Duration of cough, TB suspects’ characteristics and service factors determine the yield of smear microscopy

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Summary

OBJECTIVE To determine the efficiency of routine tuberculosis (TB) case detection by examining sputum smear positivity for acid-fast bacilli in relation to duration of cough, characteristics of TB suspects examined and health service factors.

METHOD We combined patient interviews with routine data from laboratory registers in 6 health care facilities in San Juan de Lurigancho district, Lima, Peru. A TB case was defined as a TB suspect with at least one positive sputum smear. We calculated adjusted odds ratios with 95% confidence intervals for the association between smear positivity and health service and patient’s characteristics.

RESULTS Smear positivity was 7.3% (321/4376). Of the 4376 adults submitting sputa, 55.3% (2418) reported cough for <14 days. In this group, smear microscopy yielded 3.2% (78/2418) positive results vs. 12.4% (243/1958) in patients coughing for 14 or more days. Having cough for >2 weeks, being referred by health care staff, attending a secondary-level health care facility, male sex and age between 15 and 44 years were independent determinants of smear positivity.

CONCLUSIONS Routine case detection yields a low proportion of smear-positive cases because of the inclusion of a high proportion of patients without cough or coughing for <2 weeks. Adherence to the national TB control programme guidelines on the selection of TB suspects would have a positive impact on the smear positivity rate, reduce laboratory costs and workload and possibly improve the reading quality of smear microscopy.

KEYWORDS tuberculosis, case detection, cough, Peru, smear positivity

Introduction

World Health Organisation (WHO) aims to detect at least 70% of infectious tuberculosis (TB) cases and cure 85% of detected cases as this is considered a cost-effective policy to control TB (Currie et al. 2005). In high-incidence countries, the lack of resources limits the implementation of new and improved diagnostic techniques; even culture can often not be routinely performed (WHO 2009a). In these settings, smear microscopy constitutes a simple, inexpensive and fast method for TB diagnosis which requires minimal equipment – a microscope – that can also be used for other diagnostic tests.

WHO guidelines recommend passive case detection. Two sputum specimens are collected from pulmonary TB suspects, who are persons with persistent cough for at least 2 weeks (WHO 2009b). Specimens are submitted to microscopic examination for acid-fast bacilli (AFB) through Ziehl–Neelsen staining. This screening is meant to increase the probability of ascertaining a TB case and is considered an efficient trade-off between maximal detection of infectious cases and acceptable workload for TB programs (WHO 1998). Screening of the general population is not encouraged, even in high-incidence countries. Diagnostic evaluation for pulmonary TB in a person without a persistent cough is a clinical, not a public health, activity.

For optimal results of sputum smear AFB examination, good-quality sputum samples and adherence to standard laboratory procedures are required, in addition to adequate selection of patients (Luelmo 2004). This assumes the existence of an efficient quality assurance system and properly trained staff. Work overload and inappropriate or incorrectly applied procedures result in a low quality of AFB smear microscopy and fewer TB cases detected (Van Cleef et al. 2003).

The strengthening of the Peruvian National TB Program (NTP) since 1990 has had a positive impact on TB control.
TB incidence has steadily fallen since 1992 and, by 2006, it had dropped to 110 per 100,000 inhabitants (Suárez et al. 2001; Peruvian National Tuberculosis Program 2006). The directly observed therapy short course (DOTS) strategy now covers more than 99% of public health services in Peru. The NTP guidelines define TB suspects, called respiratory symptomatics, as patients coughing for 14 or more days.

In 2005, 2.1 million diagnostic sputum smears were read in Peru; by 2006, this had increased to 2.5 million (Peruvian National Tuberculosis Program 2006). However, the proportion of positive diagnostic sputum smears in the same period decreased from 2.3% to 1.7% (Peruvian National Tuberculosis Program 2004). The large number of slides read could have affected the quality of AFB smear examination because of work overload in general laboratories and may reflect non-compliance with guidelines in the selection of TB suspects. To test this last hypothesis, we studied the characteristics and the duration of cough of patients tested for TB in Lima and related these to the smear-positive proportion.

