DIAGNOSIS OF TB END-POINTS IN VACCINE TRIALS: METHODOLOGICAL ISSUES
(OR DO YOU HAVE A PET TORTOISE?)

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Conflicts of Interest

- Most of the trials I am involved in are funded by the Aeras Foundation (USA) who are in turn mainly funded by the Bill and Melinda Gates Foundation.
- I acted once as a consultant to GSK in a meeting on endpoints.
- I am co-chair of the Taskforce on Clinical Research Issues in TB Vaccine Development of the STOP TB Working group on TB vaccines.

Background

- BCG is the existing vaccine against TB.
- Consistent efficacy against severe forms of TB in children but variable efficacy against pulmonary TB in adults.
- 15 new TB vaccines in clinical trials.
- No correlate of protection as yet.
- Clinical endpoints needed for efficacy trials.

DIAGNOSING TB

- In adults/ adolescents and HIV infected persons:
  - Smear, culture, GeneXpert, CXR, special investigations for extra-pulmonary TB.
- In young children:
  - Pauci-bacillary disease – scoring systems – symptoms, CXR and TST.
  - Induced sputum/ gastric aspirate/ naso-pharyngeal aspirate – smear, culture and GeneXpert.

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HISTORICAL ENDPOINTS (BCG TRIALS)*

TABLE 6.—*Distribution of cases and deaths from tuberculosis according to type of case at time first observed and at most severe stage observed*

Type of case [1]	Cases [2]				Tuberculosis deaths			
	At time first observed		At most severe stage observed		By type of case as first observed		By type of case at most severe stage observed	
	BCG	Control	BCG	Control	BCG	Control	BCG	Control
Enlarged hilar glands	21	122	19	99	3	14	----	----
With a parenchymal lesion	13	92	11	74	----	13	----	----
Without a parenchymal lesion	8	30	8	25	----	1	----	----
Minimal	10	29	8	20	----	4	----	----
Advance [3]	1	2	6	29	----	1	2	12
Extrapulmonary [4]	2	8	3	19	1	8	2	16
Pleural effusion	6	24	4	18	----	1	----	----
Total	40	185	40	185	4	28	4	28

[1] Type as determined by X-ray diagnosis, except for extrapulmonary cases.
[2] Includes deaths from tuberculosis.
[3] Includes moderately and far advanced cases.
[4] Includes intestinal, military, osseous, meningeal tuberculosis, and tuberculous cervical adenitis.

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*Experience with BCG vaccine in the control of tuberculosis among North American Indians. Joseph D Aronson and Carrol E Palmer
Public Health Reports Vol 61, June 7, 1946

SCORING SYSTEMS FOR PAEDIATRIC TB*

Table 4. **Observed agreement[a] among nine structured approaches for diagnosing tuberculosis, South Africa, 2001–2006**

System	MASA	Migliori	SATVI	Osborne	Stoltz–Donald	Kibel	Fourie	WHO–Harries	Stegen–Toledo	No. (%) diagnosed with tuberculosis
MASA		65.2	55.7	17.7	78.0	36.8	69.9	87.3	53.4	99 (6.9)
Migliori	0.19		72.7	51.1	71.0	61.3	68.3	64.4	85.3	602 (41.7)
SATVI	0.13	0.46		58.3	77.7	67.3	58.8	54.9	76.4	739 (51.1)
Osborne	0.02	0.13	0.15		37.9	76.9	38.6	20.6	61.9	1289 (89.2)
Stoltz–Donald	0.31	0.38	0.66	0.07		53.8	62.6	69.4	70	417 (28.9)
Kibel	0.06	0.27	0.34	0.33	0.21		52.7	39.2	70.7	1011 (70.0)
Fourie	0.09	0.32	0.18	0.06	0.10	0.18		73.8	59.0	440 (30.4)
WHO–Harries	0.18	0.18	0.11	0.02	0.08	0.08	0.24		53.4	145 (10.0)
Stegen–Toledo	0.12	0.71	0.53	0.19	0.42	0.38	0.20	0.12		772 (53.4)
No. (%) diagnosed with tuberculosis	99 (6.9)	602 (41.7)	739 (51.1)	1289 (89.2)	417 (28.9)	1011 (70.0)	440 (30.4)	145 (10.0)	772 (53.4)	1445 (100)

K, kappa statistic; MASA, Medical Association of South Africa; SATVI, South African tuberculosis Vaccine Initiative; WHO, World Health Organization.
[a] Observed percentage agreement for paired individual observations ($n = 1445$) is above diagonal spaces; K values are below diagonal spaces.

***Structured approaches for the screening and diagnosis of childhood tuberculosis in a high prevalence region of South Africa.**
Hatherill M, Hanslo M, Hawkridge T, Little F, Workman L, Mahomed H, Michele Tameris, Sizulu Moyo, Hennie Geldenhuys, Willem Hanekom, Lawrence Geiter, Gregory Hussey. Bull World Health Organ 2009;88:312-320.

