Optimism bias, inflated accuracy estimates, and contradicted findings in TB diagnostic research

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Les meilleurs soins pour la vie
The Best Care for Life

Context

There is some evidence that:

- Initially stronger effects and subsequent contradictions are not infrequent in highly cited research of clinical interventions and their outcomes.
- Claims from highly cited observational studies persist and continue to be supported in the medical literature despite strong contradictory evidence from randomized trials.
- Newly discovered true (non-null) associations often have inflated effects compared with the true effect sizes.
- Publication bias is a major concern and may be more widespread than we think; some have also challenged the conventional publishing model
- Even within published studies, selective reporting of positive outcomes in randomized trials as well as observational studies appears to be frequent
- Lack of replication of research findings and over-interpretation of findings are other concerns, especially in some fields (e.g. biomarkers)
- All of these likely result in "optimism bias" —unwarranted belief in the efficacy of new tools or interventions, and overinterpretation of the applicability of findings

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

Context Controversy and uncertainty ensue when the results of clinical research on the effectiveness of interventions are subsequently contradicted. Controversies are most prominent when high-impact research is involved.

Objectives To understand how frequently highly cited studies are contradicted or find effects that are stronger than in other similar studies and to discern whether specific characteristics are associated with such refutation over time.

Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature were examined.

Main Outcome Measure The results of highly cited articles were compared against subsequent studies of comparable or larger sample size and similar or better controlled designs. The same analysis was also performed comparatively for matched studies that were not so highly cited.

Results Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly-cited nonrandomized studies had been contradicted or had found stronger effects vs 9 of 39 randomized controlled trials ($P=.008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($P=.009$) than replicated or unchallenged studies although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than highly cited studies, but they included more studies with "negative" results.

Conclusions Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes. The extent to which high citations may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones.

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CLINICAL RESEARCH ON IMPORTANT questions about the efficacy of medical interventions is sometimes followed by subsequent studies that either reach opposite conclusions or suggest that the original claims were too strong. Such disagreements may upset clinical practice and acquire publicity in both scientific circles and in the lay press. Several empirical investigations have tried to address whether specific types of studies are more likely to be contradicted and to explain observed controversies. For example, evidence exists that small studies may sometimes be refuted by larger ones.[1,2]

Similarly, there is some evidence on disagreements between epidemiological studies and randomized trials.[3-5] Prior investigations have focused on a variety of studies without any particular attention to their relative importance and scientific impact. Yet, most research publications have little impact while a small minority receives

Persistence of Contradicted Claims in the Literature

Athina Tatsioni, MD
Nikolaos G. Bonitsis, MD
John P. A. Ioannidis, MD

Context Some research findings based on observational epidemiology are contradicted by randomized trials, but may nevertheless still be supported in some scientific circles.

Objectives To evaluate the change over time in the content of citations for 2 highly cited epidemiological studies that proposed major cardiovascular benefits associated with vitamin E in 1993; and to understand how these benefits continued being defended in the literature, despite strong contradicting evidence from large randomized clinical trials (RCTs). To examine the generalizability of these findings, we also examined the extent of persistence of supporting citations for the highly cited and contradicted protective effects of beta-carotene on cancer and of estrogen on Alzheimer disease.

Data Sources For vitamin E, we sampled articles published in 1997, 2001, and 2005 (before, early, and late after publication of refuting evidence) that referenced the highly cited epidemiological studies and separately sampled articles published in 2005 and referencing the major contradicting RCT (HOPE trial). We also sampled articles published in 2006 that referenced highly cited articles proposing benefits associated with beta-carotene for cancer (published in 1981 and contradicted long ago by RCTs in 1994-1996) and estrogen for Alzheimer disease (published in 1996 and contradicted recently by RCTs in 2004).

Data Extraction The stance of the citing articles was rated as favorable, equivocal, and unfavorable to the intervention. We also recorded the range of counterarguments raised to defend effectiveness against contradicting evidence.

Results For the 2 vitamin E epidemiological studies, even in 2005, 50% of citing articles remained favorable. A favorable stance was independently less likely in more recent articles, specifically in articles that also cited the HOPE trial (odds ratio for 2001, 0.05 [95% confidence interval, 0.01-0.19; $P<.001$] and the odds ratio for 2005, 0.06 [95% confidence interval, 0.02-0.24; $P<.001$], as compared with 1997), and in general/internal medicine vs specialty journals. Among articles citing the HOPE trial in 2005, 41.4% were unfavorable. In 2006, 62.5% of articles referencing the highly cited article that had proposed beta-carotene and 61.7% of those referencing the highly cited article on estrogen effectiveness were still favorable; 100% and 96%, respectively, of the citations appeared in specialty journals; and citations were significantly less favorable ($P=.001$ and $P=.009$, respectively) when the major contradicting trials were also mentioned. Counterarguments defending vitamin E or estrogen included diverse selection and information biases and genuine differences across studies in participants, interventions, cointerventions, and outcomes. Favorable citations to beta-carotene, long after evidence contradicted its effectiveness, did not consider the contradicting evidence.

Conclusion Claims from highly cited observational studies persist and continue to be supported in the medical literature despite strong contradictory evidence from randomized trials.

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Why Most Discovered True Associations Are Inflated

John P. A. Ioannidis

Abstract: Newly discovered true (non-null) associations often have inflated effects compared with the true effect sizes. I discuss here the main reasons for this inflation. First, theoretical considerations prove that when true discovery is claimed based on crossing a threshold of statistical significance and the discovery study is underpowered, the observed effects are expected to be inflated. This has been demonstrated in various fields ranging from early stopped clinical trials to genome-wide associations. Second, flexible analyses coupled with selective reporting may inflate the published discovered effects. The vibration ratio (the ratio of the largest vs. smallest effect on the same association approached with different analytic choices) can be very large. Third, effects may be inflated at the stage of interpretation due to diverse conflicts of interest. Discovered effects are not always inflated, and under some circumstances may be deflated—for example, in the setting of late discovery of associations in sequentially accumulated overpowered evidence, in some types of misclassification from measurement error, and in conflicts causing reverse biases. Finally, I discuss potential approaches to this problem. These include being cautious about newly discovered effect sizes, considering some rational down-adjustment, using analytical methods that correct for the anticipated inflation, ignoring the magnitude of the effect (if not necessary), conducting large studies in the discovery phase, using strict protocols for analyses, pursuing complete and transparent reporting of all results, placing emphasis on replication, and being fair with interpretation of results.

(*Epidemiology* 2008;19: 640–648)

prognostic studies, and so forth. I start here with the assumption that a research finding is indeed true (non-null), ie, it reflects a genuine association that is not entirely due to chance or biases (confounding, misclassification, selection biases, selective reporting, or other). The question is: do the effect sizes for such associations, at the time they are first discovered and published in the scientific literature, accurately reflect the true effect sizes?

The article has the following sections: a brief literature review on inflated early-effect sizes based on theoretical and empirical considerations; a description of the major reasons why early discovered effects are inflated and the major countering forces that may occasionally lead to deflated effects (underestimates); and suggestions on how to deal with these problems.

Evidence About Inflated Early-Effect Sizes

Table 1 cites articles suggesting that early studies give (on average) inflated estimates of effect.[2–34] I list here only selected evaluations that cover either many different articles/effects or a whole research domain or method. This list is nowhere close to exhaustive. For some topics, such as the inflation of regression coefficients for variables selected through stepwise statistical-significance-based processes, the literature is

Comparison of Effect Sizes Associated With Biomarkers Reported in Highly Cited Individual Articles and in Subsequent Meta-analyses

John P. A. Ioannidis, MD, DSc
Orestis A. Panagiotou, MD

Context Many biomarkers are proposed in highly cited studies as determinants of disease risk, prognosis, or response to treatment, but few eventually transform clinical practice.

Objective To examine whether the magnitude of the effect sizes of biomarkers proposed in highly cited studies is accurate or overestimated.

Data Sources We searched ISI Web of Science and MEDLINE until December 2010.

Study Selection We included biomarker studies that had a relative risk presented in their abstract. Eligible articles were those that had received more than 400 citations in the ISI Web of Science and that had been published in any of 24 highly cited biomedical journals. We also searched MEDLINE for subsequent meta-analyses on the same associations (same biomarker and same outcome).

Data Extraction In the highly cited studies, data extraction was focused on the disease/outcome, biomarker under study, and first reported relative risk in the abstract. From each meta-analysis, we extracted the overall relative risk and the relative risk in the largest study. Data extraction was performed independently by 2 investigators.

Results We evaluated 35 highly cited associations. For 30 of the 35 (86%), the highly cited studies had a stronger effect estimate than the largest study; for 3 the largest study was also the highly cited study; and only twice was the effect size estimate stronger in the largest than in the highly cited study. For 29 of the 35 (83%) highly cited studies, the corresponding meta-analysis found a smaller effect estimate. Only 15 of the associations were nominally statistically significant based on the largest studies, and of those only 7 had a relative risk point estimate greater than 1.37.

Conclusion Highly cited biomarker studies often report larger effect estimates for postulated associations than are reported in subsequent meta-analyses evaluating the same associations.

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MANY NEW BIOMARKERS ARE continuously proposed[1-3] as potential determinants of disease risk, prognosis, or response to treatment. The plethora of statistically significant associations[4,5] increases expectations for improvements in risk appraisal.[6] However, many markers get evaluated only in 1 or a few studies.[7] Among those evaluated more extensively, few reach clinical practice.[8]

This translational attrition requires better study. Are the effect sizes proposed in the literature accurate or overestimated?[9] It is interesting to address this question in particular for biomarker studies that are highly cited. Many of these risk factors are also evaluated in meta-analyses[10] that allow overviews of the evidence. However, some meta-analyses may suffer bias from selective reporting, especially among small data sets[11-13]; then large studies may provide more unbiased evidence.

The Thin Line Between Hope and Hype in Biomarker Research

Patrick M. M. Bossuyt, PhD

BIOMARKERS HAVE BECOME A POPULAR TOPIC IN medicine, and investigations of putative molecular indicators of a specific biological state have started to occupy a considerable part of health research. In the past decades, advances in molecular biology coupled with progress in genomics, proteomics, and metabolomics have fueled hope for the development of new medical tests. Biomarkers should enable clinicians to make an earlier or more definitive diagnosis, identify persons at risk of developing disease, develop more precise estimates about prognosis, and fine-tune treatment selection, thereby approaching a form of stratified, or even personalized, medicine.

