IMPACT OF TESTS ON DIAGNOSTIC THINKING AND CLINICAL DECISIONS

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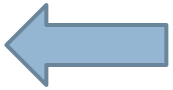
Phased evaluation of medical tests: Diagnostic thinking efficacy

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

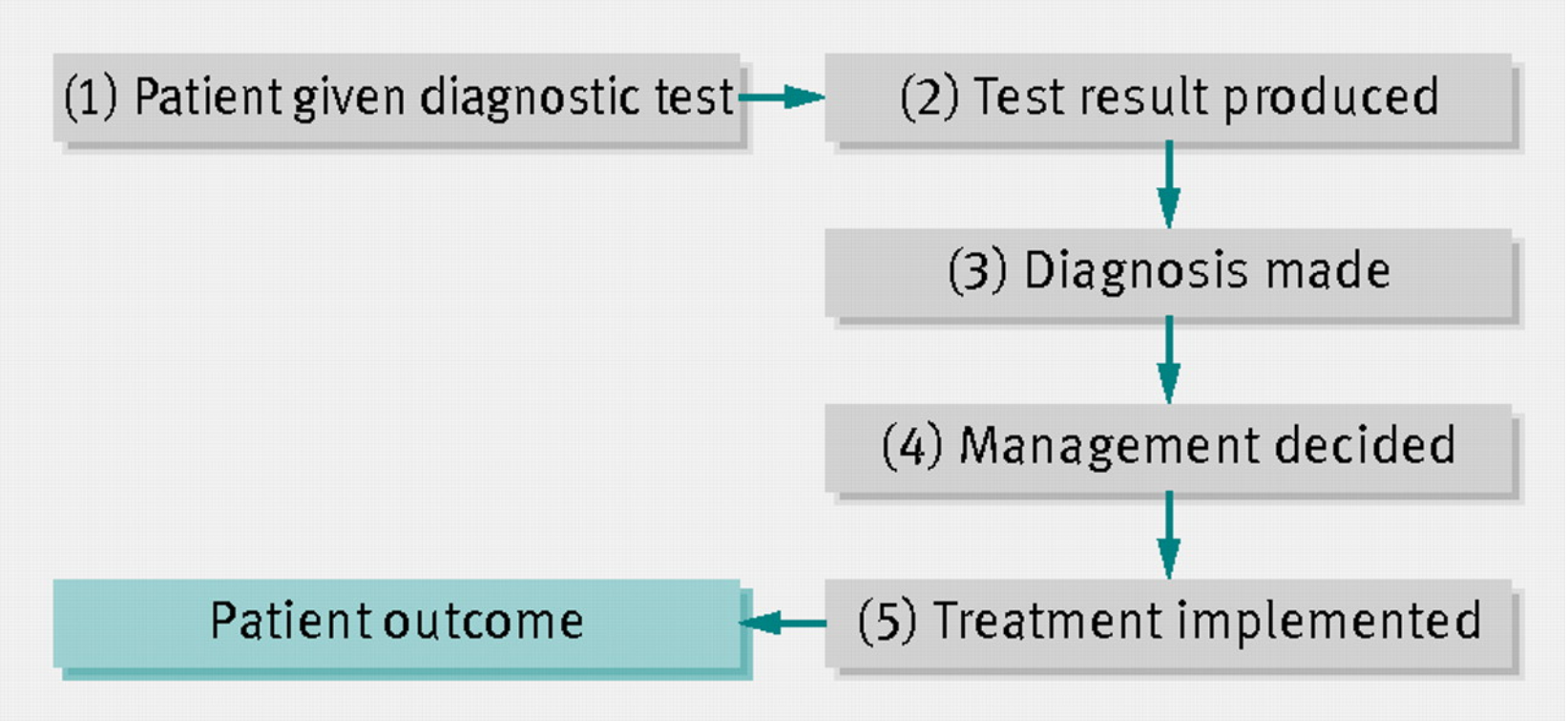
Jeroen G. Lijmer, MD, PhD, Mariska Leeflang, PhD, Patrick M. M. Bossuyt, PhD

Med Desic Making 2009

Why does it matter?

- Why order tests if the results do not make any difference to clinical/treatment decisions? ["intention to test is intention to treat"]
- 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!

