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ORIGINAL ARTICLE

Trends in sputum smear conversion among smear-positive pulmonary tuberculosis patients

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Sputum smear conversion during pulmonary tuberculosis treatment is an important indicator of patient response to therapy and as such determines the direction of TB patient care. This retrospective review assessed the trends in sputum smear evaluation and conversion rates among follow up pulmonary tuberculosis patients presenting to the Tamale Teaching Hospital from January 2004 to December 2012. A total of 8,238 sputum smear cases comprising of 6,892 (83.7%) diagnoses and 1,346 (16.3%) follow-up cases were recorded. The 1,346 follow-up cases comprised of 57.8% (778/1346) males and 42.2% (568/1346) females. The percentage proportion of follow up cases that had their month of follow up, residential addresses, ages and smear results reported are 93.8% (1262/1346), 95.2% (1281/1346), 98.2% (1322/1346) and 97.8% (1309/1346) respectively. The cumulative median age was 43years (IQR: 30 to 55years) with the minimum and maximum ages being 14 and 80 years recorded in 2008 and 2012 respectively. Thirty eight percent (511/1,346) of follow-up cases were from the intensive phase (month 2) evaluation period. One hundred and eleven (111) of the follow up cases were smear positive representing a cumulative positivity rate of 8.5% (111/1309). This comprised of 75(67.6 %) males and 36(32.4%) females. Generally males were observed to be significantly more likely to delay smear conversion during treatment (OR = 1.560; p = 0.035, 95% CI=1.032- 2.359) compared to females. The ages of the positive cases ranged from 14 to 75 years with a median age of 45.5 years. The intensive phase (month 2) positivity rate was 8.1% (63/776) representing a conversion rate of 91.9%. Significant proportion (15.4%) of males were smear positive and were more likely to remain positive after two months of therapy compared to their female counterparts (OR = 2, p = 0.02, CI = 0.098 – 1.299). Periodic surveillance of regional sputum smear late/non conversion among PTB patients on treatment would be useful in supporting Tb management in Ghana.

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INTRODUCTION

The control of pulmonary tuberculosis (PTB) involves an early detection and treatment of infected persons in order to reduce the transmission of infection within communities (Borgdorff *et al.*, 2002; Caetano Mota *et al.*, 2012; Harries *et al.*, 2012). In resource limited countries, patients with suspected symptoms of PTB are normally diagnosed based on sputum smear microscopy (SSM) (Schaaf *et al.*, 2010). Those with positive sputum smears are then put on standard anti-tuberculosis regimen comprising Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) in intensive phase of two/three months, and HR in continuation phase of four months 2(HRZE)+4(RHE) (WHO 2009).

These drugs, rapidly kill actively multiplying bacilli and further sterilize infected host tissues so as to prevent clinical relapse and drug resistance (Kochi

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et al., 1993). With full patient compliance and strict adherence to therapeutic instructions, it is anticipated that 80 to 90% of infected patients will respond to therapy and become smear negative within two/three months of treatment (Mitchison, 1990; Frieden, 2004). Notwithstanding this fact, it is estimated that more than 20% of smear-positive patients remain infectious after 2 months of treatment (Singla *et al.*, 2003; Wang *et al.*, 2009) with an annually estimated 500,000 cases of *M. tuberculosis* not responding to the two most important first line anti-tuberculosis drugs (Isoniazid and Rifampicin) (Kochi *et al.*, 1993). The emergence and ushering-in of such multi-drug resistant-tuberculosis (MDR-TB) and extremely drug resistant-tuberculosis (XDR-TB) pose critical challenges to global TB control efforts (Chihota *et al.*, 2012).

In assessing the effectiveness of treatment and infectiousness of patients' during anti-TB therapy in new patients (category I) and those requesting re-treatment (category II), sputum specimen are evaluated three times in the course of treatment for smear conversion (Clancy, 1990). Under the DOTS guidelines, smear evaluation for new smear positive PTB patients are conducted at the end of the intensive phase (month 2), extended intensive phase (Month 3) that is if month 2 SSM is positive, the continuation phase (month 5) and at the end of the continuation phase (month 6). For patients undergoing re-treatment, evaluation of smear positivity is conducted at the end of months 3, 5 and 8 respectively. Smear conversion is determined by the first negative smear in a series of previously positive smears (WHO, 2003; WHO, 2009).