With few exceptions, most of these promises have yet to be fulfilled. Only a small number of biomarkers are being used in routine clinical practice.[1] No new major cancer biomarkers have been approved for clinical use for at least 25 years.[2] Most clinical decisions still rely on more conventional forms of medical testing, such as existing laboratory measurements and imaging studies.

There are several reasons for the relatively slow progress. For example, molecular biomarkers for many conditions have yet to be identified. Other issues involve problems with characterization and control of the preanalytical variability[2] and suboptimal design of studies used for marker discovery and validation. Many biomarker studies have major methodological shortcomings, in particular in the selection of appropriate study groups; for instance, some studies include only extreme cases and contrast them with healthy controls. Despite these concerns, hope has been high, and hype has never been far away.

For instance, in a 1994 study on cancer risk in 33 families with evidence of linkage to *BRCA1* carriers, the authors compared cancer cases other than breast or ovarian cancer with national incidence rates and reported a 4.11 relative excess risk for colon cancer among *BRCA1* carriers.[4] A study published 11 years later, in which data were summarized from more than 30 epidemiologic studies on cancer incidence in *BRCA1* mutation carriers, found that all of the studies on colon cancer that had appeared after the 1994 study had reported smaller, and often nonsignificant, relative risks.[5] One of these, published in 2004, reported a nonsignificant odds ratio of 1.24.[6] However, this study has received only 26 citations so far, compared with 1051 for the initial 1994 article.[4]

Likewise, in a 1991 article, the authors reported high peak serum levels of homocysteine in 16 of 38 patients with cerebrovascular disease, in 7 of 25 with peripheral vascular disease, and in 18 of 60 with coronary vascular disease, but in 0 of 27 normal adults, and reported a statistically significant odds ratio of 23.9 for coronary vascular disease in patients with hyperhomocysteinemia.[7] A meta-analysis of hyperhomocysteinemia, published 9 years later and including 33 studies and more than 16 000 patients,[8] reported a summary odds ratio for cardiovascular disease of 1.58. The initial report has received 1451 citations, whereas to date, the meta-analysis has had 37 citations.

It is difficult to estimate how often a study that publishes a more extreme effect receives more attention than larger studies of the same marker, or than meta-analyses, which provide a summary estimate based on all available evidence, after critical appraisal. The review by Ioannidis and Panagiotou[3] is not based on an "inception cohort," ie, a group of studies of a biomarker defined from the first evalu-

Publication bias and selective publication

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

ABSTRACT

BACKGROUND

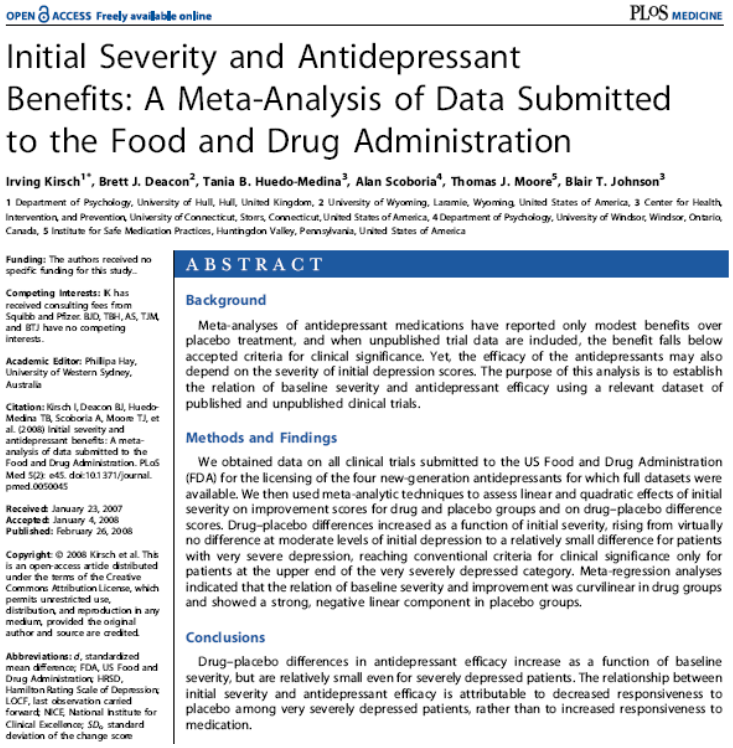
Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.

METHODS

We obtained reviews from the Food and Drug Administration (FDA) for studies of 12 antidepressant agents involving 12,564 patients. We conducted a systematic literature search to identify matching publications. For trials that were reported in the literature, we compared the published outcomes with the FDA outcomes. We also compared the effect size derived from the published reports with the effect size derived from the entire FDA data set.

RESULTS

Among 74 FDA-registered studies, 31%, accounting for 3449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.



OPEN ACCESS Freely available online PLoS MEDICINE

Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration

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Competing Interests: IK has received consulting fees from Squibb and Pfizer. BJD, TBH, AS, TJM, and BTJ have no competing interests.

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Citation: Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, et al. (2008) Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. PLoS Med 5(2): e45. doi:10.1371/journal.pmed.0050045

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Abbreviations: *d*, standardized mean difference; FDA, US Food and Drug Administration; HRSD, Hamilton Rating Scale of Depression; LOCF, last observation carried forward; NICE, National Institute for Clinical Excellence; SD_d, standard deviation of the change score

ABSTRACT

Background

Meta-analyses of antidepressant medications have reported only modest benefits over placebo treatment, and when unpublished trial data are included, the benefit falls below accepted criteria for clinical significance. Yet, the efficacy of the antidepressants may also depend on the severity of initial depression scores. The purpose of this analysis is to establish the relation of baseline severity and antidepressant efficacy using a relevant dataset of published and unpublished clinical trials.

Methods and Findings

We obtained data on all clinical trials submitted to the US Food and Drug Administration (FDA) for the licensing of the four new-generation antidepressants for which full datasets were available. We then used meta-analytic techniques to assess linear and quadratic effects of initial severity on improvement scores for drug and placebo groups and on drug–placebo difference scores. Drug–placebo differences increased as a function of initial severity, rising from virtually no difference at moderate levels of initial depression to a relatively small difference for patients with very severe depression, reaching conventional criteria for clinical significance only for patients at the upper end of the very severely depressed category. Meta-regression analyses indicated that the relation of baseline severity and improvement was curvilinear in drug groups and showed a strong, negative linear component in placebo groups.

Conclusions

Drug–placebo differences in antidepressant efficacy increase as a function of baseline severity, but are relatively small even for severely depressed patients. The relationship between initial severity and antidepressant efficacy is attributable to decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication.

While almost all trials with "positive" results on antidepressants had been published, trials with "negative" results submitted to the US Food and Drug Administration, with few exceptions, remained either unpublished or were published with the results presented so that they would appear "positive"

Non-replicated studies and publication bias – especially in genetic and biomarker studies

Human Heredity

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Non-Replication and Inconsistency in the Genome-Wide Association Setting

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available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

EJC

Almost all articles on cancer prognostic markers report statistically significant results

Panayiotis A. Kyzas[a], *Despina Denaxa-Kyza*[a], *John P.A. Ioannidis*[a,b,c,*]

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2

As researchers in tuberculosis we asked the question:

"is there evidence for 'optimism bias' in TB diagnostic research?"

We present several case studies to answer this question

Several new diagnostics are in the pipeline
But do they work? Will optimism bias prove to be a big issue?

Case study 1:

How much evidence is sufficient for commercialization?

Promising new Point of Care test: LAM antigen detection

ELSEVIER

Journal of Microbiological Methods 45 (2001) 41–52

Journal of Microbiological Methods

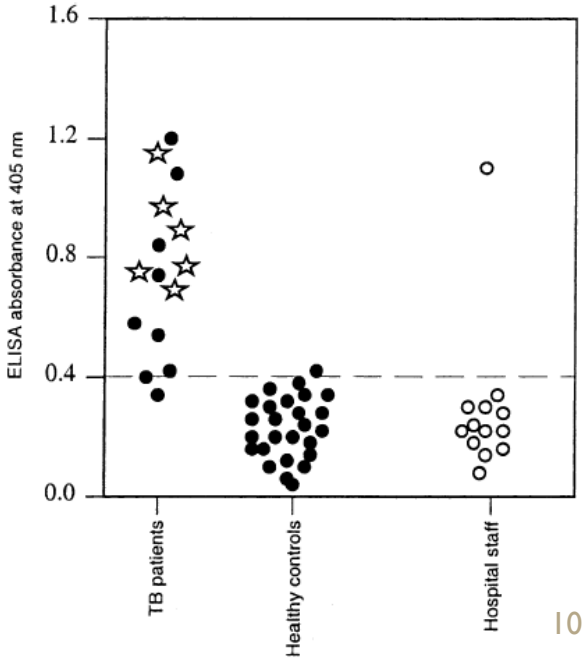
www.elsevier.com/locate/jmicmeth

Rapid diagnosis of tuberculosis by detection of mycobacterial lipoarabinomannan in urine

