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Reliability of the MODS assay decentralisation process in three health regions in Peru

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SUMMARY

OBJECTIVE: To deliver rapid isoniazid (INH) and rifampicin (RMP) drug susceptibility testing (DST) close to the patient, we designed a decentralisation process for the microscopic observation drug susceptibility (MODS) assay in Peru and evaluated its reliability.

METHODS: After 2 weeks of training, laboratory staff processed ⩾120 consecutive sputum samples each in three regional laboratories. Samples were processed in parallel with MODS testing at an expert laboratory. Blinded paired results were independently analysed by the Instituto Nacional de Salud (INS) according to predetermined criteria: concordance for culture, DST against INH and RMP and diagnosis of multidrug-resistant tuberculosis (MDR-TB) ⩾ 95%, McNemar's $P > 0.05$, kappa index (κ) ⩾ 0.75 and contamination 1–4%. Sensitivity and specificity for MDR-TB were calculated.

RESULTS: The accreditation process for Callao (126 samples, 79.4% smear-positive), Lima Sur (n = 130, 84%) and Arequipa (n = 126, 80%) took respectively 94, 97 and 173 days. Pre-determined criteria in all regional laboratories were above expected values. The sensitivity and specificity for detecting MDR-TB in regional laboratories were >95%, except for sensitivity in Lima Sur, which was 91.7%. Contamination was 1.0–2.3%. Mean delay to positive MODS results was 9.9–12.9 days.

CONCLUSION: Technology transfer of MODS was reliable, effective and fast, enabling the INS to accredit regional laboratories swiftly.

KEY WORDS: MODS assay; decentralisation; MDR-TB; Peru

DESPITE the implementation of the DOTS strategy in 100% of health services in Peru since 1992, multidrug-resistant tuberculosis (MDR-TB) has continued to emerge, and Peru has the highest incidence of MDR- and extensively drug-resistant tuberculosis (XDR-TB) in the Americas.[1–5] In settings with highly prevalent drug-resistant TB, such as Peru, the broadening of access to rapid drug susceptibility testing (DST) against rifampicin (RMP) and isoniazid (INH) is strongly recommended in the current World Health Organization (WHO) guidelines[6] as a useful measure for controlling MDR-TB.

The microscopic observation drug susceptibility (MODS) assay has been developed and validated in Peru,[7,8] and replicated in other countries,[9–11] showing high performance. However, as rapid tests for INH and RMP DST need to be available close to patients to be useful, we decided to decentralise the MODS assay to regional laboratories in Peru.

With the participation of the Peruvian Ministry of Health, represented by the National Institute of Health (Instituto Nacional de Salud [INS]), the National TB Control Programme (NTP; Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis [ESNPCT]) and the Regional Laboratories Network in three health regions, and the Universidad Peruana Cayetano Heredia (UPCH), where MODS was developed, we designed a MODS decentralisation process with the aim of enabling regional laboratories to start delivering a highly reliable MODS service with a minimum start-up delay.

The present study presents the results of the MODS assay decentralisation process under programme conditions in the health regions of Callao, Lima Sur and Arequipa, Peru.

METHODS

Study area and participants

The health regions of Callao and Lima Sur (populations 863 793 and 1 903 527, respectively) are located in the city of Lima; both comprise mainly urban

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areas. Arequipa health region (population 1 225 791) is located in the south of Peru; Arequipa is the second most highly populated city in the country. The TB incidence rate per 100 000 population and the prevalence of MDR-TB among new TB patients for Callao, Lima Sur and Arequipa were respectively 122.2 and 10.8%, 136.3 and 10.8%, and 66.8 and 5.0%, according to the 2008 NTP report and the 2006 report of the National Surveillance of Drug Resistance in Peru, respectively.[12,13] The Lima Sur and Arequipa regional laboratories routinely perform TB culture in Ogawa media and first-line DST using the proportion method in Löwenstein-Jensen (LJ) media; the Callao regional laboratory performs culture in Ogawa and LJ media, and not DST.

