IMPACT OF TESTS ON DIAGNOSTIC THINKING AND CLINICAL DECISIONS

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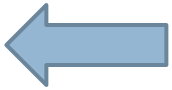
Phased evaluation of medical tests: Diagnostic thinking efficacy

Levels/Phases
Technical efficacy
Intended use
Diagnostic accuracy
Usual range
Subgroups
Clinical
population
Diagnostic thinking efficacy
Therapeutic efficacy
Patient outcome efficacy
Societal efficacy



Proposals for a Phased Evaluation of Medical Tests

Jeroen G. Lijmer, MD, PhD, Mariska Leeflang, PhD, Patrick M. M. Bossuyt, PhD

Med Desic Making 2009

Why does it matter?

- Why order tests if the results do not make any difference to clinical/treatment decisions?
- Test results will have an impact on patient outcomes, provided they correctly guide clinical and treatment decisions made by physicians
  - Not easy to study: if all doctors followed sound evidence-based guidelines on disease management, then testing MUST clearly influence treatment decisions and there is no need to study it!
- Reality: "empirical" management of syndromes in the absence of any diagnostic confirmation
  - Big difference between resource-limited vs. resource-constrained settings
    - In resource-rich settings, over-testing and overdiagnoses may be problem!
  - Lack of access to good diagnostics is another big problem
  - If medical practice is mostly non-evidence based, then there can be no real connection between testing and outcomes!

