Impact of point-of-care implementation of Xpert® MTB/RIF: product vs. process innovation

S. G. Schumacher,*† B. Thangakunam,‡ C. M. Denkinger,*†§ A. A. Oliver,‡ K. B. Shakti,‡ Z. Z. Qin,*†
J. S. Michael,¶ R. Luo,# M. Pai,*† D. J. Christopher‡

*McGill University Department of Epidemiology & Biostatistics, Montreal, †McGill International TB Centre, Montreal, Quebec, Canada; ‡Department of Pulmonary Medicine, Christian Medical College Vellore, India; §Division of Infectious Disease, Beth Israel Deaconess Medical Centre, Boston, Massachusetts, USA; ¶Department of Microbiology, Christian Medical College, Vellore, India; #Department of Pathology, Stanford University, Stanford, California, USA

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BACKGROUND: Both product innovation (e.g., more sensitive tests) and process innovation (e.g., a point-of-care [POC] testing programme) could improve patient outcomes.

OBJECTIVE: To study the respective contributions of product and process innovation in improving patient outcomes.

DESIGN: We implemented a POC programme using Xpert® MTB/RIF in an out-patient clinic of a tertiary care hospital in India. We measured the impact of process innovation by comparing time to diagnosis with routine testing vs. POC testing. We measured the impact of product innovation by comparing accuracy and time to diagnosis using smear microscopy vs. POC Xpert.

RESULTS: We enrolled 1012 patients over a 15-month period. Xpert had high accuracy, but the incremental value of one Xpert over two smears was only 6% (95%CI 3–12). Implementing Xpert as a routine laboratory test did not reduce the time to diagnosis compared to smear-based diagnosis. In contrast, the POC programme reduced the time to diagnosis by 5.5 days (95%CI 4.3–6.7), but required dedicated staff and substantial adaptation of clinic workflow.

CONCLUSION: Process innovation by way of a POC Xpert programme had a greater impact on time to diagnosis than the product per se, and can yield important improvements in patient care that are complementary to those achieved by introducing innovative technologies.

KEY WORDS: tuberculosis; diagnostic test; process assessment

THE GLOBAL BURDEN of tuberculosis (TB) remains considerable, with almost 9 million new cases and 1.5 million deaths each year.[1] An estimated 3 million cases went undiagnosed or unreported in 2013.[1] This is thought to be due in part to the shortcomings of the conventional diagnostic tests: smear microscopy is insensitive and cannot detect drug resistance, while culture results frequently do not influence treatment decisions and patients are lost to follow-up before culture results become available.[2–4] The Xpert® MTB/RIF assay (Cepheid Inc, Sunnyvale, CA, USA) is more sensitive than smear microscopy, can also detect rifampicin (RMP) resistance and provides results within 2 h.[5,6] This makes it a promising tool both to increase diagnostic yield and for implementation in point-of-care (POC) testing programmes,[7–9] which may reduce pre-treatment loss to follow-up.[10]

The accuracy of Xpert in the diagnosis of adult pulmonary TB has been studied extensively;[11] however, accuracy is only a surrogate measure for patient-important outcomes such as reduced time to diagnosis or improved treatment decisions.[12,13] More direct evidence that a new test will benefit patients is important for decisions about scale-up,[12] as the impact of a test might be heavily dependent on context and implementation strategy.[14–17] Two randomised controlled trials recently compared treatment initiation with Xpert vs. smear microscopy,[18,19] and showed that increased sensitivity might not directly translate into proportional improvements in patient-important outcomes.

The effect of different Xpert implementation strategies to maximise patient outcomes and cost-effectiveness has been modelled,[14,16,17,20] but empirical data are limited. Few studies have evaluated

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SGS and BT contributed equally to this article.

Xpert use in a POC programme, and no study to date has directly compared routine, laboratory-based implementation with POC implementation of Xpert.[18,21–23]

We aimed to assess 1) the impact of product innovation by evaluating the technical performance of Xpert performed outside of a routine laboratory by a minimally trained health worker compared to smear microscopy and liquid culture, and 2) the impact of process innovation by evaluating the effect of implementing Xpert within a POC programme compared to its use as a routine laboratory test on reductions in diagnostic delay.