Decentralisation design

The regional laboratories were first evaluated to identify their needs in terms of human resources, facilities, equipment, biosecurity and laboratory supplies. Before decentralisation, a programme to strengthen the laboratories was undertaken: adequate biosecurity (BS) was ensured (at least BS level II, with level III certified biological safety cabinets and protocols), donations for equipment and MODS supply were procured, the number of staff was increased and training was conducted at the INS and the UPCH over 2 weeks. At least one biologist and one technician in each regional laboratory were dedicated to developing the decentralisation process.

Each regional laboratory had to process at least 120 consecutive sputum samples (with the target of 80% acid-fast bacilli [AFB] smear-positive) from newly diagnosed pulmonary TB patients before initiating TB treatment. The laboratories performed concentrated Ziehl-Neelsen staining and MODS assay according to current guidelines, freely available at www.modsperu.org.

Briefly, broth cultures were prepared in 24-well tissue-culture plates (Falcon®, BD, Sparks, MD, USA), each containing decontaminanted sample, Middlebrook 7H9 broth (Difco®, BD), oleic acid, albumin, dextrose, and catalase (OADC, BD), and polymyxin, amphotericin B, nalidixic acid, trimethoprim, and azlocillin (PANTA, BD). For each sample, four wells were used: in two culture wells no drug was added, and each of the remaining two wells contained INH (0.4 μg/ml) and RMP (1 μg/ml). The cultures were examined under an inverted light microscope at a magnification of 40× on days 5, 7, 9, 11, 15, 17 and 21 after inoculation (except Saturday and Sunday). At 21 days, samples showing no growth were considered negative. To detect cross-contamination, every plate contained a third column that was not inoculated with any sample (negative control); any growth in these wells would require plate discard and re-culture of samples due to the possibility of cross-contamination. To reduce occupational exposure, plates were permanently sealed inside plastic ziplock bags after inoculation and were subsequently examined within the bag.

Positive cultures were identified by cord formation characteristic of *Mycobacterium tuberculosis* growth in liquid medium in drug-free control wells, as described previously.[7,14] Drug-resistant strains were identified when at least two colony-forming-units (cfus) were observed in a drug-containing well. The result was indeterminate if only one cfu was seen in the well. Contamination was recognised by the characteristic timing and morphology of bacterial and fungal overgrowth.

A post-decontamination back-up for each sample was processed in parallel reference MODS testing at the Laboratorio de Investigación de Enfermedades Infecciosas at UPCH, where the MODS assay was developed.[7] The MODS results of the regional laboratories and the UPCH laboratory were sent separately and blinded to the National Mycobacteria Reference Laboratory in the INS where agreement in

