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Sputum, sex and scanty smears: new case definition may reduce sex disparities in smear-positive tuberculosis

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SUMMARY

SETTING: Urban clinic, Nairobi.

OBJECTIVES: To evaluate the impact of specimen quality and different smear-positive tuberculosis (TB) case (SPC) definitions on SPC detection by sex.

DESIGN: Prospective study among TB suspects.

RESULTS: A total of 695 patients were recruited: 644 produced ⩾1 specimen for microscopy. The male/female sex ratio was 0.8. There were no significant differences in numbers of men and women submitting three specimens (274/314 vs. 339/380, $P = 0.43$). Significantly more men than women produced a set of three 'good' quality specimens (175/274 vs. 182/339, $P = 0.01$). Lowering thresholds for definitions to include scanty smears resulted in increases in SPC detection in both sexes; the increase was significantly higher for women. The revised World Health Organization (WHO) case definition was associated with the highest detection rates in women. When analysis was restricted only to patients submitting 'good' quality specimen sets, the difference in detection between sexes was on the threshold for significance ($P = 0.05$).

CONCLUSIONS: Higher SPC notification rates in men are commonly reported by TB control programmes. The revised WHO SPC definition may reduce sex disparities in notification. This should be considered when evaluating other interventions aimed at reducing these. Further study is required on the effects of the human immunodeficiency virus and instructed specimen collection on sex-specific impact of new SPC definition.

KEY WORDS: tuberculosis; microscopy; sputum; diagnosis; sex; gender; HIV

UNTIL NEW DIAGNOSTICS become available, global tuberculosis (TB) control will remain reliant on sputum smear microscopy.[1] Smear microscopy is an insensitive technique, dependent upon large numbers of acid-fast bacilli (AFB) being present in sputum. However, a recently described mathematical model has indicated that considerable public health impact may accrue from improving patient access to a smear-based diagnosis.[2] In 2006, only 61% of the world's predicted sputum smear-positive cases (SPCs) were detected.[3]

Until recently, international guidelines recommended the examination of three sputum specimens for AFB in the investigation of suspected pulmonary TB. These guidelines defined a positive smear as ⩾10 AFB per 100 high-power microscopic fields (HPF), and an SPC as a person with at least two positive smears.[4–6] Smears containing few bacilli (1–9 AFB/100 HPF) are termed 'scanty' smears. They are not uncommon, and can account for 10% of all smears from TB suspects presenting to microscopy centres.[7] There is good evidence that among clinical TB suspects in endemic countries, scanty smears are indicative of true positivity.[7,8]

In a study conducted in Nairobi, our group showed that lowering the thresholds for defining a positive smear to include scanty smears and for defining an SPC to a single positive smear considerably increased the number of cases detected.[9]

The World Health Organization (WHO) recently changed its policy with respect to the definitions of a positive smear from 10 AFB/100 HPF to 1 AFB per smear and an SPC from a patient with two positive smears to a patient with a single positive smear.[10,11] These changes are likely to increase the number of SPCs being diagnosed and/or notified.

In most countries, SPC notification rates are higher in men than in women.[3] The reason for the disparate sex ratio is unclear, but is likely to be a complex mixture of biological, epidemiological and socio-cultural determinants, compounded in some settings by inequitable access to health systems.[12–22] It has been reported that women are more likely than men to submit poor quality specimens.[23,24] Specimen quality is a critical

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determinant of smear microscopy performance, and poor quality specimens (as judged macroscopically) are associated with lower concentrations of AFB.[25,26]

It is important to understand whether recent changes in definitions, in addition to increasing the total number of reported SPCs, may affect sex disparities in case detection. This is important to ensure that the evaluation of other initiatives aimed at reducing sex disparities can be properly interpreted in the light of the changed definitions.