Smear conversion is an important indicator of patient response to therapy and as such determines the next direction of patient care (Caetano Mota *et al.*, 2012). A patient who successfully completes treatment is declared cured if all follow-up smears or subsequent smears after months 2 or 3 positive remain negative up until the end of the continuation phase (WHO, 2009; Caetano Mota *et al.*, 2012).

Sputum culture is not routinely performed in resource-limited countries thus making SSM and smear conversion the cardinal measure of response to treatment during chemotherapy and a vital indicator of treatment outcome (WHO, 2009; Caetano Mota *et al.*, 2012). Positive smear outcome during follow-up (conversion delay/failure) gives an indication of either patient non-compliance to treatment regimen and/or sub-optimal therapy. Non-compliance to treatment regimen is attributable to poor supervision and hence conversion delay/failure of new smear positive PTB patients at the end of the intensive phase (month 2) requires re-examination at month 3 (WHO 2009). SSM outcome at the end of the continuation phase (month 6) remains an important indicator of the treatment schedule with positive smear results indicating treatment failure (Caetano Mota *et al.*, 2012). To date, there is paucity of data analyzing trends in follow-up cases and their smear conversion in Ghana as a country and regionally. This retrospective study therefore seeks to assess trends in sputum smear conversion among smear-positive pulmonary tuberculosis patients presenting to the Tamale Teaching Hospital from January 2004 to December 2012.

MATERIALS AND METHODS

Study design

This hospital-based retrospective study comprised a review of available data (January 2004 to December 2012) from the Bacteriology unit of the Laboratory Department of the Tamale Teaching Hospital (TTH). TTH is the main referral hospital to the inhabitants of the northern region and the two upper regions (Upper East and Upper West) of Ghana. The hospital runs six clinical departments including the Chest clinic/ward which attends to patients with complicated respiratory tract infections including TB. SSM in the laboratory is carried out by trained and certified staff following approved national standard operating procedures (SOP) with all results being documented in a designated laboratory register (TB04). The unit has documented internal quality control in SSM and participates in onsite evaluations (regional and national) and blinded rechecking external quality assessment programme. The unit also participates in international SSM proficiency testing conducted by the National

Institute of Communicable Diseases/National Health Laboratories (NICD/NHL) in South Africa. Approval for the study was obtained from the Research Unit of TTH.

Data extraction

Demographic data and follow-up results for Ziehl-Neelsen (ZN) stained sputum smears for Acid Fast Bacilli (AFB) for smear-positive PTB patients recorded from January 2004 to December 2012 were retrieved from the TB Laboratory Registers (TB04).

Case definition

Follow-up cases were defined as sputum specimen submitted by PTB patients on treatment for assessment of smear conversion. Sputum conversion rate (SCR) was defined as the proportion of new patients and patients requesting retreatment for pulmonary smear-positive cases that had converted to pulmonary smear-negative at the end of the intensive phase

Data analysis

Demographic and smear outcome data retrieved from TB laboratory registers were entered into Microsoft Excel and cleaned for duplicate entries. Normality of data was tested using Kolmogorov-Smirnov normality test ($\alpha > 0.05$). Descriptive statistics was employed to explain the general distribution of data. The Chi-square test statistic was used to compare the statistical significance of proportions and a *p-value* < 0.05 was considered significant. Binary logistic regression analysis was performed to assess associations between sputum smear conversion results and independent variables such as sex, age and geographical location of patients. Odds ratios with 95% confidence intervals were reported. .All data were analyzed using GraphPad Prism® Version 5.0 for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

During the period under review, a total of 8,238 cases were retrieved from the records which comprised of 6,892 (83.7%) diagnoses and 1,346 (16.3%) follow-up cases. Out of the total number of diagnoses cases, 776 were smear positive representing a cumulative positivity rate of 11.3%. Males were predominately positive with a rate of 62.1% (482/776). Out of the 1,346 follow-up cases recorded, 57.8% (778/1346) were males and 42.2% (568/1346) females representing a female to male ratio of 1:1.4. Table 1 presents the year-on-year percentage pro-

