b. Si, pero esta persona concurrente no tenía una tos persistente  
c. No → *Pase a la pregunta 18*  
d. NS16. ¿Dónde compartió este ambiente con alguien infectado con TBC?  
a. NA  
b. Trabajo  
c. Casa  
d. Hospital  
e. Otro: \_\_\_\_\_

17. ¿Por cuantos días compartió este ambiente con la persona con TBC comprobada? \_\_\_\_\_

18. Aparte de usted, ¿alguien mas en casa esta actualmente recibiendo medicinas para la TBC?  
a. Si → Quien: \_\_\_\_\_  
b. No  
c. NS

## Creencias y Conocimiento de la Enfermedad

19. ¿Dónde escuchó de la TBC por primera vez?  
a. Familia  
b. Amigos  
c. Colegio  
d. Puesto de Salud  
e. TV  
f. Radio  
g. NS20. ¿Puede alguien con TBC y tos infectar a sus familiares?  
a. Si  
b. No  
c. NS

Cuestionario Inicial Para Todos Los Participantes







1

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.






Código del paciente: \_\_\_\_\_  
 Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

21. ¿Qué tan contagiosa cree que es la TBC?
- a. Nada
  - b. Poquito
  - c. Mucho
  - d. Bastante
  - e. Lo mas
22. ¿Qué tan seria cree que es la TBC?
- a. Nada
  - b. Poquito
  - c. Mucho
  - d. Bastante
  - e. Lo mas
23. En general, ¿qué puede hacer uno por si mismo para protegerse de contraer la TBC? [Marcar el factor más importante, no sugerir repuestas].
- a. Vacunarse
  - b. Comer
  - c. Dormir bien, descansar
  - d. Vivir una vida ordenada
  - e. Mantenerse alejado de la gente con TBC
  - f. Educarse
  - g. Otro: \_\_\_\_\_
  - h. NS
24. ¿Cuales son los síntomas de la TBC? [Marcar los factores, no sugerir repuestas].
24. Tos mencionada Si  No
25. Hemoptysis mencionada Si  No
26. Fiebre mencionada Si  No
27. Baja de peso mencionada Si  No
28. Fatiga, decaimiento mencionada Si  No
29. Palidez, un cierto semblante mencionada Si  No
30. ¿Qué debe hacer una persona con TBC para mejorarse? [Marcar el factor más importante, no sugerir repuestas].
- a. Tomar sus medicinas, asistir a controles
  - b. Comer mas, comer mejor
  - c. Descansar
  - d. Tener fe
  - e. Abrigarse
  - f. Otro: \_\_\_\_\_
  - g. NS
31. ¿Cómo puede hacer una persona con TBC para no contagiar la TBC a otros? [Marcar el factor más importante, no sugerir repuestas].
- a. Cubrirse la boca al toser
  - b. Quedarse en casa, mantenerse alejado
  - c. Seguir el tratamiento
  - d. Separar cubiertos
  - e. Otro: \_\_\_\_\_
  - f. NS
32. ¿Se puede curar la TBC?
- a. Siempre
  - b. Normalmente sí
  - c. A veces
  - d. Raramente
  - e. Nunca

**Instrucciones:** Marque una X sobre la línea la posición que escoges.  
 Ejemplo: -----□-----

33. Con que frecuencia esta tosiendo hoy, en un promedio de 24 horas?
- |       |   |   |   |  |   |
|-------|---|---|---|--|---|
| 0     | 1   | 2   | 3 | 4  | 5 |
| nunca | poquito   | mucho   |   | casi siempre   |   |
|       |  |   |   |    |   |

**Instrucciones:** Marque una X, en el cuadrado, todas las alternativas que corresponden.  
 Ejemplo:

34. Que indicadores utilizó para escoger a que posición poner sus X?
- Los números: 1, 2, 3, 4, 5
  - Las palabras: nunca, poquito, mucho, casi siempre
  - Las figuras:  ,  ,  ,  , 

Cuestionario Inicial Para Todos Los Participantes

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

Código del paciente: \_\_\_\_\_

Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

**Instrucciones:** Marque con X la alternativa que corresponde.Ejemplo: 

35. ¿Comparado con hace tres días, tiene más frecuencia de tos el día de hoy?

- a.  Tosiendo ahora menos  
 b.  Tosiendo ahora igual  
 c.  Tosiendo ahora más

37. Si tiene tos, ¿a que hora en el día tiene más frecuencia: *mañana, tarde o noche*?

- a.  Mañana  
 b.  Tarde  
 c.  Noche

36. El día de hoy, ¿ha tenido *solo tos, tos con flema o solo flema*?

- a.  Solo tos  
 b.  Tos con flema  
 c.  Solo flema

38. Qué tan frecuentemente tose?

- a.  Cada pocos segundos  
 b.  Cada pocos minutos  
 c.  Cada pocas horas  
 d.  No tose

**Instrucciones:** Marque el numero de días en total que tiene los siguientes síntomas desde que se enfermó. Marque 0 si ningún día.

39. ¿Cuántos días usted ha tenido los siguientes síntomas?

- a. Tos seca \_\_\_\_\_  
 b. Tos con flema \_\_\_\_\_  
 c. Tos con sangre \_\_\_\_\_  
 d. Fiebre \_\_\_\_\_  
 e. Falta de aire \_\_\_\_\_  
 f. Perdida de peso \_\_\_\_\_  
 g. Cansancio o decaimiento \_\_\_\_\_  
 h. Sudor nocturno \_\_\_\_\_  
 i. Falta de apetito \_\_\_\_\_

**Instrucciones:** Responde a la pregunta en el lugar indicado.

40. Actualmente, ¿como se siente? (0 = mal, 10 = bien): \_\_\_\_\_

41. Cuando tiene tos, ¿cuántas toses tiene por hora? \_\_\_\_\_

42. Preguntas sobre VIH

- |   | Manifiesto del paciente | Historia clínica |
|---|-------------------------|------------------|
| a. Usted ha sido diagnosticado por VIH? | _____                   | _____            |
| b. Fecha de Diagnostico:                | _____                   | _____            |
| c. Ultima Carga Viral:                  | _____                   | _____            |
| d. Fecha de ultima Carga Viral:         | _____                   | _____            |
| e. Ultimo resultado CD4:                | _____                   | _____            |
| f. Fecha de Ultimo resultado CD4:       | _____                   | _____            |
| g. Tiempo tomanda TARGA (años)          | _____                   | _____            |

