**Diagnosis of respiratory illness using non-contact sound recordings.**

***The Breathe Easy Study protocol***

***Study Site*: Joondalup Health Campus**

This study has been registered on the ANZCTR (ACTRN12618001521213)

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**1. INTRODUCTION**

Diagnosis of respiratory conditions in paediatric populations in resource-poor communities remains difficult and suboptimal. Current diagnosis and treatment algorithms used by the World Health Organisation and other NGO’s have a significant error rate and result in misdiagnoses, inappropriate use of antibiotics and unacceptable morbidity and mortality rates. Pneumonia, asthma, bronchiolitis, pertussis, bronchitis and chronic lung disease are readily diagnosable with appropriate clinical training and support services (microbiology and diagnostic imaging). Recent advances in acoustic engineering and analysis have shown promise in being able to diagnose these conditions based on sound analysis thus eliminating the need for diagnostic support services and a higher level of training for health care providers. The potential use of an automated sound analyser in resource poor environments is significant.

During a respiratory sound event (e.g. cough), the lungs are connected to the atmosphere via a column of air, which can support a much higher bandwidth than the traditional pathway across the chest musculature. We propose to use this “Information Super Highway” to diagnose pneumonia and other respiratory diseases. Physics dictate that sounds generated inside the lungs, including disease-specific ones, should propagate outside through the air column at the speed of sound. In pneumonia, lung consolidation also modulates the sound quality received outside. These components get buried in the loud main component of a cough contributed by the vibration of upper airway, but can be used to diagnose disease if isolated.

In our approach we utilise technology akin to that used successfully in speech recognition technology: analysing cough and breath sounds and the associated respiratory sound stream as a ‘language’ with its features operating as phonemes, words and sentences.

**2. OBJECTIVE**

1. To record breath sounds (including coughs and other airway noises) in children and adults presenting with any respiratory symptoms and to use these breath sounds to develop and investigate the utility of a computerised algorithm for diagnosing respiratory illnesses such as asthma, pneumonia, croup, bronchiolitis and upper respiratory illnesses (UIRT) in children and asthma, pneumonia, bronchitis, chronic obstructive pulmonary disease (COPD) and URTI in adults.

**Study Hypothesis**

That automated cough sound analysis (index test) is non-inferior to existing standard-of-care clinical diagnosis (non-standard reference test) for identifying specified respiratory disorders in children, adolescents and adults.

**3A. BACKGROUND – PAEDIATRIC STUDY**

Pneumonia is a major cause of childhood morbidity. Pneumonia kills an estimated 1.3 million children under age 5 each year (1,2). Nearly 75% of these deaths are in Africa and South East Asia affecting the underprivileged and poor populations. The diagnosis of pneumonia requires access to appropriate clinical, radiological and laboratory support which are not readily available in remote areas. Hence the development of a low-cost, field deployable, rapid diagnostic test is one of the key challenges to combating mortality.

To assist pneumonia diagnosis in resource poor areas, the WHO have developed a clinical algorithm based on the existence of symptoms such as cough, breathing difficulty, chest indrawing and respiratory rate. The criterion has good sensitivity (77-81%) and specificity (77-80%) when combined with clinical and radiological examinations. However it has unacceptably low specificity (16-47%) in the absence of clinical or radiological support (3,4). Low specificity leads to excessive antibiotic use which has implications for the patient (side effects, drug resistance) and society (medication wastage, drug resistance).

Researchers at the University of Queensland (work supported by the Bill and Melinda Gates Foundation USA under its Grand Challenges in Global Health Explorations Grant program) have developed an innovative method to diagnose childhood pneumonia based on the automated analysis of cough sounds (5). This approach is easily automated on portable devices, easy to use and low cost making it ideal for mass deployment in remote and rural areas where clinical, radiological and laboratory supports are scarce. In addition, with sensitivity 94% and specificity 88%, this method has been shown to outperform the WHO criteria for pneumonia diagnosis in resource-poor regions (5). The technique has the added benefit of being non-invasive, is radiation free and uses a non-contact recording device which is advantageous for use in children as well for infection control and to minimize cross-contamination amongst patients.