METHODS

Setting and study population
The study was performed at the Christian Medical College Hospital (CMC) in Vellore, India. We included patients aged ⩾18 years who presented with cough of ⩾2 weeks or other symptoms suggestive of pulmonary TB at the pulmonary out-patient clinic. All routine testing was performed in the Department of Microbiology at CMC, which is accredited through the Indian Revised National TB Control Programme (RNTCP). The department has offered routine Xpert testing since August 2012, and has participated in several international, multicentre studies.[5]

Point-of-care programme
Between March 2013 and June 2014, we implemented a POC programme for Xpert testing. We deployed a new four-module Xpert machine near the pulmonary out-patient clinic, aiming to reduce diagnostic delays and enable same-day diagnosis and treatment initiation. Xpert was performed by an operator with no previous laboratory training who received 2 days of training on biosafety and Xpert testing procedures. Care delivery in the POC programme involved 1) expedited sample receipt and transport, 2) rapid testing of the sample upon arrival at the POC laboratory, 3) rapid reporting of test results by calling the physician's mobile phone, and 4) rapid follow-up of patients to communicate test results and initiate treatment for TB in Xpert-positive patients.

Study design
We performed 1) a cross-sectional study to assess the impact of product innovation and 2) a pre/post-implementation study to assess the impact of process innovation. Ethics approval was obtained from the institutional review boards of the Christian Medical College in Vellore, India, and McGill University Health Centre in Montreal, QC, Canada. Consent was obtained from all prospectively enrolled patients, and was waived for use of de-identified data from historic, routine medical records.

Impact of product innovation: cross-sectional study of Xpert
The cross-sectional study involved measuring improvements in patient care achieved by the implementation of Xpert compared to existing tests. The impact of product innovation was measured by assessing the diagnostic accuracy of Xpert for the detection of *Mycobacterium tuberculosis* and RMP resistance compared to liquid and solid culture, and the incremental value and time to diagnosis compared to smear microscopy. Time to diagnosis was defined as the interval between the day the patient presented with TB symptoms and the day the test results were communicated to the patient.

Participants were asked to provide a spot sputum sample on which Xpert and routine testing via direct fluorescence microscopy and liquid (MGIT™ 960™, BD, Sparks, MD, USA) and solid culture (Löwenstein-Jensen) were performed. Additional samples were obtained per routine clinical care for second and third sputum smears on subsequent days. Positive cultures underwent drug susceptibility testing (DST) using both liquid (MGIT SIRE) and solid culture. If patients were unable to expectorate spontaneously, an induced sputum sample was obtained using nebulised hypertonic saline (3%).

Impact of process innovation: pre/post implementation study of the POC programme
The pre/post implementation study involved measuring reductions in diagnostic delay achieved through changes in care delivery (a POC testing programme). The impact of process innovation was measured by comparing the median time to diagnosis before (routine Xpert) and after the implementation of the POC programme (POC Xpert). We defined pre-test processes as those involving sample submission and transport; laboratory processes as those involving sample reception in the laboratory, test procedures and result recording; and post-test processes as those involving reporting to physicians and patient follow-up. We also obtained time to treatment initiation through direct contact and self-report during the POC Xpert phase.

A line listing of all eligible patients from the routine Xpert phase was obtained for the period between October 2012 and February 2013 and a random sample of 120 patients was drawn using the procedure for simple random sampling in STATA, version 12 (StataCorp, College Station, TX, USA). For these patients, test results were obtained from electronic medical records and dates of patient visits as well as basic clinical and demographic information via chart abstraction.

Statistical analysis
The diagnostic accuracy of Xpert was assessed comparing to one liquid and one solid culture as

Table 1 Point-of-care study population*

Variables	n (%)
Participants total	1012
Age group, years	
18–29	177 (17)
30–49	391 (39)
50–69	376 (37)
70–120	68 (7)
Sex	
Female	303 (29)
Male	709 (71)
Cough	
Yes	933 (93)
No	68 (7)
Fever	
Yes	439 (44)
No	564 (56)
Weight loss	
Yes	500 (50)
No	501 (50
Haemoptysis	
Yes	353 (35)
No	648 (65)
Night sweats	
Yes	103 (10)
No	896 (90)
State of permanent residence	
Tamil Nadu	402 (41)
Other	578 (59)
Previous tuberculosis	
Yes	316 (31)
No	671 (66)
Induced sputum	
Yes	283 (28)
No	729 (72)

* Percentages are given out of total with known values; numbers may not add up to 1012 due to missing values; percentages do not add up to 100% due to rounding errors.

reference standard. Incremental value of Xpert over smear microscopy was calculated as the number of true-positives by Xpert minus the number of true-positives by smear microscopy divided by the number of positive culture results. Assessment of accuracy and incremental value excluded contaminated cultures, failed Xpert tests and smear-positive culture-negative test results. Plots of the Kaplan-Meier estimator were used to compare cumulative time to diagnosis.[24] Confidence intervals (CIs) around the difference in median time to diagnosis were calculated with the non-parametric bootstrap.[25] All statistical analyses were conducted using STATA.

