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The potential of a portable, point-of-care electronic nose to diagnose tuberculosis

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KEYWORDS

Tuberculosis;
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Summary *Introduction:* Tuberculosis (TB) is the leading cause of death due to an infectious disease worldwide. Especially in low-income countries, new diagnostic techniques that are accessible, inexpensive and easy-to-use, are needed to shorten transmission time and initiate treatment earlier.

Objective: We conducted a study with a handheld, point-of-care electronic nose (eNose) device to diagnose TB through exhaled breath.

Setting: This study includes a total of 110 patients and visitors of an expert centre of respiratory diseases in Asunción, Paraguay. TB diagnosis was established by culture of *Mycobacterium tuberculosis* complex and compared with the eNose results in two phases.

Results: The calibration phase, including only culture confirmed TB cases versus healthy people, demonstrated a sensitivity and specificity of 91% and 93% respectively. The confirmation phase, including all participants, showed a sensitivity of 88% and a specificity of 92%. The eNose showed high acceptance rate among participants, and was easy to operate.

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Conclusion: The eNose resulted in a powerful technique to differentiate between healthy people and TB patients. Its comfort, speed and usability promise great potential in vulnerable groups, in remote areas and hospital settings to triage patients with suspicion of TB.

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Introduction

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global emergency.¹ Since then a major effort was made to stop this epidemic. The World Health Assembly launched the WHO's 'End TB strategy'; an ambitious project to reduce TB incidence by 90% before 2035 and progress to 1 TB case per million in 2050 worldwide.² Eight priority actions were established to achieve this goal. Important actions were, among others, to address the most vulnerable and hard-to-reach groups, to undertake screening and provide treatment in TB contacts and high-risk groups, and to invest in new diagnostic tools. The real-time PCR (rt-PCR) technology to both diagnose TB and detect rifampicin resistance (Xpert[®] MTB/RIF), was the latest new development to diagnose (rifampicin resistant) TB within 2 h. The high costs and lack of sufficiently skilled laboratory technicians implicates difficulties to apply this method at a large scale.³

In recent years, breath analysis has shown potential for diagnosing a variety of different diseases non-invasively.⁴ Diagnosing TB with breath analysis is still innovative but carries great potential in remote areas to screen large cohorts or to allocate hospitalized patients who are potentially infectious to others. Subsequently Xpert[®] MTB/RIF and/or culture should be performed to confirm diagnosis and to assess drug susceptibility.⁵

Next to examining volatile organic compounds (VOCs) released from sputum, several studies have been reported on breath analysis for diagnosing tuberculosis. The technologies used are nanomaterials based electronic noses, gas chromatography–mass spectrometry, and optical detection.^{6–9} Another fascinating method to detect TB has been shown using trained African pouched rats, sniffing above pots containing heat-inactivated sputum.^{10,11}

An electronic nose (eNose) based on metal-oxide sensors, and therefore mass-producible at low cost, was used in a pilot study in Bangladesh for diagnosing TB showing high sensitivity and specificity.¹² In that study, exhaled breath was collected into a bag and investigated afterwards. However, using bags could have introduced systematic errors due to interaction of VOCs with the bags materials. Based on this experience, a dedicated eNose has been developed (Aeonose[®]) that was used in the present study. No bags are required anymore, and the unit is portable and battery powered, so truly a point-of-care device.

Until now, the Aeonose[®] has been successfully applied in discriminating exhaled breath 'smell prints' between healthy subjects and patients with asthma, COPD, Barrett's disease, and lung cancer.^{13–17} It is currently also being tested for a variety of non-pulmonary malignancies.

In this paper, the first study is being described using the Aeonose[®] for diagnosing TB. We conducted the study in a Paraguayan National Reference Centre for pulmonary

diseases (INERAM) investigating its accuracy in discriminating active TB from asthma/COPD or healthy subjects and exploring factors influencing accuracy.

Study population and methods

An observational study was conducted from June 2014 until May 2015. Adults (>18 years) with suspicion of pulmonary TB, asthma or COPD patients and healthy controls were included after signing informed consent. TB suspects not able to expectorate sputum, with respiratory failure or having received TB treatment in the past 6 months were excluded from the study. TB diagnosis was preferably established by gold standard (culture of *Mycobacterium tuberculosis* complex). In case of negative culture results, diagnosis was set by other strong supporting evidence. If a subject decided to withdraw or experienced too much difficulty to breathe during the test, another participant was recruited. In case of withdrawal it did not negatively influence the normal diagnostic workup or treatment. The study was approved by the institutional review board and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable to local regulations.