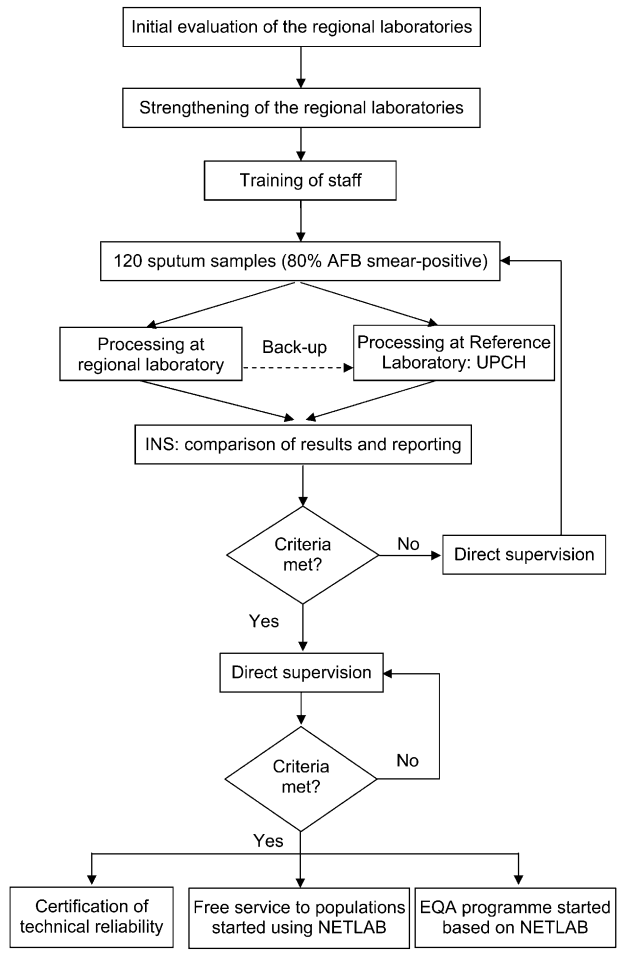

Figure 1 Decentralisation process of the MODS assay between the INS-MINSA Public Health Laboratory Network and the UPCH. AFB = acid-fast bacilli; UPCH = Universidad Peruana Cayetano Heredia; INS = Instituto Nacional de Salud of Peru; EQA = external quality assessment; MODS = microscopic observation drug susceptibility; MINSA = Ministerio de Salud.

culture, drug susceptibility and rate of contamination between UPCH and each regional laboratory were evaluated.

Each laboratory used a standard Excel spreadsheet form (Microsoft, Redmonds, WA, USA) to record their MODS results. Pre-determined criteria for successful, reliable performance were concordance for culture and susceptibility to INH and RMP of ⩾95%, McNemar's P value > 0.05, kappa index (κ) $\geqslant 0.75$ and rate of contamination between 1% and 4%. We also determined the sensitivity, specificity and predictive values for MDR-TB detection of MODS in each laboratory, using the results of the UPCH laboratory as reference.

During the accreditation period, only MODS results from the UPCH were sent to primary care practitioners in each region. The INS team subsequently performed direct supervision in each laboratory as part of the decentralisation process; resolution of any important technical issues was required prior to certification by the INS. After accreditation, the regional laboratory could initiate routine MODS service utilising the Web-based NETLAB (INS, Lima, Peru) information system for the Peruvian Laboratory Network for delivery of results and external quality assessment. The complete decentralisation design is shown in Figure 1.

Statistical analyses

Data sent to the INS in Excel spreadsheets were verified and cleaned prior to statistical analysis, which was performed using Stata version 10.1 (Statacorp, College Station, TX, USA). Between-laboratory concordance 95% confidence intervals (CIs) were calculated with McNemar P (or Exact–McNemar P for low-cell values) for paired samples, and κ indices. $P < 0.05$ was regarded as indicating a significant difference between the MODS results of the laboratories.

The protocol of the study was reviewed and approved by the INS Institutional Review Board.

RESULTS

The number of samples and the percentage of AFB smear-positive samples processed for Callao, Lima Sur and Arequipa were respectively 126 (79.4%), 130 (84%) and 126 (80%). The concordance between the UPCH laboratory and the three regional laboratories for culture, INH and RMP susceptibility and MDR-TB detection results are shown in Table 1. The global agreement for culture was 98–100%: it was 97–98% for INH susceptibility, 95–97% for RMP susceptibility, and 96.7–98% for MDR-TB detection.

The number and proportion of contaminated cultures at UPCH, Callao, Lima Sur and Arequipa were

Table 1 Verification of technical reliability in three regional laboratories and the UPCH Investigation and Development Laboratory