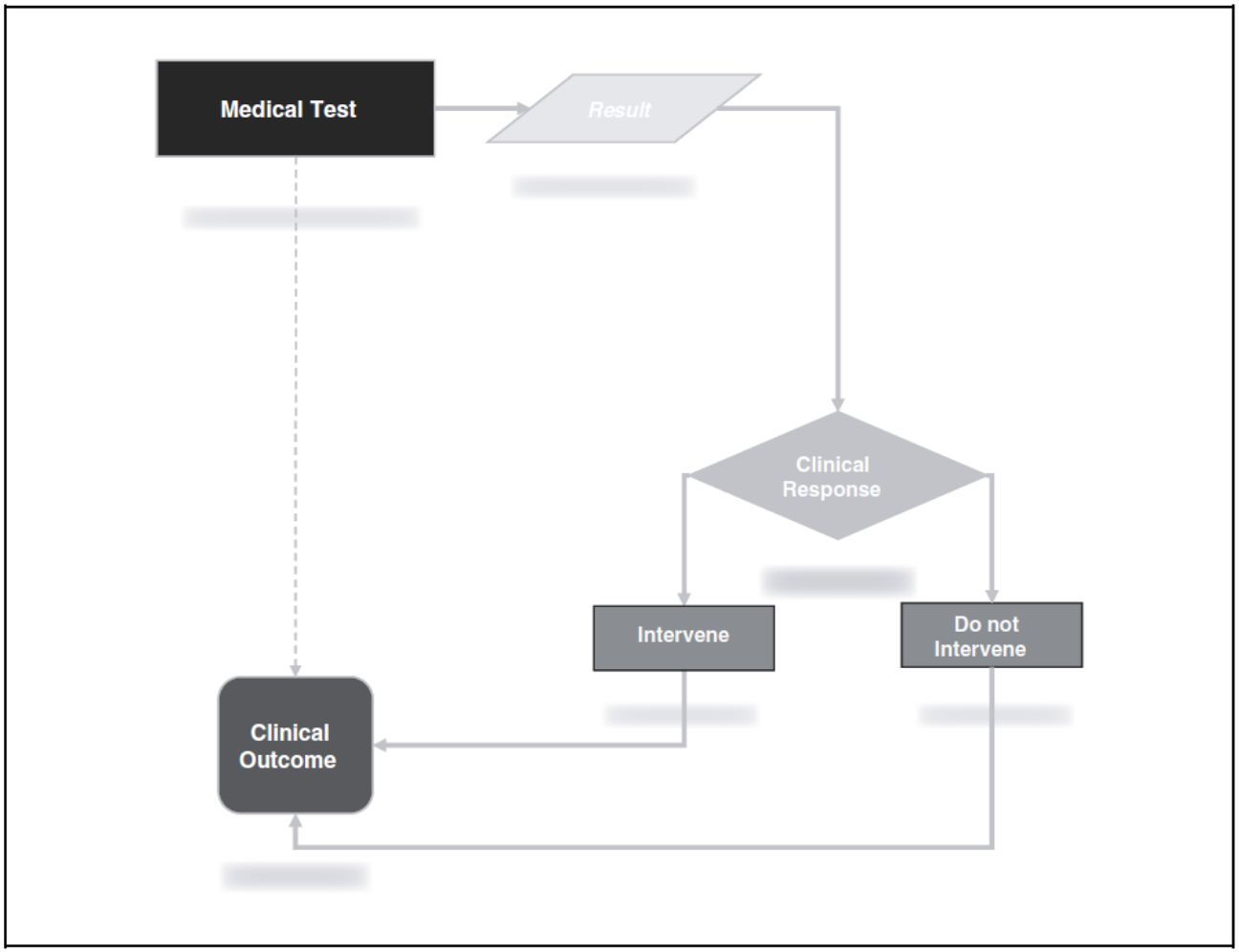


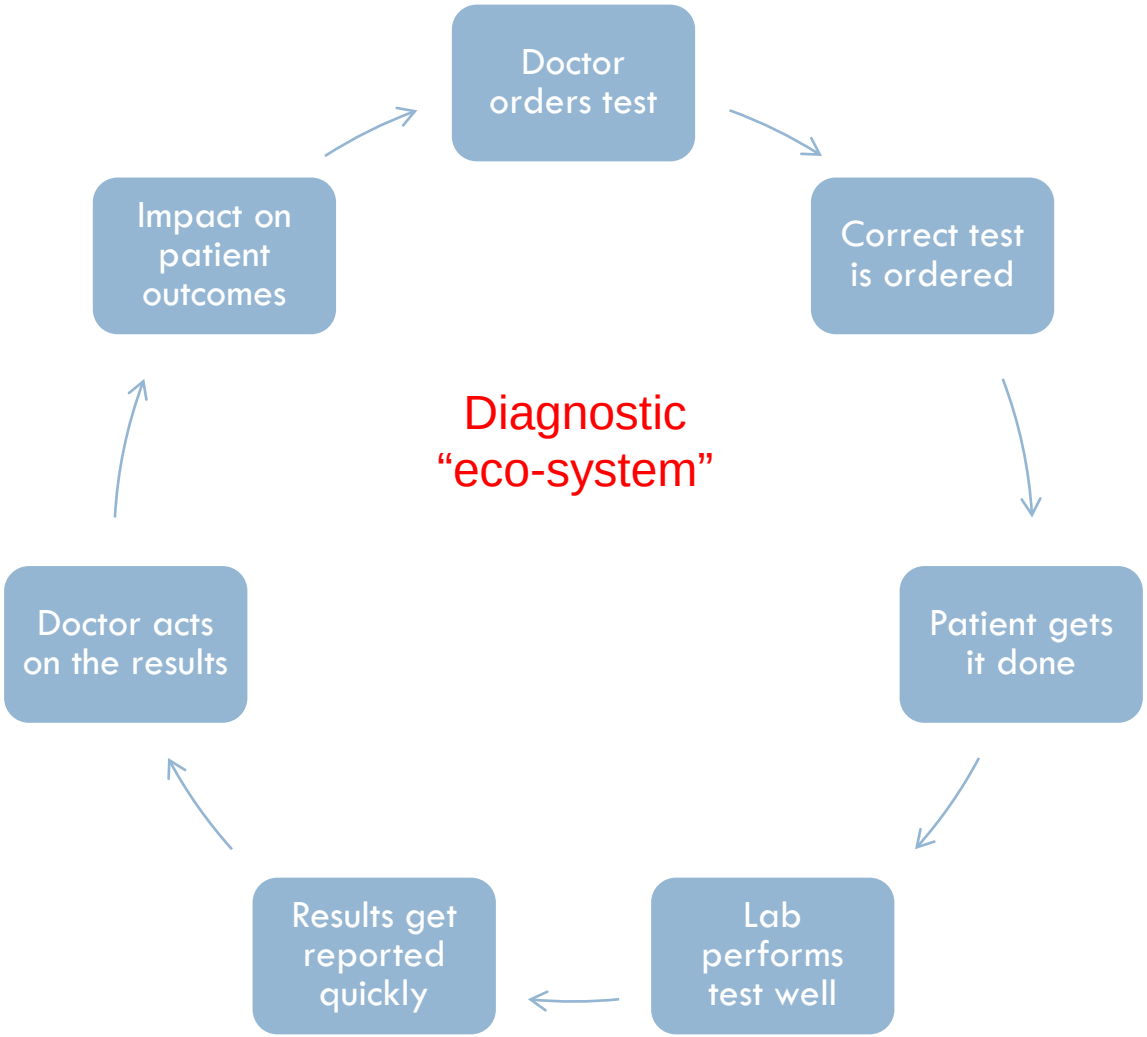
Figure 1 Direct and management effects on patient outcome.