According to the protocol, participants were divided into three groups; **Group 1** pulmonary TB, **Group 2** asthma or COPD, and **Group 3** healthy, socio-economic matched, individuals. Medical history taking (including a thorough assessment of antibiotic use) and physical examination was performed in all participants. In TB suspects, following normal hospital routine, a chest X-ray, blood chemistry and HIV test was performed. Sputum samples and/or pleural fluid was taken for microscopy and culture of *M. tuberculosis*. All TB patients were treated according to National guidelines. Final treatment outcome data were collected from the National TB Program.

All participants provided an exhaled-breath sample by in- and exhaling for 5 min, using a nose clamp, through the Aeonose[®] (see [Appendix](#) for a full description of the Aeonose[®]). The study was conducted in a room free of gases, alcohol and dust. Two devices were used. During sampling, 36 measurement cycles each containing 64 data points were recorded per sensor. In this way, each patient's measurement comprised a data matrix with thousands of records. The sensor's temperature control enables proper reproducibility of the results.¹⁸ However, even for sensors produced on the same wafer, thickness and ageing differences cause slight variations between sensors and Aeonose[®] devices over time. To cope with this phenomenon, the data are normalized. Subsequently, data are being compressed using a Tucker 3–like algorithm.¹⁹ This results into a vector of 10 components per patient while removing redundant information and noise. These resulting vectors and classification results are used to train an Artificial Neural Network (ANN). Double cross validation using the Leave-10%-Out method was applied to minimize the risk for

systematic errors. The proprietary software-package Aethena[®] used for this purpose was recently accepted for publication.²⁰ The data analysis of The eNose Company was repeated by an independent data expert from Radboud University (described in the [Appendix](#) of this article).

Based on patient characteristics and culture results, only known by the study doctors, participants were classified in Clear Positive (CP) or Likely Positive (LP) and in Clear Negative (CN) and Likely Negative (LN). The analysis by the eNose Company consisted of two phases. The first phase was the training phase (calibration) and included only culture proven TB (CP) and healthy controls (CN). The second phase (confirmation) included all participants (CP + LP + CN + LN).

Results

Patient characteristics and microbiological data

A total of 110 participants were enrolled. Baseline characteristics are shown in [Table 1](#). More than 50% of TB patients (24/47) showed cavities on the chest X-ray, no patients had human immune deficiency virus co-infection. Only few participants were current smokers or using alcohol. Thirteen TB patients used antibiotics just before establishing the

Table 2 Sputum microbiological outcomes.

	Group 1 Pulmonary TB
<i>Ziehl Neelsen staining</i>	
Positive/Negative/Not done	36/11/0
<i>GenXpert</i>	
Positive/Negative/Missing/ Not Done	12/6/11/18
<i>Culture</i>	
Positive/Negative/Missing/ Not Done	23/15/5/4

diagnosis. Nine patients used antibiotics (amoxicillin, amoxicillin-sulbactam, ampicillin, ampicillin-sulbactam), 2 cephalosporins, and 2 used a fluoroquinolone. Two participants from group 3 complained of fatigue: both female with a Body Mass Index (BMI) over 30, one presenting with night sweats without any other symptoms.

Microbiological results are shown in [Table 2](#). Although the majority (36/47) had Ziehl-Neelsen (ZN) positive sputum, only 23 patients had culture confirmed TB. Fifteen patients had negative cultures, 5 culture results were missing and in 4 patients culture was not done. Thirty-five TB patients

Table 1 Patient characteristics.

Characteristics	Group 1 Pulmonary TB	Group 2 Asthma/COPD	Group 3 Healthy controls
Number of patients	47	14	49
Mean age (years)	34.6	54.5	40.8
Sex: Female/Male	17/30	7/7	36/13
Mean Body Mass Index	21,1	25.0	25.9
Dental Status:	18/23/5/1	2/12/2	7/33/9
Good/Regular/Bad/Missing			
Habits: Smoking/Alcohol	4/2	0/2	3/1
Mean intake before test (hours) (food/drinks)	3	4	3
Comorbidity			
Asthma	1	7	0
COPD	2	7	0
Bronchitis	2	0	0
Diabetes Mellitus	4	0	0
Hypertension	3	4	9
Co-medication			
Antibiotics ^a	13	4	1
Other medication ^b	5	12	13
Chest X-ray			
Opacity	45		
Cavity	24		
Atelectasis	10		
Pleural effusion	4		

^a Definition of antibiotics use: at least three days before air sampling. Nine patients in group 1 used antibiotics from the penicillin group (amoxicillin, amoxicillin-sulbactam, ampicillin, ampicillin-sulbactam), 2 cephalosporins, and 2 used a fluoroquinolone. Four patients in group 2 used a cephalosporin for less than 7 days. Only one participant in group 3 had fever and used amoxicillin for tonsillitis.

