Serological tests for tuberculosis: the evidence is reviewed

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Chennai, December 13 2010

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Disclosure

▸ I serve as co-chair of the Evidence Synthesis subgroup of Stop TB Partnership's New Diagnostics Working Group

Overview

▸ WHO recommendations on the use of serological tests
▸ Review of the evidence
     - Background
     - Serological tests: An updated systematic review and meta-analysis
     - Cost effectiveness model of serological tests in India

WHO issues a strong recommendation *against* the use of serological tests

▸ WHO Expert Group recommended that serological tests should not be used in individuals suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status (22 July 2010)

▸ The WHO Strategic and Technical Advisory Group for TB (STAG-TB, highest policy making body for TB at WHO) endorsed the Expert Group recommendations (27 September 2010)
http://www.who.int/tb/advisory_bodies/stag_tb_report_20 10.pdf

▸ A negative WHO policy on TB serology is expected in early 2011

BACKGROUND

Serological (antibody-detection) tests for TB…

…have been around for a long time
…are attractive, especially if made into point of care tests
▸ But existing serological tests have variable accuracies and a limited clinical role (based on 3 systematic reviews)

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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[6,9*]

CLINICAL AND VACCINE IMMUNOLOGY, Feb. 2009, p. 260–276   Vol. 16, No. 2
1556-6811/09/$08.00+0   doi:10.1128/CVI.00355-08
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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]

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;62:911–918. doi: 10.1136/thx.2006.075754   6

3

WHO/TDR Laboratory-based...2008

- Rapid - test result (< 15 mins)
- Simple - 1 or 2 steps, minimal training and no equipment
- Easy to interpret - card or strip format with visual readout
- Gold standard - culture plus clinical follow-up
- Archived specimens

World Health Organization

Diagnostics Evaluation Series No.2

Laboratory-based evaluation of 19 commercially available rapid diagnostic tests for tuberculosis

Special Programme for Research & Training in Tropical Diseases (TDR) sponsored by UNICEF/UNDP/World Bank/WHO

Table 4. Performance of 19 rapid tests for pulmonary tuberculosis

	Manufacturer	Rapid Test	Sensitivity % (95% CI)	Specificity % (95% CI)
1	ABP Diagnostics	Focus Sure Check TB	8 (4-11)	95 (92-99)
2	Advanced Diagnostics	Tuberculosis Rapid Test	40 (33-46)	53 (45-61)
3	American Bionostica	Rapid Test for TB	20 (15-26)	80 (73-86)
4	Ameritek dBest	One Step TB Test	34 (27-40)	68 (61-76)
5	BioMedical Products Corp	TB Rapid Screen Test	49 (42-56)	57 (49-65)
6	Chembio	TB Stat-Pak II	32 (25-38)	83 (76-89)
7	CTK Biotech TB Antibody	Onsite Rapid Screening Test	27 (21-33)	69 (62-77)
8	Hema Diagnostic	Rapid 1-2-3 TB Test	36 (29-42)	72 (65-80)
9	Laboratorio Silanes	TB-Instantest	38 (31-44)	70 (62-77)
10	Millenium Biotechnology	Immuno-Sure TB Plus	2 (0-5)	99 (97-100)
11	Minerva Biotech	V Scan	21 (16-27)	89 (84-94)
12	Mossman Associates	MycoDot	36 (30-42)	87 (81-92)
13	Pacific Biotech	Bioline TB	19 (14-25)	95 (91-98)
14	Premier Medical Corporation	First Response Rapid TB	21 (16-27)	95 (92-99)
15	Princeton BioMeditech	BioSign M tuberculosis	1 (0-2)	99 (97-100)
16	Span Diagnostics	TB Spot ver 2.0	38 (32-45)	78 (71-85)
17	Standard Diagnostics	SD Rapid TB	21 (15-26)	96 (93-99)
18	UniMED International Inc	FirstSign MTB Card Test	60 (53-66)	58 (50-66)
19	Veda Lab	TB Rapid Test	13 (8-17)	98 (96-100)