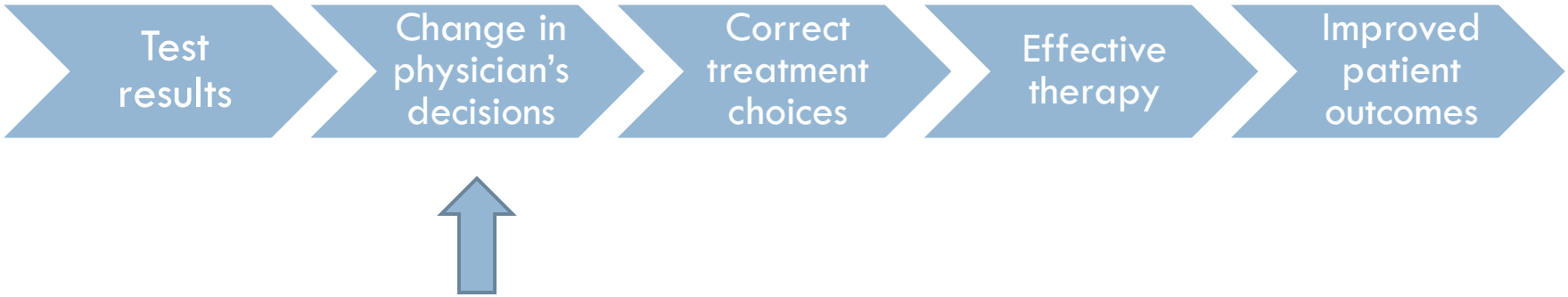
Fig 2 Simplified test-treatment pathway showing each component of a patient's management that can affect health outcomes



Ferrante di Ruffano L et al. BMJ 2012;344:bmj.e686

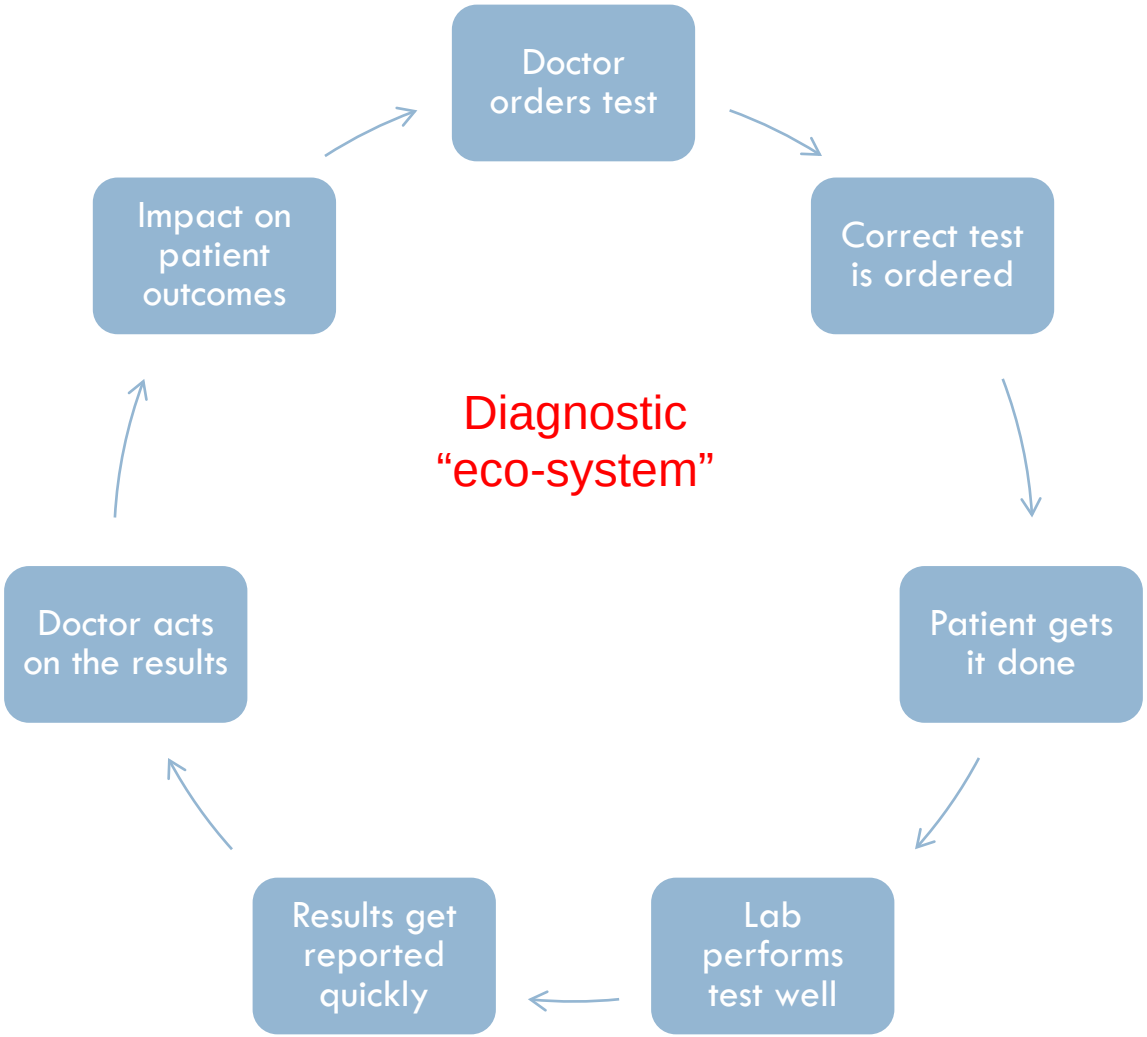
"The principal way in which testing leads to changes in a patient's health is through changes in clinical decision making and management, guided by these test results. The latter includes selecting, starting, stopping, or modifying treatment; ordering more tests; or watchful waiting." [Bossuyt et al.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

