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Incremental Yield, Safety and Positivity Predictors of Induced Sputum for Adult Pulmonary Tuberculosis Diagnosis: A Cross Sectional Study

Rendement, innocuité et facteurs prédictifs de positivité de l'expectoration induite, pour le diagnostic de la tuberculose pulmonaire: une étude transversale

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ABSTRACT

Background. The early diagnosis of pulmonary tuberculosis is one of the most effective intervention in tuberculosis (TB) control strategy, but it is still facing a high proportion of smear negative sputum. We aimed to assess the yield and safety of sputum induction (SI) for pulmonary tuberculosis (PT) diagnosis, and to seek its positivity predictors, in adults with negative analysis of spontaneous sputum. **Methods.** Adults suspected to have pulmonary tuberculosis, and who had 2 consecutive negative acid fast bacilli (AFB) and Loop-mediated isothermal amplification (TB-LAMP), were invited to undergo a unique 10% hypertonic saline inhalation. Only consenting patients who were able to undergo the inhalation procedure safely were ultimately retained. The induced sputum was analyzed through auramine AFB smear and TB-LAMP test. **Results.** A total of 110 patients were selected. The AFB smear and TB-LAMP were positive for 12 patients (10.9%). Limiting the sample to patients with salivary spontaneous sputum, salivary sputum + nodules, and salivary sputum + cavities improved diagnosis yield to 18.9%, 32.0% and 62.5%, respectively. Predictors for a positive IS analysis [adjusted odds ratio (95% confident interval), P-value] were nodules [15.2 (1.8, 132.2), 0.002] and cavities [32.7 (3.2, 336.3), < 0.001]. The procedure induced 0.9 – 1.8% minor adverse events. **Conclusion.** showed a low diagnosis yield and a good safety in this study. Selection of patients based on the type of spontaneous sputum and CXR significantly improved the diagnosis yield.

RÉSUMÉ

Introduction. Le diagnostic précoce de la tuberculose pulmonaire (TP) est une intervention majeure de contrôle de la tuberculose (TB). Cependant, il reste compromis par la proportion élevée d'analyse négative de l'expectoration. Cette étude évaluait le rendement et l'innocuité de l'expectoration induite (EI) pour le diagnostic de la TP, et recherchait les facteurs associés à sa positivité, chez des adultes présentant une analyse négative de l'expectoration spontanée. **Méthodes.** Une recherche de tuberculose était réalisée sur 2 expectorats par recherche de bacilles acido-alcoolo résistants (BAAR) et Loop-mediated isothermal amplification (TB-LAMP). Ceux présentant une recherche négative étaient invités à produire une expectoration induite par la nébulisation de chlorure de sodium à 10%. Seuls les patients consentants de participer et capables d'effectuer l'examen étaient retenus. Les analyses comportaient la microscopie à fluorescence (coloration à l'auramine) et le TB-LAMP. **Résultats.** Au total 110 patients ont été retenus. L'analyse de l'EI était positive pour 12 (10,9%) patients. L'expectorat spontané salivaire, et son association à des nodules pulmonaires ou des lésions cavitaires améliorait le rendement diagnostic à 18,9%, 32,0% et 62,5% respectivement. Les prédicteurs de positivité [rapport de cotes ajusté (intervalle de confiance à 95%), P-valeur] étaient la présence de lésions nodulaires [15,2 (1,8; 132,2), 0,002] et cavitaires [32,7 (3,2; 336,3), < 0,001]. La procédure a provoqué 0,9 à 1,8% d'effets secondaires mineurs. **Conclusion.** Le rendement de l'EI était faible et l'innocuité bonne chez les patients tout venant. L'expectoration salivaire et les lésions nodulaires ou cavitaires amélioraient significativement ce rendement.