ROC curve, commercial rapid tests for the diagnosis of pulmonary TB (n=355)
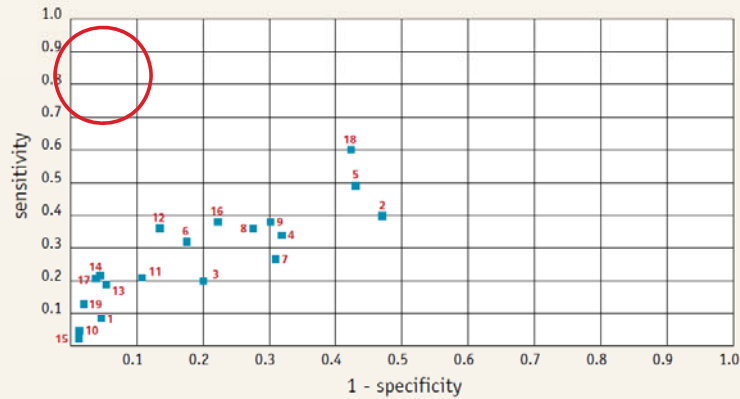
Sensitivity range: 1 to 60%
Specificity range: 53 to 99%

Current situation

▸ No serological TB test for clinical use is recommended by international guidelines nor approved by the US Food and Drug Administration

▸ Dozens of commercial serological tests based on detection of antibodies are marketed in many parts of the world, especially in developing countries with weak regulatory systems

Claims of high accuracy

▸ Package inserts are usually based on internal company data

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 Commercial 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).

American Bionostica, Inc.

SUMMARY OF CLINICAL TEST RESULTS

Specimen no./origin	ABI Test Sensitivity	ABI Test Specificity
111 Mexico	64%	98%
100 Mexico	70%	100%
85 Russia	78%	91%
341 East Europe	89%	95%
321 Estonia Group 1	88%	97%
164 Estonia Group 2	93%	95%
73 Miami	92%	93%
200 Russia	86%	92%
95 Russia	85%	94%
19 Estonia	90%	89%
33 India (all positive)	91%	N/A
73 East Europe	72%	95%

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.

11

## Based on a survey of more than 80 Indian laboratories, some preliminary estimates

• About 50 large and medium *private labs* alone are doing over 60,000 tests per month

• ~1.5 million TB serological (ELISA) tests every year

• @ $10 per test**, the market is worth at least $15 million (this is highly conservative)

**The cost is actually ~$10 per antibody (e.g. IgG). Testing for all 3 antibodies (IgG, IgA, IgM) is often done at cost of ~$30 per patient; for simplicity, we have used $10 per patient, a conservative estimate (RNTCP annual budget ~ $65 million)

Pai et al. Unpublished

12

Case report 1: A 25-year-old man from Chhattisgarh presenting with cough, fever, and weight loss for several months received a TB serology test at a community clinic. Based on a false negative test result, the patient was sent home with a Rx for vitamins and cough syrup. Within a few weeks, his condition rapidly deteriorated. Sputum smear microscopy was 3+ positive for acid-fast bacilli and the patient eventually died of his disease.
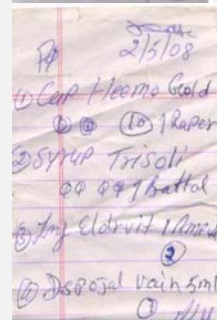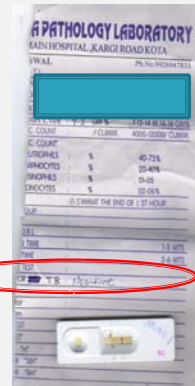
Commercial serological tests for the diagnosis of active pulmonary and extrapulmonary tuberculosis: An updated systematic review and meta-analysis

Steingart KR, Flores LL, Dendukuri N , Schiller I, Laal S, Ramsay A, Hopewell PC, Pai M