RESULTS

Study population

We prospectively enrolled 1012 consecutive, eligible patients between March 2013 and June 2014 for testing under the POC testing programme. The median age was 47 years (interquartile range [IQR] 34–60); 29% were female and most patients came from outside the province (Table 1). Many patients had symptoms suggesting relatively late-stage disease, with 17% testing culture-positive, of whom 76% were smear-positive. Almost a third of patients (31%) had been treated for TB previously and 19% reported having diabetes. More than a quarter (28%) were unable to expectorate spontaneously and underwent sputum induction. Only 50% of participants reported ever undergoing human immunodeficiency virus testing, and only 2% of those tested reported having received a positive result.

Impact of product innovation: Xpert

The sensitivity and specificity of Xpert for *M. tuberculosis* detection were respectively 85% (95%CI 78–90) and 97% (95%CI 96–98). While specificity did not vary between subgroups, sensitivity was lower in smear-negative and induced sputum samples (Table 2). Culture detected seven cases of RMP resistance and Xpert sensitivity for the detection of RMP resistance was 100% (95%CI 59–100), while specificity was 96% (95%CI 91–99). The incremental value of Xpert over smear microscopy was 6% (95%CI 3–12) when considering all available smear results (median number of smear results

Table 2 Diagnostic accuracy of Xpert® MTB/RIF compared to cultures*

Analysis	Sensitivity % (95%CI)	Specificity % (95%CI)
Overall	85 (78–90)	97 (96–98)
By smear status		
Smear-positive	95 (85–99)	—
Smear-negative	55 (32–77)	97 (95–99)
By sample type		
Spontaneous expectoration	90 (83–95)	98 (96–99)
Induced sputum	69 (50–84)	95 (91–98)

* As results from samples that tested positive on smear and negative on culture (n = 29) were excluded from the accuracy calculation, there is no specificity estimate in the smear-positive subgroup. Of 14 samples initially invalid on Xpert, we obtained a valid result for 13 on repeat testing; 2–3% of cultures were contaminated on both MGIT™ and Löwenstein-Jensen, and these were excluded from the analysis. Simultaneous stratification by smear status and sample type was omitted, as small cell numbers would lead to large imprecision in sensitivity estimates for Xpert, making meaningful inference impossible.
CI = confidence interval.

per patient was 2, IQR 2–3). The incremental value over the first smear only was 11% (95%CI 5–20).

During the pre-POC programme implementation period, i.e., when Xpert was performed in the microbiology department, the median time to diagnosis was 6 days (IQR 4–7.5) in patients who underwent smear microscopy only and 6.5 days (IQR 4–10) in patients who underwent both smear microscopy as well as Xpert (Figure, Panel A). Only 2% of patients received an Xpert result within 1 day of testing (15% by day 2 and 62% by day 7).

Impact of process innovation: POC programme

The POC programme reduced the median time from presentation at the hospital to communication of Xpert test results to patients to 1 day (IQR 0–1). This is a reduction by 5.5 days (95%CI 4.3–6.7) compared to routine Xpert testing, and a reduction of 5 days (95%CI 3.8–6.2) compared to routine smear microscopy. The reduction was due mostly to lower post-testing delays and also to the reduced turnaround time in the laboratory and pre-testing delay (Table 3).

With the implementation of the POC programme, 32% of patients were provided with their Xpert test result on the day of presentation. This proportion increased to 75% and 89% on the subsequent 2 days (Figure, Panel B). The delay of 1 or 2 days was mostly due to samples being submitted in the afternoon (40%); the test results were thus sent to the DOTS clinic the following morning.

