Making Cough Count in Tuberculosis
(and other respiratory diseases)

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Objectives

- Distinguish artificial intelligence-assisted cough detection and cough classification

- Identify the potential use cases of digital cough monitoring in tuberculosis control and respiratory medicine

About cough

Cough is a biological phenomenon in which specific sequential patterns of inspiration and expiration (without and then with air flow) create a classic "explosive" sound

There is biological rationale for coughs associated with distinct lung diseases to have distinct acoustic features

Cough is both a symptom of disease and defense mechanism

Cough is associated with many non-TB diseases so it's not perfectly specific

Cough is one of the most common symptoms of pulmonary TB but it's not perfectly sensitive either

Current ways of assessing cough are limited by recall biases, stigma, etc.

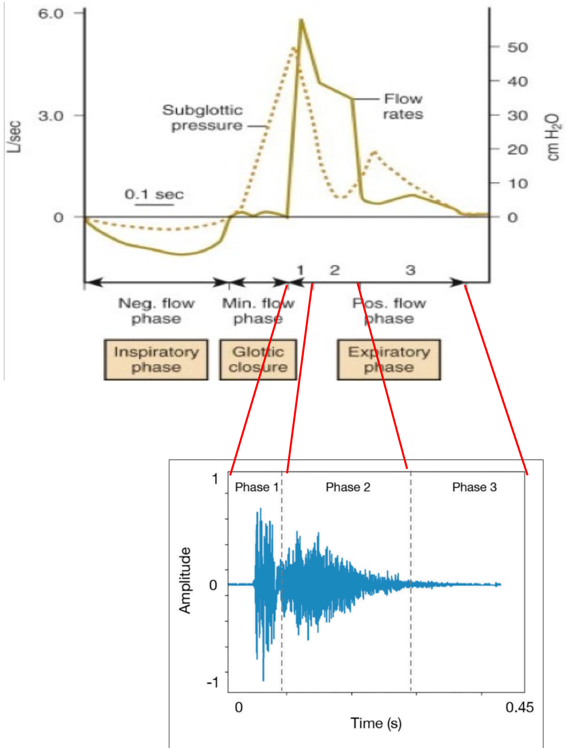


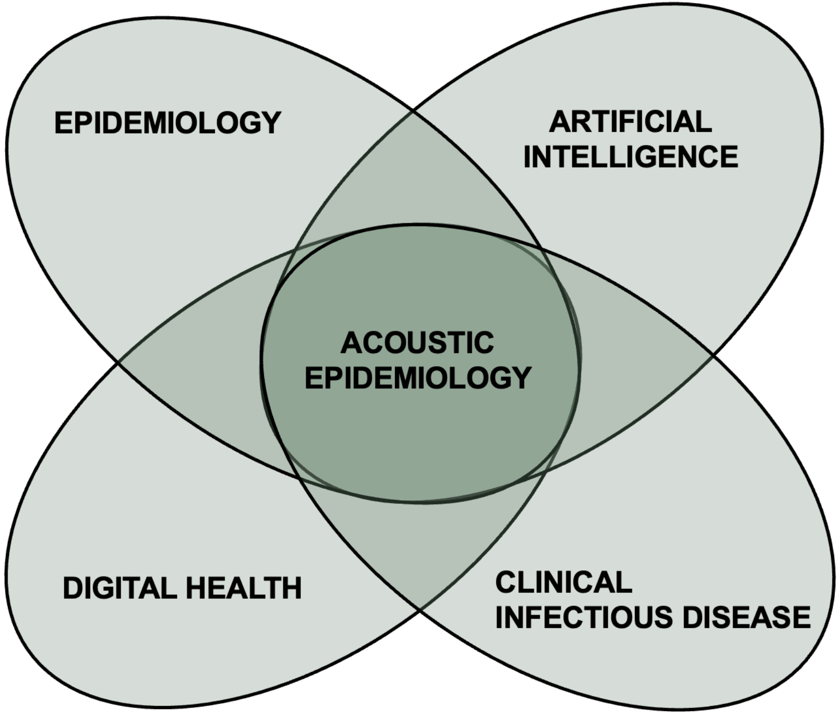
FIGURE 2 | A typical cough sound structure. There are three common patterns of cough based on the number of phase, such as three-phase cough, two-phase cough, and peal cough.