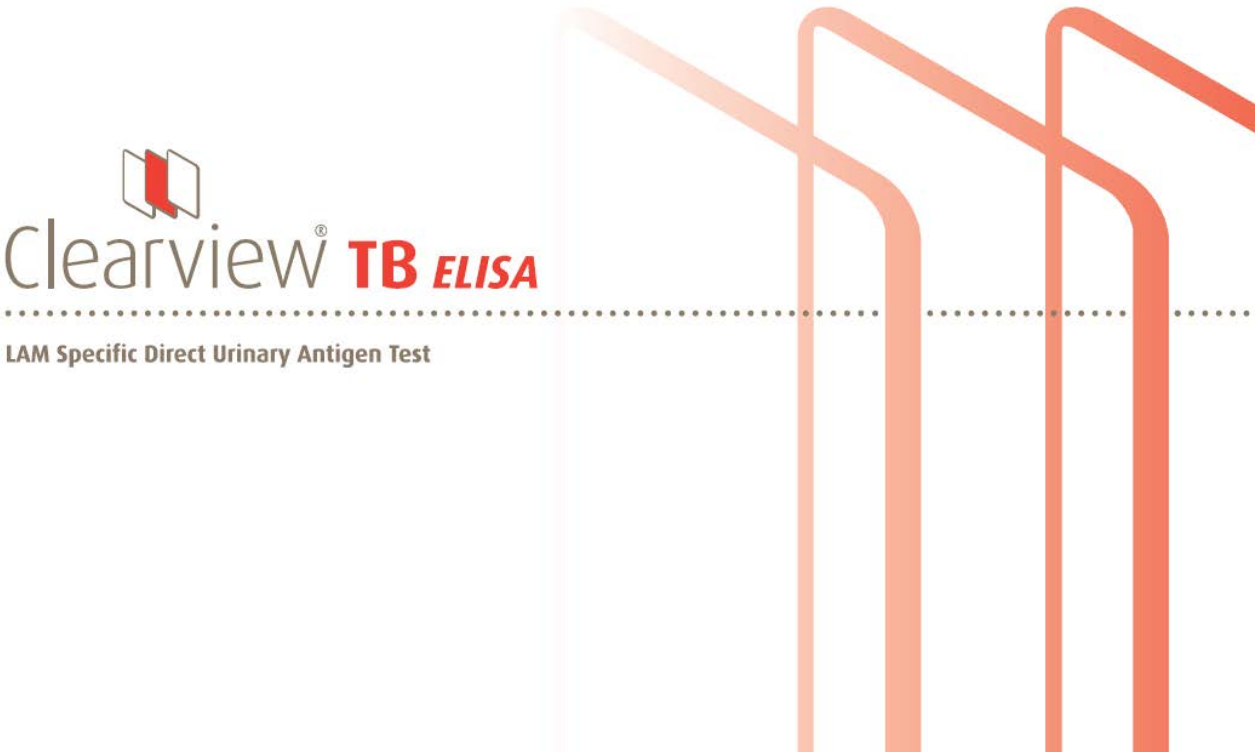
Beston Hamasur [a], Judith Bruchfeld [b], Melles Haile [a], Andrzej Pawlowski [a], Bjarne Bjorvatn [c], Gunilla Källenius [a,d], Stefan B. Svenson [a,e,*]

Sensitivity 93%

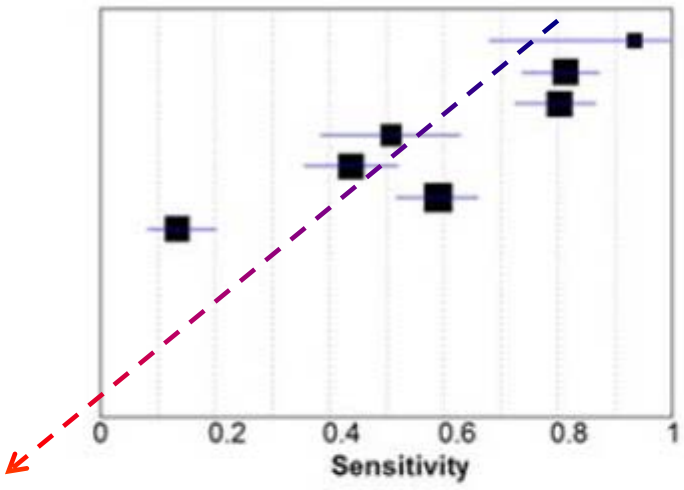
Specificity 95%



Commercialized by Chemogen and then by Inverness (now Alere)

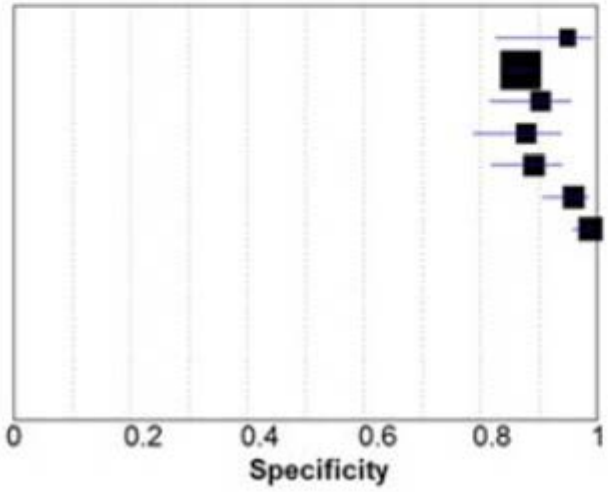


Subsequent evidence from field studies in India, S Africa, Zimbabwe, Tanzania



	Sensitivity (95% CI)
Hamasur (2001)	0.93 (0.68 - 1.00)
Tessema (2001)	0.81 (0.74 - 0.87)
Boehme (2005)	0.80 (0.72 - 0.87)
Reither (2009)	0.51 (0.38 - 0.63)
Mutetwa (2009)	0.44 (0.36 - 0.52)
Shah (2009)	0.59 (0.52 - 0.66)
Dheda (2010)	0.13 (0.08 - 0.20)

Chi-square = 202.55; df = 6 (p = 0.0000)
Inconsistency (I-square) = 97.0 %



	Specificity (95% CI)
Hamasur (2001)	0.95 (0.83 - 0.99)
Tessema (2001)	0.87 (0.84 - 0.89)
Boehme (2005)	0.90 (0.82 - 0.96)
Reither (2009)	0.88 (0.79 - 0.94)
Mutetwa (2009)	0.89 (0.82 - 0.94)
Shah (2009)	0.96 (0.91 - 0.99)
Dheda (2010)	0.99 (0.96 - 1.00)

Chi-square = 38.63; df = 6 (p = 0.0000)
Inconsistency (I-square) = 84.5 %

Minion et al. ERJ 2011

Lessons

- Rapid commercialization on the basis of early data may be problematic (especially case-control studies that can exaggerate accuracy estimates)
- Thorough field evaluation in diverse settings (e.g. varying HIV prevalence) should have been done
- This case study raises an interesting question: at what point in time after a test is introduced should meta-analyses be done?

Case study 2:

How should we design and analyze diagnostic studies?

Serologic (antibody) tests for TB

A systematic review of commercial serological antibody detection tests for the diagnosis of extrapulmonary tuberculosis

Karen R Steingart, Megan Henry, Suman Laal, Philip C Hopewell, Andrew Ramsay, Dick Menzies, Jane Cunningham, Karin Weldingh, Madhukar Pai

Thorax 2007

PLoS Medicine 2007

Commercial Serological Antibody Detection Tests for the Diagnosis of Pulmonary Tuberculosis: A Systematic Review

Karen R. Steingart[1,2], Megan Henry[3], Suman Laal[4,5,6], Philip C. Hopewell[1,2], Andrew Ramsay[7], Dick Menzies[8,9], Jane Cunningham[7], Karin Weldingh[10], Madhukar Pai[8,9*]

Performance of Purified Antigens for Serodiagnosis of Pulmonary Tuberculosis: a Meta-Analysis[▽†]

Karen R. Steingart,[1*] Nandini Dendukuri,[2] Megan Henry,[3‡] Ian Schiller,[2] Payam Nahid,[4] Philip C. Hopewell,[1,4] Andrew Ramsay,[5] Madhukar Pai,[2] and Suman Laal[6,7,8]

Clin Vaccine Immunol 2009

Why do these tests fail in field studies?

TABLE 3. Characteristics of study quality

Characteristic	No. (%) of studies
Study design	
Cross-sectional	39 (15)
Case-control	208 (82)
Nested within observational study	7 (3)
Recruitment of participants	
Consecutive or random	20 (8)
Convenience or not reported	234 (92)
Selection criteria clearly described	141 (56)
Complete verification by use of the reference standard	107 (42)
Execution of test described in sufficient detail	253 (100)[a]
Index test results blinded to reference standard?	
Yes	65 (26)
No	1 (0)
Not reported	188 (74)

[a] The description of the test execution was deemed insufficient in one study.

A large % were case-control studies

Confirmed TB cases
Vs.
Healthy controls (often from low-incidence countries)

Spectrum bias (a form of selection bias)

- Population used for evaluating the test:
  - Extreme contrast
    - Case-control design
  - Normal contrast (Indicated population)
    - Consecutively recruited patients in whom the disease is suspected

- Extreme contrast (spectrum bias) can result in overestimation of test accuracy

Clinical Chemistry 51:8
1335–1341 (2005)

Minireview

Case–Control and Two-Gate Designs in Diagnostic Accuracy Studies

Anne W.S. Rutjes,[1*] Johannes B. Reitsma,[1] Jan P. Vandenbroucke,[2] Afina S. Glas,[3] and Patrick M.M. Bossuyt[1]