The purpose of this paediatric study is firstly to collect additional data to further refine the development of the algorithm for diagnosis in childhood pneumonia; and secondly to explore the possibilities of utilising the same technology to diagnose other paediatric respiratory illnesses such as asthma, croup, bronchiolitis, pertussis and upper respiratory illnesses. There is potential for the tool to have far reaching benefits for use in remote and rural settings both within Australia and worldwide, as well as being an additional diagnostic method available to clinicians everywhere for the diagnosis of childhood respiratory illness. This will allow the development of machine intelligence technology to differentially diagnose the target diseases. Our mathematical algorithms are inspired from human speech analysis technology. We have successfully used them to develop pioneering technology in the diagnosis of sleep apnoea via snore analysis (sensitivity, specificity >92%).

We use smart phones as the sound acquisition device for multiple reasons: (i) they easily meet the acoustic requirements (bandwidth, noise levels, and transduction-sensitivity) needed for respiratory sound recording, (ii) they are ubiquitous devices even in the developing world, (iii) substantial computing power available within modern phones allow us to use them as all-in-one data acquisition, analysis and decision making devices. An instrumentation grade microphone system was chosen due to its small footprint, and the ability to capture sounds with bandwidth well beyond the human hearing range. This device will be used as a reference technology to compare smart phone devices.

**3B. BACKGROUND – ADOLESCENT AND ADULT STUDY**

Respiratory disease represents a major burden on the Australian hospital system. Acute respiratory infections represent 2.3% of the total hospital patient days in Australia and chronic respiratory diseases (mostly asthma and COPD) represent 2.0% of patient days (6). Beyond the hospital system, respiratory disease represents the largest disease outcome from a doctor visit, with an estimated 6-8 million doctor visits in Australia resulting in a diagnosis of respiratory disease, and in the US approximately 125 million ambulatory case visits are for respiratory disease.

Researchers at the University of Queensland (work supported by the Bill and Melinda Gates Foundation USA under its Grand Challenges in Global Health Explorations Grant program) have developed an innovative method to diagnose childhood pneumonia based on the automated analysis of cough sounds (5). This approach is easily automated on portable devices, easy to use and low cost. The technique has the added benefit of being non-invasive, is radiation free and uses a non-contact recording device. In an ongoing clinical study at Princess Margaret Hospital and Joondalup Health Campus in Perth, the method has recently been extended to diagnose additional childhood respiratory diseases, including bronchiolitis, croup, asthma/viral wheeze and URTI. Preliminary results from this study demonstrated that >90% sensitivity and specificity is potentially achievable for the diagnosis of these diseases in children.

The purpose of this study is to explore the possibilities of adapting this technology to diagnose adult respiratory illnesses such as asthma, pneumonia, bronchitis, COPD and upper respiratory tract illnesses. There is potential for the tool to have far reaching benefits for use in remote and rural settings (e.g. via telehealth) both within Australia and worldwide, as well as being an additional diagnostic method available to clinicians everywhere for the diagnosis of adult respiratory illness. Our mathematical algorithms are inspired from human speech analysis technology. We have successfully used similar ideas to develop pioneering technology in the diagnosis of sleep apnoea via snore analysis (sensitivity, specificity >92%).

We use smartphones as the sound acquisition device for multiple reasons: (i) they easily meet the acoustic requirements (bandwidth, noise levels, and transduction-sensitivity) needed for respiratory sound recording, (ii) they are ubiquitous devices even in the developing world, (iii) substantial computing power available within modern phones allow us to use them as all-in-one data acquisition, analysis and decision making devices.

Respiratory diseases, such as bronchitis, pneumonia, upper respiratory tract infections, asthma and chronic obstructive pulmonary disease, account for a large proportion of doctor visits. In Australia, an estimated 6-8 million doctor visits result in a diagnosis of respiratory disease (6), and in the US approximately 125 million ambulatory case visits are for respiratory disease (7). Approximately 1.4% of all hospitalisations are for respiratory infections and 1.26% for chronic respiratory disease (mostly asthma and COPD) (6). The Australian Lung Foundation estimates that respiratory infections and chronic respiratory disease accounted for ~7% of the total burden of disease in Australia in 2010.