Belkacem, et al. Front. Med. 2021

Murray and Nadel Textbook of respiratory medicine

Renewed interest in cough

Acoustic epidemiology - The analysis of human sounds (voice, coughs, sneezes, wheezing, etc) to study the determinants, patterns and distribution of disease



Acoustics and artificial intelligence

Identification of human coughs sounds among ambient sounds

i.e. transforming cough as a “symptom” in cough as a “sign”

Enables geospatial and temporal aggregation

Cough detection

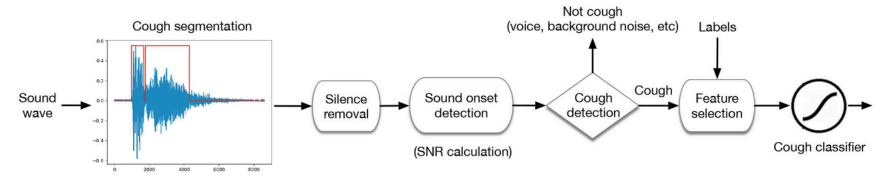


FIGURE 3 | Workflow for cough audio processing. For segmentation phase, predefined thresholds can be chosen based on the physiology of cough sounds. The raw recorded sounds contains a lot of silent fragments (with low intensity) and background noise. Therefore, silence removal phase is required for saving storage space. For signal quality check, an estimate of the signal-to-noise ratio (SNR) can be computed by taking the ratio of the power of the cough part of the signal to the ratio of the rest of the signal.

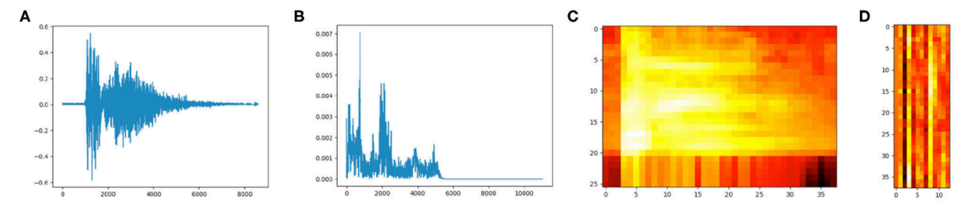


FIGURE 4 | Cough time-frequency representation analyses. **(A)** Cough signal 16-bit, frequency range 22050Hz. **(B)** Power spectrum of the cough audio frame (FFT). **(C)** Spectrogram. **(D)** MFCC.

Cough classification

Identification of cough sounds associated with specific clinical conditions or stages of disease

Belkacem, et al. Front. Med. 2021

Cough detection and classification for tuberculosis control

communications
medicine

PERSPECTIVE

https://doi.org/10.1038/s43856-022-00149-w OPEN

Making cough count in tuberculosis care

Alexandra J. Zimmer[1,2], César Ugarte-Gil[3,4], Rahul Pathri[5], Puneet Dewan[6], Devan Jaganath[7,8], Adithya Cattamanchi[7,8], Madhukar Pai[1,2] & Simon Grandjean Lapierre[2,9,10]✉