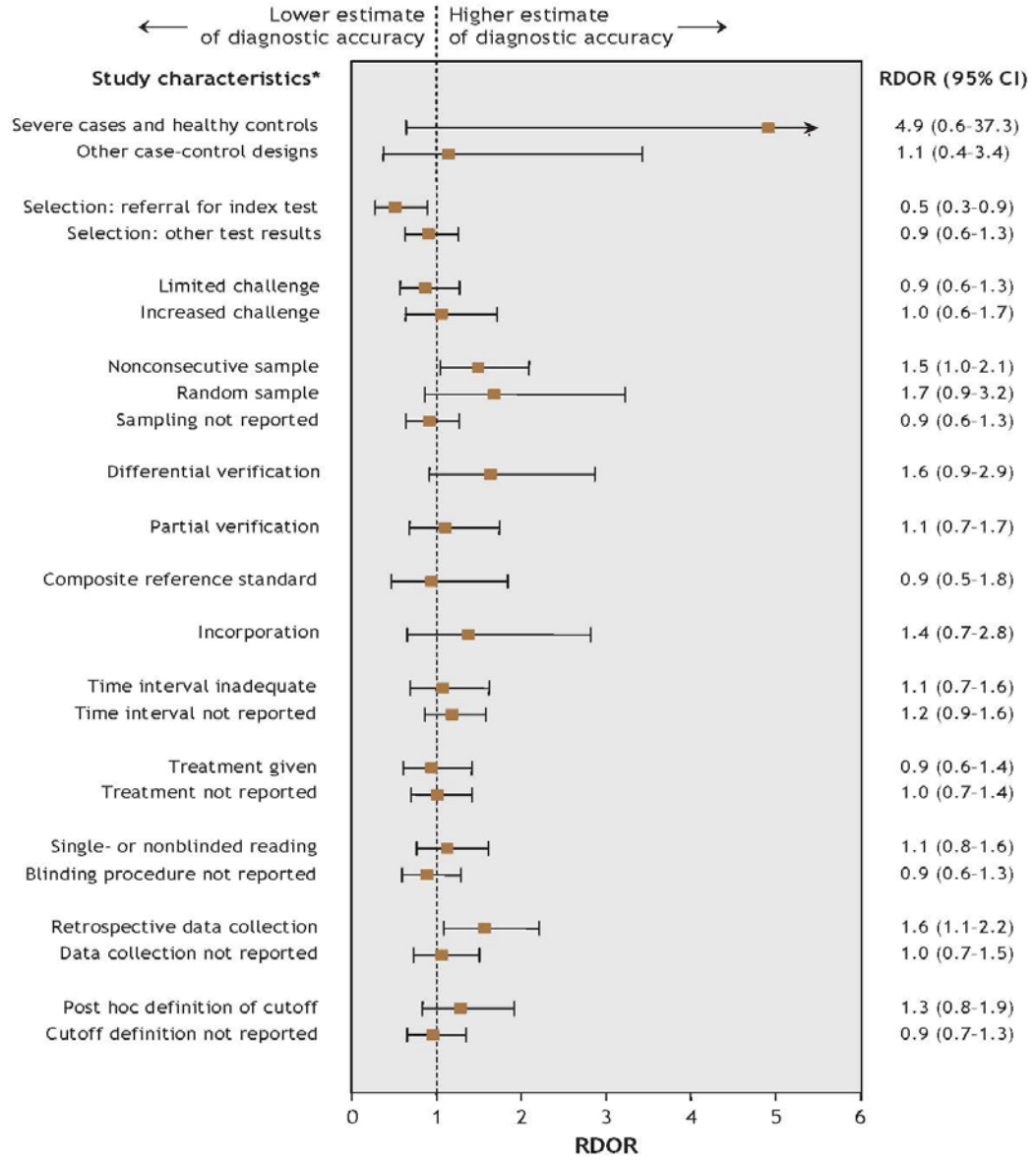


Fig. 2: Effects of study design characteristics on estimates of diagnostic accuracy. RDOR = relative diagnostic odds ratio (adjusted RDORs were estimated in a multivariable random-effects meta-epidemiologic regression model).

Case-control design results in optimistic accuracy

Rutjes et al. CMAJ 2006

We find this in TB as well: Example: PCR tests for TB meningitis

Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis

Madhukar Pai, Laura L Flores, Nitika Pai, Alan Hubbard, Lee W Riley, and John M Colford Jr

Case-control studies had a two-fold higher diagnostic odds ratios than cross-sectional studies

Table 4. Stratified analyses for the evaluation of heterogeneity among studies with in-house tests

Subgroup	Number of studies	Summary diagnostic odds ratio* (95% CI)	Test for heterogeneity† p value
Study design			
Case-control	19	86·5 (39·3, 190·2)	0·03
Cross-sectional	16	43·3 (22·5, 83·3)	0·94
Blinded interpretation of test and/or reference standard results			
Yes	21	46·9 (24·9, 88·6)	0·16
No	14	82·3 (39·8, 170·2)	0·70
Consecutive or random sampling of participants			
Yes	18	63·3 (32·8, 122·4)	0·20
No	17	46·8 (23·6, 92·8)	0·42
Prospective data collection			
Yes	18	59·9 (28·1, 127·6)	0·12
No	17	55·2 (29·9, 101·6)	0·59

*Random effects model. †χ^2 test for heterogeneity. CI=confidence interval.

Pai et al. Lancet Infect Dis 2003

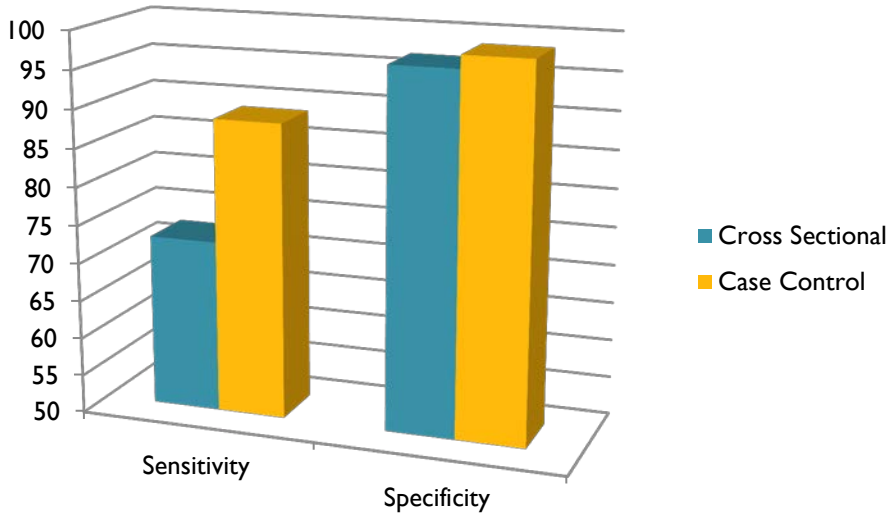
LED microscopy for sputum examination

- Cross Sectional Studies

Sensitivity 72.6%
(69.2, 75.8)
Specificity 96.9
(92.1, 98.8)

- Case Control Studies

Sensitivity 88.7%
(81.4, 93.4)
Specificity: 98.6%
(97.3, 99.3)



Minion et al. Unpublished

Analysis of diagnostic studies

- It is not uncommon to see researchers:
  - Excluding patients or controls with no definitive diagnoses ("diagnostic myopia bias")
  - Excluding indeterminate or inconclusive results
  - Perform post-hoc "discrepant" analysis to move numbers within 2 x 2 tables
- Such analyses often result in spuriously inflated accuracy estimates

Example: exclusion of indeterminates can inflate accuracy estimates

OPEN ACCESS Freely available online

PLoS one

Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals

Basirudeen Syed Ahamed Kabeer[1], Rajasekaran Sikhamani[5], Sowmya Swaminathan[2], Venkatesan Perumal[3], Paulkumaran Paramasivam[4], Alamelu Raja[1]*

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Abstract

Background: A rapid and specific test is urgently needed for tuberculosis (TB) diagnosis especially among human immunodeficiency virus (HIV) infected individuals. In this study, we assessed the sensitivity of Interferon gamma release assay (IGRA) in active tuberculosis patients who were positive for HIV infection and compared it with that of tuberculin skin test (TST).

Methodology/Principal Findings: A total of 105 HIV-TB patients who were naïve for anti tuberculosis and anti retroviral therapy were included for this study out of which 53 (50%) were culture positive. Of 105 tested, QuantiFERON-TB Gold in-tube (QFT-G) was positive in 65% (95% CI: 56% to 74%), negative in 18% (95% CI: 11% to 25%) and indeterminate in 17% (95% CI: 10% to 24%) of patients. The sensitivity of QFT-G remained similar in pulmonary TB and extra-pulmonary TB patients. The QFT-G positivity was not affected by low CD4 count, but it often gave indeterminate results especially in individuals with CD4 count <200 cells/μl. All of the QFT-G indeterminate patients whose sputum culture were positive, showed ≤ 0.25 IU/ml of IFN-γ response to phytohemagglutinin (PHA). TST was performed in all the 105 patients and yielded the sensitivity of 31% (95% CI: 40% to 22%). All the TST positives were QFT-G positives. The sensitivity of TST was decreased, when CD4 cell counts declined.

Conclusions/Significance: Our study shows neither QFT-G alone or in combination with TST can be used to exclude the suspicion of active TB disease. However, unlike TST, QFT-G yielded fewer false negative results even in individuals with low CD4 count. The low PHA cut-off point for indeterminate results suggested in this study (≤ 0.25 IU/ml) may improve the proportion of valid QFT-G results.

Citation: Syed Ahamed Kabeer B, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, et al. (2009) Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals. PLoS ONE 4(5): e5718. doi:10.1371/journal.pone.0005718

- If indeterminates are included:
  - Sens = 66%
- If indeterminates are excluded:
  - Sens = 85%

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Published by Elsevier Science Inc.

0895-4356/99/$–see front matter
PII S0895-4356(99)00101-8

Discrepant Analysis: A Biased and an Unscientific Method for Estimating Test Sensitivity and Specificity

*Alula Hadgu**

CENTERS FOR DISEASE CONTROL AND PREVENTION, DIVISION OF STD PREVENTION, ATLANTA, GEORGIA

ABSTRACT. Discrepant analysis is a widely used technique for estimating test performance indices (sensitivity, specificity, etc.) of DNA-amplification tests for detecting infectious diseases. It has recently been claimed that the discrepant analysis–based estimates of specificity are typically less biased than those based on culture and that the discrepant analysis–based specificity shows little appreciable bias. In this article, I show that those conclusions are incorrect. Using a typical example from the published literature, I show that the discrepant analysis–based estimates of sensitivity and specificity can generate a significant and clinically important overestimation of the true sensitivity and specificity values. Moreover, I demonstrate that the concept of discrepant analysis is profoundly flawed and unscientific. It violates a fundamental principle of diagnostic testing—the principle that the new test should not be used to determine the true disease status. Thus, the major problem with discrepant analysis is not only that it is biased but that it is unscientific. Therefore, discrepant analysis should not be adopted for the evaluation of any diagnostic or screening test. J CLIN EPIDEMIOL 52;12:1231–1237, 1999. Published by Elsevier Science Inc.

KEY WORDS. Discrepant analysis, sensitivity, specificity, DNA-amplification tests, *Chlamydia trachomatis*

Lessons

- Early case-control studies are often used to promote and market tests
- But a large proportion of tests fail, once they are used in real world settings (e.g. large number of failed commercial serological tests)
- Case-control studies exaggerate accuracy estimates, especially if the two-gate approach is used
- Certain data analytic approaches can also inflate accuracy estimates
- Diagnostic studies can begin as case-control studies, but need to move beyond that to prospective studies in clinically indicated populations
- Even accuracy data may be insufficient to decide on clinical impact
- Regulatory agencies should demand prospective data and not just rely on case-control accuracy studies

Case study 3:

Where should TB tests be evaluated and which populations are appropriate?

