Public Health Action

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

VOL 4 NO 4 PUBLISHED 21 DECEMBER 2014

Rollout of Xpert® MTB/RIF in Northwest Cambodia for the diagnosis of tuberculosis among PLHA

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http://dx.doi.org/10.5588/pha.14.0082

Objective: To describe the implementation and utilization of the Xpert® MTB/RIF (Xpert) assay to diagnose tuberculosis (TB) among people living with the human immunodeficiency virus/acquired immune-deficiency syndrome (HIV/AIDS, PLHA) in Cambodia.

Design: Following the rollout of Xpert, an evaluation was conducted in four provinces of Cambodia from March to December 2012 to determine the utilization, performance, and turnaround time (TAT) of Xpert among PLHA. Data were collected from paper-based patient registers.

Results: Of 497 PLHA with a positive TB symptom screen, 357 (72%) were tested with smear microscopy, and 250 (50%) with Xpert; 25 (10%) PLHA tested with Xpert were positive for TB and none were rifampicin-resistant. The utilization of Xpert increased from 23% to 75%, with a median TAT of 1 day. Across districts, utilization ranged from zero to 85%, while the TAT ranged from zero to 22 days.

Conclusion: While early data show increasing utilization of Xpert for PLHA with a positive symptom screen, most patients underwent smear microscopy as an initial diagnostic test. Training delays and challenges associated with specimen referral may have contributed to variability in Xpert uptake and TAT, particularly for sites without onsite Xpert testing. Enhanced programmatic support, particularly for specimen referral and results reporting, may facilitate appropriate utilization.

In 2010, the World Health Organization (WHO) endorsed Xpert® MTB/RIF (Cepheid, Inc, Sunnyvale, CA, USA), an automated, rapid, polymerase chain reaction (PCR) based diagnostic assay for tuberculosis (TB).[1] Although numerous clinical trials and studies have shown that Xpert has high sensitivity and specificity for the diagnosis of TB and detection of rifampicin (RMP) resistance,[2–7] it is important to assess its utilization in routine program settings, given the many logistical and health systems barriers that may influence the impact of Xpert on patient care.[5,8–10]

In 2011, Cambodia's National Center for Tuberculosis and Leprosy Control (CENAT) committed to introducing Xpert into routine practice to improve TB diagnosis among prioritized populations.[11] In accordance with WHO recommendations, the initial implementation of Xpert in Cambodia focused on people living with the human immunodeficiency virus/acquired immune-deficiency syndrome (HIV/AIDS, PLHA) presumed to have TB and those presumed to have multidrug-resistant (MDR) TB, recommending Xpert as the initial diagnostic test for both populations.[12,13]

Cambodia has been designated a high TB burden country, with a TB incidence rate of 411 per 100 000 population. While 6.3% of persons with TB are HIV-infected, Cambodia has a relatively low HIV prevalence among all adults, of 0.7%.[14–16] In addition to scaling up access to Xpert for these designated populations, several active case-finding (ACF) projects have incorporated Xpert for testing contacts of TB patients and conducting community-wide TB screening.[17–19]

The US Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) and CENAT evaluated the rollout of Xpert in routine programmatic settings for the diagnosis of TB among PLHA in preparation for the planned nationwide rollout of Xpert in these settings.

METHODS

Study population

This evaluation was conducted in four provinces in northwest Cambodia (Battambang, Bantay Meanchey, Pailin and Pursat), and included routinely collected national program data for all PLHA seen at a TB clinic in the catchment area from March to December 2012. With a population of 2.2 million, these provinces comprise approximately 16% of Cambodia's population.[20] During the evaluation period, 7612 PLHA were receiving care at HIV clinics in the catchment area.[21,22] These provinces were selected by CENAT for initial Xpert rollout, given pre-existing laboratory capacity at Battambang Provincial Referral Hospital (PRH) and established networks within these four provinces of specimen referral to the Battambang PRH laboratory for TB culture. In these four provinces, we included eight operational districts, each with a district referral hospital or PRH housing a TB clinic. The nine HIV clinics distributed throughout these eight districts routinely refer patients presumed to have TB to the co-located TB clinic for diagnostic evaluation (Figure). Xpert machines were placed at the Battambang PRH, which also provides TB culture services for the region, and the Mongkol Borei PRH to provide Xpert testing services to the four provinces.[11]

Design and methods

CENAT, the CDC, and other partners modified the recording and reporting tools and developed new diagnostic algorithms to incorporate Xpert for diagnosing

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ACKNOWLEDGEMENTS
This work was financially supported by the US Centers for Disease Control and Prevention. No direct funding was received by any of the authors for this study. No other funding bodies had any role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript. The findings and conclusions of this article are those of the authors and do not necessarily represent the views of the CDC.
Disclosure: MTE and KKE are employed by the Cambodia Ministry of Health.
Conflicts of interest: No authors have any conflict of interest or financial interest in this manuscript.