We were able to obtain the date of treatment initiation in 112 of 185 patients who tested positive on Xpert during the POC programme period. For these patients, the median time to anti-tuberculosis treatment initiation after receipt of test results was 3 days (IQR 1–8). All Xpert-positive patients were prescribed anti-tuberculosis medication at their visit to the DOTS clinic and initiated treatment either on the same day (23%) or when they reached their local DOTS centre (77%). Some of the delay was due to doctors deferring treatment initiation until results from liver function tests were available.

DISCUSSION

This study demonstrates that process innovation (e.g., in the form of a POC programme) can be more effective in reducing time to diagnosis than product innovation (e.g., a rapid test). In the study setting, the implementation of the POC programme reduced the time to diagnosis by about 6 days, while time to diagnosis remained unchanged when simply switching from smear-based to Xpert-based diagnosis. POC implementation of Xpert was feasible but required additional resources as well as substantial adaptation of clinic workflow procedures. However, the POC
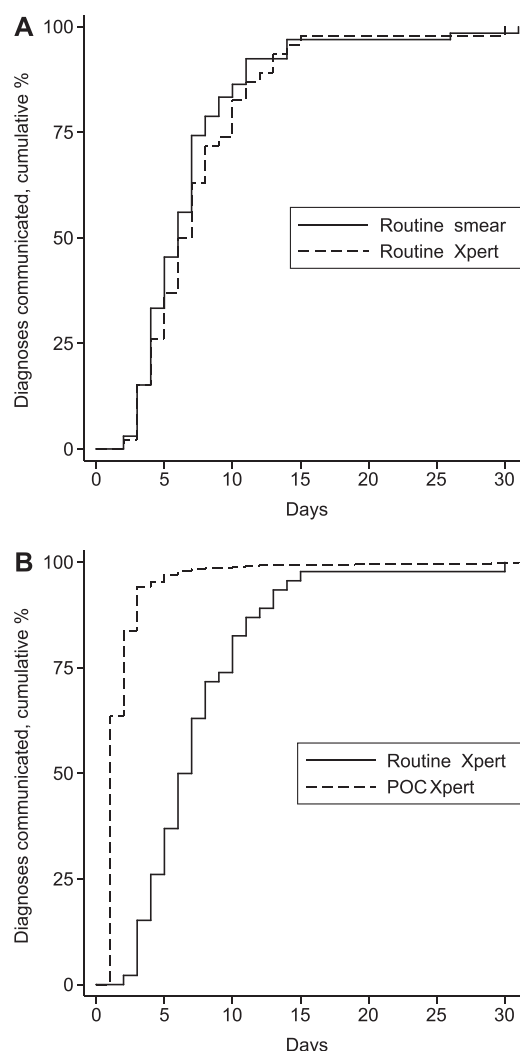

Figure Product and process impact on diagnostic delay. **A)** Time to communication of test results during the period when testing was performed according to routine procedures in the microbiology laboratory, i.e., before implementation of the POC programme. The solid line shows results for patients diagnosed using smear microscopy and the dashed line shows results for patients diagnosed using Xpert. **B)** Comparison of the time to diagnosis using Xpert pre- and post-implementation of the POC programme. The solid line shows results for patients diagnosed with Xpert according to routine procedures in the microbiology laboratory, i.e., before implementation of the POC testing programme; the dashed line shows results for patients diagnosed with Xpert within the POC testing programme. POC = point of care.

programme resulted in same-day treatment initiation in only 23% of patients.

While the sensitivity of Xpert was similar to that previously reported, our estimate was at the lower end of the spectrum compared to the recently updated meta-analysis.[11] This is likely due to the high proportion of samples obtained via sputum induction. The lower sensitivity of Xpert in such specimens has been reported previously, although in a low-burden setting.[26] The incremental number of cases

Table 3 Diagnostic delays pre- and post-implementation of a POC testing programme*

	Pre-test processes	Laboratory processes	Post-test processes	Total process
Routine Xpert (December 2012–February 2013)				
Same-day completion, %	31	0	5	0
Time to diagnosis, days, median [IQR]	1 [0–3]	1 [1–2]	4 [2–6]	6.5 [4–10]
POC Xpert (March 2013–June 2014)				
Same-day completion, %	80	73	71	32
Time to diagnosis, days, median [IQR]	0 [0–0]	0 [0–1]	0 [0–1]	1 [0–1]