It is not uncommon to see TB test evaluations where:

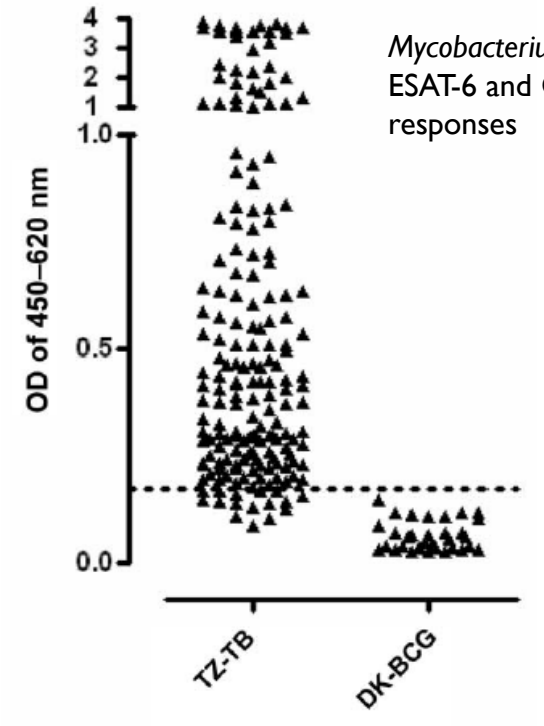
- Cases come from a high-incidence country and controls from a low-incidence country
- Tests work well in a low-incidence country and fall apart in a high-incidence country
- Tests that work well in immunocompetent persons fail in populations with high HIV prevalence

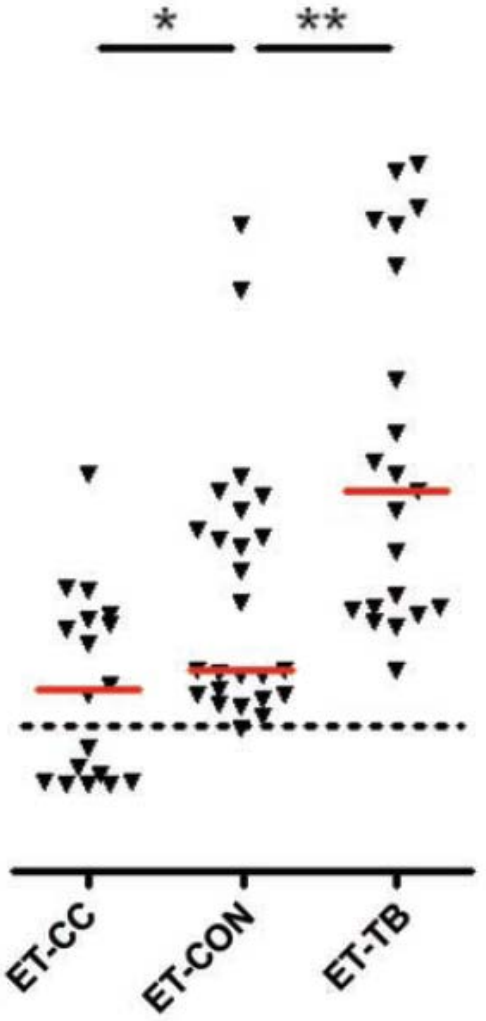
Lack of discrimination in TB endemic settings: example

Mycobacterium tuberculosis–specific ESAT-6 and CFP-10 antibody responses

Tanzanian cases

Danish controls





Ethiopia

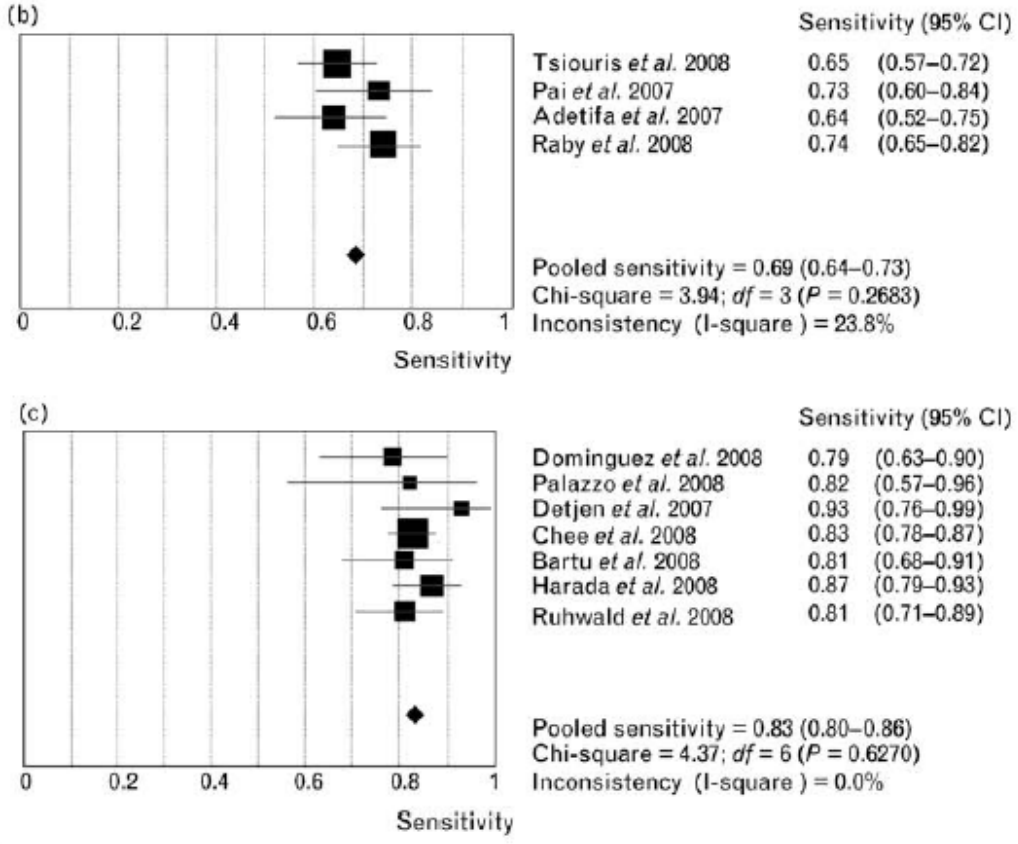
Figure 3. Dot-plot showing the optical density (OD) values obtained from 184 patients with active tuberculosis disease who resided in northern Tanzania (TZ-TB) and 32 healthy, bacille Calmette-Guérin–vaccinated, Danish resident volunteer donors with no known risk factors for tuberculosis (DK-BCG). The dotted line indicates the cutoff value, calculated as the mean OD + 3 SDs for the 32 healthy Danish resident volunteers.

Hoff et al. Clinical Infectious Diseases 2007; 45:575–82

Variation in performance in high vs low endemic countries: example

T-cell interferon-γ release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings

Keertan Dheda[a,b,c], Richard van Zyl Smit[a], Motasim Badri[a] and Madhukar Pai[d]



High incidence countries

Low incidence countries

HIV can prove to be the acid test for any test! Example of MycoDot

MycoDot was hailed to be a breakthrough because it was a simple dipstick test

Commercialized and marketed by Mossman Associates (with support of PATH)

Package insert: sensitivity of 70% and specificity of 95%

But when the test was evaluated in countries with high HIV prevalence, the performance was disastrous

Evaluation of the MycoDot™ test in patients with suspected tuberculosis in a field setting in Tanzania

G. R. Somi,* R. J. O'Brien,† G. S. Mfinanga,* Y. A. Ipuge‡

*National Institute for Medical Research, Dar Es Salaam, Tanzania, †WHO Global Tuberculosis Programme, Geneva, Switzerland, ‡National Tuberculosis and Leprosy Programme, Dar Es Salaam, Tanzania

SUMMARY

SETTING: Rapid, simple and inexpensive methods are needed to improve the diagnosis of tuberculosis in low-income countries. The MycoDot™ test has these characteristics.

OBJECTIVE: To assess the utility of the MycoDot™ test in screening patients with suspected tuberculosis.

DESIGN: Ambulatory patients presenting with symptoms of pulmonary tuberculosis were evaluated by physical examination and sputum acid-fast bacilli (AFB) microscopy. Separately, the MycoDot™ test was performed on whole blood. Patients with AFB-negative smears were treated with a 10-day course of erythromycin. Those remaining symptomatic had a chest radiograph. All sputum specimens were cultured for mycobacteria. Patients with culture-negative tuberculosis and those without a tuberculosis diagnosis were reassessed at 2 months.

RESULTS: Among the 241 patients who were evaluated, the MycoDot™ test was positive in 26% of patients with AFB-positive/culture-positive tuberculosis, 7% with AFB-negative/culture-positive tuberculosis, 7% with culture-negative tuberculosis, 19% treated for tuberculosis who did not meet study case definitions, and 16% without tuberculosis. Twenty four patients did not complete the assessment. Test sensitivity was 16%, specificity 84% and positive predictive value 45%. Sensitivity was highest (41%) in AFB-positive/HIV-negative patients and lowest (3%) in AFB-negative/HIV-positive patients.

CONCLUSION: The MycoDot™ test is not useful for the diagnosis of tuberculosis in sub-Saharan African countries, especially where HIV infection is prevalent.

KEY WORDS: tuberculosis; diagnosis; HIV; serology

Sens in HIV+ = 26%

Evaluation of a commercial immunodiagnostic kit incorporating lipoarabinomannan in the serodiagnosis of pulmonary tuberculosis in Ghana

S. D. Lawn[1], E. H. Frimpong[2] and E. Nyarko[3]

[1] *Department of Medicine, School of Medical Sciences, University of Science and Technology, Kumasi, Ghana*
[2] *Department of Microbiology, School of Medical Sciences, University of Science and Technology, Kumasi, Ghana*
[3] *National Tuberculosis Control Programme, Ministy of Health, Accra, Ghana*

Summary

We evaluated 'Mycodot', a commercially marketed immunodiagnostic test for tuberculosis which detects antibodies to lipoarabinomannan antigen. Serum was tested from 52 patients with newly diagnosed smear-positive pulmonary tuberculosis, of whom 20 were HIV-positive and 32 HIV-negative. Control sera were taken from 40 patients of whom 20 had acute non-tuberculous lobar pneumonia and 20 patients had no respiratory disease. The test was found to have a very high specificity of 97.5% (95%Cl:92.5–100%). However, the sensitivity in HIV-negative patients was 56% (95%Cl:39–73%), and was substantially lower at 25% (95%Cl:6–44%) in HIV-positive patients. In conclusion: 'Mycodot' was found to be a highly specific and easily performed assay. However, the poor sensitivity, especially in HIV- infected patients, renders it unlikely to be useful either as a primary or adjunctive diagnostic test for tuberculosis, particularly in countries with a high prevalence of HIV. A larger trial of this assay in Ghana was not deemed necessary.