We interrogated the data from the Nairobi study to determine: 1) whether women were more likely to submit poor quality specimens; 2) whether patients submitting poor quality specimens were more likely to benefit from the reduced thresholds; and 3) whether women, regardless of specimen quality, were more likely to benefit from the reduced thresholds.

STUDY POPULATION AND METHODS

The study was conducted in Mathare, Nairobi, between February and December 2005 in a clinic supported by the Kenyan Ministry of Health and Médecins Sans Frontières. The study site and methods have been described previously.[9] The clinic delivers TB-HIV (human immunodeficiency virus) care to the local community. In 2001, 50% of TB patients in Nairobi were estimated to be HIV co-infected.[27] The clinic's laboratory routinely performs sputum microscopy.

All consecutive patients aged ⩾15 years with cough >2 weeks were eligible for the study. After providing written informed consent, patients were interviewed regarding symptoms and medical history using a standard form/questionnaire. They were asked to submit three specimens over 2 consecutive days. Patients were coached by a dedicated technician in deep breathing and sputum expectoration following standard operating procedures. The on-the-spot specimens were collected out of doors under supervision.

The first specimen was collected on the spot at initial consultation, the second at home the following morning, and the third when the patient attended the clinic to deliver the second specimen. Patients submitting specimens of <1 ml in quantity were requested to produce others. Specimen appearance was assessed macroscopically. It was recognised that a mucoid or salivary specimen may not necessarily be a 'poor' specimen if the patient's illness was not causing the production of purulent or mucopurulent sputum. The specimen quality was therefore defined as 'good' if it was purulent, mucopurulent and/or blood-stained, and 'possibly poor' in the case of mucoid and salivary specimens.

Smears were stained using the hot Ziehl-Neelsen (ZN) technique (carbol fuchsin 1% and 0.1% methylene blue). Slides were examined at ×1000 magnification by two independent microscopists blind to the results of other specimens from the patient. Smears were considered negative if no AFB were seen in 100 HPFs. Positive smears were graded in accordance with the WHO/International Union Against Tuberculosis and Lung Disease system.[4,6] Where <10 AFB were seen in 100 HPFs, the exact number of AFB observed in 100 HPF was recorded.

After laboratory investigation, patients were referred back to the clinicians and decisions to treat for TB were made based on smear microscopy result, clinical presentation and chest X-ray findings.

Inter- and intra-reader reliability was assessed on a sample of 200 smears, randomly selected to be blindly re-read by a second microscopist, or by the same microscopist after a 1-day interval. Slide identification was masked by opaque tape by the study supervisor to ensure blinding. Every month, the study supervisor rechecked, blind, a random selection of 50–100% of positive and 10–20% of negative smears. At the end of the study, 100 randomly selected smears were examined blind at the TB laboratory of the Centre for Respiratory Disease Research, Kenya Medical Research Institute (KEMRI) as external quality assessment (EQA).

To assess sex differences in SPC detection, several approaches were compared. The approaches varied in the AFB cut-off used to define a positive smear, the number of positive smears required to define an SPC, and whether two or three specimens were examined. The approaches are presented in Table 1.

The proportion of TB suspects found to be SPCs was calculated for each approach and reported with a 95% confidence interval (95%CI). The SPC rate of Approaches B, C, D and E were compared with the conventional approach using McNemar's test for matched data. Patients' clinical characteristics, specimen quality and smear-positive detection rate were compared between males and females using χ^2 and *t*-tests, respectively, to compare proportions and means, and the rank sum test for non-normal distribution.

Inter- and intra-reader reliability was assessed by the calculation of the kappa (κ) coefficient, which measures the degree to which the results of both tests vary when read by two independent readers, or by the same reader after a 1-day interval. A κ coefficient of between 0.80 and 1.00 signifies an almost perfect agreement.