Table 1: General characteristics of follow up cases

Parameter	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
Gender *n=1346*										
Male	77(62.6)	71(59.7)	77(65.8)	100(64.9)	109(48.7)	90(52.9)	53(62.4)	109(64.1)	92(50)	778
Female	46(37.4)	48(40.3)	40(34.2)	54(35.1)	115(51.3)	80(47.1)	32(37.6)	61(35.9)	92(50)	568
Age *n=1322*										
Median	42	42	42	45	40	36	43	42	44	
IQR	28 -52	31 - 55	26 - 55	30 - 60	28 - 58	26 - 55	29 - 65	25 - 63	30 - 66	
Residence *n=1281*										
In Tamale	90(78.9)	87(83.7)	84(73.7)	115(75.7)	172(81.1)	117(71.8)	49(60.5)	110(67.1)	124(70.1)	948
Out of Tamale	24(21.1)	17(16.3)	30(26.3)	37(24.3)	40(18.9)	46(28.2)	32(39.5)	54(32.9)	53(29.9)	333

Data are presented as proportion; n = Number of follow up cases with indication of gender, age and residential address respectively

portions of follow-up cases and their general characteristics during the years under review.

Cases with indication of patients' residential addresses showed that 74.0% (948/1281) resided in the Tamale metropolis with the rest 26.0% (333/1281) being referral cases from other districts and regions (Table 1). The record further showed that of the 1322 cases (from a total 1,346) with indication of ages, the cumulative median age was 43years (IQR: 30 to 55years) with the minimum and maximum ages being 14 and 80 years recorded in 2008 and 2012 respectively.

The record indicated that 93.8%(1262/1346) of the 1,346 follow up cases had their month of follow up reported. Out of the 1262 cases of follow-up with indication of month of evaluation, the intensive phase comprising months 1, 2, and 3 recorded a total of 42.8% (541/1262) cases whilst 57.2% (721/1262) were recorded during the continuation phase and end of treatment period. The years 2011 and 2008 recorded the highest 75/76 (98.7 %) and the lowest 69/183 (37.7%) intensive phase smear evaluation respectively from smear positive diagnostic cases (Table 2). The records show a remarkable increase in patients reporting for end of treatment smear evaluation after six month of therapy from 2008 compared to the previous years of eight months of therapy (Table 2). The records also suggest that patients with persistent smear positivity after the extended intensive phase of therapy underwent sputum smear examination monthly during the continuation phase until the end of therapy (Table 2).

Smear results was indicated in 97.8% (1309/1346) of the follow-up cases recorded. One hundred and eleven (111) were smear positive comprising of 75 (67.6 %) males and 36(32.4%) females. This represent a cumulative positivity rate of 8.5% (111/1309) and smear conversion rate of 91.5%. Generally males were observed to be significantly more likely to delay smear conversion during treatment (OR = 1.560; p = 0.035, 95% CI=1.032- 2.359) compared to females. The ages of the positive cases ranged from 14 to 75 years with a median age of 45.5 years.

Table 2: Yearly diagnoses and follow-up cases and their month of attendance

	Diagnosis		Follow up (Month)									
Year	Total	Pos(%)	1	2	3	4	5	6	7	8	9	Total
2004	471	74(15.7)	1(0.8)	64(52.0)	5(4.1)	2(1.6)	25(20.4)	9(7.3)	1(.08)	16(13.0)	0(0.0)	123
2005	416	66(15.8)	2(1.7)	41(35.7)	7(6.1)	2(1.7)	31(27.0)	6(5.2)	4(3.5)	22(19.1)	0(0.0)	115
2006	494	66(13.4)	1(0.9)	57(48.7)	9(8.0)	6(5.1)	13(11.1)	7(6.0)	6(5.1)	17(14.2)	1(0.9)	117
2007	616	78(12.7)	0(0.0)	61(40.1)	17(11.2)	7(4.6)	18(11.4)	13(8.6)	7(4.6)	29(19.1)	0(0.0)	152
2008	890	183(20.6)	3(1.5)	69(35.1)	16(8.1)	12(6.1)	14(7.1)	72(36.5)	1(0.5)	10(5.1)	0(0.0)	197
2009	948	95(10.0)	2(1.3)	54(35.3)	10(6.5)	7(4.6)	16(10.5)	62(40.5)	0(0.0)	2(1.3)	0(0.0)	153
2010	927	58(6.3)	0(0.0)	30(41.7)	7(9.7)	3(4.2)	8(11.1)	24(33.3)	0(0.0)	0(0.0)	0(0.0)	72
2011	1026	76(7.4)	6(3.6)	75(44.6)	18(10.7)	4(2.4)	8(4.8)	50(29.8)	2(1.2)	3(1.8)	2(1.2)	168
1012	1104	80(7.2)	0(0.0)	60(36.4)	16(9.7)	3(1.8)	17(10.3)	62(37.6)	3(1.8)	2(1.2)	2(1.2)	165

NB: Yearly follow up cases reported are likely to be influenced by the previous years' cases

No patient below the age of 10 years remained smear positive during treatment within the review period (Figure 1). Generally, SSM positivity rate was relatively stable among the age groups but rose slight within the age group 50 – 60 years and declined there after. There was a steady rise in smear positivity rate with age among males during treatment. However smear positivity rate in females declined with age after peaking at age ≥10-20 years (Figure 1).