INTRODUCTION

Tuberculosis is still a very common infectious disease and the most lethal infectious one [1]. More than half (56%) of tuberculosis patients are male adults, and more than 95% of tuberculosis related deaths occur in developing countries [1]. Pulmonary tuberculosis (PT) is the most common form of the disease (75-90% of cases) and the source of its spread. PT is diagnosed by the demonstration of Koch's bacillus (KB) in respiratory secretions. This can be suspected using microscopy and confirmed on culture or identification of specific nucleic acid.

The implementation of molecular testing in recent years has improved the diagnostic accuracy of sputum analysis. One of these is the Loop-mediated isothermal amplification (TB-LAMP), recommended by the World Health Organization in resource-limited countries. TB-LAMP sensitivity ranges from 66 to 91% for KB detection in spontaneous sputum (SS) [2]. However, nearly one quarter (24.9%) of the suspected PT in Cameroon were treated without bacteriological diagnosis in 2019 (National TB control program data, unpublished). This category of patients is referred to as smear-negative pulmonary tuberculosis (PTB-). A recent study at the Jamot Hospital in Yaoundé (JHY) among PTB- revealed only 51.6% of treatments completed, up to 37.9% lost to follow-up and a 13.7% mortality rate [3]. Meanwhile, the overall lost to follow-up rate in Cameroon ranges 2.9 - 6% and mortality ranges 5-8% [4–8].

To reduce the proportion of PTB-, a flexible bronchoscopy (FB) can be performed, allowing collection of lung specimen that give the highest diagnosis yield. However, access to this procedure is limited both geographically and financially, for a large majority of the population. It is therefore not recommended by the National Tuberculosis Control Program [4]. An alternative to FB is sputum induction (SI), which is performed by the inhalation of hypertonic saline. This produces cough and/or sputum in patients unable to expectorate spontaneously. This technique has shown to be better than SS [9–12], equivalent to FB [13–16] and safe [17]. Despite these strengths, SI is not yet recommended in the national guidelines for TB management.

If the above findings were also obtained in Cameroon, SI could save time and money, increase the proportion of bacteriologically proven tuberculosis patients, ensure a reduction of lost to follow-up and less mortality. Its inclusion into the diagnostic strategy of the national strategic plan for the fight against tuberculosis could even be considered. Our aim was to provide preliminary data on SI effectiveness in a Cameroonian adult population, using a cross sectional study.

METHODS

Study setting and population

We carried out a transversal study during a 4-months period, from January 22 to May 18 2018, in the pneumology department of JHY. This department is the referral center for tuberculosis and respiratory diseases for Yaoundé and its surroundings.

Target and source populations were patients with PT suscpicion and those attending JHY, respectively. To build our study population, we prospectively invited all adults with suspicion of PT, who could not expectorate or had a negative sputum analysis (on smear and TB-LAMP), suring the study period. Only patients who consented to participated were enrolled. Exclusion criteria were: active hemoptysis, severe respiratory distress, oxygen desaturation (less than 90% on ambient air), uncontrolled heart disease, active anti-tuberculosis treatment. Since our sampling was not random, we could not calculate an appropriate sample size. However we made an approximation using OpenEpi software (www.openepi.com/SampleSize/SSPropor.htm): considering data found in the same setting one year ago (population size = 95 patients with clinically diagnozed TB, Outocme = 48.5% of patients with treatment completed) by Bitchong Ekono et al. (3), and 95% as confident interval for outcome rate, we found a minimal sample size of 77 patients.

Procedures

Pulmonary tuberculosis suspicion was based on:

1) A persistent (2 weeks or more) cough associated with any of the following symptoms: loss of weight, loss of appetite, night sweats, fatigue and fever;

2) Tuberculosis-suggestive lesions on chest x-ray (CXR).

All spontaneous sputum specimens underwent a fluorescent smear using auramine stain, for acid fast bacilli (AFB) identification, and TB-LAMP for KB nucleic acid detection. Patients with negative sputum analysis were met at the laboratory after their result disclosure, for invitation to participate to the study.