Data were double-entered using EpiData 3.1 (EpiData Association, Odense, Denmark) and analysed us-

Table 1 Approaches to assess sex differences in tuberculosis detection

Approach A	At least 2 smear-positive results out of 3, both ⩾10 AFB/100 HPF
Approach B	At least 2 smear-positive results out of 3, one ⩾10 AFB/100 HPF
Approach C	At least 2 smear-positive results out of 3, both ⩾1 AFB/100 HPF
Approach D	At least 1 smear-positive result (⩾10 AFB/100 HPF) in the 2 first specimens collected
Approach E	At least 1 smear-positive result (⩾1 AFB/100 HPF) in the 2 first specimens collected

AFB = acid-fast bacilli; HPF = high power microscopic field.

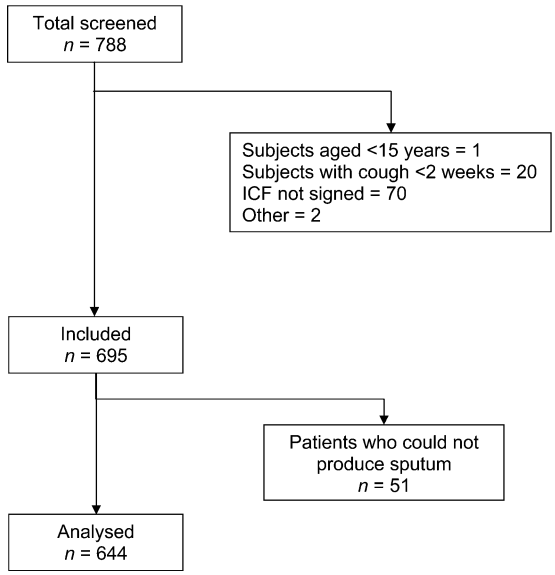

Figure Study profile. ICF = informed consent form.

ing Stata/SE 9.1 (StataCorp LP, College Station, TX, USA).

The National Ethical Review Committee of KEMRI (Nairobi, Kenya) and the Comité de Protection des Personnes (Ile de France XI, France) approved the study.

RESULTS

A total of 695 suspected TB patients were included in the study and 644 could produce at least one sputum specimen (Figure). In total, 1879 specimens were examined. One patient's sex was not recorded, 314 (45.2%) were male, and 380 (54.7%) were female. The male/female sex ratio was 0.8. The median age was 30 years (interquartile range [IQR] 25–37). Males were older than females (median age 34.1 years, IQR 26–40 vs. 30 years, IQR 25–35, $P < 0.001$).

Past TB history, intake of antibiotics in the 2 weeks prior to specimen collection and patients' clinical signs at presentation are reported in Table 2 for males and females, respectively. There were no significant differences between male and female patients in reported symptoms.

Table 2 Patient characteristics at inclusion ($N = 694$)*

	Male ($n = 314$) n (%)	Female ($n = 380$) n (%)	P value
TB past history	60 (19.1)	64 (16.8)	0.44
Course of antibiotics in past 2 weeks	17 (5.4)	25 (6.6)	0.1
Clinical presentation			
Sputum production	314 (100)	380 (100)	1
Fever	288 (91.7)	349 (91.8)	0.95
Chest pain	291 (92.8)	346 (91.0)	0.44
Night sweats	275 (87.6)	316 (83.2)	0.10
Weight loss	111 (35.3)	148 (38.9)	0.33
Haemoptysis	57 (18.1)	56 (14.7)	0.22
Loss of appetite	223 (71.0)	294 (77.4)	0.06

* One patient with sex data missing from the original 695 recruited.
TB = tuberculosis.

Among the 644 TB suspects able to produce at least one specimen, the sex ratio was also 0.8. There was no significant difference in the number of men and the number of women submitting three sputum specimens (274/314, 87.3% vs. 339/380, 89.2%, $P = 0.43$). Purulent, mucopurulent ($n = 1401$) and blood-stained ($n = 56$) specimens (i.e., 'good' quality specimens) accounted for 77.5% of all specimens (1457/1879), and mucoid ($n = 414$) and salivary ($n = 8$) specimens (i.e., 'possibly poor quality' specimens) for 22.5% (422/1879). On the basis of this macroscopic classification, significantly more men than women produced a set of three 'good' quality specimens (175/274, 63.9% vs. 182/339, 53.7%, $P = 0.01$). The proportion of males and females who failed to submit any sputum specimens was not significantly different, (8.6%, 27/314 vs. 6.3%, 24/380, $P = 0.25$).