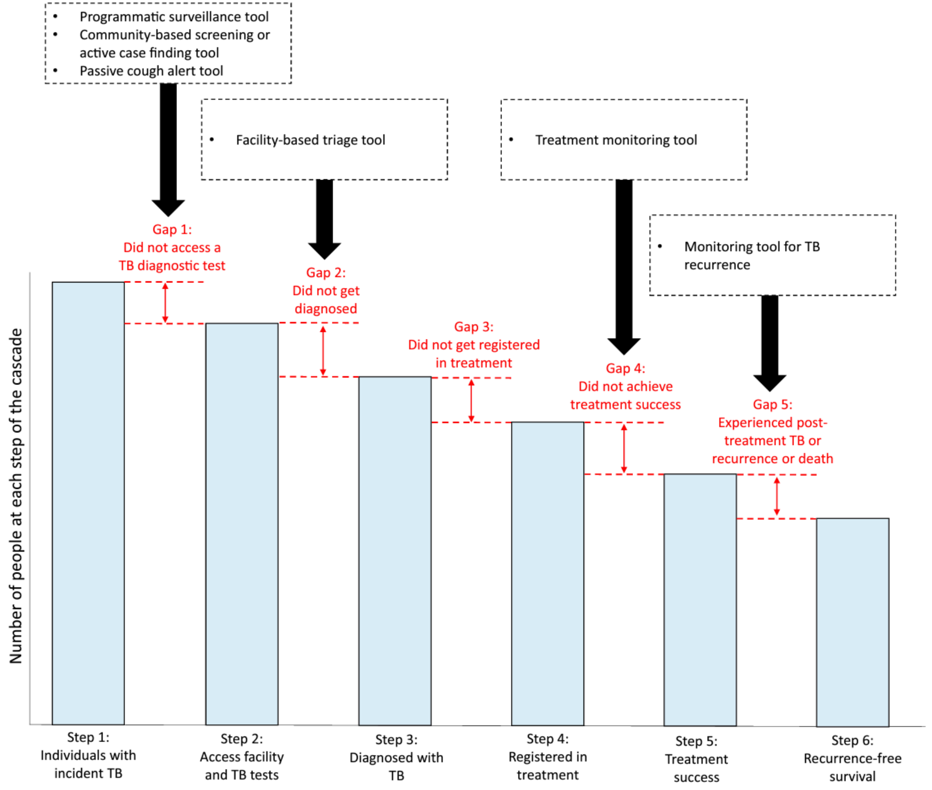


Fig. 2 Potential use cases for digital cough monitoring in the tuberculosis cascade of care. Each step in the TB care cascade is represented as a bar. The gaps in the cascade are in red between each step. Boxes pointing at the gaps represent possible digital cough-based solutions to address various gaps. The height of the bar graphs and the length of the gaps are not scaled to represent true values. They are intended to help illustrate the different steps of the care cascade and points at which people with TB may fail to benefit from care. (Cascade of care adapted from Fig. 1 of Subbaraman et al.)[49].

Syndromic surveillance works

Acoustic surveillance of cough for detecting respiratory disease using artificial intelligence

Juan C. Gabaldón-Figueira[1,2], Eric Keen[3], Gerard Giménez[3], Virginia Orrillo[4], Isabel Blavia[4], Dominique Hélène Doré[5], Nuria Armendáriz[6], Juliane Chaccour[1], Alejandro Fernandez-Montero[7], Javier Bartolomé[6], Nita Umashankar[8], Peter Small[3,9], Simon Grandjean Lapierre[5,10,12] and Carlos Chaccour[1,2,11,12]

Temporal association between aggregated cough rates and COVID « waves », both within the cohort and the population

Potential value in surveillance and preparedness ?