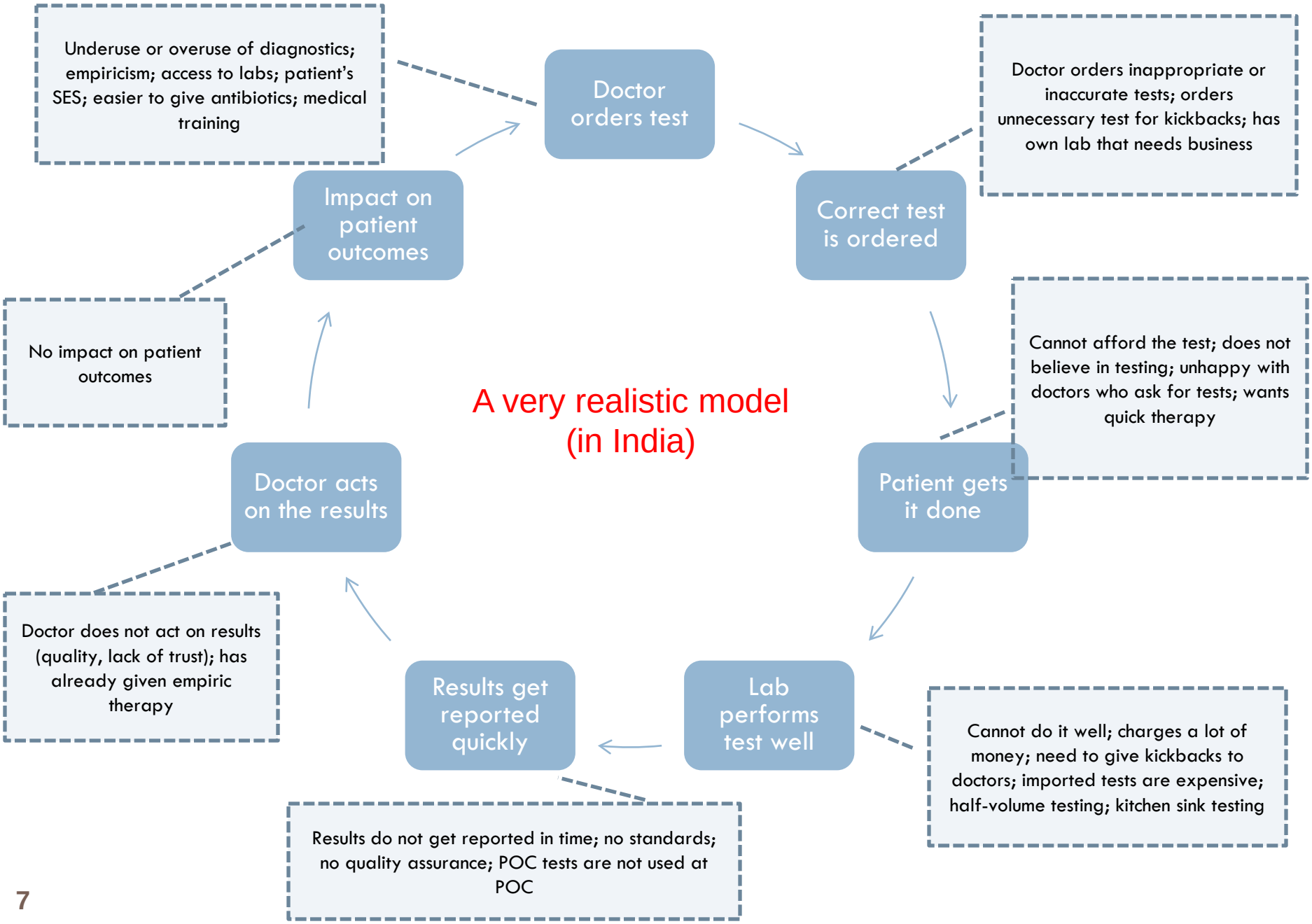
"The principal way in which testing leads to changes in a patient's health is through changes in clinical decision making and management, guided by these test results. The latter includes selecting, starting, stopping, or modifying treatment; ordering more tests; or watchful waiting." [Bossuyt et al. Med Desic Making 2009]