Diagnosis of respiratory conditions in general practice or in emergency departments can be difficult, costly and time-consuming. For example, a diagnosis of pneumonia is often confirmed using chest x-ray, which increases costs, can introduce delays and exposes patients to radiation. An inaccurate diagnosis can also cause inappropriate use of antibiotics, leading to potential side effects and drug resistance. In a telehealth setting where the patient may be located far from the clinician, diagnosis of respiratory disease is even more challenging, as the clinician is unable to listen to the lungs using a stethoscope, and imaging or lab tests can introduce significant diagnostic delays.

 We propose that an instant, clinically accurate diagnostic tool that can be used at the point of care could reduce costs, reduce time to treatment, potentially improve diagnostic accuracy and reduce inappropriate use of antibiotics for respiratory diseases in both general practice and emergency departments. We believe that the tool would greatly benefit telehealth consultations and provide much needed accurate remote diagnosis. A tool such as this could also be used effectively in resource poor environments that do not have access to lab testing and diagnostic imaging.

**4. RESEARCH PLAN**

***Study Design:***

This is a prospective, multi-centre study comparing diagnosis of paediatric respiratory illnesses using an automated cough sound analytic algorithm (index test) to clinical diagnosis (non-standard reference test). All participants will undertake both the index test and the non-standard reference test.

***Subjects:***

This study will enrol children, adolescents and adults assigned the diagnosis of any respiratory disease at participating sites during the study period (06 March 2015 to 05 March 2023.

***Sample size calculation:***

Based on expected PPA and NPA results greater than 85% from the training program, to obtain a superiority end-point of 75% (lower bound 95% CI of maximum width ±0.10) a minimum of 48 cases is required for each disease. Using the prevalence of focal pneumonia (the least prevalent targeted condition) in the training arm of 11%, and assuming a 10% attrition rate, a minimum cohort of 480 is needed.

***Inclusion criteria:***

Any child, adolescent or adult of any age (over 1 month) presenting to the ED or admitted to the ward of a participating institution with signs or symptoms of respiratory disease including rhinorrhea, cough, wheeze, dyspnoea/shortness of breath. stridor, increased work of breathing, cyanosis, additional auscultatory noises (crepitations) or low oximetry levels. Recruitment will also occur in low acuity ambulatory care units and adult respiratory medicine clinics as notified to the overseeing HREC.

A child will be considered to include any participant over 1 month and less than or equal to 144 months (12 years). Adolescents will be 145 to 263 months and adults will be 264 months (22 years) or older. For analysis, the adult group may be further divided into young adults being 264 months to 779 months and older adults being 780 months (65 years) and over.

The included subjects comprise the intended use population for the device.

***Exclusion criteria:***

* Lack of a signed consent form
* Need for ventilatory support (including non-invasive means such as CPAP, high flow nasal oxygen, BiPAP),
* Terminal disease.
* Medical contraindication to voluntary cough, including severe respiratory distress, history of pneumothorax, eye, chest or abdominal surgery within the past 3 months
* Too medically unstable to participate in study as per attending clinician.
* Structural airway disease including laryngomalacia or tracheomalacia.
* Heart failure
* Neuromuscular disease
* Lobectomy
* Participants with suspected COVID-19 or any notifiable infectious disease.

**Study Procedure:**

***Enrollment:*** Potential participants will be identified based on a search of the Emergency Department Information System (EDIS) and through inpatient censuses in use at participating hospitals using the search terms: Asthma, respiratory distress, bronchitis, COPD, bronchiolitis, croup, respiratory distress, pneumonia, pertussis, cough and wheeze in terms of presenting complaint or discharge diagnosis (if admitted to the ward). Community/staff members with an URTI may be invited to participate via newsletters.

Enrolment will be undertaken by the attending nurse or a dedicated research assistant who will approach the participant (or their parent/guardian if under 18 years of age) and explain the study, provide written information, answer any questions that may arise and obtain written consent from the participant or their parent/guardian. An explanation of the ability to withdraw from the study will be given at this time.

Consent will be sought to allow for participants cough sounds to be compiled into a “cough library” and uploaded to a website for use in clinical training. No names, identifying details or visual material will be uploaded. It will not be possible to download the cough sounds from the website.