The sputum induction was performed on a patient seated in a well-ventilated room, after a baseline clinical check was done to assess the absence of exclusion criteria. We used a branded pneumatic nebulizer Medix® AC2000 (Clément Clarke). Ten ml of hypersaline solution (10%) were initially nebulized, and each patient was instructed to breathe the steam emanating from the nebuliser, through a mouthpiece or nasolabial mask. Each nebulization lasted a maximum of 10 minutes, and was repeated if needed, for a maximum of 3 attempts. The procedure was interrupted when needed to allow cough and expectoration. It was stopped once at least 3ml of sputum was collected or side effect occurred. Sputum was collected in sterile containers and sent to HJY laboratory for AFB smear and TB-LAMP test. During the nebulization, the operator observed more than 3-meter distance from the patient, and wore an appropriate respiratory protective mask. He monitored the patient throughout the procedure, for adverse events. A clinical assessment was performed at the end and 30 minutes afterwards. Nebulization equipment (masks, nebulization chamber, tubule) was decontaminated after each session in a 2% glutaraldehyde solution for 20 minutes.

Data management and analysis

We used the CSPro software version 7.1® (United States Census Bureau) to record crude data. The analysis was then performed using IBM-SPSS version 23 software for Windows (IBM, Chicago, USA).

The yield of SI was calculated combining microscopy and TB-LAMP test, using the total number of participants as denominator. Baseline and post-procedure vital parameters (heart rate, respiratory rate, oxygen desaturation and blood pressure) were compared using paired Student test. A p-value < 0.05 was considered statistically significant. Post-

procedure adverse effects included vital signs impairment such as : desaturation or hypoxemia (oxygen hemoglobin saturation less than 90% or loss of at least 3%), tachycardia (more than 10bpm-increase in heart rate), hypotension (at list 20mmHg-decrease in systolic or 10mmHg-decrease in diastolic blood pressure) and tachypnea (at least 4 cpm-increase in respiratory rate).

In univariate analysis, the association between positive sputum and independent variables was sought using Chi square or exact Fisher tests for categorical variables, and Student test for numeric ones. Variables with a P-value < 0.10 underwent a multivariate analysis, using a stepdown multiple logistic regression process.

Ethics statements

The study was approved by the institutional ethics committee of the Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1 (Clearance number 0146/UY1/FMSB/VDRC/CSD, 17th April 2017). The head of HJY authorized patients' enrollment in his institution (Reference number 00001807/L/MINSANTE/SG/DHJY, 14th December 2017). Participants received a comprehensive information on the study, and signed a written informed consent prior to their enrollment.

RESULTS

One hundred and twenty-five patients were invited to participate, and 110 ultimately entered analysis. The flow diagram and reasons for exclusion are presented in Figure 1.

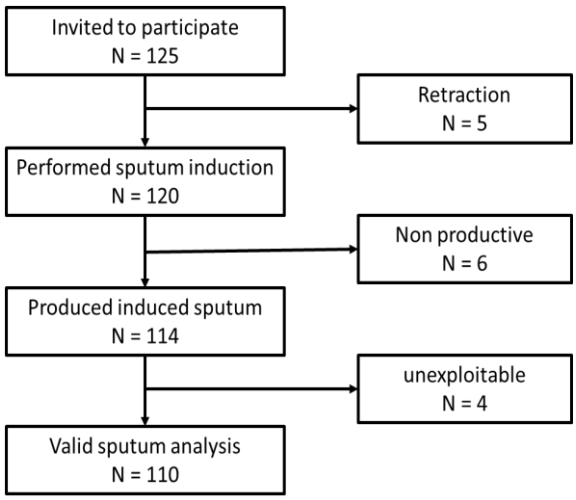

Figure 1 : Flow diagram of patients' inclusion during study for induced sputum yied study, Yaoundé, 2018

Their mean age (standard deviation) was 41.7 (13.5) years and 56 (50.9%) participants were male. Most of them were literate, more than 4/5 lived in urban area and nearly 3/4 lived alone. Pass medical history revealed mainly HIV infection. Cough and weight loss were the most frequent symptoms, while 1/3 of patients presented with pulmonary signs. The CXR was normal in 20% of patients, and cavitation was the most frequent radiological lesion (table 1).