Material and methods

Study setting

The study was conducted in 6 health care facilities in San Juan de Lurigancho, a semi-urban district in Northern Lima. In 2005, national HIV prevalence in TB patients was 1.8%, and San Juan de Lurigancho had a TB incidence of 213 per 100,000 inhabitants (Peruvian National Tuberculosis Program 2005). Five of the facilities are first-level health care centres. These centres offer outpatient services for general medicine, maternal and childcare, laboratory tests for general blood biochemistry and urine and AFB smear microscopy. At the sixth facility, the only second-level centre for the upper San Juan de Lurigancho area, inpatient care, mainly for newborns and infants, is also provided, and appendectomies, caesarean sections and other uncomplicated surgical procedures are performed there. This facility also has a pulmonary physician on its staff, carries out X-rays, performs TB cultures and is the reference facility for all the first-level centres. Smear microscopy is carried out using the Ziehl–Neelsen staining method. Routine quality control of AFB microscopy was provided by the district laboratory network.

The NTP has designated offices in all centres. A nurse and a nurse aid are permanently posted there, supervised by a physician who also has other duties in the centre. The NTP staff is responsible for the detection, notification and follow-up of TB suspects, who can consult spontaneously or can be referred by other personnel from the centre. The nurses evaluate the patients, request AFB smear microscopy when indicated and instruct the patient on sputum production. They also supervise DOT (including multi-drug-resistant TB treatment) and keep the patient records.

When a TB suspect was detected, two sputa (spot-morning) were requested. If at least one sputum sample was positive (≥1 AFB), the patient immediately started TB treatment. Only if both smears were negative and symptoms persisted, then the TB suspect was referred for medical examination, two additional samples were collected, one of which was cultured, and a chest X-ray was requested. While awaiting the culture results, a clinical-radiological TB diagnosis could be made by the physician, generally a pulmonary physician.

The NTP set for all health facilities a TB screening target of 5% of the adults consulting for any reason (Peruvian National Tuberculosis Program Guidelines 2006). This is the proportion of TB suspects expected given the estimated national TB incidence rate. The target is 6% for high-risk areas such as San Juan de Lurigancho. The proportion of TB suspects detected and screened for TB is evaluated each quarter and constitutes a key indicator of health centre performance for TB control in Peru. Health facilities in the San Juan de Lurigancho district generally reached the quarterly target and screened on a yearly basis, indeed 6% of the adults that consulted (Peruvian National Tuberculosis Program 2005).

Data collection

From August 2003 to September 2005, data were collected at the selected health care facilities. The researchers did not interfere with routine patient management to obtain an operational perspective of the TB case-detection process. Two nurse aids were trained as field workers and posted in the NTP premises at the 6 health care facilities. Each one was assigned to 3 health care facilities, spent 5 days a week in one of them and then rotated to the next. Every patient of 15 years or older who submitted a sample for AFB microscopy was invited to participate in the study. The field workers registered routinely reported data (sex, age, date of sputum submission, diagnostic or follow-up visit and sputum sample number) and additional information (duration of cough, spontaneous presentation or referral by health personnel) as reported by the patient. Subsequently, they obtained the smear results directly from the laboratory AFB register.

Statistical analysis

Data were entered in Epi-Info 3.4 (CDC, Atlanta, GA, USA) and analysed with SPSS for Windows version 13.0.
(SPSS, Inc., Chicago, IL, USA). The unit of analysis was the TB suspect, and the outcome variable was smear positivity. Smear positivity was the proportion of TB cases (defined as at least one positive smear result) of all TB suspects who submitted sputum samples during the study period. Proportions in subgroups were compared using Pearson’s chi-square test, and odds ratios (OR) were calculated with 95% confidence intervals (95% CI). To obtain adjusted OR, we constructed a logistic regression model by iterative backward elimination and forward inclusion. All variables that were statistically significant \( (P < 0.05) \) in the univariate analysis, as well as non-significant variables of interest and plausible interaction terms, were considered for inclusion in the model.