Sens in HIV+ = 25%

Despite these results, the test is still available on the market!

Lessons

- TB evaluation studies must be done in high TB incidence countries, especially in high HIV prevalent settings

- Performance outcomes from low incidence countries may be deceptive and not reflect the performance in high incidence settings where the challenges include:
  - HIV
  - Severe TB
  - High background prevalence of TB infection
  - Widespread BCG vaccination
  - Malnutrition
  - Other diseases that can affect performance (e.g. worm infestations)

- If tests perform well in TB/HIV endemic countries, then they are likely to hold up well!

Case study 4:

Who should conduct TB diagnostic studies?

Industry involvement in drug trials and its impact on study outcomes and conclusions

Scope and Impact of Financial Conflicts of Interest in Biomedical Research

A Systematic Review

Justin E. Bekelman, AB
Yan Li, MPhil
Gary P. Gross, MD

Context Despite increasing awareness about the potential impact of financial conflicts of interest on biomedical research, no comprehensive synthesis of the body of evidence relating to financial conflicts of interest has been performed.

Objective To review original, quantitative studies on the extent, impact, and management of financial conflicts of interest in biomedical research.

Data Sources Studies were identified by searching MEDLINE (January 1980-October 2002), the Web of Science citation database, references of articles, letters, commentaries, editorials, and books and by contacting experts.

Study Selection All English-language studies containing original, quantitative data on financial relationships among industry, scientific investigators, and academic institutions were included. A total of 1664 citations were screened, 144 potentially eligible full articles were retrieved, and 37 studies met our inclusion criteria.

Data Extraction One investigator (J.E.B.) extracted data from each of the 37 studies. The main outcomes were the prevalence of specific types of industry relationships, the relation between industry sponsorship and study outcome or investigator behavior, and the process for disclosure, review, and management of financial conflicts of interest.

Data Synthesis Approximately one fourth of investigators have industry affiliations, and roughly two thirds of academic institutions hold equity in start-ups that sponsor research performed at the same institutions. Eight articles, which together evaluated 1140 original studies, assessed the relation between industry sponsorship and outcome in original research. Aggregating the results of these articles showed a statistically significant association between industry sponsorship and pro-industry conclusions (pooled Mantel-Haenszel odds ratio, 3.60; 95% confidence interval, 2.63-4.91). Industry sponsorship was also associated with restrictions on publication and data sharing. The approach to managing financial conflicts varied substantially across academic institutions and peer-reviewed journals.

INDUSTRY SUPPORT OF BIOMEDICAL research in the United States increased dramatically in the last 2 decades. Industry's share of total investment in biomedical research and development grew from approximately 32% in 1980 to 62% in 2000, while the federal government's share fell.[1,2] During this period, the relationship between academic institutions and industry flourished, spawning medical advances, creating new biotechnology markets, and providing needed support for further discovery. However, an entanglement of relationships among industry, investigators, and academic institutions also emerged.

Conflicts of interest are "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly

JAMA 2003

Pharmaceutical industry sponsorship and research outcome and quality: systematic review

Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, Otavio Clark

Abstract

Objective To investigate whether funding of drug studies by the pharmaceutical industry is associated with outcomes that are favourable to the funder and whether the methods of trials funded by pharmaceutical companies differ from the methods in trials with other sources of support.

Methods Medline (January 1966 to December 2002) and Embase (January 1980 to December 2002) searches were supplemented with material identified in the references and in the authors' personal files. Data were independently abstracted by three of the authors and disagreements were resolved by consensus.

Results 30 studies were included. Research funded by drug companies was less likely to be published than research funded by other sources. Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98 to 5.51; 18 comparisons). None of the 13 studies that analysed methods reported that studies funded by industry was of poorer quality.

favourable outcome may result in biases in design, outcome, and reporting of industry sponsored research.[3]

A recent systematic review of the impact of financial conflicts on biomedical research found that studies financed by industry, although as rigorous as other studies, always found outcomes favourable to the sponsoring company.[4] However, this review looked for papers published only in English, excluded reports in letters and abstracts, and looked at studies funded by other industries. We reviewed the relation between the source of funding of the research and the reported outcomes and investigated whether quality of the methods in studies funded by pharmaceutical companies differs from that in other studies.

Methods

Study selection

We included only studies that specifically stated that they analysed research sponsored by a pharmaceutical company, compared methodological quality or outcomes with studies with other sources of funding, and reported the results in quantitative terms. Outcomes of interest were conclusions about differences in drug effectiveness,

School of Health Policy and Management, York University, Toronto, ON, Canada M3J 1P3
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Lisa A Bero *professor*

Interdisciplinary Oncology Program, H Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL 33612, USA
Benjamin Djulbegovic *associate professor*

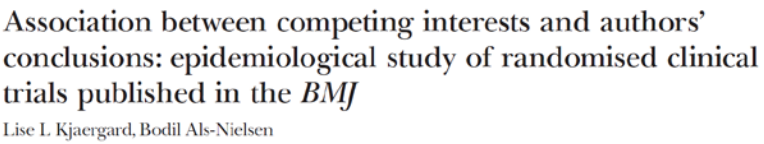
Instituto do Radium

BMJ 2003

Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials

Mohit Bhandari, Jason W. Busse, Dianne Jackowski, Victor M. Montori, Holger Schünemann, Sheila Sprague, Derek Mears, Emil H. Schemitsch, Dianne Heels-Ansdell, P.J. Devereaux

CMAJ 2004



Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the *BMJ*

Lise L Kjaergard, Bodil Als-Nielsen

BMJ 2002

Industry involvement in diagnostic studies?

OPEN ACCESS Freely available online

PLoS one

Quality and Reporting of Diagnostic Accuracy Studies in TB, HIV and Malaria: Evaluation Using QUADAS and STARD Standards

Patricia Scolari Fontela[1], Nitika Pant Pai[2], Ian Schiller[2], Nandini Dendukuri[2], Andrew Ramsay[3], Madhukar Pai[1,4]*

1 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada, 2 Department of Medicine, Division of Clinical Epidemiology, McGill University, Montreal, Canada, 3 Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland, 4 Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, Canada

Table 2. Characteristics of the studies included (N = 90).

Characteristic	Frequency (%)
Disease	
Tuberculosis	45 (50)
Malaria	18 (20)
HIV	27 (30)
Studies' origin*	
Africa	16
Asia	29
Australia and Oceania	01
Europe	27
North America	11
South America	06
Number of patients per study	
Median (interquartile range)	209 (110–555)
Number of studies with industry involvement	39 (43)
Number of studies with conflict of interest	38 (42)
Year of publication	
2004	42 (47)
2005	21 (23)
2006	27 (30)
Number of journals where included studies were published	46

About 40% of TB, HIV, Malaria diagnostic studies had industry involvement or known conflict of interest

Fontela P et al. PLoS One 2009

Industry involvement in TB diagnostic studies: example from IGRA literature

Annals of Internal Medicine | REVIEW

Systematic Review: T-Cell–based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update

Madhukar Pai, MD, PhD; Alice Zwerling, MSc; and Dick Menzies, MD, MSc

Of the 38 studies in the meta-analysis, 21 (55%) had some sort of industry involvement or support, such as sponsorship, donation of test kits, participation in advisory boards, involvement of test developers, or ownership of patents.

Industry involvement in TB, HIV, Malaria studies and likely impact: McGill-TDR/WHO study

Table 10 Multivariate logistic regression results using authors' conclusion (dependent variable) and industry involvement, disease of interest and quality assessment variables (independent variables)
[n = 153]

Variable	OR	95% CI
Industry involvement		
• No	1.0	Reference group
• Yes	4.28	1.83 - 10.02
• NR	5.11	1.77 - 14.74

Pai, Fontela, Dendukuri, Ramsay, et al.

Industry involvement in TB studies and likely impact: commercial IGRAs

- We searched for cost-effectiveness studies on commercial IFN-gamma release assays
- We found a total of 10 studies
- Of these 6 studies had industry involvement of some sort
  - 2 of 6 had CEO of a test making company as author!
- Of the 6 studies with industry involvement: ALL concluded in favor of the commercial test and claimed superior cost-effectiveness
- Of the 4 independent studies, two were in favor of the test, and two were cautious and recommended a more selective use of the test

Industry involvement in TB studies and likely impact: commercial IGRAs

Studies with industry involvement

Direct costs of three models for the screening of latent tuberculosis infection

P. Wrighton-Smith* and J-P. Zellweger#

Cost-optimisation of screening for latent tuberculosis in close contacts

R. Diel*, A. Nienhaus#, C. Lange¶ and T. Schaberg+

Cost-effectiveness of interferon-γ release assay testing for the treatment of latent tuberculosis

R. Diel*, P. Wrighton-Smith# and J-P. Zellweger¶

Cost-effectiveness of Interferon-γ Release Assay Screening for Latent Tuberculosis Infection Treatment in Germany*

Roland Diel, MD, MPH; Albert Nienhaus, MD, MPH; and Robert Loddenkemper, MD, FCCP

Enhanced cost-benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany

R. Diel [a,*], T. Schaberg [b], R. Loddenkemper [c], T. Welte [a], A. Nienhaus [d]

Targeted screening and treatment for latent tuberculosis infection using QuantiFERON®-TB Gold is cost-effective in Mexico

J. L. Burgos,* J. G. Kahn,† S. A. Strathdee,* A. Valencia-Mendoza,‡ S. Bautista-Arredondo,‡ R. Laniado-Laborin,§ R. Castañeda,§ R. Deiss,* R. S. Garfein*

Independent studies

Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis

O. Oxlade, K. Schwartzman, D. Menzies

Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Canada

Cost-effectiveness of Interferon Gamma Release Assays vs Tuberculin Skin Tests in Health Care Workers