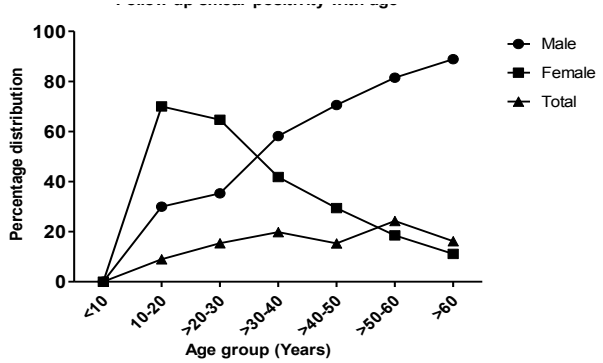

Figure 1: Follow up smear positivity rate with age

Thirty eight percent (511/1,346) of the cases with indication of follow-up were from the intensive phase (month 2) evaluation period. The intensive phase (month 2) positivity rate was 8.1% (63/776) representing a conversion rate of 91.9%. Of the 499 (97.7%) intensive phase cases with indication of gender, significant proportion (15.4%) of the males were smear positive and were more likely to remain positive after two months of therapy compared to their female counterparts (OR = 2, p = 0.02, CI = 0.098 – 1.299) (Table 3). Out of the 511 recorded cases, 481 (94.2%) had their residential addresses indicated. Smear conversion rate among patients resident in the metropolis were not significantly different from those living outside Tamale even though those resident within the metropolis had a higher likelihood of remaining smear positive (OR = 1; p = 0.932, CI= –0.637 – 0.583) after the intensive treatment (Table 3).

Four hundred and ninety three (96.5%) of the 511 cases had their ages indicated. The study showed a higher likelihood of patients >40 years presenting

Table 3: General characteristics of 2 months intensive phase smear evaluation results

Parameter		**Negative** n(%)	**Positive** n(%)	Total	OR	P *value*	CI
Gender	**n=499**						
Male		259(84.6)	47(15.4)	306(61.3)			
Female		177(91.7)	16(8.3)	193(38.7)	2	0.023	0.098 - 1.299
Age(years)	**n=493**						
up to25		89(89.9)	10(10.1)	99(20.1)			
>25-50		190(88.4)	25(11.6)	215(43.6)			
>50		151(84.4)	28(15.6)	179(36.3)		0.1525	
Residence	**n=481**						
Within Tamale		313(87.2)	46(12.8)	359(74.6)			
Outside Tamale		106(86.9)	16(13.1)	122(25.4)	0.974	0.932	--0.637-0.583

N= Number of follow up cases with indication of gender, age and residential address respectively

with delayed/non smear conversion even though this association was not statistically significant (p = 0.1525) (Table 3).

DISCUSSION

In spite of the advances made in achieving universal access of care for all TB patients, TB remains a global economic and public health problem especially in resource limited countries (WHO, 2010). The situation is compounded by the emergence of HIV and the multiple-drug-resistant tuberculosis in these countries (Harries *et al.*, 2012; Norbis *et al.*, 2013). Regular evaluation of patient sputa for smear conversion during anti-TB therapy is an important tool for effective patient management (Horne *et al.*, 2010). This review was conducted to assess trends in sputum smear conversion among smear-positive pulmonary tuberculosis patients at the Tamale Teaching Hospital in Ghana.

The current study reported a total of 776 (11.3%) newly diagnosed smear positive pulmonary tuberculosis cases from 2004 to 2012 of which 65.9% (511/776) reported for intensive phase evaluation representing a 34.1% lost to follow-up. The lost to follow up rate in the current study is higher than the 7.9% and 16% rates obtained in the national studies conducted in Burkina Faso and in Fiji by Dembele *et al.,* (2007) and Ram *et al.,* (2012) respectively. However the estimated rate from this current study is lower than the 38% pre-treatment regional lost to follow-up reported by Afutu *et al.,* (2012) in the Greater Accra Region of Ghana.