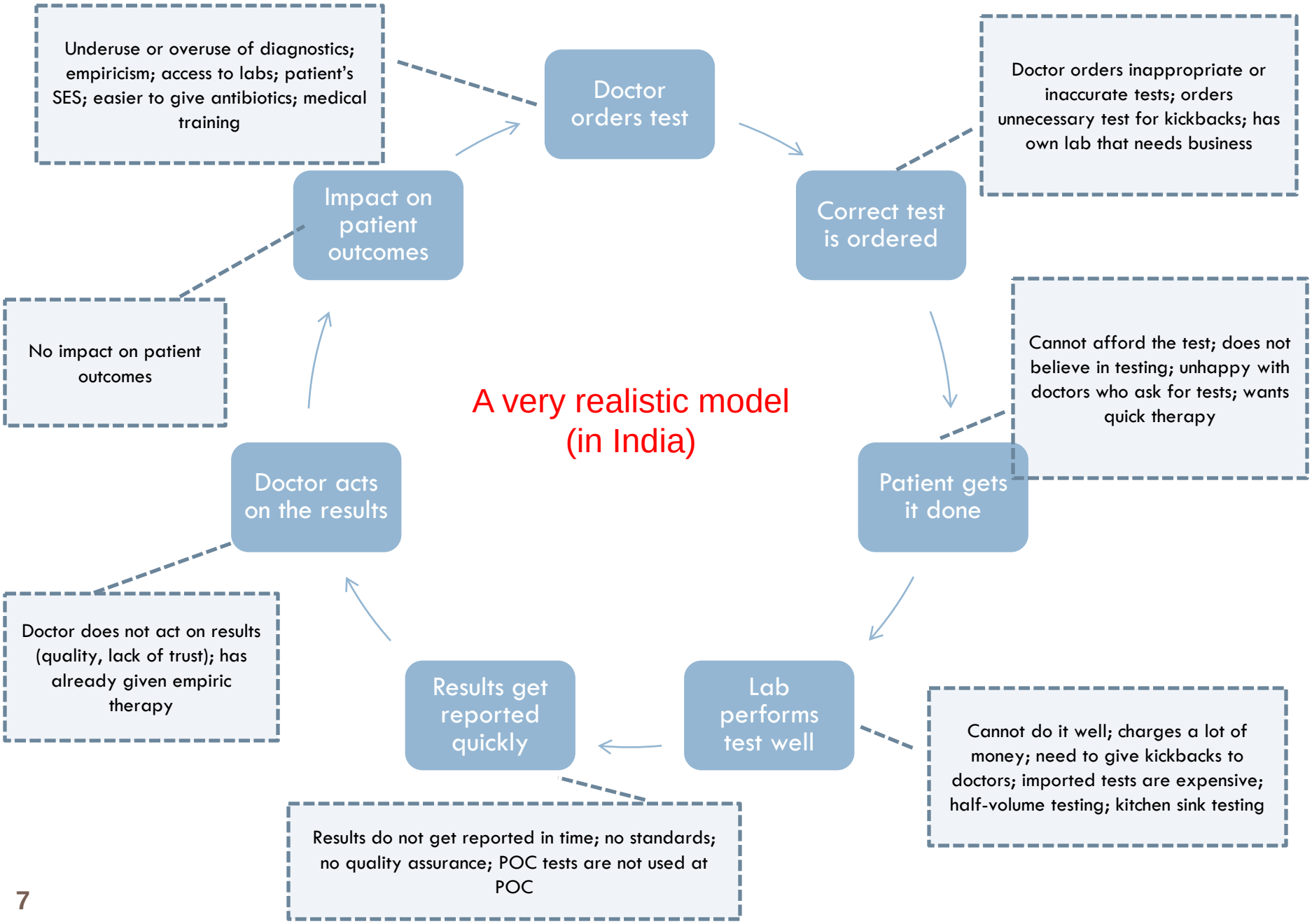
Change in physician's decisions or behavior is an intermediate step for improvement in patient outcomes