Commercial serological tests, framing the question

Population - adults and children with and without HIV infection suspected of active TB, all countries
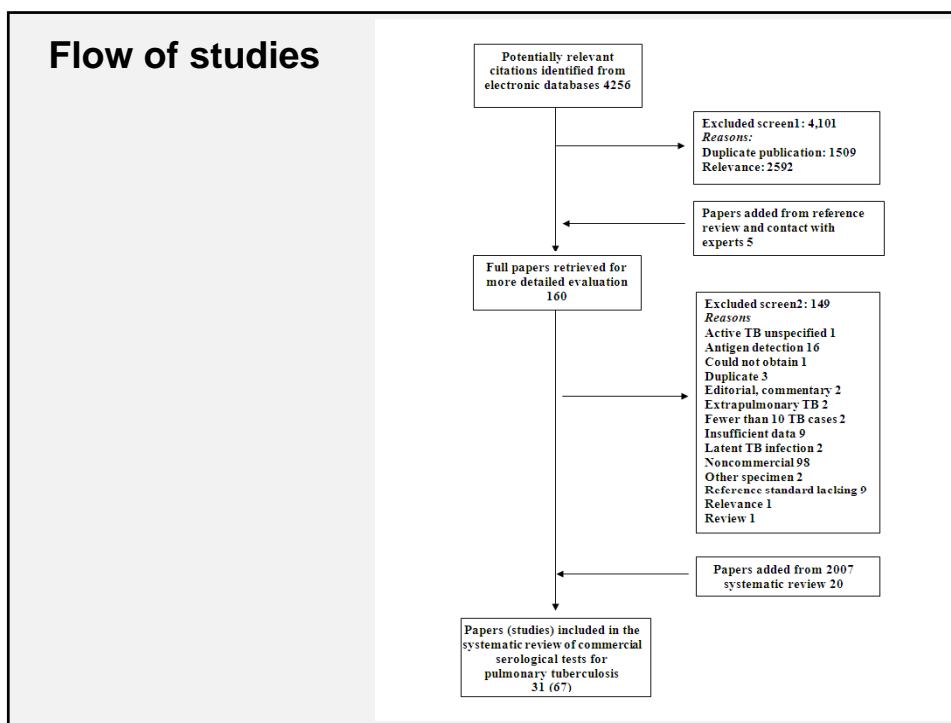
Intervention - commercial serological test

Comparison - no test/smear microscopy

Outcomes - sensitivity and specificity
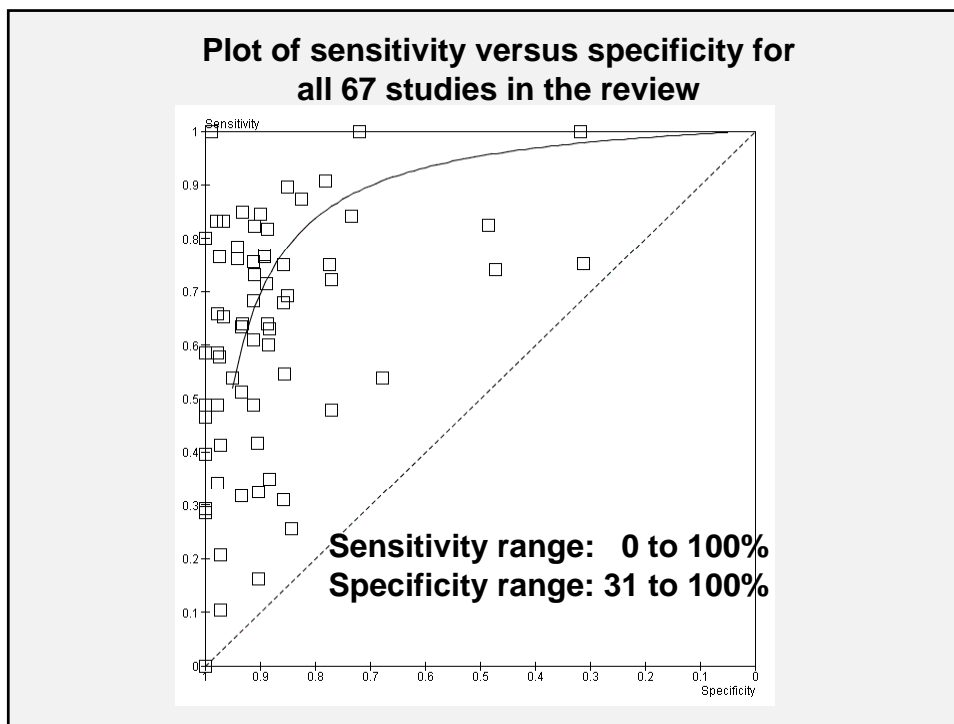
Reference standard - culture (either solid or liquid)