This observed rate of lost to follow-up from the current study could have been impacted upon by the fact that the estimated 25.4% of the patients reporting to the teaching hospital from outside the Tamale metropolitan area might have reported back to their districts for therapeutic continuation. Evaluation would therefore have been conducted locally at the districts or there could have been the possibility of some patients dropping out before treatment or after treatment had begun. Lost to follow-up at pre-treatment and during treatment is an indication that the healthcare worker is unable to evaluate the effectiveness of therapy and this has been identified as a major threat to tuberculosis control (Afutu *et al.*, 2012). Such individuals pose a significant public health risk through increased disease transmission, disease reactivation, development of drug-resistance and high rates of morbidity and mortality (Squire *et al.*, 2005; Barrett *et al.*, 2011; Zachariah *et al.*, 2012). The major reasons identified leading to pre-treatment and during treatment lost to follow-up include inadequate support for aged patients and low effort in actively tracing patients who reside in geographical locations different from the TB treatment and diagnostic centres (Gopi *et al.*, 2005; Schaaf *et al.*, 2010; Ram *et al.*, 2012). Therefore continuous monitoring and evaluation of follow up smear evaluation attendance will be useful not only to understand the magnitude of the problem but to guide management practices.

The intensive phase completion conversion rate of 91.9% recorded by this study compares well with the expected rate (80 to 90%) among patients who are put on appropriate therapy and comply fully to treatment instructions (Frieden, 2004). However rates observed from multicentre studies conducted in countries such as Cameroon (86.6%) (Kuaban *et al.*, 2009), Burkina Faso (82.9%) (Dembele *et al.*, 2007), Tanzania (72%) (Senkoro *et al.*, 2010), Uganda (76%) (Bwire *et al.*, 1999) and India (84%) (Bawri *et al.*, 2008) indicated that the current study showed a remarkably higher conversion rate but relatively lower rate compared to the 95% and 95.03% rates observed by (Khalid *et al.*, 2013) in Morocco and (Harish Kumar *et al.*, 2013) in India respectively. Meanwhile at the end of the extended intensive phase (3rd month) smear positivity rate increased marginally to 9.5% (74/776) resulting in a reduced conversion rate of 90.5% compared to 93.3% obtained by Parikh *et.al.,* (2012) among patient evaluated after the extended intensive phase**.**

The current study agrees with other studies that showed that pulmonary tuberculosis sputum smear late/non-conversion and hence patients' infectiousness after the intensive phase of therapy is impacted by male gender and age (Telzak *et al.*, 1997; Pungrassami *et al.*, 2002; Gopi *et al.*, 2006; Guler *et al.*, 2007; Dembele *et al.*, 2007 ; Senkoro *et al.*,

2010). Reasons put forward indicated that males are more likely to experience infection reactivation because they indulge in activities such as smoking and excessive alcohol consumption that exposes them to immunodeficiency. Moreover as one ages there is the tendency of reduction in immune defense against infection and clearing of infectious agents from the infected site resulting in delayed clearing of these organisms from the body. There is also the possibility of reduced therapeutic compliance and health care seeking activities among the aged which might lead to disease progression (Liu *et al.*, 1999; Arora *et al.*, 2003; Domínguez-Castellano *et al.*, 2003 ; Singla *et al.*, 2006; Kuaban *et al.*, 2009). However this study found no significant association between late/non-conversion and age of patients (Khalid *et al.*, 2013).

Smear non-conversion among TB patients have been associated with infection with drug resistant strains (primary resistance) or initially susceptible strains acquiring resistance through drug mismanagement and misuse in both new and previously treated patients (Warren *et al.*, 2004; van Rie *et al.*, 2005). There could also be the phenomenon of repeated exogenous re-infection with new strains and mixed infections involving different strains during the treatment period. Drug resistant TB is a major challenge to the control of TB especially in lower income countries (Richardson *et al.*, 2002; Warren *et al.*, 2004; Andrews *et al.*, 2008). Therefore strict monitoring and evaluation of drug adherence especially among transferred patients and periodic surveillance of regional drug resistant status among TB patients would be useful in guiding retreatment regimen.

CONCLUSION

The study shows a remarkable increase in PTB patients reporting for smear evaluation during and at the end of therapy. A significant proportion of these patients with persistent smear positivity were males. It is therefore recommended that periodic drug adherence surveillance among these patients be organized to improve TB management in the region.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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