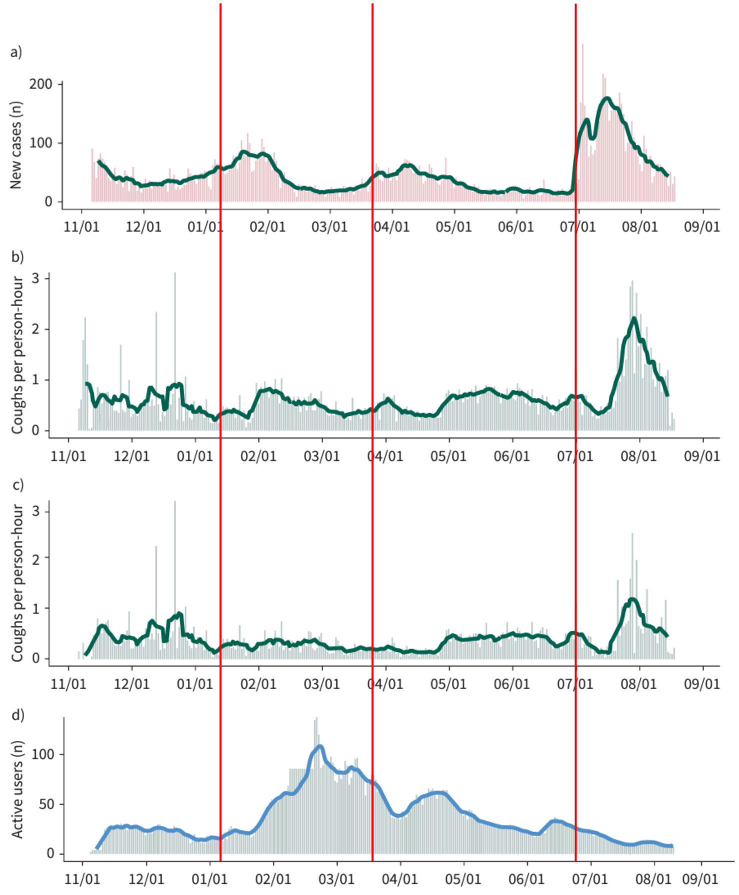
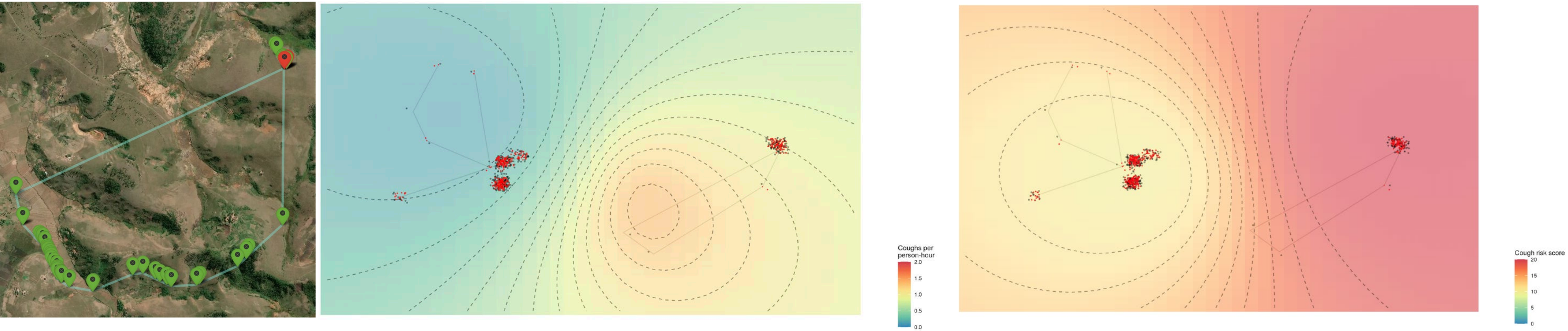


FIGURE 3 Cough and usage trends compared to coronavirus disease 2019 (COVID-19) incidence. Incidence of COVID-19 in a) the entire study area compared to b) the evolution of cough trends in the monitored cohort; c) after the exclusion of the participant with chronic cough; and d) compared to the number of active users. The continuous line represents the 7-day rolling average.

Syndromic surveillance works



Real-time temporal and geospatial aggregation of cough events among TB patients

Potential value in secondary case finding?

Tsang et al. Unpublished

Cough detection measures treatment response

Longitudinal passive cough monitoring and its implications for detecting changes in clinical status

Juan C. Gabaldón-Figueira[1], Eric Keen[2], Matthew Rudd[2,3], Virginia Orrilo[4], Isabel Blavia[4], Juliane Chaccour[1], Mindaugas Galvosas[2], Peter Small[2,5], Simon Grandjean Lapierre[6,7,10] and Carlos Chaccour[1,8,9,10]

Digital cough monitoring data corelates with clinically significant events

Potential value in treatment response monitoring?