KEY WORDS
program evaluation; new diagnostics; performance; tuberculosis

Received 8 August 2014
Accepted 1 October 2014

PHA2014;4(4):216–221

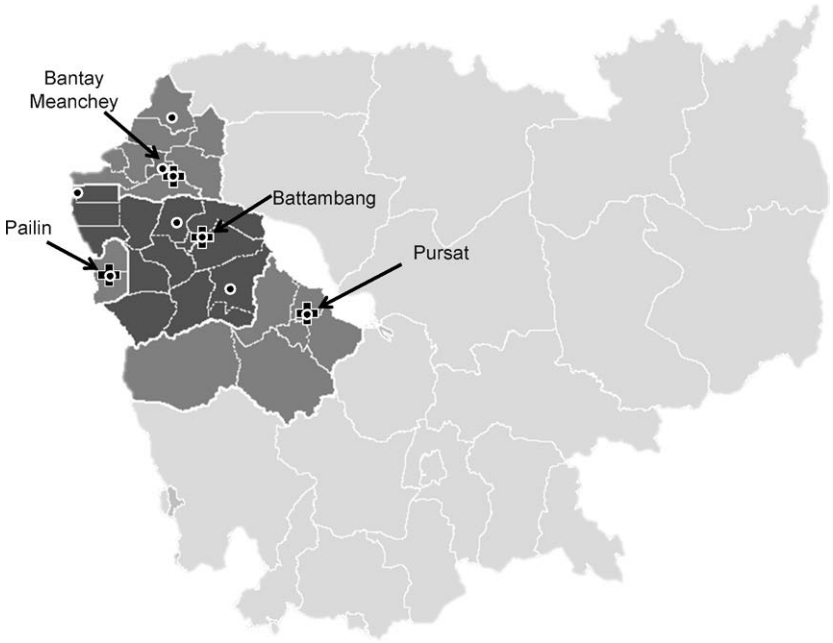

FIGURE TB-HIV co-located facilities and provincial referral hospitals in evaluation provinces and districts in Cambodia. • = TB-HIV collocated facilities; ⊕ = provincial referral hospitals; TB = tuberculosis; HIV = human immunodeficiency virus.

TB among PLHA presumed to have TB. Since 2010, national guidelines for PLHA have required screening for TB at monthly HIV clinic visits based on the presence of any fever, cough, weight loss, or >2 weeks of drenching night sweats. Guidelines recommend that patients with a positive symptom screen be referred to the TB clinic for a diagnostic evaluation.[23] Prior to Xpert rollout, diagnostic evaluation of PLHA with a positive symptom screen included a clinical evaluation, smear microscopy of three sputum specimens, chest radiograph (CXR), and TB culture if the patient was smear-negative. Most district facilities had smear microscopy and CXR on site, while TB culture was only available at Battambang PRH and CENAT's central laboratory. Under the new algorithms developed for the rollout of Xpert, eligible PLHA were to undergo a clinical evaluation, CXR, and Xpert on a single sputum specimen to replace smear microscopy. While CXR could still be performed at the district health facilities, Xpert was only available at Battambang and Mongkol Borei PRHs. According to the new algorithm, culture and drug susceptibility testing were performed only if RMP resistance was detected on the initial Xpert result. Specimens were collected from patients at the district health facilities and transported to the nearest PRH by district staff or courier. The distance from the Xpert testing to district health facilities ranged from 25 to 146 km, from Thmar Khoul and Sampov Loun, respectively.

Laboratory staff were trained in the use of Xpert modules and cartridges, specimen handling, management of invalid or error results, new recording and reporting tools, and the interpretation of results. Program staff, district and provincial TB program managers, and clinicians were trained in the new diagnostic algorithm and procedures for specimen referral.

Delays in procurement and calibration of one of the two Xpert machines led to staggered placement. On 21 February 2012, an Xpert machine was placed at the Battambang PRH, which provides TB culture services to all four northwest provinces. On 6 June 2012, a second Xpert machine was placed at the Mongkol Borei PRH laboratory, which had previously only performed smear microscopy. Collectively, these laboratories provided Xpert testing services for all eight districts.