Change in physician's decisions or behavior is an intermediate step for improvement in patient outcomes

A simplistic model

A more complex model




Underuse or overuse of diagnostics; empiricism; access to labs; patient's SES; easier to give antibiotics; medical training
Doctor orders test
Doctor orders inappropriate or inaccurate tests; orders unnecessary test for kickbacks; has own lab that needs business
Impact on patient outcomes
Correct test is ordered
No impact on patient outcomes
Cannot afford the test; does not believe in testing; unhappy with doctors who ask for tests; wants quick therapy
A very realistic model (in India)
Doctor acts on the results
Patient gets it done
Doctor does not act on results (quality, lack of trust); has already given empiric therapy
Results get reported quickly
Lab performs test well
Cannot do it well; charges a lot of money; need to give kickbacks to doctors; imported tests are expensive; half-volume testing; kitchen sink testing
Results do not get reported in time; no standards; no quality assurance; POC tests are not used at POC

Therefore, a key consideration

- Changes (or lack thereof) in physician or provider "behaviour" is necessary but is plagued problems:
  - Doctors may know something (knowledge), say something (intent), and do (practice) something else altogether!
    - E.g. prescription studies vs. audits vs. incognito standardized patient based methods

Example: influenza RIDTs

Impact of Rapid Diagnosis on Management of Adults Hospitalized With Influenza

ARCHIVES EXPRESS

Ann R. Falsey, MD; Yoshihiko Murata, MD, PhD; Edward E. Walsh, MD

Background: Rapid influenza testing decreases antibiotic and ancillary test use in febrile children, yet its effect on the care of hospitalized adults is unexplored. We compared the clinical management of patients with influenza whose rapid antigen test result was positive (Ag+) with the management of those whose rapid antigen test result was negative or the test was not performed (Ag0).

Methods: Medical record review was performed on patients with influenza hospitalized during 4 winters (1999-2003). Hospital policy mandated influenza testing (antigen or culture) for all patients with acute cardiopulmonary diseases admitted from November 15 through April 15. A subset of patients participated in an epidemiological study and had reverse-transcriptase polymerase chain reaction or serologic testing performed. Clinical data from Ag+ and Ag0 patients were compared.

Results: Of 166 patients with available records, 86 were Ag+ and 80 were Ag0. Antibiotic use (74 [86%] of 86 patients vs 79 [99%] of 80 patients; $P=.002$) was less and antibiotic discontinuance (12 [14%] of 86 patients vs 2 [2%] of 80 patients; $P=.01$) was greater in Ag+ compared with Ag0 patients. No significant differences in antibiotic days, length of hospital stay, or antibiotic complications were noted. Antiviral use (63 [73%] of 86 patients vs 6 [8%] of 80 patients; $P<.001$) was greater in Ag+ than Ag0 patients. Antigen status was independently associated with withholding or discontinuing antibiotics in multivariate analysis. Of 44 Ag+ patients deemed low risk for bacterial infection, 27 continued to receive antibiotics despite positive influenza test results. These patients more commonly had pulmonary disease and had significantly more abnormal lung examination results ($P=.005$) compared with those in whom antibiotics were withheld or discontinued.

Conclusions: Rapid influenza testing leads to reductions in antibiotic use in hospitalized adults. Better tools to rule out concomitant bacterial infection are needed to optimize the impact of viral testing.

Arch Intern Med. 2007;167:354-360

Example: malaria RDTs

Kyabayinze *et al. Malaria Journal* 2010, **9**:200
http://www.malariajournal.com/content/9/1/200

MALARIA JOURNAL

RESEARCH Open Access

Use of RDTs to improve malaria diagnosis and fever case management at primary health care facilities in Uganda

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Abstract

Background: Early and accurate diagnosis of malaria followed by prompt treatment reduces the risk of severe disease in malaria endemic regions. Presumptive treatment of malaria is widely practised where microscopy or rapid diagnostic tests (RDTs) are not readily available. With the introduction of artemisinin-based combination therapy (ACT) for treatment of malaria in many low-resource settings, there is need to target treatment to patients with parasitologically confirmed malaria in order to improve quality of care, reduce over consumption of anti-malarials, reduce drug pressure and in turn delay development and spread of drug resistance. This study evaluated the effect of malaria RDTs on health workers' anti-malarial drug (AMD) prescriptions among outpatients at low level health care facilities (LLHCF) within different malaria epidemiological settings in Uganda.