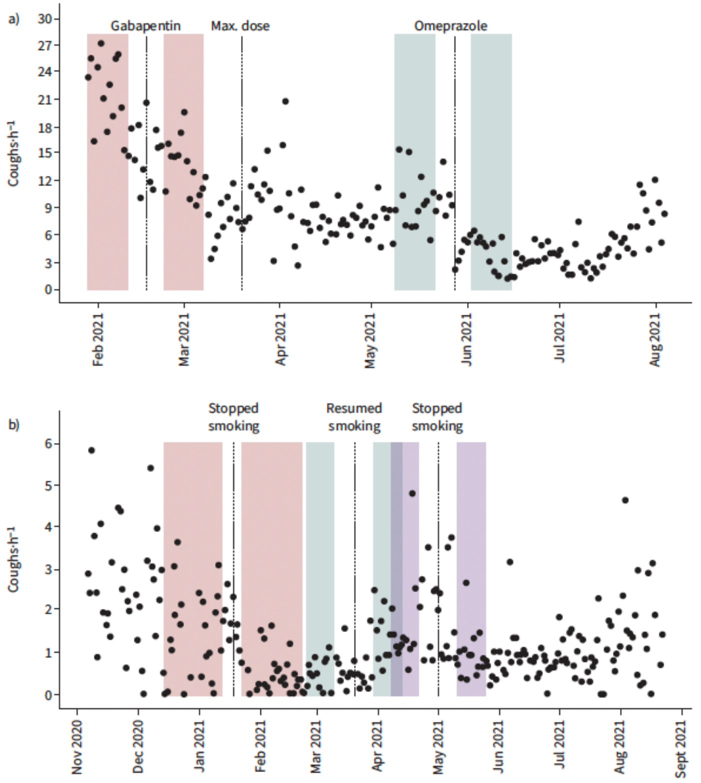


FIGURE 5 Changes in cough rates for two selected participants following specific interventions. a) A participant treated for a refractory chronic cough (Case 1) and b) a chronic smoker attempting to quit (Case 2). The dotted lines indicate the date of specific interventions. The shaded areas represent the periods used to calculate the pre- and post-intervention mean cough rates surrounding a buffer period.

Cough detection measures treatment response

Both the cough rate and circadian variability rapidly regress with TB therapy

What would we see in case of failure?

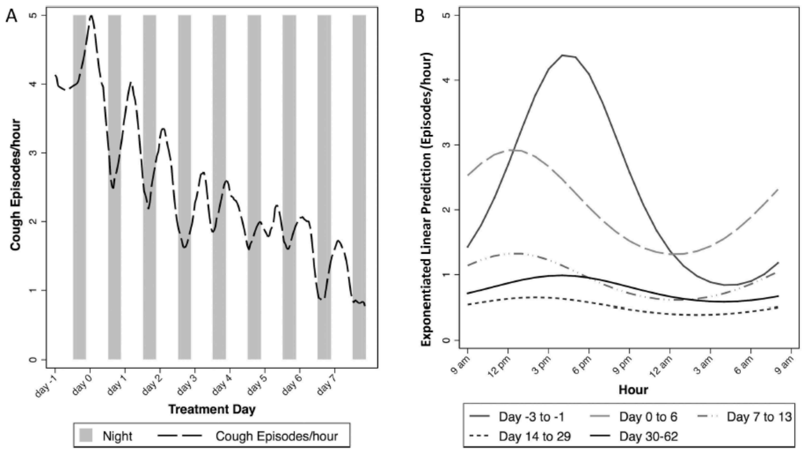


Figure 2. Circadian cycle of cough frequency during treatment for study group. *A*, Smoothed trends in cough from day –1 to day 7 of treatment. Each day begins at 9 AM, as this is the time when recordings began. *B*, Separate negative binomial generalized estimating equation models fitted for each day following treatment. All recordings, regardless of total length, were included (n = 12 108 hours of recording). Random-effects modeling was used to adjust for study participant. Circadian cycles of cough were reflected by sine/cosine terms.

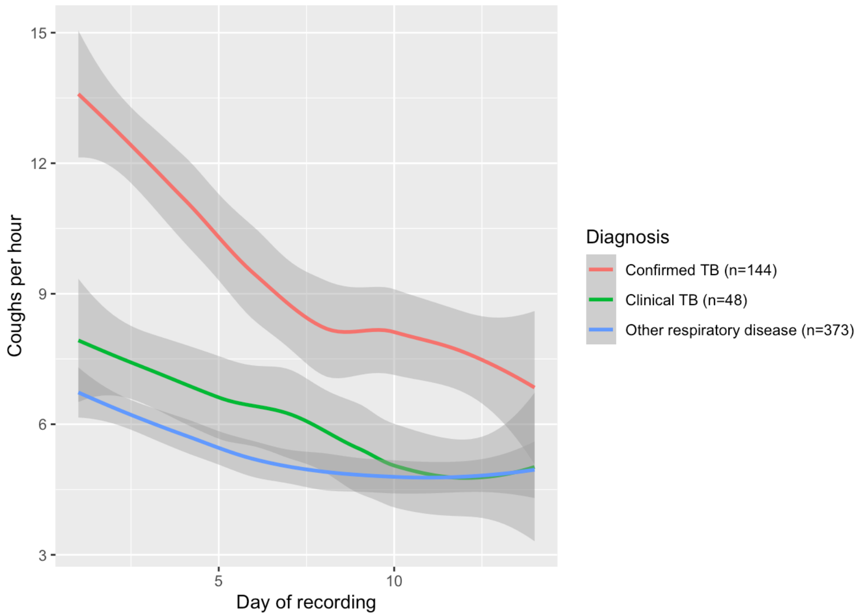
Proano et al. Clin. Inf. Dis 2017

Cough detection measures treatment response

Participants with microbiologically confirmed TB have significantly higher median cough per hour than participants with non-TB respiratory diseases.