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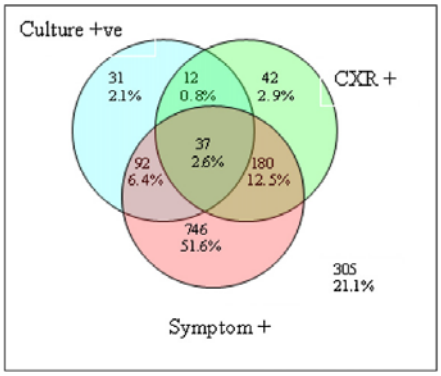
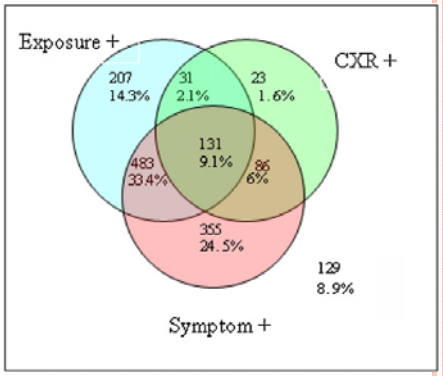
VENN DIAGRAM*





***Phenotypic variability in childhood TB: Implications of diagnostic endpoints in tuberculosis vaccine trials.**
Mulenga H, Moyo S, Workman L, Hawkridge T, Verver S, Tameris M, Geldenhuys H, Hanekom W, Mahomed H, Hussey G, Hatherill M. Journal of Vaccine 2011. Jun 10;29(26):4316-2

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"CONSENSUS" STATEMENT*

- "Lack of consensus was noted for
  (1) significance of isolated culture of Mycobacterium tuberculosis and
  (2) the need for evidence of prior tuberculosis exposure to support a diagnosis of tuberculosis disease.
  Reservations were expressed regarding use of interferon-gamma release assays and the clinical relevance, and potential for misclassification, of primary complex tuberculosis."
- "The Workshop did not achieve consensus on a single primary end-point definition. Tuberculosis disease phenotypes with optimal diagnostic certainty will be uncommon in the study population.
- Criteria for composite or multiple end points were identified, and we propose a hierarchy of end-point criteria, based on rate of occurrence, clinical relevance, and diagnostic certainty."

***Consensus Statement on Diagnostic End Points for Infant Tuberculosis Vaccine Trials.**
Hatherill M, Verver S, Mahomed H; the Taskforce on Clinical Research Issues, Stop TB Partnership Working Group on TB Vaccines. Clin Infect Dis. 2011 Dec 5. [Epub ahead of print]

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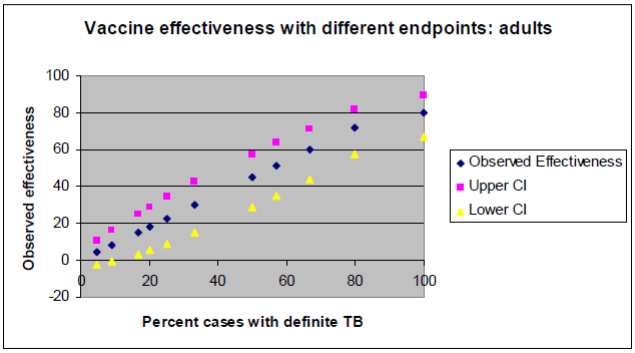
SENSITIVITY AND SPECIFICITY - EXAMPLE

100% specific endpoint, 60% vaccine efficacy, 5% incidence rate			
	Placebo	Vaccine	Efficacy
Cases	50	20	
Sample	1000	1000	
Rate	0.05	0.02	60%
Using a more sensitive but less specific definition and more cases are added but some of which are not true TB			
Cases	50	20	
New genuine cases	25	10	
Not true cases	25	25	
Rate	0.1	0.055	45%

MODELLING OF EFFECT OF MISCLASSIFICATION ON VACCINE EFFECTIVENESS

Figure 2. Effect of misclassification on vaccine with 80% efficacy in an adult TB study of 20,000 subjects, assuming that culture is 87% sensitive for diagnosis of TB



Choice of end-points in tuberculosis vaccine trials: trade-offs between power, precision and bias
Marcel A Behr, Kevin Schwartzman, Madhukar Pai (unpublished)

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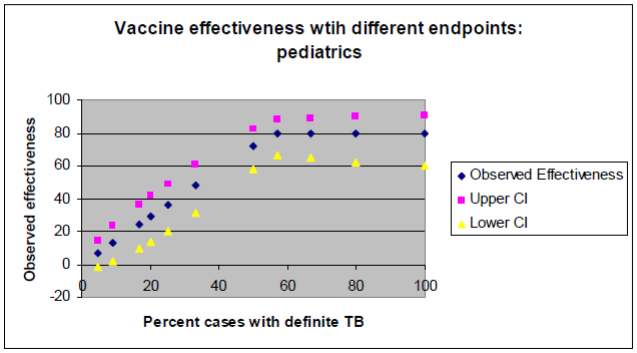
CONTINUED

Figure 3. Effect of misclassification on vaccine with 80% efficacy in a pediatric TB study of 20,000 subjects, assuming that culture is 50% sensitive for diagnosis of TB.