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

Daniel J Kyabayinze*[1], Caroline Asiimwe[1], Damalie Nakanjako[2], Jane Nabakooza[3], Helen Counihan[4] and James K Tibenderana[1,5]

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

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

M Taegtmeyer,[1] N J Beeching,[1] J Scott,[2] K Seddon,[2] S Jamieson,[3] S B Squire,[1] H C Mwandumba,[1] A R O Miller,[1] P D O Davies,[3] C M Parry[2]

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.

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.

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.

METHODS

The Department of Microbiology of the Royal

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

INT J TUBERC LUNG DIS 15(5):641–646

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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

INT J TUBERC LUNG DIS 15(3):405–407

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
    - POC tests should have a bigger impact on clinical decisions than regular tests
  - 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 ("Hawthorne effect")
  - 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!
    - If we can directly measure outcomes, do we still need to study change in behaviors??

INTERFERON-GAMMA RELEASE ASSAYS FOR CHILDHOOD TUBERCULOSIS: DO THEY IMPACT DIAGNOSTIC AND TREATMENT DECISIONS BY PEDIATRIC RESPIROLOGISTS?

July 10, 2012

Daphne I. Ling, Claire A. Crépeau, Marieke Dufresne, Shazia Khan, Caroline Quach, Nandini Dendukuri, Kevin Schwartzman, Dick Menzies, Larry C. Lands, Madhukar Pai

(Accepted by the *Pediatric Infectious Disease Journal*)

Rationale

- Meta-analyses of IGRA performance in children show that they have increased specificity and similar sensitivity compared to the TST
- Many national guidelines in low-incidence countries (including Canada) recommend the use of IGRAs in conjunction with the TST in children
- IGRAs are increasingly being used in low-incidence settings, but there are limited data on how test results influence clinical management

Objectives

- To evaluate prospectively the performance of the QFT in children with TST results, stratified by clinically-relevant subgroups

- To determine the impact of QFT results on diagnostic and treatment decisions made by pediatric respirologists in routine clinical practice

L'Hôpital de Montréal pour enfants
The Montreal Children's Hospital
Centre universitaire de santé McGill
McGill University Health Centre

MEMORANDUM

June 2009

In summary, the indications for pediatrics are as follow:

1. In support for the diagnosis of active tuberculosis in children (<18 years), in combination with other microbiological tests

2. Children in contact with a case of active infectious tuberculosis with a positive PPD

3. Immunocompromised children defined as:
    a. Receiving Prednisone (2 mg/kg/day) for 14 days or more
    b. Current chemotherapy or received in the past 3 months
    c. Pre or post- bone marrow transplant
    d. HIV positive children

   In whom a clinician is still concerned about the possibility of LTBI even after a negative PPD

4. Patients with inflammatory diseases prior to starting anti-TNF medication

5. Children with positive TST who are considered to have low probability of LTBI or low risk of progression to active disease

Study Enrollment

- Referrals to the TB Clinic included:
  - Other hospital departments (gastroenterology, ID, rheumatology, multicultural)
  - Public health agencies for child contacts
  - Community health clinics for post-landing immigration screening
  - School-based screening

- We categorized the children into the following subgroups:
  - Active TB suspects
  - Contacts of TB cases (TST+ only)
  - Immunocompromised children
  - Children starting anti-TNF treatment
  - Children from targeted screening programs (TST+ only)

Data collection

- Information on patient characteristics and TB history were routinely collected by the TB nurse, using a standard data abstraction form

- On another questionnaire, the pediatric respirologist was asked to document whether or not the QFT had any impact on his/her clinical decision

Clinical impact questionnaire

1) My Final Diagnosis (after work-up):

____ Latent TB infection (LTBI) ____ Active TB disease __X__ No TB infection or disease

2) Did QFT test play any role in making the above DIAGNOSIS?