Methods: All health workers (HWs) in 21 selected intervention (where RDTs were deployed) LLHF were invited for training on the use RDTs. All HWs were trained to use RDTs for parasitological diagnosis of all suspected malaria cases irrespective of age. Five LLHCFs with clinical diagnosis (CD only) were included for comparison. Subsequently AMD prescriptions were compared using both a 'pre - post' and 'intervention - control' analysis designs. In-depth interviews of the HWs were conducted to explore any factors that influence AMD prescription practices.

Results: A total of 166,131 out-patient attendances (OPD) were evaluated at 21 intervention LLHCFs. Overall use of RDTs resulted in a 38% point reduction in AMD prescriptions. There was a two-fold reduction (RR 0.62, 95% CI 0.55-0.70) in AMD prescription with the greatest reduction in the hypo-endemic setting (RR 0.46 95% CI 0.51-0.53) but no significant change in the urban setting (RR1.01, p-value = 0.820). Over 90% of all eligible OPD patients were offered a test. An average of 30% (range 25%-35%) of the RDT-negative fever patients received AMD prescriptions. When the test result was negative, children under five years of age were two to three times more likely (OR 2.6 p-value <0.001) to receive anti-malarial prescriptions relative to older age group. Of the 63 HWs interviewed 92% believed that a positive RDT result confirmed malaria, while only 49% believed that a negative RDT result excluded malaria infection.

Conclusion: Use of RDTs resulted in a 2-fold reduction in anti-malarial drug prescription at LLHCFs. The study demonstrated that RDT use is feasible at LLHCFs, and can lead to better targetting of malaria treatment. Nationwide deployment of RDTs in a systematic manner should be prioritised in order to improve fever case management. The process should include plans to educate HWs about the utility of RDTs in order to maximize acceptance and uptake of the diagnostic tools and thereby leading to the benefits of parasitological diagnosis of malaria.

Some TB examples

Potential Clinical Impact of Nucleic Acid Amplification Testing

At hospital discharge, only 25 (33%) of 75 AFB smear-negative patients ultimately diagnosed with culture-positive TB had been prescribed TB treatment. Had results of the more sensitive of the two NAATs, the MTD, been made available to clinicians within 24 hours of sputum collection, 18 additional TB patients could have been correctly started on TB treatment, while only two patients with negative mycobacterial cultures would have been inappropriately started on treatment. Thus, availability of MTD results would have lead to an absolute increase in sensitivity for TB of 24%, and a relative increase of 72% in early TB case detection among the Ziehl-Neelsen AFB-smear-negative population (43 TB patients if MTD results had been available compared to 25 TB patients when MTD results were not available). Instead of waiting for culture results to initiate TB treatment, these patients could have been started a median of 27 days (range 15–42 days) earlier. Unfortunately, 10 of these 18 smear-negative, MTD-positive, culture-positive TB patients died a median of 8.5 days (range 4–13 days) after enrollment, and it is unknown whether earlier initiation of treatment for these patients would have improved their outcomes.

Did not directly estimate change in clinical decisions, but indirectly estimated it

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PLoS one

Nucleic Acid Amplification Tests for Diagnosis of Smear-Negative TB in a High HIV-Prevalence Setting: A Prospective Cohort Study

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Abstract

Background: Nucleic acid amplification tests are sensitive for identifying Mycobacterium tuberculosis in populations with positive sputum smears for acid-fast bacilli, but less sensitive in sputum-smear-negative populations. Few studies have evaluated the clinical impact of these tests in low-income countries with high burdens of TB and HIV.

Methods: We prospectively enrolled 211 consecutive adults with cough ≥2 weeks and negative sputum smears at Mulago Hospital in Kampala, Uganda. We tested a single early-morning sputum specimen for Mycobacterium tuberculosis DNA using two nucleic acid amplification tests: a novel in-house polymerase chain reaction targeting the mycobacterial secA1 gene, and the commercial Amplified® Mycobacterium tuberculosis Direct (MTD) test (Gen-Probe Inc, San Diego, CA). We calculated the diagnostic accuracy of these index tests in reference to a primary microbiologic gold standard (positive mycobacterial culture of sputum or bronchoalveolar lavage fluid), and measured their likely clinical impact on additional tuberculosis cases detected among those not prescribed initial TB treatment.