Data sources

We collected data from three paper-based patient registers located at different levels of the health system to capture data on the diagnostic evaluation and treatment for PLHA eligible for Xpert. Several paper-based registers were newly introduced or modified for Xpert rollout in early 2012: 1) PLHA TB Suspect Registers at TB clinics co-located with HIV clinics to document the evaluation of symptom screen-positive PLHA, 2) pre-existing TB Treatment Registers at district level to capture TB treatment data for PLHA, and 3) TB Laboratory Registers modified to incorporate Xpert testing for PLHA.

Data collection and analysis

Data were collected retrospectively from paper-based registers for patients registered from March to December 2012. Register pages were photographed, and the photos were uploaded to a secure, password-protected computer. Patient-level data were entered into two password-protected databases which were reconciled to minimize entry errors. Patients were assigned a unique study ID after linking patient entries across program registers using name, age, sex, and address. The analytic data set contained no patient identifiers. Turnaround time (TAT) was defined as the interval between the date of TB screening, at which point a specimen for Xpert testing should have been collected, and the date the health facility received the Xpert test result. Data were analyzed using SAS 9.3 (Statistical Analysis Institute, Cary, NC, USA).

Ethics approval

The evaluation was reviewed by both the CDC and the director of CENAT. The CDC and CENAT determined the study to be a program evaluation and not research involving human participants; institutional review board approval was therefore not required.

TABLE 1 Demographic and baseline clinical characteristics of registered PLHA with a positive symptom screen

Demographic and clinical characteristics	*N* = 497 *n* (%)
Male	227 (46)
Age, years, median [IQR]	37 [32–45]
On ART	235 (47)
TB symptoms reported on screening*	
Cough	357 (72)
Fever	409 (82)
Weight loss	240 (48)
>2 weeks of night sweats	200 (40)

*Patients were asked about symptoms in the previous month.
PLHA = people living with HIV/AIDS; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome; IQR = interquartile range; ART = antiretroviral therapy; TB = tuberculosis.

RESULTS

Between 1 March and 31 December 2012, 497 PLHA with a positive symptom screen were recorded in the PLHA TB Suspect Registers in the four provinces. Approximately half of those registered were male, with a median age of 37 years (IQR 32–45), and 235 (47%) PLHA were on antiretroviral therapy (ART). Among patients who reported symptoms, 357 (72%) reported cough, 409 (82%) reported fever, 240 (48%) reported weight loss and 200 (40%) reported >2 weeks of night sweats (Table 1).

Xpert testing was performed for 250 (50%) of the 497 PLHA with a positive symptom screen; of those tested, 25 (10%) were positive for *Mycobacterium tuberculosis* (Table 2). Only 17 (3%) PLHA underwent Xpert as the initial diagnostic test in accordance with national guidelines. Smear microscopy was performed for 357 (72%) of the PLHA with a positive symptom screen, of whom 31 (9%) were smear-positive. Of the 353 (71%) PLHA who had a CXR, 103 (29%) had findings consistent with TB according to the reviewing clinician. Only 22 (4%) PLHA had a sputum culture performed, of whom four (18%) were positive for *M. tuberculosis* and six (27%) were positive for non-tuberculous mycobacteria (NTM). Of the PLHA with a positive symptom screen, 65 (13%) had no documented result for Xpert, smear microscopy, CXR or culture. Of those with no diagnostic evaluation recorded, one (2%) was diagnosed with smear-negative TB and six (9%) with extra-pulmonary TB (EPTB). Of the 25 Xpert tests positive for *M. tuberculosis*, 24 (96%) were susceptible to RMP, and one had an indeterminate result for RMP resistance (Table 3). All patients with a positive Xpert result were diagnosed with pulmonary TB (PTB). Only three (1%) Xpert tests were reported as invalid or indeterminate for *M. tuberculosis*.

TABLE 3 Xpert results among PLHA with a positive symptom screen

	n (%)
M. tuberculosis-positive, RMP-susceptible	24 (10)
M. tuberculosis-positive, RMP-indeterminate	1 (0)
M. tuberculosis-negative	222 (89)
Invalid/error	3 (1)
Total Xpert tests	250

PHLA = people living with HIV/AIDS; RMP = rifampicin.