Marie A. de Perio, MD; Joel Tsevat, MD, MPH; Gary A. Roselle, MD; Stephen M. Kralovic, MD, MPH; Mark H. Eckman, MD, MS

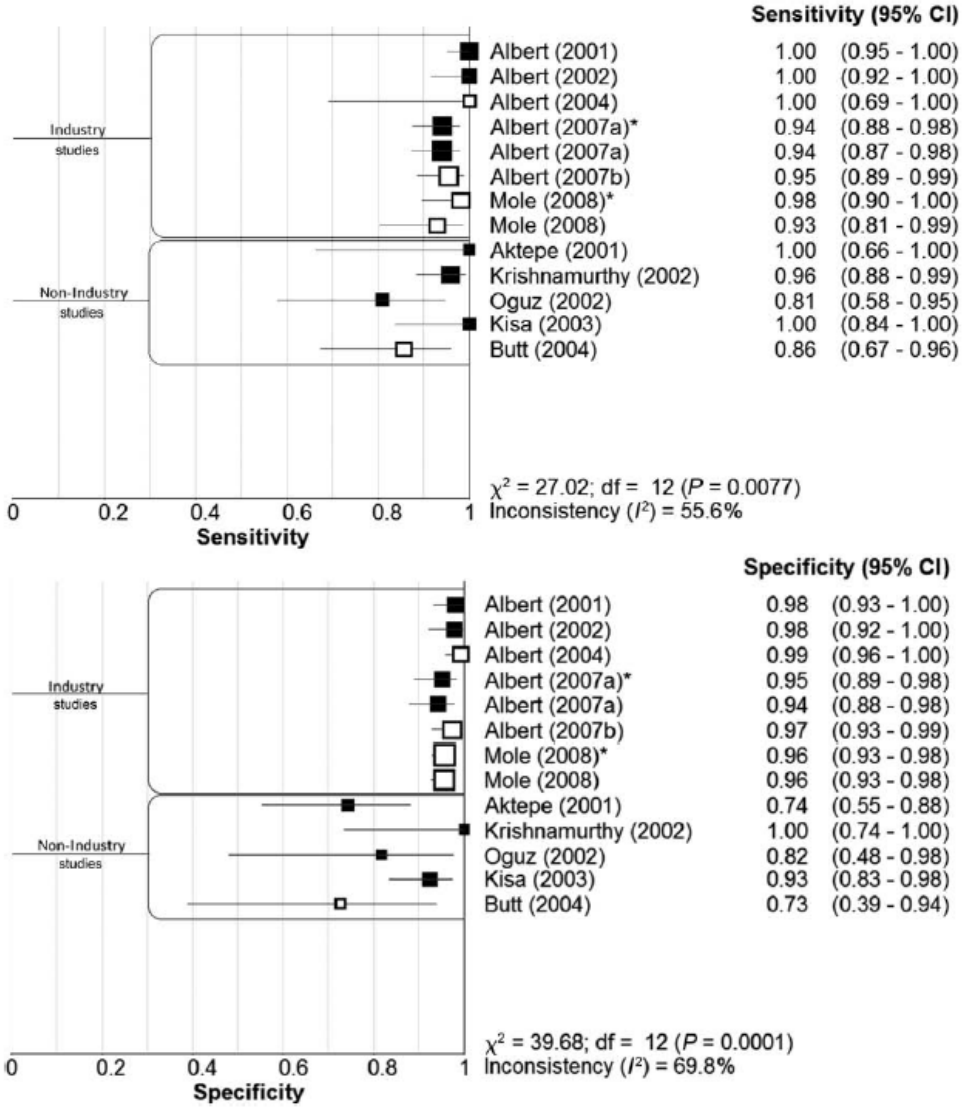
Cost-effectiveness of a new interferon-based blood assay, QuantiFERON®-TB Gold, in screening tuberculosis contacts

F. Marra,*† C. A. Marra,*‡ M. Sadatsafavi,* O. Morán-Mendoza,§¶ V. Cook,*† R. K. Elwood,*† M. Morshed,*† R. C. Brunham,*† J. M. FitzGerald*#

Cost Effectiveness of Interferon-γ Release Assay for Tuberculosis Contact Screening in Japan

Akiko Kowada,[1] Osamu Takahashi,[2] Takuro Shimbo,[3] Sachiko Ohde,[4] Yasuharu Tokuda[2] and *Tsuguya Fukui[2]*

FASTPlaque tests for drug-resistant TB



Minion J et al. ITJLD 2010

Lessons

- When test developers do the studies, test performance is always good; performance is less optimal when others try to replicate the results
  - may be suppression of unfavourable data
  - may just be a learning curve issue (test developers, by definition, understand the test better and know how to make it work!)
- While industry is critical for test development and commercialization, test evaluations should, at least in the later stages, be done independent of industry support
- At the very least, industry involvement should be clearly disclosed in all publications and presentations
- Industry and test developers should definitely not be involved in guideline and policy development
  - At least 25 countries have guidelines and statements on IGRAs
  - Vast majority of these guidelines had no disclosures on conflicts of interest (Denkinger et al. CMI 2011)

Case study 5:

Can we trust the package insert?

Serology package inserts are uniformly positive!

SEROCHECK-MTB	Rapid Test for Antibodies to *Mycobacterium tuberculosis* in serum/ plasma/whole blood
Application	• As a additional diagnostic tool in tuberculosis smear negative, culture positive suspects and tuberculosis smear negative, culture negative suspects • Extrapulmonary TB suspects • Pediatric cases • Diagnosis of suspect TB cases in HIV uninfected individuals
Principle	Self performing, rapid , semi-quantitative two-site sandwich immunoassay , lateral flow device
Sensitivity	100%
Specificity	100%

Sensitivity = 100%
Specificity = 100%

SD STANDARD DIAGNOSTICS, INC.
156-68 Hagal-dong, Giheung-gu, Yongin-si, Kyonggi-do, Korea
Tel : 82-31-899-9700 Fax : 82-31-899-9740 http://www.standardia.com

2) Comparison SD Rapid TB vs. a commercial anti-TB ELISA
The SD Rapid TB have tested with positive and negative clinical samples tested by a leading commercial ELISA test. The result shows that the SD Rapid TB is very accurate to other commercial ELISA test.

		A Commertial PHA		Total Results
		Positive	Negative	
A commercial anti-M.tuberculosis ELISA kit	Positive	112	2	114
	Negative	1	350	351
Total Results		113	352	465

In a comparison of the SD Rapid TB versus a leading commercial ELISA test, results gave sensitivity of 98.2% (112/114), a specificity of 99.7 % (350/351), and a total agreement of 99.35% (462/465).

Sensitivity = 98%
Specificity = 100%

TASHIMA Inc.

PERFOMANCE CHARACTERISTICS:

Sensitivity : Sera were collected from patients under anti TB treatment. Results of sputum examination were not available. Among 75 sera collected, samples were positive by the TB onsite Rapid screening Test Thus, the test sensitivity is 93%.

Specificity : In 53 sera derived from Northern America, all the samples were negative.

Sensitivity = 93%
Specificity = 100%

Commercial package inserts always provide data on test accuracy: can we trust them?

2009 package insert

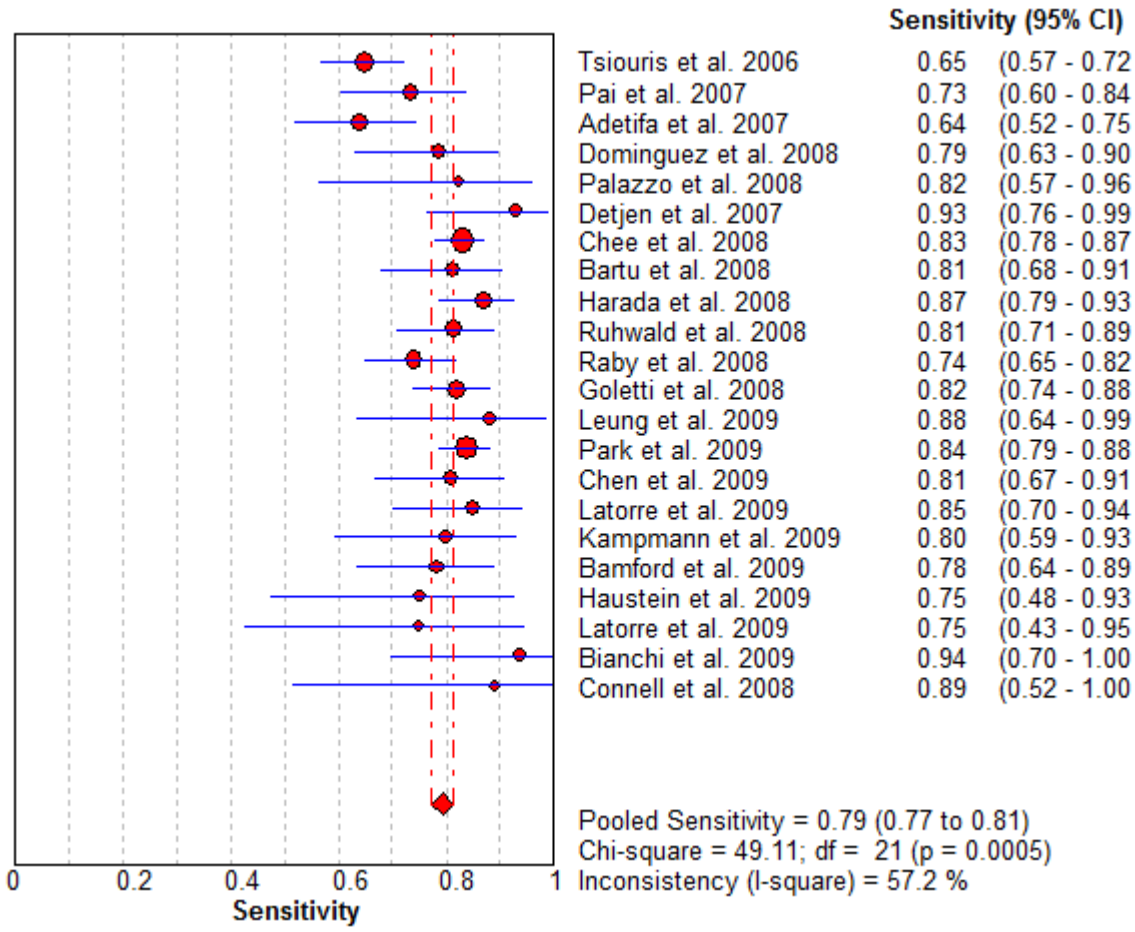
TABLE 8. QuantiFERON®-TB Gold IT: Summary of results from clinical studies of subjects with culture-confirmed *M. tuberculosis* infection.