A subset of those already included in the study (prior to 13 July 2018) will be retrospectively, contacted (via letter) to ask for their permission for their (previously recorded) cough sounds to be compiled into a “cough library” and uploaded to a website for use in clinical training. No names, identifying details or visual material will be uploaded. It will not be possible to download the cough sounds from the website. The researchers will ensure that participants who may have had a traumatic experience in hospital or who have since died, are not approached to participate.

***Data Collection:***

*Acquisition of patient cough/breath sounds*

Previous work indicates that 5-11 coughs are sufficient for the mathematical algorithms to make a decision about the existence of pneumonia.

Respiratory-related sounds are to be collected using three different types of devices: iPhone/iPads, Android phones (e.g. Samsung Galaxy S5), and free-field microphones (e.g. G.R.A.S.S. high bandwidth, instrumentation grade microphones). These devices are battery operated (<5 volts) and do not require physical contact with the subjects. The devices are mounted securely on a single small, table-top stand and placed within a 25-50cm radius from the patient’s head directed toward the patient. Ambient noise should be minimised, within reason for clinical needs.

Sound recordings are collected as follows:

|  |
| --- |
|  **1.** 1. **Voluntary Cough/Breathing Sounds** (only if patient is old enough to cooperate and is willing) |
| ☐ | Ask the patient to open the mouth and breathe deeply. (5 -10 breath cycles).  | * Keep sound recording equipment directly in front of subjects, within a 25-50cm radius.
* Microphones should point towards patients.
 |
| ☐ | Ask the patient for voluntary coughs (5-10 cough events).  |

|  |
| --- |
| **1.** 2. **Spontaneous Cough/Respiratory Sounds**  |
|  ☐ | Record spontaneous cough sounds as long as possible or until >10 coughs uncorrupted by background sounds are recorded. Record for up to one hour. Stop recording if patient distressed. | * Keep sound recording equipment directly in front of subjects, within a 25-50-cm radius.
* Microphones should point towards patients.
 |
|  ☐ | Record other respiratory sounds if available (stridor, wheeze, croup, cry) as long as possible. |

To assess whether sough sounds are impeded when transmitted through masks or other barriers, a subset of participants will be requested to provide at least five discernible cough-sounds (ie discrete cough sounds detected by the in-built cough-detector) both with and without impedance (total of ten discernible coughs) according to the above protocols. Cough recordings obtained with- and without-impedance will be compared (via the in-built diagnostic application installed on the iPhone – the index test) for equivalence. The application delivers a dichotomous result (“DISEASE PReSENT” or “DISEASE ABSENT”. There will be no requirement to ascertain clinical diagnosis for these participants and thus no requirement to access medical records, perform lung-function tests or undergo a physical examination. No results will be provided to participants.

Results from participant will yield five paired results for adolescents and adults: LRTD, pneumonia/LRTI, asthma exacerbation, COPD exacerbation, COPD and five or six paired results for children: (LRTD, asthma/RAD, croup, pneumonia, URTI or bronchiolitis (<2 years only).

If participants are unwilling to cooperate in the active component of the study, abandon the attempt.

**Data Collected:**

Data will be obtained from the patient medical notes – either from ED presentation or inpatient notes and entered onto an electronic data base/Case Report Form.

Collected cough and breath sounds (analysed by algorithm as per below)

**ED Diagnosis (Index Test)**

Diagnosis **–***as per medical discharge summary/EDIS discharge diagnosis*

* + Initial Clinical diagnosis
	+ Final diagnosis as per treating team after laboratory / imaging data is obtained (when appropriate).

**Other Data Collection:**

***Demographic data***

* Age
* Gender
* Height
* Weight

***Past Medical History***

* Respiratory or Cardiac disease
* Smoking History (collected for participants over 10 years at research nurse discretion)
* Medications

***Symptoms and Signs***

* Presence of respiratory symptoms and signs including wheeze, stridor, cough, fever, increased work of breathing, cyanosis, decreased oximetry, subcostal retractions, upper respiratory tract signs (runny nose).
* Length of illness, fever, vomiting, diarrhea, conscious level.
* Use of antibiotics or asthma medications (bronchodilators, steroids)
* Auscultatory findings

**Clinical Diagnosis Definitions (Non-standard Reference Test)**

The clinical diagnostic team have access to all clinical details including all investigations. For the clinical diagnosis, possible outcomes for each disease: “YES”, “NO” or “UNSURE”, where “UNSURE” indicated that the case definition was not entirely met or where symptoms had been significantly altered by treatment prior to enrolment.