Inter- and intra-reader reliability was very good, with a κ coefficient of respectively 0.83 (95%CI 0.76–0.86) and 0.91 (95%CI 0.88–0.94). Among the 200 smears blindly and randomly selected for inter-observer reliability assessment, nine smears were

Table 3 Results of internal quality control by study supervisor

Month 2005	Smears controller-positive n	Smears controller-negative n	Total n	Sensitivity %	Specificity %	Errors by controlled microscopists
February	13	17	30	100	100	1 minor
March	45	31	76	100	100	2 minor
April	34	41	75	100	100	2 minor
May	36	41	77	100	95	2 major (false-positive)
June	35	42	77	100	95	2 major (false-positive)
July	31	38	69	100	100	2 minor
August	31	32	63	100	100	3 minor
September	52	24	76	100	100	1 minor
October	22	14	36	100	100	2 minor
November	28	18	46	100	100	1 minor
December	20	15	35	100	100	2 minor
Total	347	313	660	Mean 100	Mean 99.1	16 minor, 4 major

Table 4 Results of external quality assessment by Tuberculosis Laboratory, KEMRI, Nairobi, Kenya*

Controller (KEMRI)	Controlled microscopists					
	Negative	Scanty	1+	2+	3+	Total
Negative	83	1	0	0	0	84
Scanty	0	3	2	0	0	5
1+	0	0	8	2	0	10
2+	0	0	1	9	3	13
3+	0	0	0	2	6	8
Total	83	4	11	13	9	120

* Total number of errors = 11 minor errors.
KEMRI = Kenya Medical Research Institute.

graded as scanty by the first observer. The second observer graded six as scanty, one 1+ and two negative. Among the 200 smears blindly and randomly selected for intra-observer variation, six were graded as scanty on the first day by the observer. The same observer also graded these six smears as scanty on the following day. In terms of smear positivity/negativity, internal quality control found 95–100% agreement between the study microscopist and the controller, and EQA agreement was 99% (Tables 3 and 4).[9]

The use of 1 AFB/100 HPF threshold to define a positive smear detected significantly more positive smears compared to the use of 10 AFB/100 HPF as threshold (19.9%, 374/1879 vs. 16.0%, 301/1879, $P < 0.001$). Table 5 presents positive smear detection rates in the group of 'good' and 'possibly poor' quality specimens. The detection rate was significantly higher for specimens of 'good' quality compared to those of 'possibly poor' quality, regardless of which AFB threshold was used. The increase in detection using a more sensitive threshold was significantly more important in the group of 'possibly poor' quality specimens ($P = 0.004$).

The standard approach (A) detected 105 SPCs among 644 TB suspects (16.3%). The proportions of TB suspects found to be SPCs by the different approaches (A–E) are reported in Table 6 for men and women. They all detected significantly more SPCs than Approach A ($P < 0.001$). Regardless of the approach, significantly more men than women were found to be smear-positive. There were 20/45 (44.4%) and 10/59 (16.9%) extra cases detected by Approach E compared to Approach A in women and men, respectively. The increase in detection was significantly higher for women ($P < 0.002$). When we selected only patients

Table 7 Proportions of SPCs found among male and female tuberculosis suspects able to produce a set of three 'good' quality specimens and two 'good' quality specimens for approaches based on collection of three and two specimens, respectively (difference of positivity rate between males and females)