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TEST X EXAMPLE (DO YOU HAVE A PET TORTOISE?)

Test X	Culture_GenXprt		
	Pos	**Neg**	**Total**
Pos	0	5 1.15	5
Neg	14	429 **98.85**	443
Total	14	434	448

SATVI/ AERAS endpoint definitions for infant TB vaccines clinical trials (composite endpoint)

- **TB Case Definition Endpoint #1**
- Any of the following numerical categories

1. Isolation of *M. tuberculosis* from any site.
2. Identification of *M. tuberculosis* by an approved molecular diagnostic technique from any site.
3. Histopathology diagnostic for tuberculosis disease (such as caseating granulomas)
4. Choroidal tubercle diagnosed by an ophthalmologist
5. Miliary pattern on chest X ray in a HIV negative infant

Endpoint 1 continued

6. Clinical diagnosis of tuberculous meningitis (CSF protein >0.6 g/L and pleocytosis >50/mm3 with mononuclear cell >50%) with features of basal meningeal enhancement and hydrocephalus on head CT.
7. Vertebral spondylosis
8. A single smear/histology specimen positive for acid fast (or auramine positive) bacilli from a normally sterile body site.

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9. One of the following:

- a) Two acid fast or auramine smears positive each from a separate collection morphologically consistent with mycobacteria from either sputum or gastric aspirate that are not found to be non-tuberculous mycobacteria bacteria on culture , OR
- b) QuantiFERON conversion from negative or indeterminate to positive, OR
- c) Tuberculin skin test ≥15 mm
- AND
- One of the following compatible radiographic features:
- a) Calcified Ghon focus, OR
- b) Pulmonary cavity, OR
- c) Hilar/mediastinal adenopathy, OR
- d) Pleural effusion, OR
- e) Airspace opacification,
- AND
- One of the following clinical manifestations:
- a) Cough without improvement for longer than two weeks, OR
- b) Weight loss of at least 10% of body weight for at least 2 months, OR
- c) Failure to thrive (crossing at least one entire major centile band downward) for at least 2 months, where the major centile bands are defined as <97th–90th, <90th–75th, <75th–50th, <50th–25th, <25th–10th, and <10th–3rd weight-for-age centiles*.

PNEUMONIA VACCINE TRIALS*

- The predefined primary end points were a first episode of **invasive pneumococcal disease** and **an episode of radiologically confirmed pneumonia** that occurred at least 14 days after the third dose in children without HIV infection who were included in the per-protocol analyses. Invasive pneumococcal disease was defined on the basis of the isolation from blood, cerebrospinal fluid, or both of a pneumococcal serotype included in the vaccine

*A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection.
Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N; Vaccine Trialists Group.
N Engl J Med. **2003** Oct 2;349(14):1341-8.

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Table 2. First Episodes of Invasive Pneumococcal Disease.*

Variable	Vaccinated Group	Control Group	P Value	Vaccine Efficacy (95% CI)
	no. of episodes			*percent*
HIV-negative children				
Invasive pneumococcal disease	11	19	0.2	42 (–28 to 75)
Vaccine-serotype pneumococci	3	17	0.003	83 (39 to 97)
Non–vaccine-serotype pneumococci	4	1	0.38	–300 (–19,599 to 60)
Vaccine-related–serotype pneumococci	4	1	0.38	–300 (–19,599 to 60)

Table 4. Efficacy of the Vaccine against First Episodes of Radiologically Confirmed Pneumonia.*

Variable	Vaccinated Group	Control Group	P Value	Vaccine Efficacy (95% CI)
	no. of episodes			%
HIV-negative children	169	212	0.03	20 (2 to 35)
HIV-positive children	182	209	0.19	13 (–7 to 29)
All children	356	428	0.01	17 (4 to 28)

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Conclusion

- Clinical trial endpoints are needed for TB vaccine efficacy trials.
- While specificity is very important, caution should be exercised in how the endpoints are selected.
- Only an efficacious vaccine will tell us whether our endpoints are sound.

Acknowledgments

- Mark Hatherill, Sizulu Moyo and SATVI team.
- STOP TB Working group on TB vaccines: Taskforce on Clinical Research Issues in TB Vaccine development.
- M Pai and M Behr