For paediatric trials two Paediatricians will provide a final diagnosis with a third Paediatrician adjudicating if there is a disagreement.

For adult trials the clinical diagnosis will be based upon formal lung function tests when available, consensus clinical diagnosis between at least two clinicians and a full review of clinical notes and investigations.

For children over six years of age and for adults, spirometry represents the best, currently available, objective test for lung function. The collection of lung function parameters via spirometry represents an objective comparator against which the diagnostic algorithm under investigation may be compared. Spirometry will be performed on all willing participants over six years of age.

The following clinical diagnoses definitions will be used for the Paediatric Trial:

|  |  |
| --- | --- |
| Disease | Required features to reach a clinical diagnosis |
| Upper respiratory tract disease (URTD) | * Nasal congestion, rhinorrhoea or a sore throat.
 |
| Lower respiratory tract disease (LRTD) | * One or more of the following:
* Wheezing or silent chest (in the setting of obstruction) at the time of recording
* Any auscultatory findings, including crackles, bronchial breath sounds, or focally decreased breath sounds
* Increased work of breathing unless purely associated with stridor
* A productive cough > 5 days
 |
| Asthma/RAD | * Wheeze or silent chest at the time of recording
* Responsive to bronchodilators during this illness
* Diagnosis is Unsure if:
* No bronchodilator test1 administered
* Pre-treated with bronchodilators with wheeze resolved at the time of recording
 |
| Bronchiolitis | * Age < 24 months
* Must have both:
	+ A persistent cough and
	+ Diffuse wheeze that is non-responsive to bronchodilator (if administered) and/or diffuse crackles
 |
| Pneumonia (Focal) | At least one feature from both of the following categories:1. History of: (i) fever in prior 48 hours or fever at the time of examination, (ii) cough, (iii) dyspnoea, or (iv) chest pain
2. Either focal2 examination findings including crackles, bronchial breath sounds, focal decreased breath sounds; OR

A chest radiograph with new consolidation with normal auscultation findings |
| Croup | * Typical seal-like barking cough on the cough recording.
 |

1 Bronchodilator test: administration of Salbutamol MDI via spacer up to 3 times over one hour at the following doses: 6 puffs for children < 6 yrs., 12 puffs for children > 6 yrs.

2 Pneumonia (Focal) implies the absence of generalised findings on auscultation reflecting generalised LRTD such as RAD and bronchiolitis.

**Clinical Diagnosis Definitions (Non-standard Reference Test)**

The clinical diagnostic team have access to all clinical details including all investigations.

For adult trials the clinical diagnosis will be based upon formal lung function tests when available, consensus clinical diagnosis between at least two clinicians and a full review of clinical notes and investigations.

The following clinical diagnoses definitions will be used for the Adult Trial:

|  |  |
| --- | --- |
| Disease | Required features to reach a clinical diagnosis |
| URTD | - Nasal congestion, rhinorrhoea or a sore throat as seen in URTI’s, nasal allergy or sinusitis. |
| Lower RespiratoryTract Disease (LRTD) | - All LRTDs (asthma, COPD, bronchiectasis, emphysema, ILD, LRTI, pneumonia, cystic fibrosis, chronic bronchitis, pulmonary hypertension, sarcoidosis, asbestosis, pulmonary fibrosis) but excludes spirometry confirmed controlled asthma. |
| Controlled asthma | - No clinical symptoms, FEV1 > 0.8 predicted on formal spirometry |
| Pneumonia/LRTI | Must have both:- New Respiratory symptoms (SOB, cough, chestpain less than one week) and acute fever (history)- And,o Pneumonia: New Infiltrate (or more) on the radiographo LRTI: No infiltrate on CXR. Does not require fever history. |
| Acute Asthma | Must have:- Symptom are consistent with asthma: Cough, SOBand wheeze.- Wheeze on clinical exam- Positive response to BDT |
| Fixed asthma | - Symptoms consistent with acute asthma- Spirometry FEv1/FVC <0.7 (actual) post BDT testand not co-morbid COPD |
| COPD Exacerbation | - Previously diagnosed as having COPD (must havesmoking history)- Worsening symptoms of SOB, cough- New Lower-Respiratory symptoms (SOB, cough, chest pain less than one week) or acute fever (history) |
| COPD | Must have all of the following:- If spirometry available then ratio FEV1/FVC <0.7on the best test (after bronchodilator if given)- If spirometry unavailable then, historical diagnosisof COPD and history of smoking or otherenvironmental exposure- Respiratory symptoms consistent with COPD |