	Females		Males		
	n	% (95%CI)	*n*	% (95%CI)	*P* value
Three specimens	($n = 182$)		($n = 175$)		
Approach A	32	17.6 (12.3–23.9)	45	25.7 (19.4–32.8)	0.06
Approach B	34	18.7 (13.3–25.1)	48	27.4 (21.0–34.7)	0.05
Approach C	37	20.3 (14.7–26.9)	51	29.1 (22.5–36.5)	0.05
Two specimens	($n = 218$)		($n = 201$)		
Approach D	39	18.0 (13.0–23.6)	52	25.9 (20.0–32.5)	0.05
Approach E	46	21.1 (15.9–27.1)	59	29.3 (23.2–36.2)	0.05

SPC = smear-positive tuberculosis case; CI = confidence interval.

Table 5 Smear-positive results according to specimen quality ($N = 1879$)

	Purulent, mucopurulent and blood-stained ($n = 1457$)		Mucoid and salivary ($n = 422$)			
	n	% (95%CI)	*n*	% (95%CI)	*P* value	Total
⩾10 AFB/100 HPF	267	18.3 (16.4–20.4)	34	8.1 (5.6–11.1)	<0.001	301
⩾1 AFB/100 HPF	325	22.3 (20.2–24.5)	49	11.6 (8.7–15.1)	<0.001	374
Increase in detection	58	21.7	15	44.1	0.004	

CI = confidence interval; AFB = acid-fast bacilli; HPF = high power microscopic field.

Table 6 Proportion of TB suspects found to be SPCs using different approaches to define an SPC (difference of positivity rate between male and female)*

	Total ($N = 644$)†		Female ($n = 356$)		Male ($n = 287$)		
	n	% (95%CI)	*n*	% (95%CI)	*n*	% (95%CI)	*P* value
Approach A	105	16.3 (13.5–19.4)	45	12.6 (9.4–16.5)	59	20.6 (16.0–25.7)	0.007
Approach B	116	18.0 (15.1–21.2)	52	14.6 (11.1–18.7)	63	21.9 (17.3–27.2)	0.006
Approach C	126	19.6 (16.6–22.8)	58	16.3 (12.6–20.5)	67	23.3 (18.6–28.7)	0.01
Approach D	117	18.2 (15.3–21.4)	54	15.2 (11.6–19.3)	62	21.6 (17.0–26.8)	0.03
Approach E	135	21.0 (17.9–24.3)	65	18.3 (14.4–22.7)	69	24.0 (19.2–29.4)	0.03

* Comparison between different approaches: A vs. B, $P \leqslant 0.01$; A vs. C, $P \leqslant 0.01$; A vs. D, $P \leqslant 0.01$; A vs. E, $P \leqslant 0.01$.
† One patient with sex data missing.
SPC = smear-positive TB case; CI = confidence interval; TB = tuberculosis.

who were able to produce a set of 'good' quality specimens, the difference in detection between men and women was on the threshold for significance ($P = 0.05$). Table 7 shows the proportion of TB suspects found to be SPCs among males and females able to produce a set of three 'good' quality specimens and two 'good' quality specimens for approaches based on the collection of three and two specimens, respectively.

HIV status was not determined for all patients, but 153/696 (22.0%) were HIV-infected patients referred for TB investigation by the HIV clinic. Significantly more women than men had been referred (107/380, 28.2% vs. 46/314, 14.6%, $P < 0.001$).

DISCUSSION

This study suggests that using lower thresholds to define positive smears and SPCs may also result in a reduction in the sex disparities seen in SPC notifications in some settings. This is achieved primarily through increased finding of positive smears in 'possibly poor' quality specimens.

Our findings indicate that: 1) men and women were both significantly more likely to be classified as SPCs using the reduced thresholds; 2) patients submitting 'possibly poor' quality specimens were significantly more likely to be classified as SPCs using the reduced thresholds; 3) women were significantly more likely than men to produce 'possibly poor' quality specimens; and 4) although women were significantly more likely than men to be classified as smear-positive using the reduced threshold, this sex- or gender-specific effect may not be significant when 'possibly poor' quality specimens were removed from the analysis ($P = 0.05$).