**Ethical considerations**

This study was approved by the Institutional Ethics Committee at Universidad Peruana Cayetano Heredia. All data were processed anonymously.

**Results**

During the study period, we enrolled 5946 patients who submitted 1, 2 or 3 samples in the 6 health care facilities. A total of 4376 (73.6%) patients that submitted sputum samples for diagnostic purposes were included in the analysis. Of these 87.5% (3831/4376) submitted two sputum samples and 6.3% (276/4376) submitted three samples. The remaining 1570 submitted a follow-up sample and were already receiving TB treatment. Overall, there were 7.3% (321/4376) smear-positive patients. Mean age of the population was 33.3 years (SD ± 15.7) for all the patients. No age difference was observed by smear results: 29.9 years (SD ± 12.5) for the smear-positive patients vs. 33.6 years (SD ± 15.9) for the smear-negative patients. Male patients accounted for 47.4% (2075/4376) of the population but predominated among the smear-positive patients, 61.1% (196/321).

Duration of cough had an asymmetric distribution with a median of 10 days (IQR 0–15) for all patients; 15 days (IQR 15–29) for smear-positive patients, and 10 days (IQR 0–15) for smear-negative patients.

The proportion of screened patients stratified by duration of cough and smear positivity, and the number of patients to be tested to obtain a positive case is shown in Table 1. Of the patients tested, 55.3% (2418/4376) did not conform with the Peruvian NTP definition of a TB suspect, and 83.9% (3673) had less than 21 days of cough. Smear positivity increased from 1.5% in patients reporting no cough at all to 15.5% for persons coughing for 21 days or more, and from 3.2% in non-TB suspects to 12.4% in TB suspects as defined by the NTP.

Examining eight persons coughing for 14 or more days would yield one TB case, while 31 persons would have to be tested to find one TB case if these had cough from one to 13 days.

Table 2 shows the variables associated with smear positivity. Ninety-seven of the 4367 patients were excluded from this analysis because of missing data on referral status. Duration of cough was the factor most strongly associated with smear positivity (AOR 6.3, 95% CI 4.2–9.4). Attending a second-level health care centre also had a strong association (AOR 3.1, 95% CI 1.9–4.9). Referral for smear microscopy by health staff, sex and age were further independent predictors. We found an interaction between the effect of duration of cough on smear positivity and the level of health facility consulted: the effect of cough was stronger in the five first-level health centres than in the second-level centre. We did not find an interaction between duration of cough and referral by health staff, or between level of service consulted and referral.

<table>
<thead>
<tr>
<th>Duration of cough (days)</th>
<th>Patients screened ( n = 4376 ) (%)</th>
<th>No of positive cases</th>
<th>Smear positivity % (95% CI)</th>
<th>OR (95% CI)</th>
<th>No of persons tested to find one positive case % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1156 (26.4)</td>
<td>17</td>
<td>1.5 (0.8–2.2)</td>
<td>1</td>
<td>67.9 (35.9–100.0)</td>
</tr>
<tr>
<td>1–6</td>
<td>348 (8.0)</td>
<td>15</td>
<td>4.3 (2.2–6.4)</td>
<td>3.0 (1.5–6.1)</td>
<td>23.3 (11.7–34.7)</td>
</tr>
<tr>
<td>7–13</td>
<td>914 (20.9)</td>
<td>46</td>
<td>5.0 (3.6–6.5)</td>
<td>3.5 (2.0–6.2)</td>
<td>20.0 (14.3–24.5)</td>
</tr>
<tr>
<td>14–20</td>
<td>1255 (28.7)</td>
<td>134</td>
<td>10.7 (9.0–12.4)</td>
<td>8.0 (4.8–13.3)</td>
<td>9.4 (7.9–10.9)</td>
</tr>
<tr>
<td>≥21</td>
<td>703 (16.1)</td>
<td>109</td>
<td>15.5 (12.8–18.2)</td>
<td>12.3 (7.3–20.7)</td>
<td>6.4 (5.3–7.6)</td>
</tr>
<tr>
<td>&lt;14</td>
<td>2418 (55.3)</td>
<td>78</td>
<td>3.2 (2.5–3.9)</td>
<td>1</td>
<td>31.0 (24.2–37.8)</td>
</tr>
<tr>
<td>≥14</td>
<td>1958 (44.7)</td>
<td>243</td>
<td>12.4 (11.0–13.9)</td>
<td>4.1 (3.2–5.4)</td>
<td>8.1 (7.1–9.0)</td>
</tr>
</tbody>
</table>
In this study, more than half of the patients screened for TB in a semi-urban district in northern Lima did not comply with the NTP operational definition for a TB suspect (i.e. patients coughing for 2 or more weeks). Moreover, the rate of smear positivity in this group (3.2%) was quite inferior to the one in the group fulfilling such definition (12.4%).