Table I: Clinical and radiological characteristics of patients, 2018, Yaoundé, Cameroun N=110

Group	Variables and categories		Values[1]
Socio demographic data	Age, years		41.7 (13.5)
	Gender	Male	56 (50.9)
		Female	54 (40.1)
	Highest educational level	None	4 (3.6)
		Primary	45 (40.9)
		Secondary	42 (38.2)
		Higher	19 (17.3)
	Place of residence	Rural	26 (23.6)
		Urban	84 (76.4)
	Marital status	Single	68 (61.8)
		Married	30 (27.3)
		Widowed/divorced	12 (10.9)
Past medical history	HIV positive		33 (37.1)
	Asthma		1 (0.9)
Clinical presentation	Duration of symptoms	Less 1 month	37 (33.6)
		1 – 3 months	43 (39.1)
		More 3 months	30 (27.3)
	Cough		103 (93.6)
	Weight loss		91 (82.7)
	Fever		
	Night sweats		77 (70)
	Evening fever (N=80)		35 (43.8)
	Dyspnea		31 (28.2)
Radiological presentation	Pulmonary signs		37 (33.6)
	Cavitation		64 (61.5)
	Infiltrates		20 (18.2)
	Pleural effusion		15 (13.6)

[1] Continuous data are presented as mean (standard deviation), categorical data are presented as frequencies (proportion in %).

Sputum induction efficacy and safety

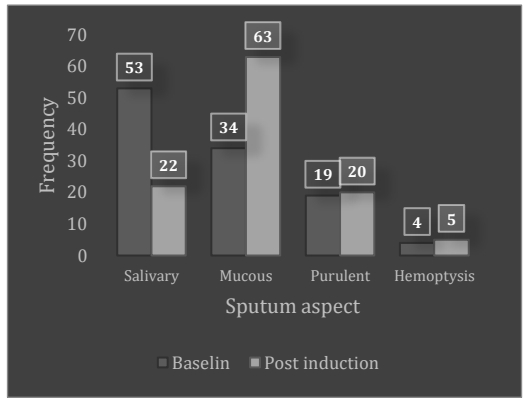

Figure 2 : Frequencies of sputum's aspect at baseline and after inhalation of hypertonic saline solution, Yaoundé, 2018 (N = 110)

At baseline, almost half of patients (48.2%) presented with salivary or mucous/mucopurulent sputum. These proportions were changed after SI, such that 75.5% of patients produced an adequate sputum afterwards. Out of the 53 patients with salivary sputum at baseline, 38 (71.7%) switched to mucous or mucopurulent after hypertonic saline

inhalation. Changes in type of sputum's frequencies are shown on figure 2.

Table II: Tolerance and safety of sputum induction among patients suspected for pulmonary tuberculosis, Jamot Hospital of Yaoundé, 2018 (N=110)

Variables and categories		Values[1]	P-value[2]
Procedure related discomfort	Absent	72 (65.5)	/
	Mild	36 (32.7)	
	Moderate	2 (1.8)	
	Severe	0 (0.0)	
Discomfort type	Respiratory	13 (11.8)	/
	Throat tingling or irritation	9 (8.2)	
	Length of procedure	2 (1.8)	
	Cough worsening	1 (0.9)	
	Retrosternal tingling	1 (0.9)	
	Imprecise	11 (10.0)	
Objective adverse event	Tachycardia	2 (1.8)	/
	Tachypnea	1 (0.9)	
	Hypotension	1 (0.9)	
	Hypoxemia	1 (0.9)	
	Vomiting	1 (0.9)	
Mean heart rate	Baseline	91.1 (15.2)	0.270
	Post sputum induction	91.4 (15.2)	
Mean respiratory rate	Baseline	24.0 (6.1)	0.035
	Post sputum induction	24.2 (6.1)	
Mean oxygen saturation	Baseline	98.0 (1.9)	0.090
	Post sputum induction	97.9 (2.2)	
Mean systolic blood pressure	Baseline	108.9 (14.7)	0.175
	Post sputum induction	109.2 (14.7)	
Mean diastolic blood pressure	Baseline	67.0 (10.5)	0.234
	Post sputum induction	66.6 (9.8)	