The proportion of PLHA with a positive symptom screen who underwent Xpert testing increased from 23% in the second quarter to, respectively, 75% and 73% in the third and fourth quarters. The proportion of PLHA tested with Xpert varied by district, ranging from zero to 85% (Table 4). The median TAT from clinic visit to receipt of Xpert result was 1 day, although this ranged from zero to 22 days. Two sites were co-located with a laboratory performing Xpert testing; one had a median TAT of 0 days, while the other had a median TAT of 7 days. Delays in collecting specimens from patients and lack of real-time results reporting contributed to this delay. Sites that were not co-located had a median TAT of 12 days.

In program registers, a 'final diagnosis' indicates a clinical decision and patient classification based on pre-defined categories (TB ruled out, smear-positive PTB, smear-negative PTB and EPTB). A final diagnosis was recorded for 417 (84%) PLHA with a positive symptom screen, of whom 123 (29%) were diagnosed with any form of TB. Among PLHA diagnosed with TB, 34 (28%) were recorded as smear-positive PTB, 63 (51%) as smear-negative PTB and 26 (21%) as EPTB.

Among 417 PLHA with a positive symptom screen and a final diagnosis, 222 had documented results for both smear microscopy and Xpert (Table 5). Results were concordant for 204 (92%) patients; for 13 (6%) smear and Xpert were positive, while for 191 (94%) both smear and Xpert were negative. All patients with positive results for both tests were diagnosed with PTB. Of those with a negative smear and a negative Xpert test, 153 (80%) were not diagnosed with TB, four (2%) were diagnosed with EPTB and 34 (18%) were diagnosed with PTB. There were no culture results for these 34 patients, but 32 (94%) had CXR findings consistent with TB.

There were 18 discordant results between smear microscopy and Xpert, including eight (44%) patients with a positive smear and negative Xpert, eight (44%) with a negative smear and a positive Xpert and two (11%) with a negative smear and an invalid Xpert. Four (50%) patients with a positive smear and a negative Xpert had culture results available; two were found to have NTM and two had negative cultures. Of the patients with discordant results, 17 (94%) were diagnosed with PTB (Table 5).

TABLE 2 Utilization and results of TB diagnostic evaluation among PLHA with a positive symptom screen in 2012

	PLHA registered *n*	AFB+ / total sputum smears *n/N* (%)	CXR+ / total CXR *n/N* (%)*	Culture+ / total culture *n/N* (%)	Xpert+ / total Xpert *n/N* (%)
March†	22	0/8 (0)	2/8 (25)	0/0	0/0
April–June	201	12/147 (8)	46/163 (28)	3/10 (30)	12/46 (26)
July–September	159	9/113 (8)	33/129 (26)	0/7 (0)	4/120 (3)
October–December	115	10/89 (11)	22/51 (43)	1/5 (20)	9/84 (11)
Total	497	31/357 (9)	103/351 (29)	4/22 (18)	25/250 (10)

*CXR+ = CXR consistent with TB per clinician.
†The PLHA TB Suspect Registers were introduced in March 2012.
TB = tuberculosis; PLHA = people living with HIV/AIDS; AFB = acid-fast bacilli; + = positive; CXR = chest radiograph.

TABLE 4 Xpert testing and turnaround time for PLHA with a positive symptom screen from clinic visit date until the Xpert result was returned to the clinic

District	Xpert tests/ symptom screen + PLHA *n/n* (%)	TAT Median days*	TAT Range [IQR]
Battambang†	39/92 (42)	7	0–16 [1–8]
Sampov Loun	4/14 (29)	5	N/A
Mong Russey	25/53 (47)	17	0–104 [9–35]
Thmar Khoul	17/20 (85)	6	0–24 [3–12]
Mongkol Borei†‡	161/256 (63)	0	0–35 [0–1]
Thmar Puok	1/10 (10)	N/A	N/A
Sampov Meas	3/46 (7)	22	N/A
Pailin	0/6 (0)	N/A	N/A
All	250/497 (50)	1	0–104 [0–7]

*Of 250 Xpert tests, the date the Xpert result was received by the clinical site was documented for 209 (84%) patients.
†Health facilities in these operational districts were co-located with a laboratory performing Xpert testing.
‡Mongkol Borei district houses two facilities providing TB services for PLHA: Mongkol Borei Referral Hospital and Serei Siphon District Referral Hospital.
PLHA = people living with HIV/AIDS; TAT = turnaround time; IQR = interquartile range; N/A = not applicable.