UPCH results	Callao (n = 126)*		Lima Sur (n = 130)†		Arequipa (n = 126)*	
Mycobacterial culture	Positive	Negative	Positive	Negative	Positive	Negative
Positive	91	0	94	0	96	0
Negative	0	26	1	17	2	20
P value‡	1.0		1.0		0.5	
Concordance, %	100		99.1		98.3	
κ index	1.0		0.97		0.94	
Isoniazid susceptibility	Resistant	Susceptible	Resistant	Susceptible	Resistant	Susceptible
Resistant	25	1	17	2	6	0
Susceptible	1	64	1	74	2	88
P value‡	1.0		1.0		0.5	
Concordance, %	97.8		96.8		97.9	
κ index	0.95		0.9		0.86	
Rifampicin susceptibility	Resistant	Susceptible	Resistant	Susceptible	Resistant	Susceptible
Resistant	21	1	13	2	5	0
Susceptible	2	67	3	76	3	88
P value‡	1.0		1.0		0.25	
Concordance, %	96.7		94.7		96.9	
κ index	0.91		0.81		0.75	
MDR-TB detection	MDR-TB	Non-MDR-TB	MDR-TB	Non-MDR-TB	MDR-TB	Non-MDR-TB
MDR-TB	19	1	11	1	5	0
Non MDR-TB	2	69	2	80	2	89
P value‡	1.0		1.0		0.5	
Concordance, %	96.7		96.8		97.9	
κ index	0.91		0.86		0.82	
Sensitivity, % (95%CI)	95 (85.5–100)		91.7 (76–100)		100 (100–100)	
Specificity, % (95%CI)	97.2 (93.3–100)		97.6 (94.2–100)		97.8 (94.8–100)	
PPV, % (95%CI)	90.5 (77.9–100)		84.6 (65.0–100)		71.4 (38.0–100)	
NPV, % (95%CI)	98.6 (95.8–100)		98.8 (96.4–100)		100 (100–100)	

*8 cultures were not comparable with UPCH results (2 due to contamination and 6 due to indeterminate results).
†18 cultures were not comparable with UPCH results (9 due to contamination and 9 due to indeterminate results).
‡McNemar.
UPCH = Universidad Peruana Cayetano Heredia; MDR-TB = multidrug-resistant tuberculosis; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

Table 2 Comparison of laboratory processing time of MODS assays with positive culture results between the regional laboratories and the UPCH laboratory by smear result

Smear results	*n**	Regional laboratories mean ± SD days	UPCH laboratory mean ± SD days	*P* value†
Negative	6	8.63 ± 1.37	8.17 ± 2.4	0.52
Positive +	130	10.1 ± 3.76	8.55 ± 3.19	0.0004
Positive ++	80	8.58 ± 3.2	7.93 ± 3.19	0.026
Positive +++	78	8.08 ± 2.61	7.18 ± 2.29	0.026
Total	296	9.16 ± 3.45	8.04 ± 3.02	<0.001

*Positive culture in regional laboratories.
†Wilcoxon matched pairs signed-rank test.
MODS = microscopic observation drug susceptibility; UPCH = Universidad Peruana Cayetano Heredia; SD = standard deviation.

respectively 14 (2.7%), 1 (0.8%), 3 (2.3%) and 2 (1.6%). No cross-contamination was detected. Time to culture positivity of smear-positive samples was marginally shorter (<1 day) at UPCH; mean time to positive MODS results (for all smear-positive and -negative samples taken together) was 8 ± 3.02 days for UPCH and 9.16 ± 3.45 days for the regional laboratories ($P < 0.001$; Table 2). Of the 58 smear-negative samples, six (10.34%) had positive MODS results at a regional laboratory.

The time required to complete the decentralisation process, including accreditation, was respectively 94, 97 and 173 days for Callao, Lima Sur and Arequipa. This culminated in INS certification of the technical reliability of the MODS assay in all three regional laboratories, which were able to implement free services for their regions using NETLAB. Complementary educational interventions for health care providers were undertaken in the three regions, and posters and leaflets were distributed to educate patients about the availability of this rapid diagnostic TB test (Figure 2).

Figure 2 Poster promoting universal access to rapid testing for MDR-TB in pulmonary TB patients in Callao, Lima Sur and Arequipa, Peru. MDR-TB = multidrug-resistant tuberculosis.

Translation: Health care centre. "If you have been diagnosed with TB, beware! It could be drug-resistant." "Before starting treatment, ask for the rapid TB test to check for drug-resistant TB." "Rapid testing is free. Ask for it at your local health care clinic or hospital." "Remember: drug-resistant TB is curable if it is diagnosed early."