Lowering the thresholds for defining a positive smear to include scanty smears, and the threshold for defining an SPC to a single positive smear, considerably increased the number of cases detected.[9] The considerable increase in the number of cases detected could be achieved even when reducing the number of specimens examined from three to two, thus reducing the laboratory workload and, potentially, the number of patient visits required.[9] Reducing the workload could help increase case detection by allowing more time for the examination of smears.[28,29] Reducing the number of patient visits required could help increase case detection through reducing patient drop-out during the diagnostic investigation. TB suspect drop-out rates of between 13% and 95% during the diagnostic process have been reported.[30,31]

Smear microscopy is dependent upon relatively large numbers of AFB being present in the sputum. Paucibacillary pulmonary TB leading to smear-negative results is common where rates of TB-HIV co-morbidity are high, due most likely to altered pathological processes in the immunocompromised host.[32] Any sex/gender disparities in HIV prevalence are likely to be reflected in TB notification due to the association of HIV with a reduced probability of smear-based diagnosis.

There may be other reasons for the under-notification of female SPCs. A study in Kenya that reported a lower sensitivity of ZN microscopy in women found that it was not significantly lower in women (after adjustment for HIV).[22] Interestingly, in the same study, the use of fluorescence microscopy—recently shown to be 10% more sensitive on average than ZN microscopy—reduced the sex differences.[22,33]

Absence, or reduced numbers, of AFB in sputum can be due to poor quality specimens.[25,26] Undernotification of female SPCs may be expected if women are less likely to produce 'good' quality sputum specimens.[23,24]

Improving the specimen quality by providing patients with clear sputum collection instructions has been reported to markedly increase the sensitivity of ZN microscopy.[23,34] A recent study in Pakistan reported that such instructions reduced the frequency of submission of poor quality specimens and substantially increased the number of women being considered SPCs (in accordance with the previous WHO definition).[23] The large increase in sensitivity could not be explained wholly through the increased submission of higher quality sputum specimens.[23] The effect of instruction on smear positivity in men was less, and was not statistically significant.[23]

There were limitations associated with our study. First, sputum quantity was not recorded. Sputum quantity may be important: in this study, 51 patients were excluded because they could not produce sputum specimens of at least 1 ml. The quantity of specimen (above the minimum 1 ml) submitted by patients was not recorded. It has been reported that in the absence of instruction, men submit larger volume specimens and that specimens of at least 5 ml have a higher probability of testing smear-positive.[23,35] However, a study in Kenya reported no significant difference between the sexes in the volume of specimen submitted (Professor Paul Klatser, personal communication), and found that specimen volume was associated with neither smear nor culture positivity.[22] Second, HIV status was not determined for all subjects. Significantly more of the female patients recruited had been referred from the HIV clinic and were known to be HIV-infected. The effect of HIV co-infection on the rate of submission of 'possibly poor' quality specimens needs further investigation. Finally, sputum samples were not cultured.

CONCLUSIONS

It is clear from this study that, even where patients are well-instructed in sputum collection and where microscopy services are of high quality, the lowering

of thresholds for defining a positive smear and an SPC results in more patients, particularly more female patients, being considered smear-positive cases.

The effects of HIV co-infection, coaching in specimen production, specimen volume and fluorescence microscopy on the sex- or gender-specific impact of reduced thresholds for case definition require further study. Studies should also look at whether lowering the thresholds for defining an SPC results in more patients receiving treatment for TB, or whether the increase in SPCs detected is only of significance in notification and the monitoring and evaluation of TB control activities.