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

**Radiologic Interpretation Data Form**

Date of read: \_\_\_\_\_

Radiologist Name: \_\_\_\_\_

Radiologist Signature: \_\_\_\_\_

Patient code: \_\_\_\_\_

Patient gender:  male  female

Patient age: \_\_\_\_\_

**1. Type of film:**

AP  PA  Lateral from R  Lateral from L  Thoracic CT without contrast  Other: \_\_\_\_\_

2. Date of film: Day: \_\_\_\_\_ Month: \_\_\_\_\_ Year: \_\_\_\_\_

3. Rotation: \_\_\_\_\_

4. Adequacy of inhalation: \_\_\_\_\_

	Site	a. Consolidation?	b. Cavitation?	c. Pneumatocele?	d. Atelectasis?
5	Right upper lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
6	- anterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
7	- apical	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
8	- posterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
9	Right middle lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
10	Right lower lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
11	- superior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
12	- basal	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
13	Left upper lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
14	- anterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
15	- apical	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
16	- posterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
17	Lingula	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
18	Left lower lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
19	- superior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
20	- basal	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no

21. Pleural effusion?  yes  no  
 left?  small  medium  large  
 right?  small  medium  large

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

22. Miliary spread?  yes  no

23. Pneumothorax?  yes  no

where and size: \_\_\_\_\_

24. Lymphadenopathy:  yes  no

which lymph nodes groups

hilar  mediastinal

25. Pericardial effusion?  yes  no

left?  small  medium  large

26. Bronchiectasis?  yes  no

where: \_\_\_\_\_

27. Fibrosis?  yes  no

where: \_\_\_\_\_

any retractions, deviations? \_\_\_\_\_

28. Mediastinal thickening?  yes  no

29. Any tree-in-bud pattern? Where? \_\_\_\_\_

30. Cavitation: For each cavity, please describe:

Cavity # 1:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  think  thick smooth nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 2:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  think  thick smooth nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity #3:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 4:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 5:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

More cavities?  yes: please use another sheet to describe  no

Other findings such as fractures, cardiac abnormalities, exudative / fibrotic densities, bronchogenic spread, mass-like lesions (calcified vs. non-calcified), please describe:

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31. Normal film?  yes  no

# BMJ Open

## A protocol for studying cough frequency in people with pulmonary tuberculosis

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<b>Primary Subject Heading</b>:	Global health
Secondary Subject Heading:	Respiratory medicine, Infectious diseases, Global health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Cough, Monitoring

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## ABSTRACT

*Introduction:* Cough is a key symptom of tuberculosis (TB) as well as the main cause of transmission. However, a recent literature review (Turner et al. 2015, J Infect Dis) found that cough frequency (number of coughs per hour) in patients with TB has only been studied once, by Loudon in 1969 (Loudon et al. 1969, Am Rev Respire Dis). The main aim of this study is to describe cough frequency patterns before and after the start of TB treatment and to determine baseline factors that affect cough frequency in these patients. Secondly, we will evaluate the correlation between cough frequency and TB microbiological resolution.

*Methods:* This study will select participants with culture confirmed TB from two tertiary hospitals in Lima, Peru. Based on Loudon's results, we estimated that a sample size of 107 patients was sufficient to detect clinically significant changes in cough frequency. Participants will initially be evaluated through questionnaires, radiology, MODS broth TB-culture, auramine smear microscopy, and cough recordings. This cohort will be followed for the initial 60 days of anti-TB treatment, and throughout the study several microbiological samples as well as 24-hour recordings will be collected. We will describe the variability of cough episodes and determine its association with baseline laboratory parameters of pulmonary TB. In addition, we will analyse the reduction of cough frequency in predicting TB cure, adjusted for potential confounders.

*Ethics and dissemination:* Ethical approval has been obtained from the ethics committees at A.B. PRISMA in Lima, Peru, the Universidad Peruana Cayetano Heredia in Lima, Peru, and Johns Hopkins University, in Baltimore, USA. We aim to publish and disseminate our findings in peer-reviewed journals. We also expect to create and maintain an online repository for TB cough sounds as well as the statistical analysis employed.

### Strengths and limitations of this study

- The algorithm employed in this project has been validated specifically for patients with pulmonary tuberculosis, which enables us to use this algorithm in our patients.
- A strength of this project is that its results will reflect actual cough frequency episodes in pulmonary tuberculosis by utilising 24-hour recordings in the patients' normal-day settings (traffic, dogs barking, etc.). We expect that this will generate a novel method of evaluating cough in TB that can be used in real-world scenarios.
- Our study has the limitation that recordings have been processed through a semi-automated algorithm. To decrease time constraints our long-time goal is to create a fully automated processing system. We anticipate that experience gained with semi-automated analysis will aid us in developing future algorithms.

## INTRODUCTION

Tuberculosis (TB) is an infectious disease, and was responsible for 9.6 million new cases and 1.5 million deaths in 2014.[1] TB is transmitted in the air[2 ,3] and cough is the most important cause of transmission.[4] Cough in people with pulmonary TB disease arises as a result of the inflammatory response to mycobacterial pulmonary infection. A reduction in cough is assumed to represent adequate response to treatment, and to result in decreased risk of spread of infection. Despite its crucial role in TB transmission, a recent literature review[5] reported that cough frequency during TB therapy has not been studied since work carried out by Loudon in the 1960s.[6 ,7] Thus, longitudinal cough frequency studies in TB are needed.

Loudon described cough frequency in eight-hour overnight periods for nine weeks. All sounds with amplitude and frequency consistent with possible cough events were recorded and then manually reviewed.[8] His findings show a two-fold reduction in the first two weeks of treatment, from a mean of 13.6 to 4.75 coughs/hour.[7] *Mycobacterium TB* colony forming units (CFU) also reduced significantly, from  $10^6$  at baseline to  $10^3$  two weeks later.[9 ,10] This evidence led to the idea that drug-susceptible TB patients become sufficiently non-infective by the second week of treatment that they no longer pose a risk to others. This and other evidence led to the often-used policy that two weeks was the necessary duration of respiratory isolation for newly diagnosed patients commenced on appropriate treatment. Current evidence[11] and guidelines affirm this position;[12-14] however, this two week policy has been criticised.[15 ,16] Our group has shown that drug-susceptible TB patients re-