DISCUSSION

We were able to decentralise the MODS assay to regional laboratories in the Peruvian Public Laboratory Network under reliable criteria and operational conditions. Considering the implications of early, accurate MDR-TB diagnosis for appropriate treatment and improved clinical outcome, it is important to guarantee the most accurate diagnosis in the shortest time possible. Timely diagnosis of new cases of MDR-TB has been shown to improve the clinical outcomes of these patients,[15] and mathematical models have shown that the expansion of currently available culture and DST services is likely to have a important impact on the control of MDR-TB and TB in developing countries.[16] For these reasons, we believe that the MODS assay should improve the outcome of these patients, and in the medium to long term contribute significantly to MDR-TB control in Peru. Following certification by the INS, the regional laboratories started delivery of free MODS services for all pulmonary TB patients before treatment in the three regions.

In view of the in-house nature of the current non-commercial MODS assay, it was necessary to develop a robust but agile process for decentralising MODS in developing countries that permitted accurate definition of the technical performance of the new MODS laboratories without the need to undertake a completely new evaluation of assay performance at each new site. The time required to complete the decentralisation process was 3 months in the Lima regions and 6 months in Arequipa, due to the lower TB incidence in Arequipa.

In addition to rapid direct DST for INH and RMP, the liquid-culture MODS assay can be used to diagnose both pulmonary and extra-pulmonary TB in patients with or without the human immunodeficiency virus,[17–19] as well as in treatment follow-up; however, due to limitations in laboratory capacity and funding, post-accreditation focused only on the use of MODS for the detection of MDR-TB in pulmonary

TB patients prior to starting treatment, regardless of sputum smear status. The education campaigns thus reflected only this specific use of MODS, although it is clear that continuing education and monitoring of use in the field are necessary to avoid laboratories becoming overwhelmed by requests for MODS testing for this wider range of potential proven indications.

The marginal difference in the delay before MODS cultures were regarded as positive reflects experience in plate-reading; delays fall when laboratories start to perform MODS frequently.

The main limitation in the design of this process was the small number of drug-resistant isolates, which resulted because the samples were collected consecutively and non-selectively. However, this did not affect the outcomes because the purpose was not to undertake yet another evaluation of MODS against other DST methods, as has already been done repeatedly with several reference DST methods, such as the LJ proportion method,[8,20] proportion in agar 7H10 in plates,[9,21] MB BacT[8] and MGIT media.[22] This intervention differs from the WHO/IUATLD Supranational Reference Laboratory Network processes as they work with strains (culture) and not with samples,[23] as MODS and other direct tests need to achieve an appropriate number of certified resistant strains for quality control. As we needed to perform decentralisation in the shortest possible time, we had to work with patient samples before they received TB treatment; as MDR-TB prevalence is 10% in Lima and Callao and 5% in other provinces, we expected only 12 MDR-TB patients from 120 samples and six from Arequipa. This problem could have been overcome if sputum samples with known susceptibility to INH and RMP from banks had been used. Unfortunately, this type of bank is not available internationally, and creation of our own bank would require considerable time. This problem would be encountered in countries with MDR-TB prevalence similar to or lower than that in Peru, but it may be more manageable in settings with prevalence exceeding 20% in never-treated cases.

The present intervention constitutes an excellent example of integration between the national health care system, the university and the support of international agencies. The validity of this approach to laboratory accreditation (using MODS performed at an expert laboratory as the reference) was demonstrated using a molecular assay (Genotype® MTBDR-plus, Hain Lifescience, Nehren, Germany) in work previously reported in this *Journal*.[24] New devices are currently being created to replace the conventional inverted microscope to allow manual or digital evaluation, and tele-diagnosis through the internet is under development.[25]

Finally, this design is transferable to similar settings elsewhere to quickly evaluate the technical reliability of laboratories for implementation of this and other new rapid tests. An external quality assurance programme is currently in place in the three regions included in this study; we hope to continue to decentralise the assay to other regions and major hospitals in Peru, where TB and drug-resistant TB are serious problems and where the need is greatest.