Excluded studies published before 1990 and studies with < 10 TB cases

Results - Pulmonary TB

Flow of studies

```
                    Potentially relevant
                    citations identified from
                    electronic databases 4256

                                          Excluded screen1: 4,101
                                          Reasons:
                                          Duplicate publication: 1509
                                          Relevance: 2592

                                          Papers added from reference
                                          review and contact with
                                          experts 5

                    Full papers retrieved for
                    more detailed evaluation
                    160
                                          Excluded screen2: 149
                                          Reasons
                                          Active TB unspecified 1
                                          Antigen detection 16
                                          Could not obtain 1
                                          Duplicate 3
                                          Editorial, commentary 2
                                          Extrapulmonary TB 2
                                          Fewer than 10 TB cases 2
                                          Insufficient data 9
                                          Latent TB infection 2
                                          Noncommercial 98
                                          Other specimen 2
                                          Reference standard lacking 9
                                          Relevance 1
                                          Review 1

                                          Papers added from 2007
                                          systematic review 20

                    Papers (studies) included in the
                    systematic review of commercial
                    serological tests for
                    pulmonary tuberculosis
                    31 (67)
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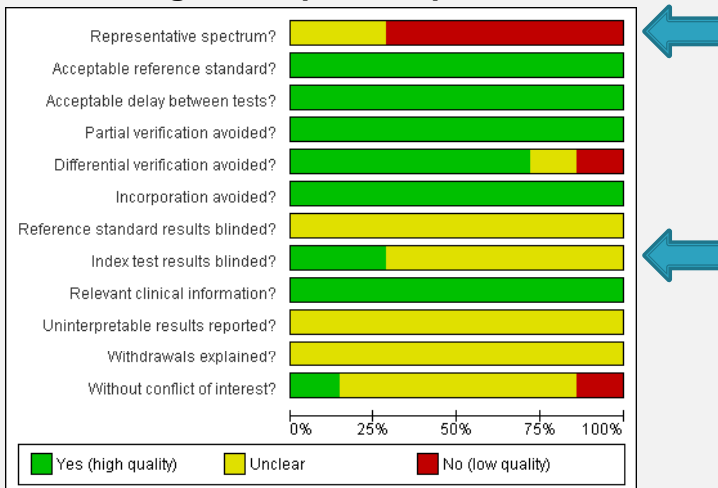
Study characteristics

- 67 studies used 18 different serological tests (anda-TB IgG most common, 19% of studies)

- 32 (48%) studies in low/middle-income countries

- Zero studies involved children; 1 study involved HIV-infected individuals

- Median TB patients 41 (IQR 33, 54)

- Studies were considered low quality (only 28% included a representative patient spectrum; only 51% reported blinding of the serological test result)

- No studies reported on patient-important outcomes
  - increased number of TB patients detected
  - decreased number false-positive TB patients treated