STUDY	QuantiFERON®-TB Gold IT			QuantiFERON®-TB Gold (liquid antigen)			TST (5mm)*	
	Pos	Neg	Ind	Pos	Neg	Ind	Pos	Neg
Australian	24	3	0	20	7	0	–	–
USA	47	11	3	34	10	6	60	19
Japanese	86	6	8	78	14	8	–	–
Overall Sensitivity	89% (157/177)			81% (132/163)			76% (60/79)	

Pos – Positive; Neg – Negative; Ind – Indeterminate
* In the U.S. study of 86 *M. tuberculosis* patients, TST results were missing for 4 and invalid for 3.

According to the company, this test has 89% sensitivity in active TB

Updated meta-analyses on sensitivity of QuantiFERON-TB Gold In Tube



Pooled estimate was about 79%

More examples...

Test	Package insert sens	Package insert spec	Meta-analysis sens	Meta-analysis spec
FASTPlaque-Response	96 – 100%	99 – 100%	95%	95%
Anda-TB IgG	85 - 90%	85 - 100 %	60 - 75%	~90%
MycoDot	70%	95%	26% - 76%	84% - 97%
Clearview TB ELISA	81% (HIV+)	93 – 98%	56% (HIV+)	95%
GenoType MDTBDrplus	99%	99%	98%	99%
Gen-Probe MTD	97% (S+) 72 (S-)	100% (S+) 99% (S-)	97% (S+) 76% (S-)	96% (S+) 95% (S-)

Lessons

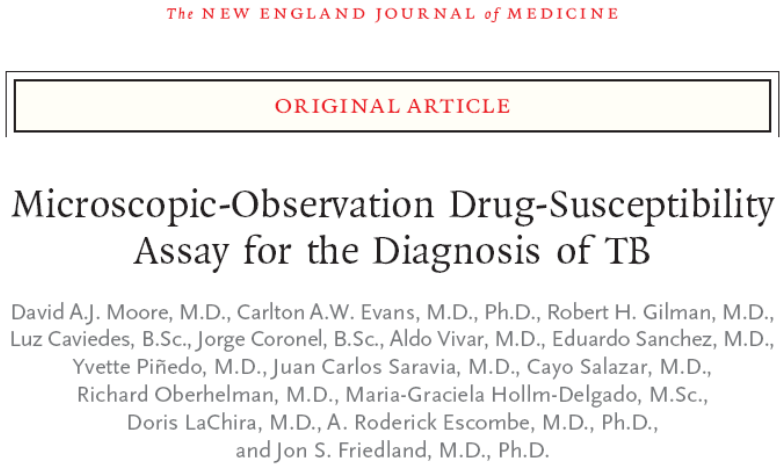
- Company package inserts often present optimistic estimates based on small in-house evaluations that are usually sponsored by the companies
- Lab professionals and clinicians must be critical of advertised estimates of accuracy and performance
- Even when contradictory data are published, companies may not revise their package inserts or advertisements
- There is very little post-marketing surveillance of diagnostics and devices
  - Regulatory agencies may not require companies to revise their package inserts
  - Poorly performing tests may, in fact, never get pulled off the market

Case study 6:

Should we expect tests to be transferable and replicable?

Transferability: technologies that work well in the hands of developers will not necessarily work well everywhere

Eg. MODS, phage assays



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Microscopic-Observation Drug-Susceptibility Assay for the Diagnosis of TB

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MODS: developed in Peru – performs excellent

Sensitivity better than LJ (98 vs. 84%)

Fast turnaround time (1 week vs. 6 weeks+)

Implemented in India – performs poorly

Sensitivity 80%

Issues with contamination

Issues with reliability

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Diagnostic accuracy of the microscopic observation drug susceptibility assay: a pilot study from India

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Simple, phage-based (*FASTPlaque*) technology to determine rifampicin resistance of *Mycobacterium tuberculosis* directly from sputum

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SUMMARY

SETTING: Cape Town, South Africa.
OBJECTIVE: To evaluate the performance of a simple, manual, phage-based test for determining rifampicin (RMP) resistance of *Mycobacterium tuberculosis* directly from smear-positive sputum specimens.
DESIGN: A comparative study of the performance of the *FASTPlaque* (phage amplification) technology to determine RMP resistance directly from smear-positive sputum compared with isolation and the conventional indirect Middlebrook 7H11 agar proportion method.
RESULTS: The *FASTPlaque* direct RMP test achieved sensitivity, specificity and overall accuracy of 100% (11/11), 100% (134/134) and 100% (145/145), respectively, compared with the conventional indirect susceptibility test method (resolved data). The *FASTPlaque* direct RMP test reported results within 2 days from receipt of the specimen, while the conventional method took between 27 and 103 days (mean ± SD 33.2 ± 7.2 days).
CONCLUSION: *FASTPlaque* technology applied directly to smear-positive sputum offers performance comparable to conventional methods, with results available in 2 days instead of weeks to months. The test may form a useful part of DOTS-Plus programmes to combat multidrug-resistant tuberculosis, improving patient prognosis and reducing ongoing transmission of disease. It does not require specialised equipment, making it appropriate for high-burden countries.
KEY WORDS: *FASTPlaque*; phage amplification; multidrug-resistant tuberculosis; rifampicin resistance; susceptibility testing

FASTPlaque phage assay – performed well when done by industry

100% sens
100% spec

Implemented in Kenya – performs poorly

Despite upgrading the lab:

Low accuracy (31% sens; 95% spec)

Issues with contamination (nearly have were not interpretable)

Evaluation of *FASTPlaque*TB™ to diagnose smear-negative tuberculosis in a peripheral clinic in Kenya

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SUMMARY

OBJECTIVE: To evaluate the performance and feasibility of *FASTPlaque*TB™ in smear-negative tuberculosis (TB) suspects in a peripheral clinic after laboratory upgrading.
DESIGN: Patients with cough ⩾2 weeks, two sputum smear-negative results, no response to 1 week of amoxicillin and abnormal chest X-ray were defined as smear-negative suspects. One sputum sample was collected, decontaminated and divided into two: half was tested with *FASTPlaque*TB in the clinic laboratory and the other half was cultured on Löwenstein-Jensen medium in the Kenyan Medical Research Institute. Test sensitivity and specificity were evaluated in all patients and in human immunodeficiency virus (HIV) infected patients. Feasibility was assessed by the contamination rate and the resources required to upgrade the laboratory.
RESULTS: Of 208 patients included in the study, 56.2% were HIV-infected. Of 203 *FASTPlaque*TB tests, 95 (46.8%) were contaminated, which interfered with result interpretation and led to the interruption of the study. Sensitivity and specificity were respectively 31.2% (95%CI 12.1–58.5) and 94.9% (95%CI 86.8–98.4) in all patients and 33.3% (95%CI 9.9–65.1) and 93.9% (95%CI 83.1–98.7) in HIV-infected patients. Upgrading the laboratory cost €20 000.
CONCLUSION: *FASTPlaque*TB did not perform satisfactorily in this setting. If contamination can be reduced, in addition to laboratory upgrading, its introduction in peripheral clinics would require further assessment in smear-negative and HIV co-infected patients and test adaptation for friendlier use.
KEY WORDS: tuberculosis; phage-based test; smear microscopy; diagnosis; developing countries

Replication

- There are many examples of novel tests for TB that show great promise, but do not get replicated
- Or subsequent results are disappointing and commercialization is abandoned
- Or test may be quite good, but impossible to develop and manufacture in a cost-effective way
- Results in a graveyard of inexplicably abandoned diagnostics

Example: MPB64 skin patch test (Sequella Inc.)

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MPB64 mycobacterial antigen: a new skin-test reagent through patch method for rapid diagnosis of active tuberculosis

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SUMMARY

SETTING: A collaborative study between the Japan BCG Laboratory, Tokyo, Japan, and the Infectious Disease Section, Philippine General Hospital, Manila, the Philippines. Tuberculosis patients from four clinics in the vicinity of Manila, Our Lady of Grace Parish, Sto. Niño de Tondo Parish, the Canossa Health and Social Center, and the Health Care Development Center, were examined.

OBJECTIVE: To develop a new, simple and rapid diagnostic method for active tuberculosis. Subjects were tested for skin reaction to a special antigen, MPB64, by the patch test method instead of intradermal injection of purified protein derivative (PPD).

DESIGN: Fifty-three active tuberculosis patients and 43 healthy PPD-positive controls were tested to determine whether or not the reaction to MPB64 was positive only in active tuberculosis patients.

RESULTS: Fifty-two of the 53 active tuberculosis patients showed a positive reaction to MPB64, while none of the 43 PPD-positive controls did. The specificity of MPB64 to active tuberculosis was 100%, and the sensitivity was 98.1%. The efficacy of the test was 98.9%.

CONCLUSION: The patch test with MPB64 is a promising method for the diagnosis of active tuberculosis, distinguishing tuberculous patients from those who are infected but have not developed the disease, and also from BCG-vaccinated individuals. This new skin test is a subject for further evaluation and it is important to compare the results with PPD Mantoux.

KEY WORDS: MPB64; patch skin test; rapid diagnosis; active TB

Early data in 1998:

Sensitivity: 98%
Specificity: 100%

In 2011, still not commercially available

Pai M et al. Exp Rev Mol Diagn 2006;6(3):423-432; Image courtesy Sequella Inc.

Lessons

- Many novel tests and biomarkers are bound to fail
- We need to appreciate the "failure rate" of new tests and interventions
- Replication, in diverse settings, is required, before proceeding with commercialization and clinical use
- Transferability of technologies must receive attention; tests need to be robust if they have to work well in all settings
- Tests that work well in the hands of developers may not work well in field settings, especially in resource-limited countries
- Single studies are never sufficient for policy and guideline development; we need more extensive evidence
- Even accuracy data are not sufficient for evidence-based policies