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RÉSUMÉ

CONTEXTE : Une clinique urbaine de Nairobi, Kenya.
OBJECTIFS : Evaluer l'impact de la qualité des crachats et de différentes définitions de cas de tuberculose (TB) à frottis positifs (SPC) sur le taux de détection de SPC chez les hommes et les femmes.
MÉTHODE : Etude prospective parmi les patients suspects de TB.
RÉSULTATS : Un total de 695 patients ont été recrutés : 644 ont produit >1 spécimen pour l'examen microscopique. Le sex-ratio (homme/femme) était de 0,8. Il n'y a pas eu de différence significative entre les hommes et les femmes pouvant soumettre trois spécimens (274/314 vs. 339/380 ; $P = 0{,}43$). Significativement plus d'hommes que de femmes (175/274 vs. 182/339 ; $P = 0{,}01$) ont soumis un lot de trois échantillons de « bonne » qualité. La réduction des seuils de positivité pour définir un SPC en incluant les frottis faiblement positifs (« scanty ») s'est accompagnée d'une augmentation de la détection de SPC chez les hommes et les femmes. L'augmentation a été significative chez les femmes. La définition révisée du SPC de l'Organisation Mondiale de la Santé (OMS) s'est accompagnée de la meilleure proportion de SPC chez les femmes. Quand l'analyse se limite aux patients ayant soumis un lot de spécimens de « bonne » qualité, la différence de détection entre les hommes et les femmes a été à la limite de la signification statistique ($P = 0{,}05$).
CONCLUSIONS : Des taux de SPC supérieurs chez les hommes sont classiquement décrits. La révision de définition de l'OMS du cas peut réduire la disparité de notification de SPC entre les hommes et les femmes, et ceci est à prendre en compte pour l'évaluation d'autres interventions visant à réduire cette disparité. Les effets de la coinfection par le virus de l'immunodéficience humaine et de l'accompagnement pour la collecte des crachats, sur l'impact de la réduction des seuils de positivité pour définir un SPC chez les hommes et les femmes doivent encore être étudiés.

RESUMEN

MARCO DE REFERENCIA : Un consultorio urbano en Nairobi, Kenia.
OBJETIVOS : Evaluar la repercusión de la calidad de la muestra de esputo y de las diferentes definiciones de caso de tuberculosis (TB) con baciloscopia positiva (SPC), sobre la detección de tales casos en hombres y mujeres.
MÉTODOS : Fue este un estudio prospectivo de pacientes con presunción clínica de TB.
RESULTADOS : Se incluyeron en el estudio 695 pacientes, de los cuales 644 aportaron como mínimo una muestra de esputo para estudio microscópico. El cociente entre hombres y mujeres fue de 0,8. No se observó una diferencia estadísticamente significativa entre los hombres y las mujeres que aportaron tres muestras (274/314 vs. 339/380 ; $P = 0{,}43$). Más hombres que mujeres aportaron tres muestras de 'buena calidad' (175/274 vs. 182/339 ; $P = 0{,}01$). Cuando se bajó el umbral de la definición de SPC y se incluyeron las muestras con escasos bacilos, se observó una mayor detección de casos en ambos sexos. El aumento de la detección fue significativamente mayor en las mujeres. La definición de SPC revisada de la Organización Mundial de la Salud (OMS) se asoció con las tasas más altas de detección en las mujeres. Cuando se restringió el análisis a los pacientes que aportaron varias muestras de buena calidad, la diferencia en la detección de casos entre hombres y mujeres alcanzó apenas el nivel de significación estadística ($P = 0{,}05$).
CONCLUSIONES : Es frecuente una mayor tasa de notificación de SPC en los hombres. La definición revisada puede disminuir las diferencias de notificación entre los sexos. Es importante considerar este aspecto cuando se evalúan otras intervenciones cuyo objetivo es reducir estas discrepancias. Es necesario estudiar con más detenimiento los efectos de la coinfección por el virus de la inmunodeficiencia humana y las indicaciones sobre la recogida del esputo, en la repercusión, específica de género, de la disminución del umbral de número de bacilos en definición de caso.