^b Other medications: group 1: two patients use insulin and 1 metformine, 2 with enalapril and one patient use salbutamol during crisis. Group 2: three patient use IECA (enalapril) and one with diuretic (spironolactone) for hypertension. SABA/LAMA were use in five patient; only SABA in 3 participants. Group 3: nine patients were treated for hypertension (five use enalapril, 3 losartan and two with aspirin also); three woman with oral contraceptives; two patients use levothyroxine.

showed clinical and bacteriological improvement and were considered cured by the National TB Program. Five patients had persistent positive *M. tuberculosis* culture after the initial phase. Two patients were lost to follow up, one participant abandoned treatment, and 7 were transferred out. No patients died.

Electronic nose results

Four participants were excluded from the analysis due to erroneous use of the Aeonose®.

The calibration phase included 69 participants: 23 culture proven TB (CP) and 46 healthy controls (CN). The analysis resulted in three false positive individuals and two false negative, yielding a sensitivity of 91% and a specificity of 93% (Figs. 1 and 2). The two false negative TB patients both had ZN positive and culture proven TB. One of them received antibiotics (ampicillin) during six days before TB diagnosis was set. The three false positives were females, 2/3 had a BMI >30 and 2/3 suffered from arterial hypertension (treated with ACE inhibitors). None of these women presented clinical symptoms compatible with TB.

The confirmation phase, predicting TB in all (n = 106) participants, showed five false positives and five false negatives (88% sensitivity and a specificity of 92%) (Figs. 3 and 4). The five false positives showed only two patients with a normal BMI, two showed overweight (BMI >25) and one was even obese (BMI 33). Two females suffered from caries, one participant used ACE inhibitors and one presented with chronic bronchitis.

All 5 false negative TB patients received antibiotics before TB diagnosis was established. Although 3/5 patients had ZN positive sputum and 4/5 showed cavities on the chest X ray, 4/5 were culture negative. According to the National TB Program final treatment results showed cure in all 5.

Discussion

This study showed excellent results of a low-cost, hand-held and easy to use eNose device (Aeonose®) to detect TB in a hospital population. Both in culture confirmed TB (calibration phase) and in all TB suspects (confirmation phase) with ROC curves comparable to culture of *M. tuberculosis*, the gold standard.¹² With this technology, a preliminary TB

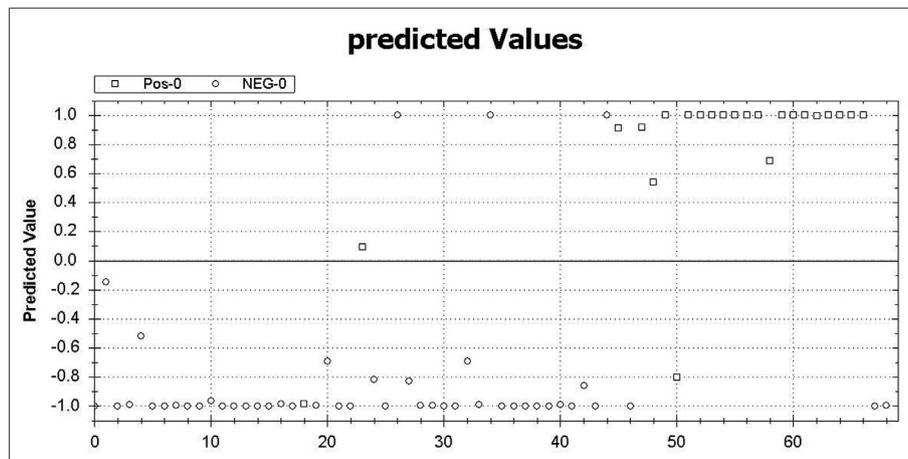


Figure 1 Predicted values of calibration phase (Clear Positives versus Clear Negatives).