TABLE 5 Diagnostic results by final diagnosis: AFB sputum smear microscopy and Xpert results among the 222 eligible PLHA with a final diagnosis recorded in program registers*

Final diagnosis	AFB+ Xpert+ *n* (%)	AFB+ Xpert– *n* (%)	AFB– Xpert+ *n* (%)	AFB– Xpert– *n* (%)	AFB– Xpert invalid *n* (%)	Total *n* (%)
Not TB	0	0	0	153 (80.1)	1 (50)	154 (69.4)
AFB+ PTB	13 (100)	8 (100)	5 (62.5)	0	0	26 (11.7)
AFB– PTB	0	0	3 (37.5)	34 (17.8)	1 (50)	38 (17.1)
EPTB	0	0	0	4 (2.1)	0	4 (1.8)
Total	13	8	8	191	2	222

*Among 417 patients with a documented final diagnosis, only 222 had documented results for both sputum smear microscopy and Xpert.
AFB = acid-fast bacilli; PLHA = people living with HIV/AIDS; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome; + = positive; – = negative; TB = tuberculosis; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis.

Limitations

Our evaluation was limited to districts offering TB and HIV services; the experience of these districts may not address issues specific to districts without existing clinical TB-HIV services or reflect the capacity of other provincial referral hospitals. This evaluation relied on routinely collected program data from CENAT registers, limiting our ability to determine whether incomplete data reflected incomplete testing or poor documentation. Very few patients underwent culture, limiting our ability to determine the incremental yield of Xpert over smear microscopy among culture-confirmed patients.

DISCUSSION

This evaluation identified a number of health system factors that may affect the impact of Xpert on patient care in northwest Cambodia, namely long TATs at some sites, low utilization of Xpert and high rates of empiric treatment. Despite the establishment of specimen referral and result-reporting mechanisms, many sites experienced delays in Xpert referral and result reporting because specimen transport could only be scheduled once a week and results were often reported only when additional specimens were delivered. In addition, due to lack of funding and personnel, five sites across three provinces experienced interruptions in specimen transport during the study period, episodically suspending Xpert testing. Where onsite testing was available, the TAT was often rapid and utilization rates high; however, even when Xpert was available on site, delays in collecting specimens from patients resulted in TATs of several days. While the utilization of Xpert increased over the course of the evaluation to 75% of eligible PLHA by the end of 2012, Xpert use varied widely across districts and did not replace smear microscopy as the initial test for most patients. Ultimately, only 3% of all eligible PLHA underwent Xpert as the initial diagnostic in accordance with national guidelines. Additional training and education for TB officers and clinicians in the new diagnostic algorithm and in reducing TATs could improve the utilization and yield of Xpert.

One suggested remedy for long TATs has been to further decentralize Xpert, placing more machines at patient point-of-care.[8] However, given the current low utilization rates at central sites, the added cost of placing machines in areas where they may not be used to capacity may lead to a higher cost per patient.[9,10,17,24] Cambodia has also explored ACF campaigns to increase access; such strategies have had variable yield and may not be sustainable for PLHA through routine service.[17–19] Depending on placement, utilization, and screening and diagnostic algorithms, Xpert can increase the cost per case of diagnosed TB by as much as US$28–151 in some settings.[24] Such costs must be weighed against the increased yield of case-finding efforts and the impact on patient outcomes to determine its desirability. A cost effectiveness analysis of Xpert in Cambodia is underway to explore per-pa-

tient costs of pre- and post-Xpert algorithms to inform future placement and testing strategies.

This evaluation found that empiric treatment for TB was high among patients without bacteriological confirmation of TB through Xpert or smear microscopy, as well as patients with discordant Xpert and smear microscopy results. Discordant results may reflect errors in the preparation and interpretation of slides, or inter-specimen variability, because smear and Xpert testing were often performed on different sputum specimens. The limited use of culture in routine practice precluded the determination of the yield of Xpert in identifying additional smear-negative TB cases. In addition, all patients with a positive smear and negative Xpert were diagnosed and treated as smear-positive PTB cases, which may indicate overtreatment of persons without active TB disease. This evaluation and previous reports[25] have found high rates of NTM in Cambodia, underscoring that Xpert may be a better initial diagnostic test than smear microscopy. The high sensitivity and specificity of Xpert over smear microscopy should enable the identification of additional, smear-negative cases and a reduction in unnecessary empiric treatment. However, these benefits may be attenuated in environments such as Cambodia with high rates of empiric treatment.[26,27]

CONCLUSION

Xpert offers an opportunity for timely and accurate initiation of anti-tuberculosis treatment in Cambodia and other high-burden settings. However, underutilization of Xpert, long turnaround times, and use of Xpert as a follow-on diagnostic may undermine the benefit of timely results with Xpert, particularly among PLHA who are at increased risk of death with a delayed TB diagnosis.[28] Strong health systems are imperative to realize the potential of Xpert, including robust specimen referral and result-reporting systems, selection of appropriate testing strategies, and careful placement of machines where they are both accessible and cost-effective.