Results: Of 211 patients enrolled, 170 (81%) were HIV-seropositive, with median CD4+ T-cell count 78 cells/μL (interquartile range 29-203). Among HIV-seropositive patients, 94 (55%) reported taking co-trimoxazole prophylaxis and 29 (17%) reported taking antiretroviral therapy. Seventy-five patients (36%) had culture-confirmed TB. Sensitivity of MTD was 39% (95% CI 28–51) and that of secA1 was 24% (95% CI 15–35). Both tests had specificities of 95% (95% CI 90–98). The MTD test correctly identified 18 (24%) TB patients not treated at discharge and led to a 72% relative increase in the smear-negative case detection rate.

Conclusions: The secA1 and MTD nucleic acid amplification tests had moderate sensitivity and high specificity for TB in a predominantly HIV-seropositive population with negative sputum smears. Although newer, more sensitive nucleic acid assays may enhance detection of Mycobacterium tuberculosis in sputum, even currently available tests can provide substantial clinical impact in smear-negative populations.

Citation: Davis JL, Huang L, Worodria W, Masur H, Cattamanchi A, et al. (2011) Nucleic Acid Amplification Tests for Diagnosis of Smear-Negative TB in a High HIV-Prevalence Setting: A Prospective Cohort Study. PLoS ONE 6(1): e16321. doi:10.1371/journal.pone.0016321

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Does solid culture for tuberculosis influence clinical decision making in India?

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SUMMARY

SETTING: Medical units at an academic tertiary referral hospital in Southern India.

OBJECTIVE: To investigate the impact of solid culture on Löwenstein-Jensen medium on clinical decision making.

DESIGN: In a retrospective review of 150 culture-positive and 150 culture-negative consecutively sampled tuberculosis (TB) suspects, treatment decisions were analysed at presentation, after the availability of culture detection results and after the availability of drug susceptibility testing (DST) culture results.

RESULTS: A total of 124 (82.7%) culture-positive patients and 35 (23.3%) culture-negative patients started anti-tuberculosis treatment prior to receiving their culture results; 101 patients (33.7%) returned for their results; two (1.3%) initiated treatment based on positive culture and no culture-negative patients discontinued treatment. DST was performed on 119 (79.3%) positive cultures: 30 (25.2%) showed any resistance, eight (6.7%) showed multidrug resistance and one (0.84%) showed extensively drug-resistant TB. Twenty-eight patients (23.5%) returned for their DST results. Based on DST, treatment was modified in four patients (3.4%).

CONCLUSION: Using solid culture, 150 cultures need to be tested for one treatment modification and 30 for DST. The cost of the widespread application of culture will need to be balanced against its impact on treatment decisions in India.

KEY WORDS: tuberculosis; culture; decision making

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PLoS one

Impact and Cost-Effectiveness of Culture for Diagnosis of Tuberculosis in HIV-Infected Brazilian Adults

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Abstract

Background: Culture of *Mycobacterium tuberculosis* currently represents the closest "gold standard" for diagnosis of tuberculosis (TB), but operational data are scant on the impact and cost-effectiveness of TB culture for human immunodeficiency (HIV-) infected individuals in resource-limited settings.

Methodology/Principal Findings: We recorded costs, laboratory results, and dates of initiating TB therapy in a centralized TB culture program for HIV-infected patients in Rio de Janeiro, Brazil, constructing a decision-analysis model to estimate the incremental cost-effectiveness of TB culture from the perspective of a public-sector TB control program. Of 217 TB suspects presenting between January 2006 and March 2008, 33 (15%) had culture-confirmed active tuberculosis; 23 (70%) were smear-negative. Among smear-negative, culture-positive patients, 6 (26%) began TB therapy before culture results were available, 11 (48%) began TB therapy after culture result availability, and 6 (26%) did not begin TB therapy within 180 days of presentation. The cost per negative culture was US$17.52 (solid media)–$23.50 (liquid media). Per 1,000 TB suspects and compared with smear alone, TB culture with solid media would avert an estimated eight TB deaths (95% simulation interval [SI]: 4, 15) and 37 disability-adjusted life years (DALYs) (95% SI: 13, 76), at a cost of $36 (95% SI: $25, $50) per TB suspect or $962 (95% SI: $469, $2642) per DALY averted. Replacing solid media with automated liquid culture would avert one further death (95% SI: −1, 4) and eight DALYs (95% SI: −4, 23) at $2751 per DALY (95% SI: $680, dominated). The cost-effectiveness of TB culture was more sensitive to characteristics of the existing TB diagnostic system than to the accuracy or cost of TB culture.

Conclusions/Significance: TB culture is potentially effective and cost-effective for HIV-positive patients in resource-constrained settings. Reliable transmission of culture results to patients and integration with existing systems are essential.