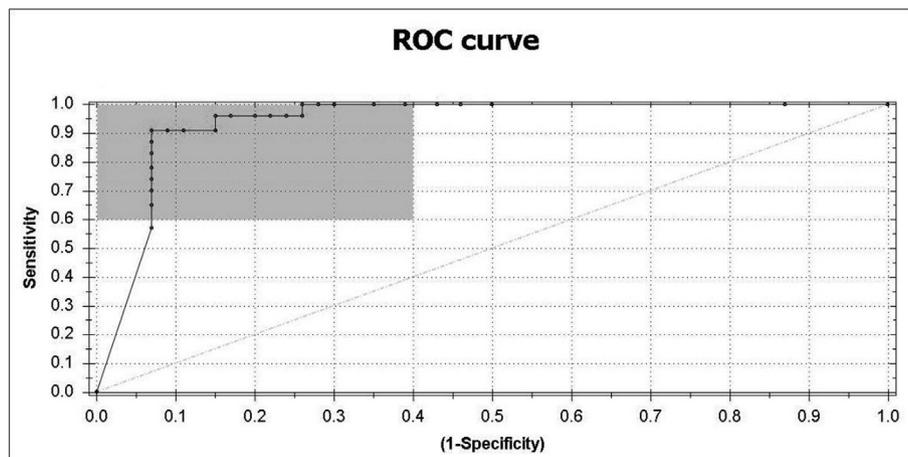


Figure 2 ROC Curve of calibration phase (Clear Positives versus Clear Negatives).

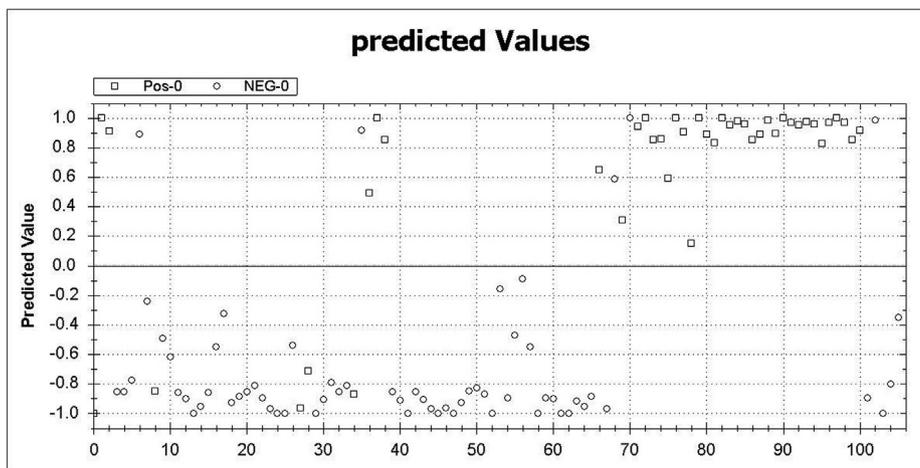


Figure 3 Predicted values of validation phase (all participants).

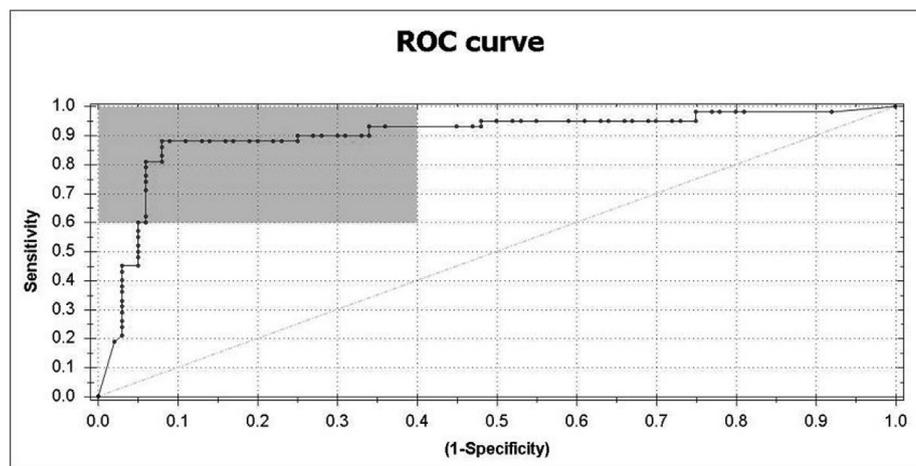


Figure 4 ROC Curve of validation phase (all participants).

diagnosis may be speeded up significantly which can be useful for indicating the need for airborne isolation or for screening persons from a vulnerable and/or hard-to-reach population. As Mycobacterial culture is needed for determination and to perform drug susceptibility testing, an eNose will not replace the current gold standard. However, the Aeonose[®] could be used as a triage instrument to use culture and/or GeneXpert techniques in a more efficient way. In general, the Aeonose[®] showed ease of operation, and no adverse effects were observed.