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3 main sputum culture positive for longer.[17 ,18] Most importantly, the assump-  
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5 tion that TB patients are no longer coughing at two weeks has never been  
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7 corroborated.  
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11 The 2015 CHEST guidelines state that acoustic parameters are the best pa-  
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13 rameter to evaluate the frequency of cough.[19] In order to ensure accurate  
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15 measurement, it is important to use a standardised method such as automat-  
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17 ed cough counting with a validated algorithm. Despite the recently growing  
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19 literature on this topic, these methods are principally being used in the field of  
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21 non-infectious chronic disease.[20-25] Whilst algorithms for cough-counting  
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23 have been validated[26-30] our research protocol appears to be the first to do  
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25 so specifically in patients with pulmonary TB.[31 ,32]  
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32 To address this knowledge gap, we have developed the Cayetano Cough  
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34 Monitor (CayeCoM) and here describe a protocol for it to be used to study  
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36 cough frequency in patients with pulmonary TB.  
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## 41 **METHODS**

### 42 **Study objectives**

43 The primary objective of this study is to describe cough frequency patterns in  
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45 adults with pulmonary TB before and after treatment initiation.  
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48 The second objective of this study is to determine baseline characteristics that  
49  
50 correlate with cough frequency, such as patient demographics, radiological  
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52 findings, presence of multi drug-resistant TB (MDR-TB), and HIV status.  
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55 The third objective of this study is to test for an association between changes  
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3 in cough frequency and microbiological resolution of TB disease during thera-  
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### 9 10 **Study design**

11 This prospective cohort study will follow adult patients with pulmonary TB  
12 throughout their treatment period in Lima, Peru.  
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18 Subjects with a confirmed or suspected diagnosis of active pulmonary TB will  
19 be referred to our study team. After obtaining written informed consent, we will  
20 record coughs prior to initiation of TB treatment. Subjects will provide us with  
21 early-morning sputum samples that will be tested for active pulmonary TB  
22 disease by testing at least one sputum sample using the microscopic-  
23 observation drug-susceptibility (MODS) broth culture assay[33-35] and au-  
24 ramine smear microscopy, to assess the bacillary load.  
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36 Patients in whom the pulmonary TB diagnosis is confirmed by MODS will re-  
37 ceive treatment delivered by the National TB Programme as per standard  
38 practice.[36] Figure 1 summarises the data to be collected at baseline and  
39 during the 60 days of follow-up.  
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### 47 **Study sites**

48 Peru has one of the highest TB incidence rates in the Americas.[37] More  
49 than one-third of the incident TB cases in the Andean region are from Peru.  
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51 With respect to rates of MDR-TB and extensively drug resistant (XDR) TB,  
52 Peru ranks first in all of the Americas. However, underreporting in the region  
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3 may contribute to Peru's overrepresentation, as shown in the latest Pan  
4 American Health Organisation (PAHO) report.[37]  
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10 Within Peru, Lima and its metropolitan area account for most cases of MDR-  
11 TB and XDR-TB.[38] Thus, we will recruit patients from two hospitals: Hospital  
12 Nacional Dos de Mayo, located in the historic centre of Lima; and Hospital  
13 Nacional Daniel Alcides Carrión, located in Callao and which belongs to Li-  
14 ma's metropolitan area.  
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21 Our main site, Hospital Nacional Dos de Mayo (HNDM), is a 650-bed teaching  
22 and public national tertiary referral hospital run by the Peruvian Ministry of  
23 Health (MINSA). It provides services to the poor population from the surround-  
24 ing inner city area. HNDM is the only hospital in Peru with a negative pressure  
25 ward available for TB patients. Our secondary site is another tertiary referral  
26 hospital run by MINSA, Hospital Nacional Daniel Alcides Carrión. This 462-  
27 bed teaching health facility lies in the Callao region.  
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#### 40 **Study population**

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42 The infectious disease and pulmonary physicians will refer subjects to the re-  
43 search team. Criteria for referral are suspicion of active pulmonary TB or a  
44 confirmed case of active pulmonary TB who has not yet started treatment. Ac-  
45 tive pulmonary TB is defined by a positive MODS culture result. Subjects will  
46 be excluded if they were less than 18 years of age, pregnant, have started a  
47 new treatment regimen for TB within the last 7 days, or are unable or unwilling  
48 to provide informed consent. If a patient changes treatment regimen, for ex-  
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ample due to treatment failure or to an adverse drug reaction, this would also be considered as a new regimen. Pregnancy is defined by a positive result on serum or urine beta human chorionic gonadotropin ( $\beta$ -hCG) assay.

### Outcomes and case definitions

The primary outcomes for this study are cough frequency and microbiological data from serial sputum samples. Cough frequency is defined as the number of cough episodes, or cough epochs, within a time period. Cough epochs are defined as cough events that are within a two-second period frame.[32]

Regarding microbiological data, participants will be entered into the study if they have a positive culture result. Treatment regimens will be adjusted as needed by the treating team based on the results of the MODS drug-susceptibility testing from their sputum. Our study team will not be involved in the treatment regimen selection.

Sputum smear conversion is defined as three consecutive smear-negative results, collected at least 8 hours apart after initial smear positivity at diagnosis.[12] Culture conversion is defined as two consecutive negative culture results, taken at least 30 days apart. This last definition is the one used in the Ministry of Health (MINSA)[36] and is recommended by the World Health Organisation (WHO).[39] The date of conversion will be considered as the date of the first negative sputum smear or culture contributing to conversion.

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3 Secondary outcomes include weight, temperature, and radiological character-  
4 istics. When possible, radiological interpretation data from chest films and tho-  
5 racic computed tomography (CT) scans will be obtained. Chest X-ray films  
6 (CXR) provide a high negative predictive value for the presence of active  
7 TB,[40] but CXR might be normal when in fact there is parenchymal dis-  
8 ease.[41] More specifically, CT scans correctly determine pulmonary TB cas-  
9 es in 91% of cases whereas CXR only in 49% of cases.[41-44] In addition, CT  
10 scans provide higher sensitivity for the detection of lymphadenopathy, early  
11 bronchogenic spread, and to evaluate cavitation and disease activity.[44]  
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### 25 **Sample size**