Citation: Dowdy DW, Lourenço MC, Cavalcante SC, Saraceni V, King B, et al. (2008) Impact and Cost-Effectiveness of Culture for Diagnosis of Tuberculosis in HIV-Infected Brazilian Adults. PLoS ONE 3(12): e4057. doi:10.1371/journal.pone.0004057

The clinical impact of nucleic acid amplification tests on the diagnosis and management of tuberculosis in a British hospital

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ABSTRACT

Background: Nucleic acid amplification tests (NAAT) based on PCR provide rapid identification of *Mycobacterium tuberculosis* and the detection of rifampicin resistance. Indications for their use in clinical samples are now included in British tuberculosis guidelines.

Methods: A retrospective audit of patients with suspected mycobacterial infection in a Liverpool hospital between 2002 and 2006. Documentation of the impact of NAAT usage in acid fast bacillus (AFB) microscopy positive samples on clinical practice and the influence of a multidisciplinary group on their appropriate use, compared with British guidelines.

Results: Mycobacteria were seen or isolated from 282 patients and identified as *M tuberculosis* in 181 (64%). NAAT were indicated in 87/123 AFB positive samples and performed in 51 (59%). *M tuberculosis* was confirmed or excluded by this method in 86% of tested samples within 2 weeks, compared with 7% identified using standard methods. The appropriate use of NAAT increased significantly over the study period. The NAAT result had a clinical impact in 20/51 (39%) tested patients. Culture results suggest the potential for a direct clinical impact in 8/36 (22%) patients in which it was indicated but not sent and 5/36 (14%) patients for whom it was not indicated. Patients managed by the multidisciplinary group had a higher rate of HIV testing and appropriate use of NAAT.

Conclusions: There were significant clinical benefits from the use of nucleic acid amplification tests in this low prevalence setting. Our data suggest that there would be additional benefit from their use with all AFB smear positive clinical samples.

METHODS

The Department of Microbiology of the Royal

due to mutations in a single gene (the *rpo*B gene), this can also be detected using a NAAT method.[8 9] Although the currently available tests for *rpo*B mutations do not detect all cases of rifampicin resistance, and will not detect isolated isoniazid resistance, the association between rifampicin resistance and MDR-TB is strong, with one report showing 95% of rifampicin resistant strains to be associated with resistance to isoniazid.[10] British guidelines therefore also advocate use of rapid diagnostic tests for rifampicin resistance if a risk assessment suggests a patient might have MDR-TB. Detection of rifampicin resistance by NAAT is taken to indicate MDR-TB until full sensitivity profiles become available.

Liverpool has a low prevalence but a rising incidence of TB, with 47 cases notified in 2002 and 86 in 2005, out of a population of approximately 650 000 which has changed little in that time period.[11] The recent increases reflect national trends[12] and coincide with Liverpool being designated as a "dispersal" centre for refugees in 2002.[13]

We conducted a retrospective analysis of the clinical impact of the use of NAAT in patients with suspected TB, who had a clinical sample that was AFB smear positive between 2002 and 2006, and we examined the influence of a multidisciplinary approach on the appropriate use of investigations in this low prevalence setting.

Clinical impact of the NAAT result

The use of NAAT had a clinical impact in 20/51 (39% (95% CI 27%, 53%)) patients for whom it was performed. Three patients who had started TB treatment were able to stop within 2 weeks and in one of these cases a major prison contact-tracing exercise was avoided; two of four patients with MDR-TB were identified promptly by NAAT; in three patients, detection of MTB confirmed the need for a hospital contact-tracing exercise; in five previously treated patients, MDR-TB was excluded; and in seven patients for whom there was uncertainty about the diagnosis, TB was confirmed and appropriate treatment continued. In addition, MDR-TB was excluded in 26 patients who originated in TB endemic countries.

If NAAT had been sent from the other 36 patients in which they were indicated, the subsequent culture results suggest it could have had an impact in 8 (22% (95% CI 11%, 38%)) by detecting one further case of MDR-TB, excluding MDR-TB in two patients previously treated, confirming TB in two patients and excluding it in three for whom there was diagnostic uncertainty. There could have been further impact by excluding MDR-TB in 26 patients in whom there were risk factors.