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RÉSUMÉ

OBJECTIF : Afin de permettre des tests de sensibilité (DST) rapides et proches des patients pour l'isoniazide (INH) et la rifampicine (RMP), nous avons élaboré au Pérou un processus de décentralisation du test de l'observation microscopique des milieux de culture (MODS) et évalué sa fiabilité.

MÉTHODES : Après 2 semaines de formation, le personnel du laboratoire a traité ⩾120 échantillons de crachats consécutifs dans chacun des trois laboratoires régionaux ; les échantillons ont été traités parallèlement avec le test MODS dans un laboratoire spécialisé. Des résultats aveugles appariés ont été analysés indépendamment par l'Instituto Nacional de Salud (INS) en fonction de critères prédéterminés : concordance avec la culture, avec le DST pour INH et RMP et avec le diagnostic de tuberculose multirésistante (TB-MDR) ⩾ 95%, *P* de McNemar > 0,05, index kappa (κ) ⩾ 0,75 et taux de contamination 1% à 4%. On a calculé la sensibilité et la spécificité à l'égard de la TB-MDR.

RÉSULTATS : Le processus d'accréditation pour Callao (126 échantillons, 79,4% de bacilloscopie positive des frottis), Lima Sud (130, 84%) et Arequipa (126, 80%) a pris respectivement 94, 97 et 173 jours. Les critères prédéterminés dans l'ensemble des laboratoires régionaux ont été supérieurs aux valeurs attendues. La sensibilité et la spécificité pour la détection de la TB-MDR dans les laboratoires régionaux ont été >95%, à l'exception de la sensibilité à Lima Sud, qui a été de 91,7%. Le taux de contamination a été de 1,0 à 2,3%. Le délai moyen avant les résultats positifs du MODS a été de 9,9 à 12,9 jours.

CONCLUSION : Le transfert de technologie du MODS est fiable, efficient et rapide, permettant à l'INS d'accréditer rapidement les laboratoires régionaux.

RESUMEN

OBJETIVO: Con la intención de que las pruebas de susceptibilidad (DST) rápida a isoniacida (INH) y rifampicina (RMP) estén más cerca al paciente, diseñamos en el Perú un proceso de descentralización de la prueba de susceptibilidad a drogas por observación microscópica (MODS) y evaluamos su fiabilidad.

METODOS: El personal de cada uno de los tres laboratorios regionales, luego de 2 semanas de entrenamiento, procesó ⩾120 muestras consecutivas de esputo. Las muestras fueron procesadas en paralelo por un laboratorio experto que sirvió de referente. Los resultados pareados y ciegos fueron analizados independientemente por el Instituto Nacional de Salud (INS) de acuerdo a criterios predeterminados: concordancia para cultivo, susceptibilidad a INH y RMP y diagnóstico de TB-MDR ⩾ 95%, valor de *P* de McNemar > 0,05, índice kappa (κ) ⩾ 0,75 y una contaminación entre 1% y 4 %. Se calculó la sensibilidad y especificidad para la detección de TB-MDR.

RESULTADOS: El proceso para acreditar los laboratorios regionales de Callao (126 muestras, 79,4% frotis positivo), Lima Sur (130, 84%) y Arequipa (126, 80%) tomó 94, 97 y 173 días. En todos los laboratorios regionales los criterios predeterminados tuvieron valores superiores a los esperados. La sensibilidad y especificidad de los laboratorios regionales para detectar TB-MDR estuvieron >95%, excepto la sensibilidad en Lima Sur, que fue de 91,7%. La contaminación varió entre 1% y 2,3%. El promedio para obtener un resultado positivo de la prueba MODS varió entre 9,9 y 12,9 días.

CONCLUSION: La transferencia tecnológica de la prueba MODS fue fiable, efectiva y rápida, permitiendo al INS una acreditación oportuna de los laboratorios regionales.