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27 In a pilot study we estimated that the frequency of cough in TB patients before  
28 receiving treatment is approximately 327 coughs during a 24-hour period with  
29 a standard deviation of approximately 50. A sample size of 97 patients would  
30 enable us to detect a conservative decrease of the mean number of coughs in  
31 the 24-hour period of at least 45 coughs after two weeks of treatment, with a  
32 5% Type I error probability and 80% power.  
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43 Under the hypothesis that TB patients before treatment experience a high  
44 cough frequency, we hypothesise that after two weeks of anti-TB treatment,  
45 there will be a clinical response accompanied by a significant reduction in  
46 cough frequency. Response is defined as at least a two-fold reduction in  
47 cough frequency. Response is defined as at least a two-fold reduction in  
48 cough frequency, which was previously shown to occur within the first 2  
49 weeks of treatment.[7] For power calculations, it is assumed that all subjects  
50 will eventually respond to treatment, according to our definition of response,  
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3 and that once cough frequency has reduced in an individual it will not rise  
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5 again. We assume that after the two weeks of treatment approximately 10%  
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7 of patients would maintain a high frequency of cough. Thus, a sample size of  
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9 97 patients will allow us to detect an odds ratio of at least 3.2 for the risk of  
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11 patients not responding to TB treatment in two weeks of therapy, under a 95%  
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13 significance and 80% power. An additional 10% of patients will be recruited, to  
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15 correct for patients who do not complete all of the study procedures. Thus, we  
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17 will aim to recruit a total of 107 patients.  
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### 23 **Study organisation**

24 The Asociación Benéfica (A.B.) PRISMA and Universidad Peruana Cayetano  
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26 Heredia in Lima, Peru will provide local administrative oversight. Overseas,  
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28 oversight will be conducted by Johns Hopkins University in Baltimore, Mary-  
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30 land, USA.  
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35 In Lima, the Pampas office of A.B. PRISMA will provide operations and lo-  
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37 gistic support for fieldwork. An additional collaborating signal processing  
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39 team will be based locally in the Universidad Nacional de Ingeniería, Lima,  
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41 Peru, as well as at Tufts University, Massachusetts, USA.  
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45 Our collaborating biostatisticians are based at Tufts University, Tulane Uni-  
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47 versity, and Universidad Peruana Cayetano Heredia, Lima, Peru. All investi-  
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49 gators are involved in protocol design and technical support and will remain  
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51 involved in the ongoing analyses.  
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### 55 **Personnel, training and logistics**

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3 Nurses have been trained by study staff to obtain sputum samples in a best-  
4 practice fashion based on previous work,[45 ,46] and to operate and trouble-  
5 shoot all recorder devices, memory cards, and battery packs. We will adhere  
6 to recommended infection prevention & control practices for TB to reduce bio-  
7 risk in healthcare professionals and patients.[47] Written informed consent is  
8 required prior to research participation. At the time of enrolment, subjects will  
9 follow the procedures outlined in Figure 1.  
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Subjects with active pulmonary TB will be followed throughout their TB treat-  
ment. After the identification of active pulmonary TB and based on conven-  
ience basis, subjects who consent will undergo CXR and a non-contrast tho-  
racic CT scan.

The first day of a new TB treatment regimen is defined as “Day 0”. An initial  
questionnaire will be completed on that day (Supplementary File 1). It should  
be mentioned that we used a 5-level ordinal scale instead of 10 to make it  
simpler for our interviewees. We have found it easier in this setting for re-  
search participants to interpret 5-levels each with defining words (never, little,  
much, almost always, always) rather than 10. This questionnaire is similar to  
the one that was employed in a previous study.[48] Baseline cough frequency  
will be obtained by performing an audio recording of the patients before they  
obtain their microbiological results, which is usually a few days prior to treat-  
ment initiation. Hence, subjects will be recorded from at least one day prior to  
treatment and throughout their first two weeks of treatment. They will subse-  
quently be recorded for 24 hours on or around days 21, 30 and 60 of treat-

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3 ment, although up to two days date deviation for Sundays and public holidays  
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5 will be allowed.  
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10 Recordings will start at 09:00 hours and will be as continuous as possible.  
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12 Occasionally incomplete recordings could be obtained due to malfunction of  
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14 equipment or patient non-compliance. On the recording days clinical data will  
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16 be gathered, including: weight, temperature, and sputum samples for smear  
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18 and MODS results. The number of days to culture positivity in the MODS liq-  
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20 uid culture assay will be recorded in order to assess the microbiological bur-  
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22 den in the patients' samples, based on prior work done with a similar tech-  
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24 nique.[49]  
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### 32 **Audio recording**

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34 Design of the audio recording equipment, the CayeCoM device, builds on  
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36 previous chronic cough ambulatory audio recordings.[27 ,50 ,51] The  
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38 CayeCoM device is a Marantz PMD 620 professional handheld recorder, us-  
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40 ing an Audio-Technica AT899 sub-mini microphone with an AT8537 micro-  
41  
42 phone power module. The microphone will be attached at the patient's lapel  
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44 as shown in Figure 2. The recorder is adapted to work with an external lithium  
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46 battery supply (Enix Energies 800040) to enable continuous 24-hour record-  
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48 ings. The audio is recorded onto a SanDisk SDHC 8 GB card, at a sample  
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50 rate of 48 kHz, encoding 64 kbps in mono in MP3 format. The audio equip-  
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52 ment is kept inside a basic pack connected to a lapel microphone. Batteries  
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54 and SD cards will be exchanged daily by the study nurses. In pilot research,  
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3 subjects tolerated the audio equipment well, wearing them 24 hours a day and  
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5 taking them off only to bathe.  
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### 9 10 **Processing of audio recordings**

11 The recorded signals will be analysed after all patient recordings are complet-  
12 ed. For cough analysis, software developed by our group and previously de-  
13 scribed in detail will be used.[31 ,32] Thus we provide only a brief review here  
14 and refer interested readers to our previous publications.  
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20  
21 Briefly, cough recordings will be analysed using a 2-step algorithm: first, event  
22 detection, followed by event classification into cough vs. non-cough. Detec-  
23 tion of acoustic events will be based on the signal energy proportional to the  
24 voltage-squared of the signal. An acoustic event will detect if the signal ener-  
25 gy exhibited a rapid increase above a time-varying baseline estimate of ambi-  
26 ent noise. The next stage of processing seeks to classify detected events.  
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30 Here, the spectral features of each time frame in the acoustic event are char-  
31 acterised using Mel frequency cepstral coefficients and their derivatives. As  
32 described in detail elsewhere,[32] a training data set will be used to develop a  
33 classifier based on the sequential minimal optimisation (SMO) algorithm.  
34  
35 Based on classifier outputs, each acoustic event will be marked as 'cough' or  
36 'not-cough'.  
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49 Isolated cough events will be automatically combined into cough epochs, or  
50 bursts of closely spaced individual coughs, following previous research.[52]  
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52 We will employ a definition of cough epochs, as defined in the 'Outcomes and  
53 case definitions' section above. Note that within the cough literature, a variety  
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3 of metrics are available for describing cough, and there is no clear evidence  
4 as to which are most clinically meaningful. We have previously published a  
5 review and discussion of these various metrics (number of individual coughs,  
6 number of cough bouts or epochs, number of 1-sec periods containing cough,  
7 etc.).[32]  
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12 We will employ a semi-automated approach in which cough epochs that are  
13 automatically detected will then be manually reviewed to eliminate false posi-  
14 tives. This is necessary as our recordings will be made in very noisy envi-  
15 ronments (outside clinical settings) and false detection rates for a fully auto-  
16 mated system remain high. For this study, a simple graphical user interface  
17 will be constructed to allow nurses to review automatically detected epochs,  
18 enabling listening to each as often as needed, and then to either accept or re-  
19 ject the detected cough. Thus, the review of automatically detected coughs  
20 acts to eliminate algorithmic false positive coughs.  
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36 *Validation:* The approach described in the paragraphs above was previously  
37 validated using as gold standard a fully manual review of 60 files (15 subjects,  
38 4 randomly selected time periods per subject) in which two nurses listened to  
39 all files in their entirety.[32] Because nurses only manually marked the start of  
40 each cough, validation was compared on the basis of the epoch definition de-  
41 scribed above. The semi-automated approach described above gave 75.5%  
42 sensitivity in detecting coughs (true positive rate of 6.8/hour) with an average  
43 false positive rate of 0.5/hour.[32] While the semi-automated approach does  
44 require time for human review, the initial automated step will remove the large  
45 majority of possible events. Thus on average, review time is reduced by near-  
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ly two orders of magnitude compared to a fully manual review in which the entire recording is reviewed. We will also maintain the privacy of subjects, as non-cough events, such as conversation, will never be reviewed by the human ear.

