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SHORT COMMUNICATION

A comprehensive study of the efficiency of the routine pulmonary tuberculosis diagnostic process in Nairobi

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SUMMARY

Tuberculosis (TB) suspects from Rhodes Chest Clinic, Nairobi, Kenya, were subjected to three sputum smear microscopy (Ziehl-Neelsen) examinations and a chest X-ray (CXR). Results were compared with Löwenstein-Jensen culture as the gold standard to establish the efficiency of the routine diagnostic process. All laboratory tests and the CXR were available for 993 (71%) of the 1398 enrolled suspects. Of these, 554 (56%) were culture-positive. The routine diagnostic process was very sensitive, able to detect 92% of culture-positive cases but missing 8%. The specificity was low (66%), and 23% of the patients started on treatment were culture-negative, mainly due to the low specificity of the CXR. It may be possible to increase the efficiency of the diagnostic process by specifying better criteria for CXR examination, improving the quality of CXR reading and counselling patients to return when complaints persist.

KEY WORDS: tuberculosis; diagnosis; sensitivity; specificity; Kenya

MANY TUBERCULOSIS (TB) programmes, particularly those in big cities, are overwhelmed by increases in patients. In Kenya, as in other sub-Saharan countries, this increase is higher in patients with sputum-negative and extra-pulmonary TB, as compared to sputum-positive cases.[1,2] The largest increase has been observed in Nairobi, which experienced an average annual growth in tuberculosis patients of 25% in the 1990s.[1]

The high number of suspects attending clinics has repercussions on adherence to routine diagnostic procedures. The time reserved for counselling may be reduced, laboratory personnel may read one or two instead of three smears, there is less time for slide reading, and more attention may be paid to the chest X-ray (CXR). Moreover, the high prevalence of human immunodeficiency virus (HIV) infection among suspects influences the diagnostic process with frequent atypical presentations. Consequently, patients may be misclassified (e.g., as smear-negative instead of smear-positive) or even misdiagnosed:[3] a study in Nairobi reported that 26% of the sputum-negative patients were actually sputum smear-positive.[2] Similar observations have been made earlier, suggesting that increased laboratory workload is a major contributing factor to misclassification and misdiagnosis.[4]

We carried out a descriptive analysis of the routine diagnostic process for TB suspects in Nairobi, Kenya, and report on the efficiency of this process when compared to culture positivity as the gold standard.

METHODS

Between March 2000 and March 2001, new TB suspects (aged 15–65 years old) were enrolled from Rhodes Chest Clinic (RCC), a big diagnostic centre in Nairobi. All patients underwent the following routine diagnostic procedures: step 1—selection of TB suspects by general health staff, based on clinical symptoms such as productive cough >3 weeks; step 2—identification of patients with smear-positive TB by asking suspects to submit three sputum specimens for smear examination; step 3—identification of patients with smear-negative TB by performing a CXR in suspects whose sputum examinations were negative.[5] Patients were counselled about the diagnostic process, with emphasis on delivering three sputum specimens and having blood taken and examined for HIV.

Three specimens (spot, early morning, spot) were collected in sterile bottles. A direct smear was made from each bottle at RCC using Ziehl-Neelsen (ZN) staining, and the bottles were then sent on to the Kenya Medical Research Institute for culture, performed on Löwenstein-Jensen (LJ) slopes.[6]

Culture was used as the gold standard for TB disease and for analysing each diagnostic outcome. A

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Table 1 Yield of detection by ZN followed by X-ray from culture-positive/-negative TB suspects

Clinical diagnosis made at RCC	Total	Culture-positive	Culture-negative
Total suspects enrolled	993	554 (56%)	439 (44%)
Total diagnosed and treated for TB	660	509 (77%)	151 (23%)
Diagnosed by ZN and treated as smear-positive TB	340	332 (98%)	8 (2%)
1st specimen	176	176	0
2nd specimen	134	129	5
3rd specimen	30	27	3
Diagnosed by CXR and treated as smear-negative TB	320	177 (55%)	143 (45%)
CXR consistent for TB	168	68	100
CXR highly consistent for TB	152	109	43
Total diagnosed not having TB and not treated	333	45 (14%)	288 (86%)

Note: calculated on the basis of 993 suspects for whom all tests on three specimens could be interpreted and X-ray was available.
ZN = Ziehl-Neelsen; RCC = Rhodes Chest Clinic; CXR = chest X-ray

patient with at least one positive culture out of three cultures was regarded as a 'proven' TB case, while a patient with three negative culture results was regarded as not having TB. In cases where the diagnosis could not be made with certainty (e.g., when cultures were contaminated) patients were excluded from the analysis.

The CXR was performed and read by the RCC radiologist, who was blinded to the laboratory results. Readings were categorised using the following four-point scoring system: 1) no pathology, 2) pathology not consistent with TB, 3) pathology consistent with TB, and 4) pathology highly consistent with TB.