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Objectif : Décrire la mise en œuvre et l'utilisation du test Xpert(R) MTB/RIF afin de diagnostiquer la tuberculose (TB) parmi des personnes vivant avec le VIH/SIDA (virus de l'immunodéficience humaine/ syndrome de l'immunodéficience acquise ; PLHA) au Cambodge.
Schéma : Après le déploiement du test Xpert, une évaluation a été réalisée dans quatre provinces du Cambodge entre mars et décembre 2012 afin de déterminer l'utilisation, la performance et le délai d'exécution du Xpert parmi les PLHA. Des données ont été recueillies à partir des dossiers papiers des patients.
Résultats : Sur 497 PLHA ayant une grille de symptômes de TB positive, 357 (72%) ont bénéficié d'une microscopie de frottis et 250 (50%) ont eu un test Xpert ; 25 (10%) PLHA testés par Xpert étaient positifs pour la TB et aucun n'était résistant à la rifampicine. L'utilisation du Xpert est passée de 23% à 75% avec un délai d'exécution médian d'un jour. Dans les districts, l'utilisation allait de zéro à 85% et le délai de mise en œuvre allait de zéro à 22 jours.
Conclusion : Si les données précoces montrent une utilisation croissante du Xpert chez les PLHA avec une grille de symptômes positive, la majorité des patients bénéficiait initialement d'un diagnostic par examen microscopique de frottis. Les délais de formation et les problèmes posés par l'envoi des spécimens peuvent avoir contribué à la variabilité du recours au Xpert et au délai de sa mise en œuvre, particulièrement dans les endroits dépourvus de possibilité de test Xpert sur place. Davantage de soutien aux programmes, notamment en termes d'envoi des spécimens et de retour des résultats, pourrait faciliter son utilisation appropriée.

Objetivo: Describir la introducción y la utilización de la prueba Xpert(R) MTB/RIF en el diagnóstico de la tuberculosis (TB) de las personas aquejadas de infección por el virus de la inmunodeficiencia humana (VIH) y sida (PLHA) en Camboya.
Método: Tras el despliegue de Xpert, se llevó a cabo una evaluación en cuatro provincias de Camboya de marzo a diciembre del 2012 con el fin de determinar el tipo de utilización, el rendimiento diagnóstico y el tiempo de obtención de los resultados de la prueba Xpert en las PLHA. Se recogieron los datos de los pacientes a partir de los registros en soporte de papel.
Resultados: De los 497 PLHA y una detección positiva de síntomas de la TB, en 357 casos se practicó una baciloscopia (72%) y en 250 la Xpert (50%); 25 de las personas examinadas con Xpert obtuvieron un resultado positivo (10%) y en ninguna se observó resistencia a rifampicina. La utilización de la prueba aumentó de 23% a 75% y la mediana del lapso hasta obtener el resultado fue un día. En los diferentes distritos, el uso de la prueba osciló entre 0% y 85% y el lapso hasta la notificación del resultado fue de cero a 22 días.
Conclusión: Los datos iniciales indicaron un aumento de la utilización de la prueba Xpert en las PLHA que presentan una detección positiva de síntomas de la TB, pero en la mayoría de los pacientes se practicó la baciloscopia del esputo como prueba diagnóstica inicial. Es posible que los retrasos en la capacitación y las dificultades relacionadas con la remisión de las muestras hayan contribuido a la variabilidad en la aceptación de la Xpert y en el tiempo de obtención de los resultados, sobre todo en los centros donde no se practica la prueba en el lugar de atención. Se podría fomentar el uso apropiado de esta prueba mediante un apoyo programático, dirigido especialmente a la remisión de las muestras y la notificación de los resultados.

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e-ISSN 2220-8372
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Contact: pha@theunion.org
PHA website: http://www.theunion.org/index.php/en/journals/pha
Article submission: http://mc.manuscriptcentral.com/pha