### **Microbiology**

The microbiological tests will be carried out in a Biosafety Containment Level 3 research laboratory situated within Universidad Peruana Cayetano Heredia in Lima, Peru. The sputum samples will be digested and decontaminated by the standard NaOH-N-acetyl cysteine method.[53] For smear microscopy, an aliquot of 100 µl is stained with Auramine O and examined with x400 magnification. Results are determined as negative, paucibacillary (1-19 acid fast bacilli [AFB] visualized in 40 fields), 1+ (20-199 AFB visualized in 40 fields), 2+ (5-50 AFB per field) and 3+ (>50 AFB per field). Culture and MODS susceptibility testing will be performed with the remaining samples, according to standard protocols.[33-35]

### **Radiology**

Radiological information will be gathered, when possible, on a convenience basis. Priority will be given to CT scans, since they have been shown to be more sensitive in general.[44] A previous study determined that the sensitivity for the prediction of active TB through CT scans was of 96%, whereas for CXR it was merely 48%.[54] Films will be read by a local radiologist and a US board-certified radiologist blinded to the patient's demographics and outcomes. They will provide an interpretation that is standardised as per our

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2  
3 study protocol to describe radiological findings including cavitation, consolida-  
4 tion, lymphadenopathy, and effusions (Supplementary File 2). We will explore  
5 whether these radiological findings are predictive of microbiological burden  
6 and cough frequency.  
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14 Cavitations will be further described by size, location, presence or absence of  
15 an air-fluid level, and cavity wall thickness based on prior work that shows the  
16 relevance of these findings to pulmonary TB and most importantly, to infectivi-  
17 ty.[7 ,55-58] It is therefore important to determine cavitations, and as Im and  
18 collaborators have shown, CT correctly identifies cavitations in 58% of cases,  
19 whereas CXR only identifies 22%.[55]  
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### 29 **Statistical methodology and analysis**

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31 All questionnaire data will be double digitised from paper forms using Visual  
32 FoxPro 9 Service Pack 2 (Microsoft Corp. Redmond, Washington, USA) and  
33 microbiological data will be double entered using Microsoft Access 2010 (Mi-  
34 crosoft Corp. Redmond, Washington, USA). These two data sets will be  
35 cross-compared for validity and errors. From these data, descriptive statistics  
36 will be tabulated and graphed.  
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47 Cough analysis processing results will be stored as Matlab (Mathworks, Inc,  
48 Natick MA) files containing information regarding each event and its  
49 timestamp. Algorithmically detected coughs will be annotated in the files. After  
50 manual review, isolated cough events will be grouped into cough epochs, or  
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3 bursts of closely spaced individual coughs within 2 seconds, following pub-  
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5 lished work on cough evaluation.[52]  
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10 For the first study objective of describing cough frequency, cough epochs will  
11 be plotted throughout the day, and cough frequency will be summarised as  
12 the frequency of cough epochs per hour. Positively-skewed cough data may  
13 be log-transformed to facilitate data visualisation and analysis. To address the  
14 second study objective, correlation of characteristics with cough frequency,  
15 we will use generalised estimating equations (GEE) based Poisson or nega-  
16 tive binomial regression with baseline microbiologic status, and trigonometric  
17 (sine/cosine) terms to model circadian periodicity, as the independent varia-  
18 bles. In addition, a multiple logistic regression in a longitudinal generalised  
19 linear model (GLM) framework analysis will evaluate a function of sputum ba-  
20 cillary load and with cough frequency that we propose as a potential predictor  
21 of TB transmissibility. In all cases we will correct for outliers, and nested mod-  
22 els will be compared using the likelihood ratio test. We will also consider vari-  
23 ables such as gender, HIV status, drug resistance, and previous history of TB,  
24 in our analysis, either by stratifying or by adjusting for these variables in our  
25 models.  
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45 To test the association between cough frequency and microbiological resolu-  
46 tion of TB disease associated with the third aim of this study, time-to-event  
47 survival analyses where the outcomes of interest are sputum smear conver-  
48 sion, and culture conversion, as defined above, and the primary predictors of  
49 interest are cough frequency at baseline, during treatment, and time to two-  
50 fold reduction in cough frequency. In addition, secondary analyses of weight,  
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3 temperature, and radiological characteristics, will be conducted using general-  
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5 ised linear models and GEE logistic regression as appropriate.  
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### 10 11 12 **Ethics and dissemination**

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14 Ethical approval has been obtained from the ethics committees at A.B. PRIS-  
15  
16 MA in Lima, Peru, the Universidad Peruana Cayetano Heredia in Lima, Peru,  
17  
18 and Johns Hopkins University, in Baltimore, USA. Written informed consent  
19  
20 will be obtained from all participants. Test results will be delivered by tele-  
21  
22 phone or at subsequent visits at which time a team physician or nurse will be  
23  
24 able to explain the results to the study participants. TB treatment remains the  
25  
26 responsibility of the medical staff in charge and the National TB Programme.  
27  
28 We aim to publish and disseminate our results, once the project is complete.  
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30 We also expect to create and maintain an online repository for TB cough  
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32 sounds as well as the statistical analysis employed.  
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### 36 37 **Discussion**