**Algorithm analysis plan (Index Test)**

The algorithm will be developed according to the protocol of University of Queensland (UQ) using cough/breathing sounds and the input of clinical parameters.

For each recording, the algorithm will determine diagnoses using cough data alone, and then using cough data plus features picked from a group of five parent/guardian-reported symptoms including the presence or absence of (i) fever (ii) rhinorrhoea (iii) wheeze (iv) hoarse voice and (v) maximum days of symptoms (i-iv). The index test delivers a binary response: “YES” or “NO” for each disease.

**Data Analysis**

As a non-reference standard test is used as the comparator, the primary measures of diagnostic agreement used will be Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA). PPA are those clinical diagnosis-positive cases who are also positive for the index test; NPA are those clinical diagnosis-negative cases who are also negative for the index test. 95% confidence intervals around these parameters will be calculated using the method of Clopper-Pearson.

**Study Blinding**

Clinical diagnoses will be determined by the clinical adjudication panel and completed prior to index test analysis. The analysis of the cough sound files plus symptom data by the algorithm will be conducted by an independent researcher and the algorithm development team. The algorithm output will be compared to the non-standard reference clinical diagnosis by an independent statistical team.

**Ethical aspects**

Ethical approval will be obtained from all participating sites.

This study does not contribute to the clinical management of patients. All clinical decisions are made by the attending team according to standard procedures.

All data will be securely stored. Paper data sheets will be stored in a locked cupboard and electronic records stored on password protected computer servers at Perth Children’s Hospital, ResApp and The University of Queensland. No identifying data will be attached to data sheets, sound recordings or analysis worksheets. Analysis of de-identified data (but not sound recordings) may also occur at Curtin University (Schools of Public Health and Nursing, Midwifery and Paramedicine).

**5. OUTCOMES AND SIGNIFICANCE**

By increasing the robustness of our algorithm in diagnosing respiratory disease we will create an accurate tool that can produce consistent results in the hands of untrained or poorly trained health care providers in the absence of diagnostic support services. The use of this tool in the developing world has great potential for improving the health of many children and to decrease the currently unacceptable level of morbidity and mortality.

By increasing the applicability of our algorithm in diagnosing respiratory disease to include adolescents and adults we hope to create an accurate tool for the diagnosis of respiratory disease in the general practice, emergency department, telehealth and low resource settings. It may be particularly useful in remote/regional areas and have a place in indigenous health.

If successful, this tool could reduce costs associated with current diagnostic tests, reduce delays, reduce patient radiation exposure and potentially decrease the inappropriate use of antibiotics.

In telehealth settings, where the patient is not physically present and a clinician is unable to use a stethoscope, this tool could provide a clinically accurate remote diagnosis where the alternative is to bring the patient to the clinician and/or send the patient for imaging or lab tests.

The use of this tool also has great potential for improving the health of many in low resource settings, where there is lack of access to trained medical staff and diagnostic support services.

The outcomes of this study will be presented at scientific forums and published in peer reviewed journals. The research sponsor, ResApp Health Ltd. will also get a summary of the results. Patient data will be anonymised before sending to University of Queensland researchers. Research reports and publications will not reveal the identity of patients in any way.

Anonymous data received by UQ will be stored within the School of Information Technology and Electrical Engineering server, behind the school’s firewall and under password control. Only the lead researcher and personnel authorised by him will have access to the data set.

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