[1] Continuous data are presented as mean (standard deviation), categorical data are presented as frequencies (proportion in %).
[2] P-value for paired Student test to compare vital signs' means before and after sputum induction.

Nearly one third of participants (34.5%) reported a procedure-related discomfort, which was mild in 94.7% of them. The discomfort was mainly felt as respiratory (11.8%) or throat tingling or irritation (8.2%). There were very few adverse events related to saline inhalation, and none of them needed to stop the procedure. The comparison of vital signs before and after the procedure showed no statistical difference, except for the mean respiratory rate which was 0.2 higher post induction (24.2 vs 24.0; p = 0.035). Details on SI tolerance and safety are presented on table 2.

Yield of induced sputum

Out of the 110 sputum samples analyzed, 12 were positive on TB-LAMP, including only 2 which were positive on microscopy. Thus, the yield of SI (95% CI) in the total study population was 10.9 (5.1, 16.7) %. That yield was improved when the denominator was adjusted according to some features, such as salivary sputum at baseline (yield = 18.9%) or the presence of salivary sputum switch (yield = 23.7%). Additional adjustment on radiologic features led to further increase of the SI yield (table 3).

Table III: Prevalence of positive smear according to sample selection, Yaoundé

Population sample	n	%	Prevalence (95% CI)[1]
Global	110	12	10.9 (5.1, 16 ;7)
Salivary spontaneous sputum	53	10	18.9 (8.3, 29.4)
Salivary sputum switch[2]	38	9	23.7 (10.2, 37.2)
Salivary and nodules	25	8	32.0 (13.7, 50.3)
Salivary and cavitation	8	5	62.5 (28.9, 96.1)

CI = confidence interval.
[1] Prevalences and their confident interval are given in %.
[2] Patient whose sputum change from salivary to non salivary after induction.

Predictors of positive sputum analysis

Table IV: Association between positive sputum induction and patients characteristics, 2018, Yaoundé, Cameroun (N=110)

Variables	Categories	n	Mean (sd) or Frequency (%)
Age, years	Positive result	12	41.7 (16.6)
	Negative result	98	41.7 (13.2)
Gender	Male	56	7 (12.5)
	Female	54	5 (9.3)
HIV positive	Negative	56	5 (8.9)
	Positive	33	6 (18.2)
Recent contact with pulmonary tuberculosis patient	No	63	6 (9.5)
	Yes	19	2 (10.5)
	Unknown	28	4 (14.3)
Duration of symptoms	≤ 1 month	37	2 (5.4)
	> 1 month	73	10 (13.7)
Night sweats	Absent	33	2 (6.1)
	Present	77	10 (13.0)
Dry cough	No	40	5 (12.5)
	Yes	64	6 (9.4)
Evening fever	Absent	45	3 (6.7)
	Present	35	5 (14.3)
Hemoptysis	Absent	10	0 (0.0)
	Present	100	12 (12.0)
Pulmonary signs	Absent	73	9 (12.3)
	Present	37	3 (8.1)
Spontaneous sputum	Non salivary	57	2 (3.5)
	Salivary	53	10 (18.9)
Normal chest X-rays	Yes	20	0 (0.0)
	No	90	12 (13.3)
Cavitation	Absent	100	7 (7.0)
	Present	10	5 (50.0)
Nodules	Absent	71	3 (4.2)
	Present	39	9 (23.2)
Infiltrates	Absent	90	10 (11.1)
	Present	20	2 (10.0)
Consolidation	Absent	78	11 (14.1)
	Present	32	1 (3.1)
Pleural effusion	Absent	95	11 (11.6)
	Present	15	1 (6.7)
Normal chest X-ray	Yes	20	0 (0.0)
	No	90	12 (13.3)

sd = standard deviation.