Thorax 2008

The Clinical And Public Health Impact Of Automated Nucleic Acid Testing For Tb Evaluation In San Francisco

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Background: In low-incidence settings, patients suspected of tuberculosis (**TB**) may be prescribed empiric treatment based on clinical and epidemiological data before results of microbiological tests are known. This may result in earlier treatment of TB patients, but may also lead to unnecessary treatment and contact investigations in patients without TB. Although the performance characteristics of nucleic acid assays (**NAA**s) have been widely reported, few studies have evaluated these tests for identifying patients who do not need treatment among those prescribed empiric treatment.

Objective: To evaluate the impact of automated NAA for TB diagnosis (GeneXpert [**GX**] Cepheid Diagnostics, Sunnyvale, CA) among patients prescribed empiric treatment.

Methods: We retrospectively studied patients starting empiric TB treatment at the San Francisco Department of Public Health TB Clinic because of moderate or high suspicion of TB. All had GX for TB performed on a NALC-NaOH concentrated pellet from the first sputum collected. We extracted data from medical records, and determined if GX results altered treatment or contact investigation decisions. We used McNemar's test for paired proportions to assess the significance of any reduction in unnecessary interventions with GX.

Results: 20 consecutive patients in whom suspicion of TB was sufficiently high that empiric treatment was initiated were tested with GX between April and August, 2010. Six had acid-fast bacilli smear-positive (**AFB**+) sputum; 5 of the 6 were GX+, and had treatment and contact investigation continued. All 5 had positive cultures for M. TB. The sixth AFB+ patient was GX-, and had treatment and contact investigation discontinued; culture confirmed M. kansasii. All 14 AFB- patients were also GX-. Based on a GX result, 11 stopped treatment and contact investigation discontinued; all were culture-negative. The remaining 3 patients had treatment continued, but contact investigation was held. All 3 were sputum culture-negative, however, one had a positive culture from bronchoalveolar-lavage fluid and one improved clinically at the 2-month visit consistent with a treatment response. Overall, GX changed management in 12/20 (60%) patients, reducing unnecessary treatments from 13/20 (65%) to 1/20 (5%) ($p<0.005$), and unnecessary contact investigations from 13/20 (65%) to 0/20 (0%) ($p<0.002$). GX failed to detect 2 smear-negative, culture-negative TB cases, but, in both cases, clinicians continued treatment based on continued high clinical suspicion.

Conclusions: This pilot evaluation suggests that automated NAA for TB could have substantial clinical and pubic health impact. Confirmation of this finding will require prospective evaluation in low-incidence settings where empiric treatment is common.

Am J Respir Crit Care Med 183;2011:A5314

TB EXAMPLE: DOES QUANTIFERON-TB GOLD HELP WITH LTBI TREATMENT DECISIONS IN CHILDREN?

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SHORT COMMUNICATION

Implementation of liquid culture for tuberculosis diagnosis in a remote setting: lessons learned

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SUMMARY

Although sputum smear microscopy is the primary method for tuberculosis (TB) diagnosis in low-resource settings, it has low sensitivity. The World Health Organization recommends the use of liquid culture techniques for TB diagnosis and drug susceptibility testing in low- and middle-income countries. An evaluation of samples from southern Sudan found that culture was able to detect cases of active pulmonary TB and extra-pulmonary TB missed by conventional smear microscopy. However, the long delays involved in obtaining culture results meant that they were usually not clinically useful, and high rates of non-tuberculous mycobacteria isolation made interpretation of results difficult. Improvements in diagnostic capacity and rapid speciation facilities, either on-site or through a local reference laboratory, are crucial.
KEY WORDS: tuberculosis; non-tuberculous mycobacteria; microscopy; liquid culture

Impact on clinical decisions are important but not easy to study

- How doctors act on tests will be influenced/confounded by:
  - Their practice environment (evidence-based/protocol-driven or not; public vs. private; HMO vs. not, developed vs. developing country, etc.)
  - How quickly test results get fed back to the doctors who need them
  - Hard to study if a test is not approved for clinical use (will need to estimate hypothetical impact)
  - Even within a health system, MDs may vary in their behaviours for the same condition ("variation in practice quality")

Impact on clinical decisions are important but not easy to study

- How doctors act on tests will be influenced/confounded by:
  - Retrospective audits can be misleading – one can never quite tell if the change in management was definitely because of the test result – unless MDs explicitly recorded the rationale for the change (quality of medical records)
  - Prospective studies are better but the study itself can potentially influence the MDs to alter their behaviours
  - If empiricism is widespread, it is hard to tease out what role, if any, a test is playing
  - Differences between knowledge and actual practice
  - Change in behaviour is only a "surrogate" for downstream patient outcomes:
    - Behaviour might change, but outcomes may not!