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39 We will determine cough frequency before and during anti-TB treatment using  
40  
41 the CayeCoM device. We will identify baseline predictors of cough frequency  
42  
43 during TB treatment and evaluate the correlation between change in cough  
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45 frequency and microbiological resolution.  
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49  
50 The medical literature currently lacks information about cough frequency in  
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52 TB. As recently noted by Turner and Bothamley,[5] cough frequency in pa-  
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54 tients undergoing TB treatment has only been studied once, almost half a  
55  
56 century ago.[6 ,7] This previous study has the limitation of only being con-  
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3 ducted within an 8-hour period, overnight, and thus there is no information on  
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5 daytime coughing or the effect of the diurnal rhythm on cough. A similar  
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7 study[58] demonstrated that the severity of cough and pathological chest x-  
8  
9 ray findings were associated with higher levels of TB transmission. However,  
10  
11 their study did not measure cough frequency but instead focused on a subjec-  
12  
13 tive characteristic: cough severity. It should be noted that to assess cough  
14  
15 frequency one must utilise objective acoustic parameters, since self-reported  
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17 cough is unreliable.[19] As reported in abstract form, the objective acoustic  
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19 Leicester Cough Monitor (LCM) has been used to evaluate 24-hour cough re-  
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21 cordings in patients with pulmonary TB before starting treatment, showing that  
22  
23 cough frequency is reduced at night.[59] This further justifies re-evaluation of  
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25 Loudon's overnight study.  
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30 Our project has several strengths and limitations. An important strength is the  
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32 generation of 24-hour cough recordings, which will provide lengthy recordings,  
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34 will enable evaluation of cough patterns at different times of day, and also has  
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36 the benefit of being recorded during a normal day in real-world settings where  
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38 we expect our device to be used in the future. Normal day recordings are con-  
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40 founded by background noise, which is a challenge for analysis of cough re-  
41  
42 cordings, considering that traffic and environmental noise (such as dogs bark-  
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44 ing, music, and television) may generate noises similar to cough. To diminish  
45  
46 this effect, we have incorporated a time-varying estimate of the noise back-  
47  
48 ground as well as a data quality control. Having a semi-automated algorithm  
49  
50 is a limitation, since it requires time and human input, but also a strength  
51  
52 since the human ear is the gold standard for determining the characteristic  
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54 sound of cough. Similar to Loudon's proposal,[8] our algorithm will help to  
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3 screen and reduce the length of the recordings to ~5% of their original length,  
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5 without affecting sensitivity and improving specificity.[32] We aim to improve  
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7 our sensitivity by fully automated processing remains a long-term goal for our  
8  
9 group, and we anticipate that experience gained with semi-automated analy-  
10  
11 sis will aid us in developing future algorithms. In addition, we are now devel-  
12  
13 oping second-generation devices where the validity is improved by employing  
14  
15 accelerometers. This study is limited by restriction to only non-pregnant adults  
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17 because this is the population for which the algorithm has been validated.  
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21 However, future research is planned to include these important vulnerable  
22  
23 populations.

24  
25 CayeCoM has been validated for 24-hour recordings,[32] whereas Pulmo-  
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27 Track (PulmoTrack-CC, KarmelSonix, Haifa, Israel) was validated for 25  
28  
29 minutes[29] and the Hull Automatic Cough Counter for 1-hour recordings.[27]  
30  
31 Other systems have also validated their algorithms for 24-hour recordings,  
32  
33 such as the LCM,[28 ,60] VitaloJAK,[30] and the LifeShirt System.[26] How-  
34  
35 ever, in contrast to our study, none of these algorithms have been validated  
36  
37 for pulmonary TB nor within real-life settings (e.g. traffic). We expect that this  
38  
39 project will generate a novel method to evaluate treatment response. In future  
40  
41 studies we intend to better assess infectiousness by additionally quantifying  
42  
43 TB in cough-generated aerosols.  
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47 Cough frequency should provide additional information regarding the evolu-  
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49 tion of the patients' medical condition. If a correlation with bacteriological  
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51 treatment response is demonstrated, then this would have the potential to  
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53 contribute to patient management without relying on a laboratory in adult pa-  
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55 tients with pulmonary TB. However, we should be careful when monitoring TB  
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3 patients since some may worsen after an initial positive response to therapy.  
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5 It could assist with decisions regarding the need for on-going respiratory isola-  
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7 tion of patients, treatment duration, and identification of patients with treat-  
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9 ment failure who may need modification of their treatment regimens. The de-  
10  
11 vice also has the potential to be used remotely, as in telemedicine. This is po-  
12  
13 tentially important in a country such as Peru, where the majority of doctors live  
14  
15 in the capital, leaving most of the country without a physician in their region.  
16  
17 Cough monitoring devices seem challenging; however, we believe that this is  
18  
19 the first step towards telemedicine in cough-TB. In Peru, many rural areas do  
20  
21 not have facilities for laboratory diagnosis, but have at least one physician or  
22  
23 healthcare professional. They may be trained in placing these devices. We  
24  
25 are also working on making devices smaller, cheaper, and easier to use.  
26  
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28

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### Contributors:

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22 and JWL directly contributed to study design and are responsible for supervi-  
23 sion of data gathering. AP, BHT, JWL, MZ and GL will be responsible for data  
24 management and statistical analysis for this project.  
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### Competing interests statement:

49 All authors declare that they have no competing interests in relation to this  
50 work.  
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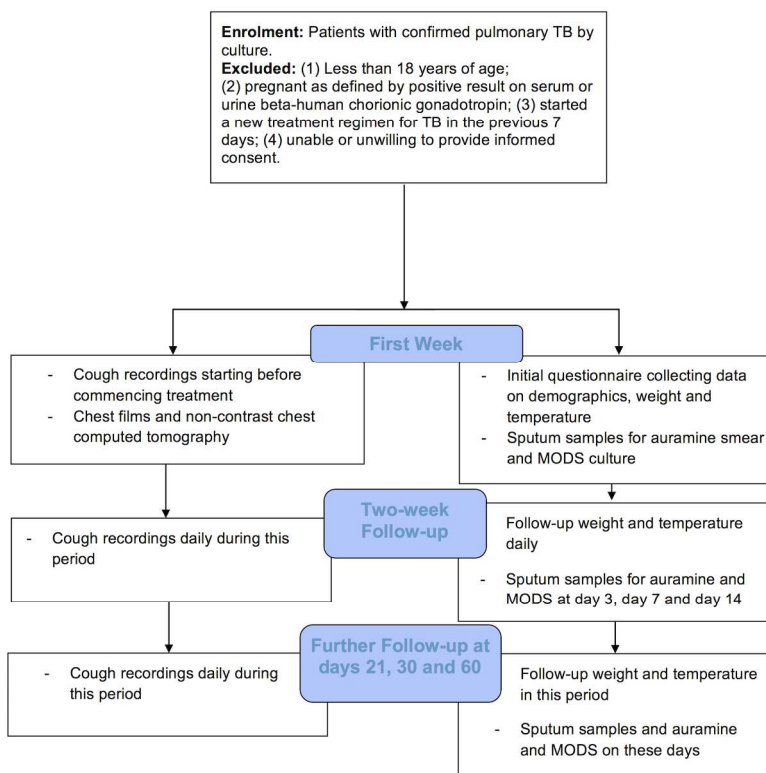