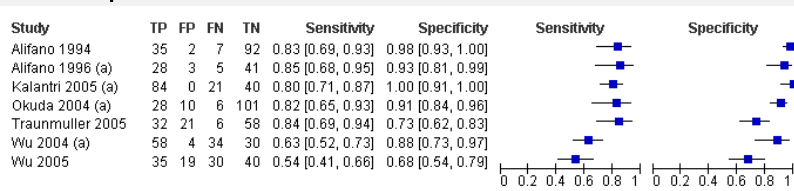 - decreased number of patients lost due to fewer visits

Plot of sensitivity versus specificity for all 67 studies in the review

anda-TB IgG (Anda Biologicals, Strasbourg, France) studies involving smear-positive patients

Representative spectrum?
Acceptable reference standard?
Acceptable delay between tests?
Partial verification avoided?
Differential verification avoided?
Incorporation avoided?
Reference standard results blinded?
Index test results blinded?
Relevant clinical information?
Uninterpretable results reported?
Withdrawals explained?
Without conflict of interest?

0%   25%   50%   75%   100%

■ Yes (high quality)   ☐ Unclear   ■ No (low quality)

Steingart et al. submitted manuscript

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anda-TB IgG

A. Smear positive

Study	TP	FP	FN	TN	Sensitivity	Specificity
Alifano 1994	35	2	7	92	0.83 [0.69, 0.93]	0.98 [0.93, 1.00]
Alifano 1996 (a)	28	3	5	41	0.85 [0.68, 0.95]	0.93 [0.81, 0.99]
Kalantri 2005 (a)	84	0	21	40	0.80 [0.71, 0.87]	1.00 [0.91, 1.00]
Okuda 2004 (a)	28	10	6	101	0.82 [0.65, 0.93]	0.91 [0.84, 0.96]
Traunmuller 2005	32	21	6	58	0.84 [0.69, 0.94]	0.73 [0.62, 0.83]
Wu 2004 (a)	58	4	34	30	0.63 [0.52, 0.73]	0.88 [0.73, 0.97]
Wu 2005	35	19	30	40	0.54 [0.41, 0.66]	0.68 [0.54, 0.79]

Sensitivity   Specificity
0 0.2 0.4 0.6 0.8 1   0 0.2 0.4 0.6 0.8 1

B. Smear negative

Study	TP	FP	FN	TN	Sensitivity	Specificity
Alifano 1996 (c)	23	3	13	41	0.64 [0.46, 0.79]	0.93 [0.81, 0.99]
Luh 1996 (b)	50	33	20	260	0.71 [0.59, 0.82]	0.89 [0.85, 0.92]
Okuda 2004 (b)	19	10	7	101	0.73 [0.52, 0.88]	0.91 [0.84, 0.96]
Wu 2004 (b)	30	4	56	30	0.35 [0.25, 0.46]	0.88 [0.73, 0.97]

Sensitivity   Specificity
0 0.2 0.4 0.6 0.8 1   0 0.2 0.4 0.6 0.8 1

**Bivariate meta-analysis, random effects, pooled estimates**
Smear+ Sensitivity = 76% (63,87); Specificity = 92% (74, 98)
Smear-   Sensitivity = 59% (10,96); Specificity = 91% (79, 96)

Steingart et al. submitted manuscript

22

Summary ROC plots for anda-TB IgG showing better performance in studies of smear-positive patients (A) than smear-negative patients (B).The red squares are summary sensitivity and specificity
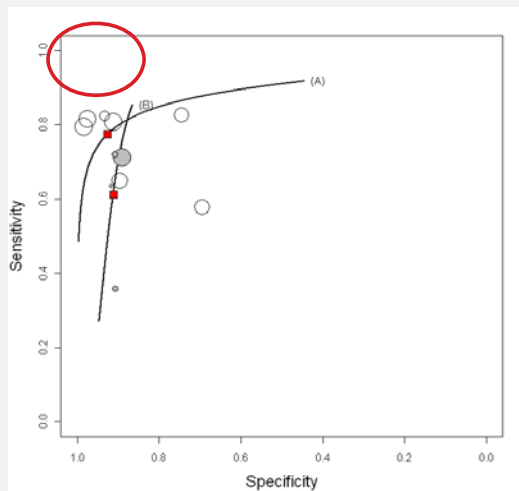
Steingart et al. submitted manuscript

Head-to-head comparison SDHO and smear microscopy, HIV-infected individuals

Test	Sensitivity % (95% CI)	Specificity (95% CI)
SDHO (Saint-Sauveur des Monts, Canada)	16 (5, 34)	90 (74, 98)
Smear microscopy	68 (49, 83)	100 (89,100)

- 55 HIV-infected pulmonary TB suspects, hospitalized and outpatient
- 31 culture-confirmed TB cases
- Median age 31
- Central African Republic

Kassa-Kelembho et al. Clin Vaccine Immunol. 2006 June; 13(6): 702–3

Discussion

The sensitivity and specificity estimates in the meta-analysis are likely to be overly optimistic for at least two reasons:

1. study quality generally suffered from lack of a representative patient spectrum and could have resulted in inflated estimates of test accuracy

2. publication bias was possible because studies with poor performance were unlikely to be unpublished

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NOVEMBER 8, 2010
THE POLITICAL SCENE
Hendrik Hertzberg and Ryan Lizza discuss the midterm results.

LETTER FROM INDIA
A DEADLY MISDIAGNOSIS
Is it possible to save the millions of people who die from TB?
by Michael Specter

Case report 2: A middle-aged woman from India complaining of cough received a serological TB test at a private medical clinic. Based on a false positive test result, the patient was misdiagnosed as having active TB disease and received a six month course of multidrug antituberculous therapy. After treatment completion, the patient's cough recurred, her condition worsened, and she was eventually diagnosed with active TB

Serological Testing for Active Tuberculosis in India is More Costly and Less Effective than Sputum Smear Microscopy

Dowdy DW, Steingart KR; Pai M

Hypothetical "Study Population"

- ▸ 1.5 million TB suspects
  - ◦ Conservative estimate of annual number of serologic tests in India
- ▸ 1 in 7 actually have TB
  - ◦ Estimate from FIND, comparable to other studies
- ▸ Among TB patients, 53% are "highly infectious"
  - ◦ Would be diagnosed with 2 sputum smears in ideal lab
- ▸ 5% HIV prevalence
  - ◦ 10% with access to ART (UNAIDS 2009); does not affect model results
- ▸ Accuracy estimates obtained from the systematic review

Dowdy et al., 2010 submitted manuscript

28

What is the cost for 1.5 million TB suspects who undergo serologic testing in India?
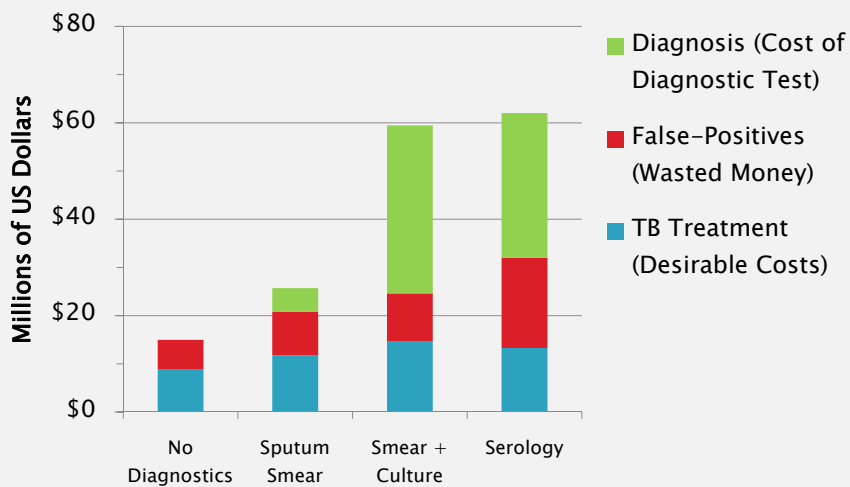
Dowdy et al., unpublished

29

Table 3. Cost-Effectiveness of Diagnostic Strategies for 1.5 Million TB Suspects in India, Relative

Diagnostic Test	Cost (US$)	Additional TB Cases Treated	Additional False-Positive Cases Treated	Secondary Cases Averted
Sputum smear microscopy	$11.9 million	44,000	36,000	443,000
Sputum smear + TB culture	$45.0 million	71,000	48,000	555,000
Serological testing	$47.5 million	58,000	157,000	411,000
Rapid molecular testing	$52.8 million	86,000	12,000	629,000

Dowdy et al., 2010 submitted manuscript

15

In conclusion

- **Published data on commercial serological tests for the diagnosis of active TB inconsistent and imprecise estimates of sensitivity and specificity**

- **Modeling study in a hypothetical cohort of 1.5 million adult Indian TB suspects suggests that serological testing for active TB is both more costly and less effective than sputum smear microscopy**

Acknowledgements
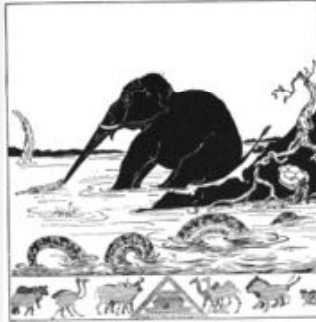
Questions?

**"Satiable curiosity…
and that means he asked ever so many questions."**

33