The clinical diagnosis was made by the clinical officer according to the guidelines of the National Tuberculosis and Leprosy Programme (NTLP):[5] smear-positive TB when at least one of the three smears was positive for ZN, and smear-negative TB when three sputum smears were negative for ZN and the CXR result was consistent with TB.

Data were entered into a computer database, and statistical analysis was carried out using Epi-Info (CDC, Atlanta, GA) and SPSS software (SPSS Inc, Chicago, IL).

RESULTS

In total, 1398 suspects were enrolled. For 169, a third culture result was missing, while for another 236 CXR results were not available. Data were complete for 993 (71%) suspects. HIV seroprevalence, which was known for 34% of the suspects, was significantly higher among women (56%) than among men (34%) ($P < 0.05$). Of the total 554 (56%) culture-positive and 439 (44%) culture-negative patients, 660 (66%) were clinically diagnosed with TB (Table 1).

The routine diagnostic process detected 509 (92%) of the culture-positive cases: 332 (60%) by ZN examination (real smear-positive patients) and 177 (32%) by CXR (real smear-negative patients). Of the ZN-positive cases, 176 (53%) were detected by the first specimen, 36% by the second early morning specimen and 8% by the third specimen. The entire diagnostic process missed 45 (8%) culture-positive cases (under-diagnosis). Of the 439 culture-negative patients, 151 (34%) were diagnosed with TB (over-diagnosis): 2% as smear-positive TB by ZN and 32% as smear-negative TB based on CXR.

The sensitivity and specificity were respectively 92% and 66% for the entire diagnostic process, 60% and 98% for ZN microscopy and 80% and 67% for CXR (on smear-negative suspects) (Table 2). The latter values on CXR changed significantly when only the score 'highly consistent with TB' was used (49% and 90%).

Logistic regression on all suspects showed that the probability of a positive culture was higher for men than for women (adjusted odds ratio [aOR] 0.64; $P < 0.001$); it decreased with age ($P < 0.001$), and was slightly higher among HIV-positive patients (aOR = 1.51; $P = 0.09$). Similarly, a positive smear was more

Table 2 Test characteristics under routine circumstances using culture as gold standard

Test system	*n**	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Pre-test probability (%)	PPV (%)	NPV (%)
The entire screening process	993	92 (90–94)	66 (63–69)	56 (53–59)	77 (75–80)	86 (84–89)
ZN (result: any positive) on all suspects	993	60 (57–63)	98 (97–99)	56 (53–59)	98 (97–99)	66 (63–69)
CXR on suspects, excluding those who were ZN-positive						
Result: consistent or highly consistent for TB	653	80 (77–83)	67 (63–70)	34 (30–38)	55 (51–59)	86 (84–89)
Result: highly consistent for TB	653	49 (45–53)	90 (88–92)	34 (30–38)	72 (68–75)	77 (74–81)

* 993 all suspect patients, 653 suspects excluding those who were ZN-positive.
CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; ZN = Ziehl-Neelsen; CXR = chest X-ray.

likely in males (aOR = 0.55; $P < 0.001$), in younger age groups ($P < 0.01$), but not in HIV-positive patients (aOR = 1.86; $P = 0.57$). When restricted to smear-negative TB suspects only, HIV was a risk factor for a positive culture (aOR = 2.27; $P = 0.02$).

DISCUSSION

The results show that a high proportion of TB suspects (over 50%) were culture-positive. A high proportion (66%) were also placed on TB treatment, which reflects the high proportion of culture-positives, but also the problem of over-diagnosis in relation to culture positivity.

The proportion of cases among suspects differs according to the type of clinic; in rural clinics it might be 10%–20%, while in specialist chest clinics it is usually higher. Laboratory reports for the whole of Kenya indicated that 19% of TB suspects had a positive smear; for Nairobi this was as high as 22%.[1] Assuming that a similar proportion of suspects might truly have smear-negative TB, the proportion of suspects with culture-positive TB could be around 40%. The 56% of suspects with culture-positive TB found in our study is therefore rather high.

The routine diagnostic process as practised at RCC, ZN combined with CXR, was very sensitive, identifying 92% of all culture-positive cases. Even if, due to poorer services, ZN had detected fewer patients, the high sensitivity of CXR would still result in a high detection rate.

The sensitivity of ZN microscopy based on three sputum smears was 60% (95% confidence interval [CI] 57%–63%). This proportion can be considered as optimal under routine circumstances, and is comparable with other reports.[6,7] The majority of smear-positive patients (53%) were detected by the first spot smear examination, while the second smear yielded almost 40% of patients and the third spot smear contributed the remaining 8%.

One of the concerns was the frequency of over-diagnosis; 23% (151/660) of the patients who were treated for TB were culture-negative. As expected, over-diagnosis of smear-positive TB cases was low (2%, 8/340), but among smear-negative patients it was very high (45%, 143/320). It was also higher among women ($P = 0.026$) and among HIV-positive patients ($P = 0.048$). In an HIV-prevalent environment, the threshold for diagnosis of TB is probably rather low.