Figure 1 – Flow Diagram for CayeCoM Study  
 175x247mm (300 x 300 DPI)

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Figure 2 – Picture of the Cayetano Cough Monitor (CayeCoM)  
175x90mm (300 x 300 DPI)

Código del paciente: \_\_\_\_\_  
 Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

Entrevistador: \_\_\_\_\_

### **Cuestionario Inicial Para Todos Los Participantes:**

#### Datos Demográficos:

1. Edad: \_\_\_\_\_
2. Sexo: \_\_\_\_\_

#### Antecedentes:

3. ¿Cuántas personas normalmente duermen en casa?: \_\_\_\_\_ Personas
4. ¿Cuántas habitaciones hay en su hogar? (sin contar baño, pasadizo, cocina, depósito, garaje): \_\_\_\_\_ habitaciones.
5. ¿Cuál es el ingreso mensual de la vivienda? S/. \_\_\_\_\_
6. ¿Cuánto gasta su familia en alimentación cada semana? S/. \_\_\_\_\_
7. ¿Cuántas personas en su vivienda comen de esos alimentos que compran semanalmente? \_\_\_\_\_ Personas
8. ¿Cuántas veces en el ultimo mes usted se ha acostado con bastante hambre porque no había comida en casa? \_\_\_\_\_ días

#### Historia de Tuberculosis:

La tuberculosis es una enfermedad que se trata con varios antibióticos a la vez, y cuyo tratamiento dura varios meses.

9. ¿Ha sido diagnosticado con TBC anteriormente?
  - a. Si
  - b. No → *Pase a la pregunta 15*
  - c. NS

10. ¿Cuántas veces? \_\_\_\_\_

11. Si recibió tratamiento para la TBC, ¿dónde recibió la mayor parte del tratamiento?
  - a. NA
  - b. Mismo distrito
  - c. Otro distrito
  - d. Otra ciudad
  - e. Otro país

12. Si recibió tratamiento para la TBC ¿por cuantos meses en total lo tomó? \_\_\_\_\_

13. Si recibió tratamiento previo, en que esquema estaba (lo mas recién): -  
 \_\_\_\_\_

14. Si recibió tratamiento para la TBC ¿cumplió con el tratamiento previo?

- a. NA
- b. Si
- c. No → \_\_\_\_\_
- d. NS

#### Factores de Riesgo

15. ¿Ha compartido un cuarto con alguien que haya tenido TBC comprobada?

- a. Si, y esta persona también tenía una tos persistente
- b. Si, pero esta persona concurrente no tenía una tos persistente
- c. No → *Pase a la pregunta 18*
- d. NS

16. ¿Dónde compartió este ambiente con alguien infectado con TBC?

- a. NA
- b. Trabajo
- c. Casa
- d. Hospital
- e. Otro: \_\_\_\_\_

17. ¿Por cuantos días compartió este ambiente con la persona con TBC comprobada? \_\_\_\_\_

18. Aparte de usted, ¿alguien mas en casa esta actualmente recibiendo medicinas para la TBC?

- a. Si → Quien: \_\_\_\_\_
- b. No
- c. NS

#### Creencias y Conocimiento de la Enfermedad

19. ¿Dónde escuchó de la TBC por primera vez?

- a. Familia
- b. Amigos
- c. Colegio
- d. Puesto de Salud
- e. TV
- f. Radio
- g. NS

20. ¿Puede alguien con TBC y tos infectar a sus familiares?

- a. Si
- b. No
- c. NS

Cuestionario Inicial Para Todos Los Participantes

1

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.



Código del paciente: \_\_\_\_\_

Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

21. ¿Qué tan contagiosa cree que es la TBC?

- a. Nada
- b. Poquito
- c. Mucho
- d. Bastante
- e. Lo mas

22. ¿Qué tan seria cree que es la TBC?

- a. Nada
- b. Poquito
- c. Mucho
- d. Bastante
- e. Lo mas

23. En general, ¿qué puede hacer uno por si mismo para protegerse de contraer la TBC? [Marcar el factor más importante, no sugerir repuestas].

- a. Vacunarse
- b. Comer
- c. Dormir bien, descansar
- d. Vivir una vida ordenada
- e. Mantenerse alejado de la gente con TBC
- f. Educarse
- g. Otro: \_\_\_\_\_
- h. NS

¿Cuales son los síntomas de la TBC?

[Marcar los factores, no sugerir repuestas].

24. Tos mencionada

Si  No 

25. Hemoptysis mencionada

Si  No 

26. Fiebre mencionada

Si  No 

27. Baja de peso mencionada

Si  No 

28. Fatiga, decaimiento mencionada

Si  No 

29. Palidez, un cierto semblante mencionada

Si  No 

30. ¿Qué debe hacer una persona con TBC para mejorarse? [Marcar el factor más importante, no sugerir repuestas].

- a. Tomar sus medicinas, asistir a controles
- b. Comer mas, comer mejor
- c. Descansar
- d. Tener fe
- e. Abrigarse
- f. Otro: \_\_\_\_\_
- g. NS

31. ¿Cómo puede hacer una persona con TBC para no contagiar la TBC a otros? [Marcar el factor más importante, no sugerir repuestas].

- a. Cubrirse la boca al toser
- b. Quedarse en casa, mantenerse alejado
- c. Seguir el tratamiento
- d. Separar cubiertos
- e. Otro: \_\_\_\_\_
- f. NS

32. ¿Se puede curar la TBC?