__X__ Yes ____ No ____ Not applicable, QFT was not requested or results were not available to me

3) If Yes to the above question, how was it useful?

Latent TB

	TST	QFT	Decision
X	+	--	I used the negative QFT to rule out LTBI
☐	--	+	I used the positive QFT to diagnose LTBI
☐	+	+	I used both the positive TST and QFT to diagnose LTBI
☐	?	+	I used the positive QFT to diagnose LTBI (regardless of TST result)
☐			Other explanation:

Active TB

	QFT	Decision
☐	+	I used the positive QFT and other signs/features to diagnose active TB
☐	--	I used the negative QFT to rule out active TB
☐		Other explanation:

Clinical impact questionnaire

4) If I had not ordered QFT, my diagnosis would have probably been:

X Latent TB infection (LTBI) ____ Active TB disease ____ No TB infection or disease

5) My Final Treatment Decision (after work-up):

X No prophylaxis for LTBI
____ LTBI prophylaxis: INH for 6 or 9 months or specify other regimen: _____
____ Active TB disease therapy

6) Did QFT test play any role in the above TREATMENT decision?

X Yes ____ No ____ Not applicable, QFT was not requested or results were not available to me

7) If Yes to the above question, how was it useful?

	TST	QFT	Decision
X	+	--	I used the negative QFT to withhold LTBI prophylaxis
☐	--	+	I used the positive QFT to initiate LTBI prophylaxis
☐	+	+	I used both the positive TST and QFT to initiate LTBI prophylaxis
☐	?	+	I used the positive QFT to initiate LTBI prophylaxis (regardless of TST result)
☐	**Active TB**	+	I used the positive QFT & other signs/features to initiate anti-TB therapy
☐			Other explanation:

Signature_____ Date_____ Chart #_____

Data analysis

- Primary outcome was the proportion of clinical changes made within each subgroup
- Logistic regression analysis to determine factors associated with a clinical change in children with discordant TST+/QFT- results
  - Dependent variable was clinical change made (yes or no)
  - Independent variables were determined *a priori*:
    - age, sex, foreign birth, recent arrival, BCG vaccination, TST induration*, multiple BCG or TST, history of contact, chest radiograph abnormalities, and year of enrollment
  - Clustered robust standard errors were calculated to account for different preferences, TB experience and QFT knowledge among respirologists

Clinical subgroups

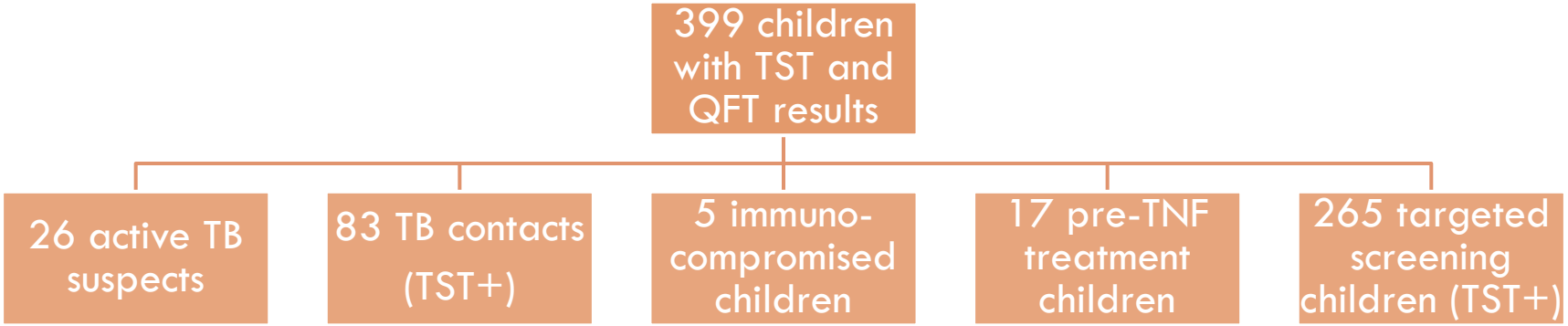

Table 1. Patient characteristics

Characteristic	Frequency (%)
Median age in years (range)	13 (0-18)
Sex	
Male	215 (54)
Female	184 (46)
Country of birth	
Canada-born	67 (17)
Foreign-born	332 (83)
BCG vaccination	
Yes	327 (82)
No	72 (18)
History of contact	
Yes	99 (75)
No	300 (25)