To make a diagnosis of smear-negative TB, the physician relies mainly on CXR; interpretation depends on the quality of the picture and the reading skills of the interpreter. The sensitivity of the combined CXR scores (consistent and highly consistent for TB) was 80%, but the specificity was low (67%), resulting in over-diagnosis.

It may be possible to reduce the rate of over-diagnosis by using only the CXR result 'highly consistent for TB'. However, this would compromise the sensitivity and therefore increase under-diagnosis. Other ways of reducing rates of over-diagnosis include 1) narrowing down the selection criteria for patients eligible for CXR, and 2) postponing the CXR examination until there has been no response to a course of non-specific antibiotics. In big clinics like RCC, such organisational changes are complicated, with the attendant risk that patients will drop out. A more feasible option is to improve the specificity of CXR by establishing a quality control system for CXR reading, as is already practised for microscopy. Finally, counselling could be improved and patients could be urged to return if complaints persist.

Whether all culture-negative patients placed on treatment really did not have TB is questionable. In the early stages, TB may give CXR abnormalities in the absence of a positive culture. In the Netherlands, around 8% of pulmonary TB cases are culture-negative.[8] Furthermore, we used positive culture on LJ medium as the gold standard. Although more sensitive methods exist, such as BACTEC, differences in recovery between these methods are not very high (10%–20%).[9] It is therefore possible that the real proportion of over-diagnosis was probably somewhat lower than the 45% reported. Nevertheless, over-diagnosis remains an issue of concern.

The diagnostic process missed 8% (45/554) of the culture-positive cases (under-diagnosis), because CXR failed to detect TB. This has been observed before, especially in HIV-positive patients.[10] The fact that culture-positive cases are missed is inherent to the screening process, but is nevertheless a concern. To subject all suspects to culture (gold standard) would be impossible. Applying these results to the whole of Kenya would mean that over 5000 culture-positive cases are missed annually. This indicates the importance of repeating examinations when complaints persist.

CONCLUSIONS

The entire routine diagnostic process at RCC is very sensitive: 92% of the culture positive cases were identified—over 50% by ZN, the remainder by CXR. Nevertheless, 8% are missed. The specificity of the diagnostic process is rather low (66%): 23% of the total and 44% of the smear-negative patients were culture-negative, and may have been wrongly diagnosed. To prevent over-diagnosis, improvements might be made by narrowing down the criteria for CXR and improving the quality of CXR reading. Improving counselling and urging patients to return when complaints persist can prevent under-diagnosis.

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RÉSUMÉ

Des sujets suspects de TB fréquentant la Clinique Thoracique de Rhodes, à Nairobi, Kenya, ont subi trois examens de microscopie des expectorations (Ziehl-Neelsen) ainsi qu'une radiographie thoracique (CXR). Les résultats ont été comparés avec les cultures sur milieu de Löwenstein-Jensen servant d'étalon pour établir l'efficience du processus de diagnostic appliqué en routine. Sur 1.398 suspects de TB, tous les tests de laboratoire ainsi que les CXR étaient disponibles pour 993 (71%). Parmi ce groupe, la culture a été positive chez 554 (56%). Le processus de diagnostic de routine était sensible, et a permis de détecter 92% des cas positifs à la culture, mais 8% ont échappé. La spécificité était basse (66%), et 23% des patients mis sous traitement avaient une culture négative, surtout en raison de la faible spécificité du CXR. Pour améliorer l'efficience du processus du diagnostic, on pourrait rendre plus sévères les critères pour le CXR, améliorer la qualité de la lecture des CXR, et encourager les patients à revenir lorsque leurs plaintes persistent.

RESUMEN

Sujetos sospechosos de TB que asisten al Dispensario de Enfermedades Respiratorias de Rhodes, Nairobi, Kenya, hubieron tres exámenes de esputo (Ziehl-Neelsen) y radiografía de tórax (CXR). Se compararon los resultados con los cultivos en medio Löwenstein-Jensen utilizados como patrón oro para establecer la eficacia del proceso de diagnóstico de rutina. Sobre 1.398 sospechosos de TB, todos los exámenes de laboratorio realizados, así como las CXR, permitían plantear el diagnóstico en 993 (71%). En este grupo, el cultivo era positivo en 554 (56%). El proceso de detección de rutina permitía detectar el 92% de los casos con cultivo positivo, mientras que el 8% escapaban. La especificidad fue baja (66%), puesto que el 23% de los pacientes puestos en tratamiento tenían cultivo negativo, debido principalmente a la baja especificidad de la CXR. Para mejorar la eficacia del proceso de diagnóstico de rutina, se podría hacer más estrictos los criterios de la CXR, mejorar la calidad de la lectura de las placas, y insistir para que los pacientes vuelvan si las molestias persisten.