Median cough per hour regresses following diagnosis and treatment initiation

What would we see in case of failure?



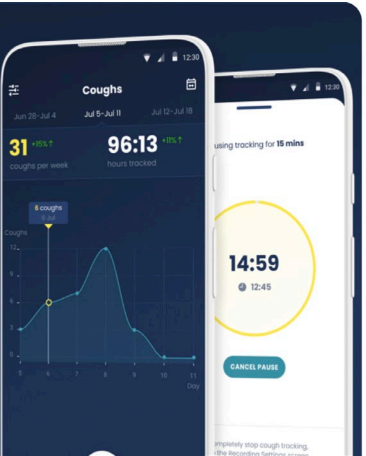
Huddart et al. Int J. Tuberc. Lung Dis. 2022

Cough detection as a pronostic biomarker

COVID-19 confirmed patients requiring hospitalization

Continuous cough monitoring in individual rooms

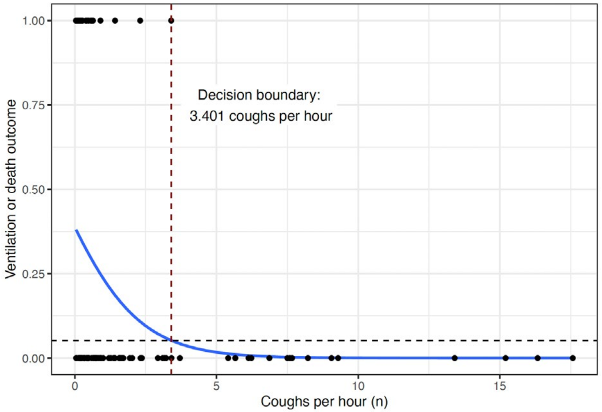
Continuous monitoring of oxygen support and categorical clinical outcomes (e.g. room air, noninvasive ventilation, intubation, death)

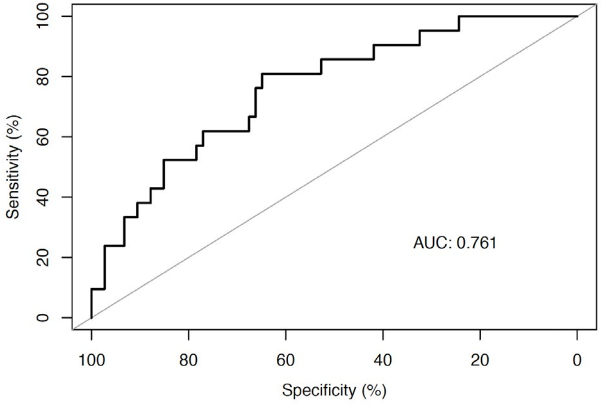


Cough detection as a pronostic biomarker

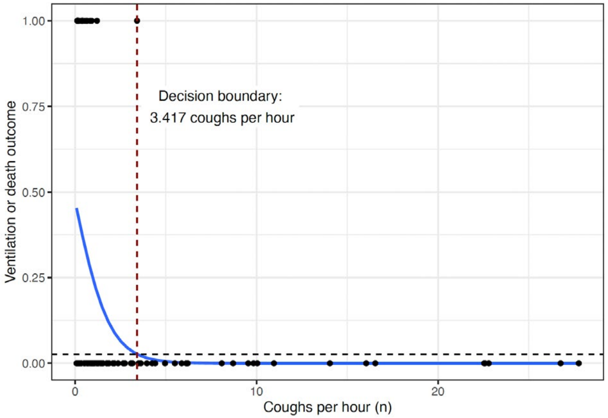
Transitional cough rate as an outcome predictor