Our definition of a TB case was a patient with at least one positive smear, without considering culture results, which is the definition currently in use by the NTP to start TB therapy. Thus, it allows evaluation of the routine case-detection process, and it gives our study direct programmatic implications.

The proportion of smear positivity in a population depends on the prevalence of TB, accessibility of the health services, selection criteria for the patients to be screened and the quality of the test execution (Harries et al. 1997; Makunde et al. 2007).

In our study population, the rate of smear positivity was 7.3%, which points to suboptimal efficiency: In high-incidence settings relying on passive detection of TB cases, 10% smear positivity is considered indicative of optimal performance (Baily et al. 1967; Rieder et al. 1997). The low smear positivity rate found in our study is a consequence of inadequately selecting individuals with short duration of cough for screening. This has also been observed in other studies (Baily et al. 1967; Harries et al. 1997; Makunde et al. 2007).

We did not find a significant difference in the smear positivity proportion of the patients coughing for 14 or more days [12.4% (95% CI 11.0–13.9%)] vs. those coughing for 21 or more days [15.5% (95% CI 12.8–18.2%)]. An earlier diagnosis is made in the former scenario which could have a positive impact on transmission. These findings support the use of 2 weeks of cough as a cut-off point for the definition of a TB suspect in high-incidence settings, as recommended by the Peruvian NTP. In a multicentric study in India, Santha et al. (2005) also compared the cut-off points of 2 vs. 3 weeks of cough and found 12% and 13% smear positivity, respectively. In another study in India, 8.8% and 9.7% of positive smears were found in persons coughing for 2 and 3 weeks, respectively, while only 0.4% was found in those who had only 1 week of cough (Baily et al. 1967). A large study in eight rural regions of Tanzania found proportions of smear-positive cases varying from 14.3% to 23.8% in persons coughing for 3 or more weeks (Ipuge et al. 1996).

Smaller proportions of smear-positive cases have been described in other settings where the prevalence of TB is lower and/or other definitions of TB cases are used (Banda et al. 1998; Shargie et al. 2006; Bastos et al. 2007; González-Ochoa et al. 2009).

Although it would have been interesting, we could not, unfortunately, investigate the reasons for the large number of non-TB suspects who submitted a sputum sample. Patients with other symptoms compatible with TB or epidemiological criteria to suspect TB might justifiably