This study showed altered smell prints in some patients with a high BMI resulting in a false-positive test result. This may be due directly to their diet influencing the VOCs or the fact that being overweight can be considered a disease.¹³ Diabetes mellitus and age are also known to influence the eNose signal.^{13,21,22} The use of an ACE inhibitor may have led to false positive results because of hepatic metabolism of the medication.²³ On the other hand, hypertension can cause systemic disease. Dental caries, meals, drinks or substance abuse did not seem to influence the accuracy of the Aeonose[®] in this study.²³

Both in prevalence studies and in clinical practice, a false-positive result will not result into severe implications

other than stigmatization but will lead to more in-depth investigation to exclude TB to prevent transmission in the community or a nosocomial infection. False-negative results may have more serious consequences, especially when a missed diagnosis might harm others. In this study, they were associated with the use of antibiotics just before TB diagnosis was established. Prior treatment with antibiotics, especially fluoroquinolones, often hampers its diagnosis by gold standard as well.^{24–26} It seems that this diagnostic delay will not be shortened by the Aeonose[®].

No comparison could be made between Paraguayan and Bangladesh data due to different operational conditions (e.g. not using bags for collecting exhaled breath, and different operating characteristics of the sensors). Therefore we are not yet able to state whether the Aeonose[®] can be used in other countries as well. In theory, each country, region or continent may have a unique smell print in TB patients as VOC's are (partly) influenced by genetic profiles, co-morbidities, smoking or alcohol intake or food. More data, also from different regions, are needed to show if restrictions are eminent.

The Aeonose[®] carries great potential to screen large groups of vulnerable and hard-to-reach people at low costs,

as the device is battery operated and measurements can be done by technically unskilled workers. To obtain an instant result, the data from the Aeonose[®], connected to a mobile phone, can be transmitted to a datacenter for analysis. This technology has already been implemented into the next model of the Aeonose[®].

This study has several limitations. The first relates to its small sample size: a larger number of positives and negatives will increase the stability of the neural network and improve classification predictions of breath profiles that were not used in training the network. The small sample size also impeded us to isolate factors influencing the accuracy of the Aeonose[®].

The second limitation was the lack of confirmation of TB diagnosis by gold standard in 50% of cases. Negative cultures were probably influenced by the prior use of antibiotics and missing microbiological data were caused by inexperience of study doctors, lack of hospital resources and laboratory logistics. The fact that out of 36 ZN positive sputa only 23 became culture positive could reflect suboptimal culture techniques. Macroscopically, no non-tuberculous mycobacteria were grown in these cases. Thirdly, we did not culture sputa for respiratory pathogens other than *M. tuberculosis* and cannot exclude false positive or negative eNose results due to either an alternative or dual diagnosis. In Paraguay, a co-infection with paracoccidiomycosis is often found in severely affected patients with pulmonary TB. This issue needs to be addressed in future studies. Finally, we only included patients with suspicion of active TB and compared them with healthy people and patients with a stable chronic pulmonary disease. In a future (blinded) validation study, either patients with a community acquired pneumonia and TB, presenting with symptoms and radiology, should be included.

To elucidate the potential of the Aeonose[®] to detect extra-pulmonary TB cases more research is needed. In a next study, we will amplify inclusion criteria slightly in order not to miss patients who started TB treatment for a few days. It is not to be expected that VOC's in a TB patient will change rapidly as recovery normally takes a much longer period.

Conclusion

In this study, the Aeonose[®] showed an excellent sensitivity and specificity to diagnose TB and may prove a helpful tool to support the WHO post 2015 global strategy. Follow-up studies are currently being conducted to validate these results and to evaluate whether the Aeonose[®] is capable to detect extra-pulmonary TB. These studies will also evaluate other important issues as whether the Aeonose[®] can speed-up and lower the costs of current diagnostic pathways.

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Disclaimer

The eNose Company was involved in analysing the smell prints without having access to patient characteristics or microbiological results. An independent researcher of Radboud University repeated the analysis using different data analysis techniques. This researcher was also blinded to patient characteristics and microbiological results. The eNose Company supplied technical information for the [Methods](#) section and [Appendix](#) of this manuscript. They did not decide to submit the article for publication.

Conflict of interest statement

The researcher have no conflicts of interest. They investigated the accuracy of the Aeonose with no type of influence by the eNose company.

The authors from the eNose company only analysed the signals and provided the tekst of technical aspects of the electronic nose device.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jinf.2017.08.003>.

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