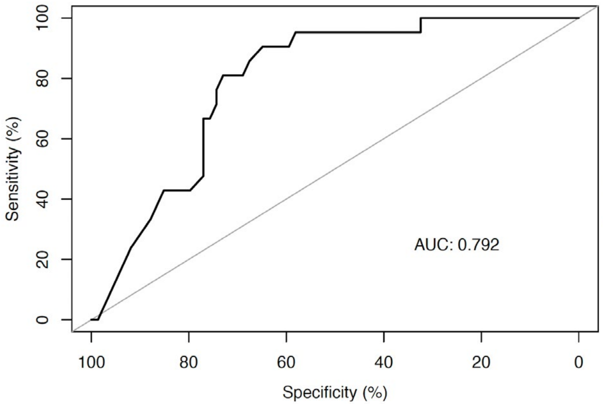
Total enrollement



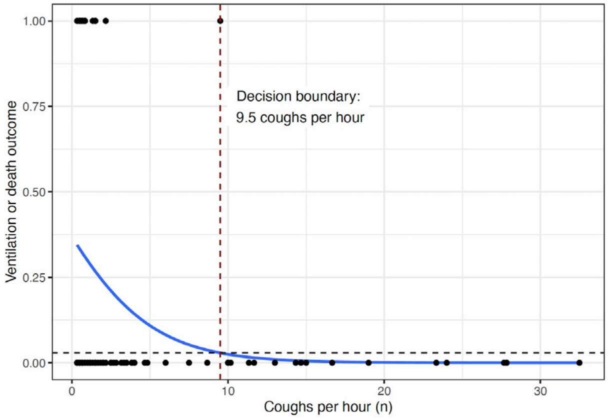


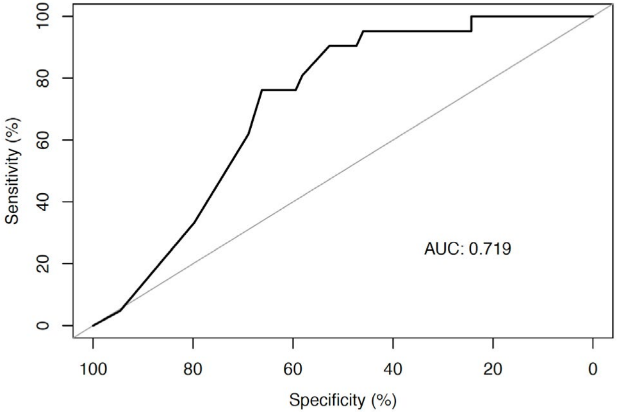
Initial 24 hours





Initial 6 hours





COugh Diagnostic Algorithm for Tuberculosis

CODA TB DREAM Challenge

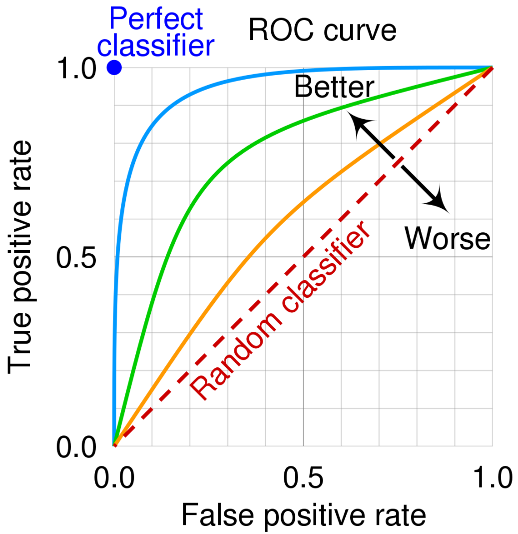
- Diagnostic cohort of > 2100 TB suspects self referred to care for TB diagnostics
- High quality solicited cough sounds recording and clinical parameters
- Well characterized TB disease using composite diagnostic based on Xpert & culture

https://www.synapse.org/#!Synapse:syn31472953/wiki/

Assessing cough classification performance

Predicted Class

Actual Class		Positive	Negative	
	Positive	True Positive (TP)	False Negative (FN) **Type II Error**	**Sensitivity** $\frac{TP}{(TP+FN)}$
	Negative	False Positive (FP) **Type I Error**	True Negative (TN)	**Specificity** $\frac{TN}{(TN+FP)}$
		Precision $\frac{TP}{(TP+FP)}$	**Negative Predictive Value** $\frac{TN}{(TN+FN)}$	**Accuracy** $\frac{TP+TN}{(TP+TN+FP+FN)}$



$$\text{F1-score} = \frac{TP}{TP+\frac{1}{2}(FP+FN)}$$

Receiver operating characteristic (ROC) curve
Area Under the Curve (AUC)