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Smear positive</th>
<th>Smear negative</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>124 (5.5)</td>
<td>2132 (94.5)</td>
<td>1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>196 (9.7)</td>
<td>1827 (90.3)</td>
<td>1.8 (1.5–2.3)</td>
<td>1.8 (1.5–2.4)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–29</td>
<td>197 (8.7)</td>
<td>2067 (91.3)</td>
<td>1</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30–44</td>
<td>80 (7.7)</td>
<td>960 (92.3)</td>
<td>0.87 (0.67–1.14)</td>
<td>0.84 (0.63–1.11)</td>
<td></td>
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<tr>
<td>45–59</td>
<td>31 (5.0)</td>
<td>583 (95.0)</td>
<td>0.56 (0.38–0.82)</td>
<td>0.54 (0.36–0.81)</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>12 (3.3)</td>
<td>349 (96.7)</td>
<td>0.36 (0.19–0.63)</td>
<td>0.26 (0.14–0.47)</td>
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<tr>
<td>Referral by health staff</td>
<td></td>
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<tr>
<td>No</td>
<td>153 (6.0)</td>
<td>2415 (94.0)</td>
<td>1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>167 (9.8)</td>
<td>1544 (90.2)</td>
<td>1.7 (1.4–2.1)</td>
<td>1.8 (1.4–2.3)</td>
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<tr>
<td>Duration of cough (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–13</td>
<td>78 (3.3)</td>
<td>2259 (96.7)</td>
<td>1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥14</td>
<td>242 (12.5)</td>
<td>1700 (87.5)</td>
<td>4.1 (3.2–5.4)</td>
<td>6.3 (4.2–9.4)</td>
<td></td>
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<tr>
<td>Level of service</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>167 (6.2)</td>
<td>2512 (93.8)</td>
<td>1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>Second</td>
<td>153 (9.6)</td>
<td>1447 (90.4)</td>
<td>1.6 (1.3–2.0)</td>
<td>3.1 (1.9–4.9)</td>
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<td>Interaction term:</td>
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<td>2nd level of service</td>
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<tr>
<td>duration of cough S ≥14 day</td>
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</table>

### Discussion

In this study, more than half of the patients screened for TB in a semi-urban district in northern Lima did not comply with the NTP operational definition for a TB suspect (i.e. patients coughing for 2 or more weeks). Moreover, the rate of smear positivity in this group (3.2%) was quite inferior to the one in the group fulfilling such definition (12.4%). Our definition of a TB case was a patient with at least one positive smear, without considering culture results, which is the definition currently in use by the NTP to start TB therapy. Thus, it allows evaluation of the routine case-detection process, and it gives our study direct programmatic implications.

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We did not find a significant difference in the smear positivity proportion of the patients coughing for 14 or more days [12.4% (95% CI 11.0–13.9%)] vs. those coughing for 21 or more days [15.5% (95% CI 12.8–18.2%)]. An earlier diagnosis is made in the former scenario which could have a positive impact on transmission. These findings support the use of 2 weeks of cough as a cut-off point for the definition of a TB suspect in high-incidence settings, as recommended by the Peruvian NTP. In a multicentric study in India, Santha et al. (2005) also compared the cut-off points of 2 vs. 3 weeks of cough and found 12% and 13% smear positivity, respectively. In another study in India, 8.8% and 9.7% of positive smears were found in persons coughing for 2 and 3 weeks, respectively, while only 0.4% was found in those who had only 1 week of cough (Baily et al. 1967). A large study in eight rural regions of Tanzania found proportions of smear-positive cases varying from 14.3% to 23.8% in persons coughing for 3 or more weeks (Ipuge et al. 1996).

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Although it would have been interesting, we could not, unfortunately, investigate the reasons for the large number of non-TB suspects who submitted a sputum sample. Patients with other symptoms compatible with TB or epidemiological criteria to suspect TB might justifiably
have been tested without persistent cough. However, those reasons can hardly explain why more than 50% of those screened did not comply with the definition of TB suspects. This large proportion may have been a consequence of health care workers’ will to reach the target of screening 6% of all adult outpatients in high risk areas, set by the NTP in 2000 as an indicator of good performance and still applicable today. Imposing such target with almost fixed resources and under declining TB prevalence rates could be counterproductive and place an excessive workload on health staff. Patients with <14 days of cough who are screened are wrongly registered as TB suspects attending a health centre, which biases the TB indicators.

Adherence to the still current NTP definition of TB suspect (cough ≥14 days) would reduce laboratory workload and increase the positive predictive value of smear microscopy, even if a small number of patients that do have TB would not be diagnosed before 2 weeks of cough. We also recommend that the current Peruvian TB screening target be revised. Sputum smear microscopy will give an optimal yield of infectious TB cases and be efficient provided that the operational definition of TB suspects – 2 weeks of cough- is consistently implemented.

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Yield of AFB sputum smear microscopy

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