* Pre-test processes may lead to delays due to sample submission and transport; laboratory processes may lead to delays due to sample reception in the laboratory, test procedures and result recording; post-test processes may lead to delays due to result reporting to physicians and patient follow-up.
POC = point of care; IQR = interquartile range.

detected over smear microscopy, and not accuracy, is the key parameter for gauging the value of Xpert for TB case finding, and was significantly lower than the ~30% one might expect based on global estimates of the proportion of pulmonary TB cases that are smear-negative[1] and Xpert sensitivity in smear-negative samples.[11] This was likely a result of the good quality fluorescence smears performed by the highly experienced technicians in the microbiology department as well as the spectrum of patients seen in a tertiary care facility. While Xpert yielded only modest benefits over smear microscopy in our setting, we stress that the population was skewed towards later-stage disease and smear positivity. Greater gains would be expected on average and in settings with more RMP resistance. Furthermore, while same-day smear microscopy is possible in principle, it is rarely implemented as batching results in large time savings. This is not the case for Xpert, which is inherently more amenable to POC use.

Although previous studies have reported on POC implementation of Xpert,[18,21–23] this is the first study designed to tease apart the impact of the 'product' (Xpert) from that of the 'process' (POC programme) on time to diagnosis. We found that it was the system around the test, rather than the test itself, that reduced diagnostic delays in our out-patient hospital setting, and that this was mostly due to reductions in post-testing delays. The two principal reasons for delays in routine testing were as follows: 1) the microbiology department received a large number of samples each day from multiple departments within the hospital as well as from the public sector, and during the study period only one 4-module Xpert machine was available, limiting throughput; and 2) the doctors learnt the Xpert result only when checking the electronic medical records on the patient's follow-up visit, commonly scheduled 3–7 days after the initial presentation. Simply scheduling same-day or next-day patient follow-up, combined with rapid reporting of test results directly to the physician by mobile phone led to reductions in delay within the POC programme. This has now become routine practice in the hospital's pulmonary out-patient clinic.

Same-day diagnosis and treatment initiation was not achieved in most patients, similar to a recently published randomised trial,[18] but unlike the other three studies that evaluated POC Xpert implementation.[21–23] The main reasons for this shortcoming was the work hours of doctors and study staff (usually 8 am to 4.30 pm), combined with patients presenting late in the day. Treatment would usually only be initiated on the same day if patients lived in the vicinity of the hospital, as they would otherwise be referred to their local DOTS centre.

The strengths of our study include the direct comparison of two Xpert implementation strategies (routine vs. POC), the large prospective cohort for Xpert POC implementation and the focus on clinical impact in addition to accuracy. Our data also add value to the ongoing discussion on spontaneous vs. induced samples.[26]

Our study also has limitations. First, while some of the general conclusions may broadly hold, the generalisability of the specific results will be limited to similar hospital settings with low rates of loss to follow-up and empiric treatment, as this was not observed in the study population. Second, analyses based on pre/post comparisons could lead to confounding if factors influencing time to diagnosis (other than implementation of the POC programme) change from the pre to the post implementation period. However, this is unlikely, as the delays in this setting were mostly a result of standard sample processing and clinic operating procedures, and these processes did not change for reasons other than the intervention itself. Lastly, time to diagnosis and even time to treatment—while downstream of diagnostic accuracy—are still only surrogate outcomes for patient outcomes and public health benefits, which could not be measured in this study. While reductions in delay should lead to reduced loss to follow-up, transmission and improved patient outcomes, we cannot be certain of the magnitude of such benefits.

CONCLUSIONS

Our study has two key implications beyond those for the study site itself. First, the finding that changes in

the system rather than introduction of a new technology led to reduced delays highlights the potential for process innovation to improve patient outcomes. When introducing novel tests, adaptation of all processes involved from diagnosis to treatment initiation (and possibly beyond) should be carefully considered to reap the full benefits that improved technology may offer. The World Health Organization policy on same-day smear diagnosis is driven by the process innovation approach to reduce loss to follow-up and increase the likelihood of same-day diagnosis and treatment.[27–29] The application of mHealth technology may vastly improve the efficiency and feasibility of POC programmes.[30–32]

The second key implication highlighted by this research is that the impact of Xpert—or any other diagnostic technology—heavily depends on the context: in our setting the high quality of smear microscopy together with the low prevalence of both drug resistance and paucibacillary disease led to a relatively limited impact of Xpert, while the pre-existing clinic operating procedures allowed for the implementation of the POC programme to lead to significant reductions in diagnostic delay. We note that these results could go in the opposite direction in a different context. Operational research can thus help inform how to implement new tests and to focus implementation where the impact is likely be the greatest.[33–35]

While many studies have estimated the diagnostic accuracy of Xpert, few studies have explored different implementation strategies, and this study has shown that POC implementation is feasible and provides complementary benefit to the technology itself. There has been little research into the impact of process innovation, and given its potential, more research in this area is needed to optimise the impact of existing and new tools.