TB cough classification

Subchallenge 1:

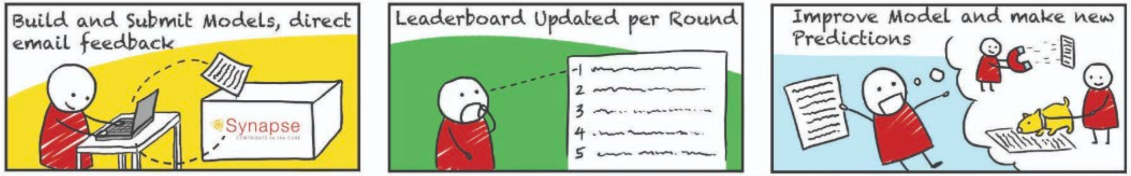
Predict ‘positive’ TB diagnosis using cough recordings only.

Subchallenge 2:

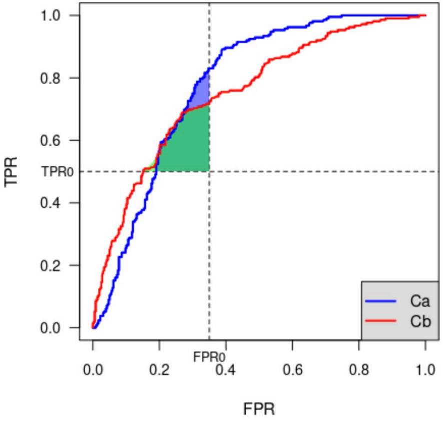
Predict ‘positive’ TB using cough recordings and additional demographic/clinical variables (Age, Sex, Height, Weight, BMI, Smoking, Reported Duration of Cough, Prior TB, Hemoptysis, Heart Rate, Temperature, Fever, Night Sweats, and Weight loss).

Assessment

Submissions will be scored using the two-way partial area under the receiver operator characteristic curve (pAUROC) [1] with Sensitivity (TPR) $\geq$ 0.8 and 1 - Specificity (FPR) $\leq$ 0.4



Images courtesy of ICGC-TCGA DREAM Somatic Mutation Calling Challenge Project Team



Characteristic	Minimal requirements
1 Diagnostic sensitivity	Overall sensitivity should be >90% compared with the confirmatory test for pulmonary TB
2 Diagnostic specificity[a]	Specificity should be > 70% when compared with the confirmatory test

WHO 2019

TB cough classification

Subchallenge 1

	name	status	submitterid	auc_roc
	model-c1-5	ACCEPTED	Blue Team	0.6687056737588651
	my-model-c1-6	ACCEPTED	Blue Team	0.6618794326241135
	my-model-c1-4 (endpoint)	ACCEPTED	Blue Team	0.6418439716312057
	syn50896810	ACCEPTED	Blue Team	0.6416666666666666
	syn49187199	ACCEPTED	LCL	0.6415780141843972

Subchallenge 2

round	name	status	submitterid	auc_roc
5	syn51037332	ACCEPTED	AI-Campus High School Team	0.7462765957446809
5	syn51009842	ACCEPTED	Yuanfang Guan Lab Team	0.7457446808510638
5	my-model-c2-6	ACCEPTED	Blue Team	0.7422872340425531
5	syn50999655	ACCEPTED	Metformin-121	0.739804964539007
5	syn49187199	ACCEPTED	LCL	0.6415780141843972

Over 150 participants – Approximately 10 teams submitting classification models in the last rounds

Selected preliminary leaderboard results confirm that there is a TB acoustic signature

Final results and complementary / sub-group analyses to come

Discussion

Acoustic epidemiology is an emerging field of research

There are multiple potential niches for digital cough monitoring in TB control and respiratory medicine

Results from cough detection studies suggest that TB treatment clinical response can be objectively measured

Technological improvements are needed to facilitate unobtrusive longitudinal monitoring

Specific thresholds / patterns suggesting clinically relevant events (e.g. treatment failure) need to be identified and validated

Results from cough classification studies suggest the existence of an acoustic signature for pulmonary TB

Existing classification models can be further improved

Existing classification models could be combined with other biomarkers

The impact of cough classification for TB triage needs to be modeled and prospectively validated

Acknowledgements

CODA TB DREAM Challenge collaborators and other clinical research sites

Other academic partners

Industry and start-ups

Funders