- a. Siempre
- b. Normalmente sí
- c. A veces
- d. Raramente
- e. Nunca

**Instrucciones:** Marque una X sobre la línea la posición que escoges.

Ejemplo: -----

33. Con que frecuencia esta tosiendo hoy, en un promedio de 24 horas?

0                      1                      2                      3                      4                      5

nunca

poquito

mucho

casi siempre

**Instrucciones:** Marque una X, en el cuadrado, todas las alternativas que corresponden.Ejemplo: 

34. Que indicadores utilizó para escoger a que posición poner sus X?

 Los números: 1, 2, 3, 4, 5 Las palabras: nunca, poquito, mucho, casi siempre Las figuras:

Cuestionario Inicial Para Todos Los Participantes

2

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

Código del paciente: \_\_\_\_\_  
 Fecha de Entrevista: \_\_\_/\_\_\_/\_\_\_ Iniciales del Entrevistador: \_\_\_\_\_

**Instrucciones:** Marque con X la alternativa que corresponde.

Ejemplo:

35. ¿Comparado con hace tres días, tiene más frecuencia de tos el día de hoy?
- Tosiendo ahora menos
  - Tosiendo ahora igual
  - Tosiendo ahora más
37. Si tiene tos, ¿a que hora en el día tiene más frecuencia: *mañana, tarde o noche*?
- Mañana
  - Tarde
  - Noche
36. El día de hoy, ¿ha tenido *solo tos, tos con flema o solo flema*?
- Solo tos
  - Tos con flema
  - Solo flema
38. Qué tan frecuentemente tose?
- Cada pocos segundos
  - Cada pocos minutos
  - Cada pocas horas
  - No tose

**Instrucciones:** Marque el numero de días en total que tiene los siguientes síntomas desde que se enfermó. Marque 0 si ningún día.

39. ¿Cuántos días usted ha tenido los siguientes síntomas?
- Tos seca \_\_\_\_\_
  - Tos con flema \_\_\_\_\_
  - Tos con sangre \_\_\_\_\_
  - Fiebre \_\_\_\_\_
  - Falta de aire \_\_\_\_\_
  - Perdida de peso \_\_\_\_\_
  - Cansancio o decaimiento \_\_\_\_\_
  - Sudor nocturno \_\_\_\_\_
  - Falta de apetito \_\_\_\_\_

**Instrucciones:** Responde a la pregunta en el lugar indicado.

40. Actualmente, ¿como se siente? (0 = mal, 10 = bien): \_\_\_\_\_

41. Cuando tiene tos, ¿cuántas toses tiene por hora? \_\_\_\_\_

42. Preguntas sobre VIH

	Manifiesto del paciente	Historia clínica
a. Usted ha sido diagnosticado por VIH?	_____	_____
b. Fecha de Diagnostico:	_____	_____
c. Ultima Carga Viral:	_____	_____
d. Fecha de ultima Carga Viral:	_____	_____
e. Ultimo resultado CD4:	_____	_____
f. Fecha de Ultimo resultado CD4:	_____	_____
g. Tiempo tomanda TARGA (años)	_____	_____

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

### **Radiologic Interpretation Data Form**

Date of read: \_\_\_\_\_

Radiologist Name: \_\_\_\_\_

Radiologist Signature: \_\_\_\_\_

Patient code: \_\_\_\_\_

Patient gender:  male  female

Patient age: \_\_\_\_\_

#### 1. Type of film:

AP  PA  Lateral from R  Lateral from L  Thoracic CT  
without contrast  Other: \_\_\_\_\_

2. Date of film: Day: \_\_\_\_\_ Month: \_\_\_\_\_ Year: \_\_\_\_\_

3. Rotation: \_\_\_\_\_

4. Adequacy of inhalation: \_\_\_\_\_

	Site	a. Consolidation?	b. Cavitation?	c. Pneumatocele?	d. Atelectasis?
5	Right upper lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
6	- anterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
7	- apical	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
8	- posterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
9	Right middle lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
10	Right lower lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
11	- superior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
12	- basal	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
13	Left upper lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
14	- anterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
15	- apical	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
16	- posterior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
17	Lingula	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
18	Left lower lobe	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
19	- superior	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
20	- basal	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no

21. Pleural effusion?  yes  no  
left?  small  medium  large  
right?  small  medium  large

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

22. Miliary spread?  yes  no

23. Pneumothorax?  yes  no

where and size: \_\_\_\_\_

24. Lymphadenopathy:  yes  no

which lymph nodes groups

hilar  mediastinal

25. Pericardial effusion?  yes  no

left?  small  medium  large

26. Bronchiectasis?  yes  no

where: \_\_\_\_\_

27. Fibrosis?  yes  no

where: \_\_\_\_\_

any retractions, deviations? \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

28. Mediastinal thickening?  yes  no

29. Any tree-in-bud pattern? Where? \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

30. Cavitation: For each cavity, please describe:

Cavity # 1:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  think  thick smooth nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 2:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  think  thick smooth nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity #3:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

La asociación de la frecuencia de la tos con la dinámica microbiológica de la tuberculosis en pacientes con tuberculosis pulmonar activa.

CODIGO PACIENTE: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 4:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

Cavity # 5:

location: \_\_\_\_\_

size (in mm) cephalic: \_\_\_\_\_

size (in mm) caudal: \_\_\_\_\_

size (in mm) anterior-posterior: \_\_\_\_\_

presence of air/ fluid level?:  yes  no

Cavity wall:  thin  thick  smooth  nodular

Cavity Wall Thickness(in mm): \_\_\_\_\_

More cavities?  yes: please use another sheet to describe  no

Other findings such as fractures, cardiac abnormalities, exudative / fibrotic densities, bronchogenic spread, mass-like lesions (calcified vs. non-calcified), please describe:

\_\_\_\_\_  
\_\_\_\_\_  
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\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

31. Normal film?  yes  no

## Correction

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Proaño A, Bravard MA, Tracey BH, *et al.* Protocol for studying cough frequency in people with pulmonary tuberculosis. *BMJ Open* 2016;6:e010365. The segmentation of the eighth author's name is incorrect. This author's last name is Lee, and middle name is O'Neill.

*BMJ Open* 2016;6:e010365corr1. doi:10.1136/bmjopen-2015-010365corr1



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## Correction

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Proaño A, Bravard MA, Tracey BH, *et al.* Protocol for studying cough frequency in people with pulmonary tuberculosis. *BMJ Open* 2016;6:e010365. The segmentation of the tenth author's name is incorrect: his first name is Jose, middle name is Luis and last name is Cabrera, and he should be cited as Cabrera JL.

*BMJ Open* 2016;6:e010365corr2. doi:10.1136/bmjopen-2015-010365corr2



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