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RESUME

CONTEXTE : Le devenir des patients pourrait être amélioré à la fois grâce à l'innovation du produit (des tests plus sensibles) et à l'innovation du processus (par exemple un programme de tests réalisés sur place [POC]).

OBJECTIF : Etudier les contributions respectives des innovations en matière de produit et de processus dans l'amélioration du devenir des patients.

SCHÉMA : Nous avons mis en œuvre un programme de POC basé sur le Xpert® MTB/RIF dans une consultation externe d'un hôpital de soins tertiaires d'Inde. Nous avons mesuré l'impact de l'innovation du produit en comparant le délai de diagnostic entre le système de routine contre le test POC. Nous avons également mesuré l'impact de l'innovation du produit en comparant l'exactitude du diagnostic et le délai requis entre frottis et Xpert faits sur place.

RÉSULTATS : Nous avons enrôlé 1012 patients pendant une période de 15 mois. Le Xpert a eu une grande précision, mais la valeur ajoutée d'un test Xpert par rapport à deux frottis n'a été que de 6% (IC95% 3–12). La mise en œuvre du Xpert comme test de laboratoire de routine n'a pas réduit le délai de diagnostic par comparaison au diagnostic basé sur un frottis. En contraste, le programme POC a réduit le délai de diagnostic de 5,5 jours (IC95% 4,3–6,7), mais a nécessité un personnel affecté à cette tâche et une adaptation substantielle de l'organisation du travail des structures de santé.

CONCLUSIONS : L'innovation du processus par le biais d'un programme d'Xpert POC a eu un impact plus important sur le délai de diagnostic que le produit en lui-même et peut apporter une importante amélioration à la prise en charge des patients ; ce progrès compléterait celui obtenu par l'introduction de techniques innovantes.

RESUMEN

MARCO DE REFERENCIA: La innovación de los productos (por ejemplo, pruebas más sensibles) y también de los procedimientos (como el programa de pruebas de diagnóstico inmediato en el punto de atención [POC]) puede mejorar los desenlaces clínicos de los pacientes con tuberculosis.

OBJETIVO: Examinar las contribuciones respectivas de la innovación de los productos y de los procedimientos en el progreso de los desenlaces clínicos.

MÉTODO: Se introdujo un programa de análisis diagnósticos en el POC con el uso de la prueba Xpert® MTB/RIF en un consultorio ambulatorio de un hospital de atención terciaria en la India. Se midió la repercusión de la innovación del procedimiento al comparar el lapso hasta obtener el diagnóstico con las pruebas ordinarias y con el programa de pruebas en el POC. Se midió la repercusión de la innovación de los productos al comparar la precisión y el tiempo hasta establecer el diagnóstico de las baciloscopias y la prueba Xpert realizadas en el laboratorio.

RESULTADOS: Participaron en el estudio 1012 pacientes durante un período de 15 meses. La prueba Xpert ofreció una gran precisión, pero la utilidad incremental de una prueba Xpert comparada con dos baciloscopias fue solo 6% (IC95% 3–12). La introducción de la prueba Xpert como un análisis sistemático de laboratorio no disminuyó el lapso hasta obtener el diagnóstico cuando se comparó con el diagnóstico basado en la baciloscopia. Al contrario, el programa de pruebas inmediatas disminuyó en 5,5 días el lapso hasta el diagnóstico (IC95% 4,3–6,7), pero exigió la presencia de personal dedicado a las pruebas y una adaptación considerable del flujo de trabajo clínico.

CONCLUSIÓN: La innovación de los procedimientos mediante un programa con la prueba Xpert de diagnóstico inmediato ejerció un mayor efecto sobre el lapso hasta el diagnóstico que uso del producto por sí mismo y este programa puede aportar progresos considerables a la atención de los pacientes, que complementarían de los avances logrados con las tecnologías innovadoras.