Table 1 (Continued)

Characteristic	Frequency (%)
TST (recommended cut-offs)*	
Positive	367 (92)
Negative	32 (8)
QFT	
Positive	82 (21)
Negative	311 (78)
Indeterminate	6 (1)
Chest radiography	
Abnormalities present	27 (7)
No abnormalities	367 (92)
Not done (i.e. negative TST)	5 (1)
Year of study	
Year 1	202 (51)
Year 2	197 (49)

* 5 mm for contacts and immunocompromised children; 10 mm for all others

Concordance

Active TB suspects (n=26)		
	TST +	TST -
QFT +	6	0
QFT -	11*	9

* 5 of 11 TST+/QFT- children were treated for active TB based on abnormal chest radiography and history of contact; only 2 of these 5 cases were positive on culture

Concordance

TST+ TB contacts (n=83)	
	TST +
QFT +	29
QFT -	52*
QFT indeterminate	2

* 7 contacts who had converted to a positive result on the 2nd TST done 12 weeks later remained negative on the 2nd QFT

Concordance

TST+ targeted screening children (n=265)	
	TST +
QFT +	46
QFT -	218
QFT indeterminate	1

Clinical changes

- TB contacts: In 52 TST+/QFT- children, INH was prescribed based on the positive TST result in 49 (94.2%) children. The negative QFT result was used to withhold INH in the remaining 3 children, who were considered contacts with minimal exposure.

- Targeted screening children: In 201 TST+/QFT- children who returned for their follow-up visit, the negative QFT result was used to withhold INH in 145 (72.1%) children.

Multivariable analysis (n=250)

Covariate	Odds Ratio (95% CI)
Age in years	0.98 (0.90, 1.07)
Male	0.60 (0.33, 1.08)
Foreign-born	1.01 (0.29, 3.57)
Recent arrival (≤2 years)	0.70 (0.27, 1.82)
BCG vaccinated	0.48 (0.16, 1.45)
Multiple BCG/TST	3.93 (0.68, 22.55)
History of contact	0.01 (0.003, 0.08) *
TST 10-14 mm	1 (reference)
TST 15-19 mm	0.57 (0.30, 1.09)
TST ≥20 mm	0.27 (0.15, 0.49) *
CXR abnormalities	2.52 (0.68, 9.32)
Year of study (1st vs 2nd)	0.87 (0.25, 3.03)

Follow-up results

- Phone calls were made 1 year later to the homes of TST+/QFT- children who did not receive INH. Parents were asked about:
  - Travel to endemic countries
  - Contact with TB cases
  - Presence of TB symptoms
  - Reasons for doctor or ER visits in the past year
- A total of 96 calls were made:
  - 59 (61.5%) successfully contacted
  - 24 (25%) could not be reached after 3 attempts
  - 13 (13.5%) had moved
- As of January 2012, we are not aware of any child that has developed active disease

Study strengths

- Many studies have evaluated factors associated with discordant TST/QFT results; our study evaluates factors associated with actual clinical changes

- By asking for clinical decisions before and after the QFT, we were able to go beyond medical charts by providing the explicit rationale behind management decisions

- The Hawthorne effect was not a major issue:
  - One respirologist relied on the TST alone and did not use the QFT
  - If intention to test means intention to treat or not treat, then the QFT was not used in strict accordance with the clinical indications in child contacts

Study limitations

- Study design does not allow us to answer: what would happen if respirologists were given QFT first then TST?
- Large number of TST+ children from school screenings and low number in other subgroups are not representative of all children investigated for LTBI
- Our findings cannot be generalized to primary-care settings with physicians who are not highly experienced in TB management
- The study could only assess short-term outcomes (clinical changes) and not long-term patient outcomes (progression to active TB)

Conclusions

- History of contact and TST induration ≥20mm were associated with reducing the likelihood of a clinical change based on a negative QFT
- Given their suboptimal sensitivity, a negative QFT result cannot be used to rule out active TB
- QFT may be useful in reducing the number of low-risk children considered for INH treatment
- Further research is needed to discover new biomarkers that will identify those who will benefit most from preventive therapy

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