On univariate analysis, there was no difference in mean age between the positive and negative sputum groups. Although

the yield appeared higher in HIV patients than non-HIV patients (18.2 vs 8.9) %, the difference was not significant. None of the symptoms nor the presence of pulmonary signs was associated to a positive analysis of induced sputum. The salivary aspect of the sputum (18.9% vs 3.5%, p = 0.022), the presence of cavitation (50.0% vs 7.0%, p < 0.001) and nodules (23.2% vs 4.2%, p = 0.006) on CXR were associated to positive IS. Details of univariate analysis are presented in table 4. In the initial logistic regression model, salivary sputum lost its significancy [adjusted odds ratio (aOR) (95% CI) =2.73 (0.5,14.89), p = 0.221]. It was however maintained in the model, since its removal generated a significant change on cavitation's aOR (32.7 to 43.6, change = 33.3%), and there was an association between the 2 variables in univariate analysis (Chi 2 = 3.2, p = 0.07); suggesting a confounding effect of salivary sputum on cavitation. Thus, nodules [aOR (95% CI) = 19.0 (2.2, 160.7), p < 0.001] and cavitation [aOR (95% CI) = 43.6 (4.4, 430.6), p < 0.001] were definitely defined as independent predictors of a positive sputum analysis, while baseline salivary sputum was considered as confounder (table 5).

Table V: Crude and adjusted odds ratios for predicting positive analysis of induced sputum, 2018, Jamot Hospital, Yaoundé (N=110)

	Univariate analysis	Multivariate analysis	P-value
Variables	**cOR (95%CI)**	**aOR (95%CI)**	
Salivary spontaneous sputum	6.4 (1.3, 30.7)	2.7 (0.5, 14.9)	0.221
Nodular lesions on Chest X-ray	**6.8 (1.7, 26.9)**	**15.2 (1.8, 132.2)**	**0.002**
Cavities on Chest X-ray	**13.3 (3.1, 57.1)**	**32.7 (3.2, 336.3)**	**< 0.001**

c = crude, a = adjusted, OR = odds ratio, CI = confident interval

DISCUSSION

Our study intended to estimate the yield of sputum induction among adult who did not initially produce an adequate sputum. We showed a 10.9% diagnosis yield. Limiting the sample to patients who switched their sputum from salivary to non salivary doubled this yield. Cavities and nodules on CXR appeared to be independent predictors of induced sputum analysis positivity, and salivary spontaneous sputum was a confounding factor.

The capacity to bring out respiratory secretions non-invasively is one of the strongest advantages of SI. Up to 95% of patients will produce adequate sputum after induction [18]. Our proportion was quite low (75.5%), probably for epidemiological and/or methodological reasons. Most of the studies published on this topic come from Asia (especially India), Latin America or South Africa, and not from our sub-region (Central Africa). Tobacco habits and population age in those regions may favor alternative causes of productive cough, such as malignancies. On the other hand, HIV prevalence, which is higher in our context, is known to increase the non-productive cough rate.

The SI's good tolerance and safety is another advantage that has been highlighted in the literature. One can assume that higher saline concentration would lead to more adverse events. This has been refuted in the present study, where a 10% saline was used. In fact, our adverse events rate (less than 2% for each) was lower than other authors' who used mainly a 3% solution in adult population. The most frequent (rate range) observed are tachycardia (1 – 16.6%), dyspnea (2 – 4.4%), chest pain (1.6 – 2%), nausea and headache (4.4%), cough (1 – 2%); while respiratory distress (5%), hypoxemia (3.3%) and bronchospasm requiring rescue (11,3%) were found in only one study each [15,17,19–21].

The diagnosis yield of SI varies in the literature, according to the numerator (Auramine fluorescent smear, Ziehl-Nielsen Smear, molecular tests, mycobacterial culture, combined definition, etc.), the denominator (all-coming, smear negative sputum only, positive Mycobacterium tuberculosis culture, final diagnosis of tuberculosis based on treatment success, etc.) and the number of procedures (1, 2, 3 or more). Our study was lead in the less favorable scenario regarding the denominator (all patients with sputum smear negative were included in the calculation) and the procedure (a unique SI procedure was performed). This may partly explain why our yield (10.9%) was lower than those found in recent studies, ranging 13% – 63.3% [9,13–15,18,21,22]. However, when we limited our sample to participants producing only salivary specimens (meaning inability to expectorate adequate sputum), our diagnosis yield reached 18.9%. This is close to the one Park et al. found in Korea (17.9%), combining microscopy and PCR- test after a single SI procedure, on adults unable to expectorate [9].

Repetition of procedures improve the diagnosis yield of induced sputum, as shown by Brown et al. [22] in UK (SI yield on culture : 30% for one SI, 33% for 2 and 39% for 3), and Lawn et al. [10] during south-African HIV patients' screening (incremental yield of 5.1% after 1 IS and 14.9% with a second sample obtained by SI). Chew et al. also found in Singapore a slight superiority of 2 pooled IS to a single one [23]. Nonetheless, Brown showed that performing more than 3 SI provided no additional benefit on diagnosis yield [22]. His study also illustrated the superiority of the mycobacterial culture to the smear alone: the yield of 3 pooled SI dropped from 39% for mycobacterial culture to 11.2% for sputum AFB smear, close to our 10.9% yield. Other authors have found a lower yield difference between direct microscopy and culture after Si, such as Jiang in China (17% vs 28%) [12], and Keeratichananont in Thaïland (13% vs 17%) [21].

We found no study presenting predictors of positive IS analysis. On this topic, we expected 2 types of factors : 1) those known as predictive of tuberculosis such as night sweat, evening fever, weight loss, apical location or cavitation on CXR; and 2) those known to decrease positivity rate of SS, such as HIV infection, dry cough, nodular or miliary lesions on CXR. None of the expected symptoms were eventually associated with IS positivity, may be due to their lack of specificity. The salivary aspect of sputum was highly associated with positive IS only on univariate analysis, and appeared to be a confounder for the cavities on CXR. The presence of cavity on CXR yielded the strongest association with diagnosis of tuberculosis after SI, in patients with AFB smear negative SS. Data on table 3 show an almost six-fold increase in diagnosis yield, from the all-coming AFB smear negative sputum to patients with inadequate sputum + cavity on CXR. This could be used to

consider a clinical algorithm, in a time- and cost-saving purpose.

CONCLUSION

The yield of SI for PT diagnosis appeared to be low in this study, where all patients with negative analysis of spontaneous sputum and with unknown ultimate diagnosis were used as denominator. It also appeared to be safe in this population sample, and significantly associated with some features such as a salivary spontaneous sputum, nodules and cavities on CXR. SI could therfore be encouraged primarily for patients who do not produce adequate sputum when tuberculosis is suspected.

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Conflict of interest

Authors declare no coflict of interest related to this study.

Contributions of authors

Massongo Massongo designed the study, selected and followed study participants, monitored the field work, analyzed data and drafted the manuscript. Ngah Komo ME, Balkissou DA and Bitchong Ekono CF selected and followed study participants and revised the manuscript.
Ebanembang Ze D performed data collection.
Pefura Yone EW and Afane Zé E supervised the entire process. All authors read and approved the manuscript.

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