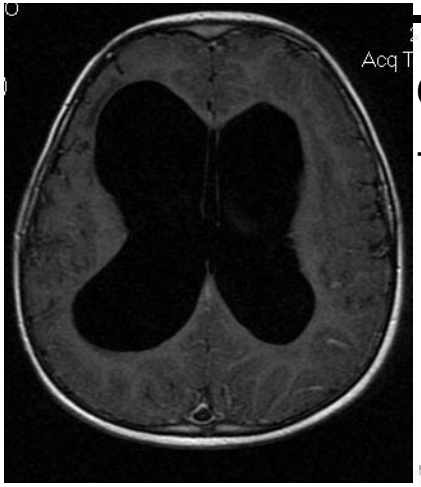
REFERENCE STANDARDS FOR EXTRAPULMONARY TB DIAGNOSTIC EVALUATIONS

Maxine Caws

mcaws@oucru.org

MAIN SITES OF EXTRAPULMONARY TUBERCULOSIS



Central nervous system
-Meningitis

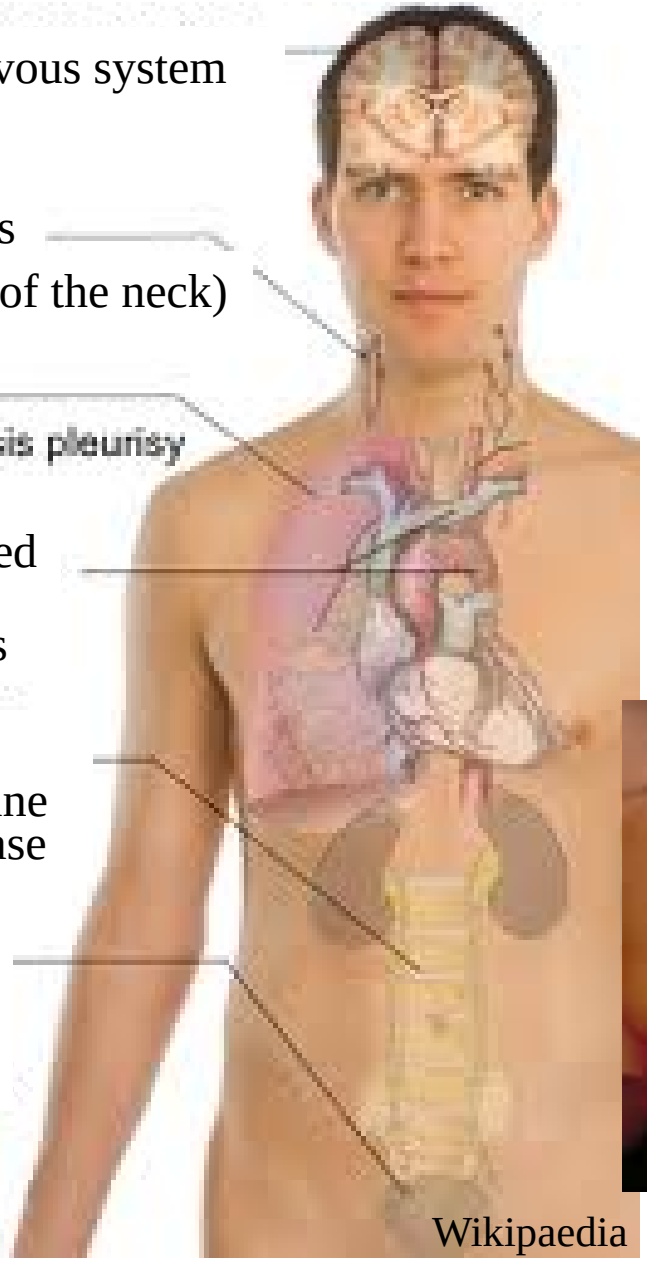
Lymphatics
-Scrofula (of the neck)

Pleura
- Tuberculosis pleurisy

Disseminated
-Miliary tuberculosis

Bones and joints of spine
–Potts disease

Genito-Urinary
-Urogenital tuberculosis

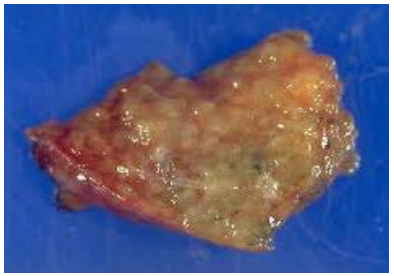


Wikipaedia

SAMPLE TYPE APPROPRIATE DEPENDS ON SITE OF SUSPECTED DISEASE

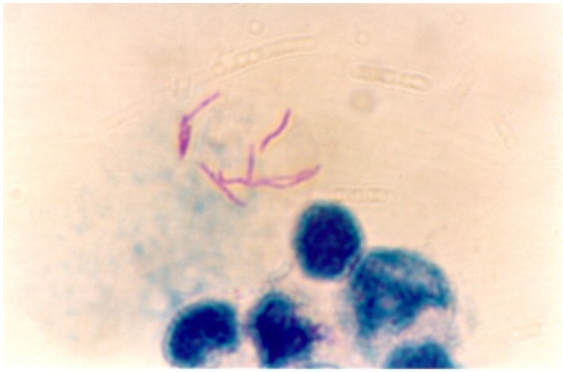
-PLEURAL FLUID

-PERICARDIAL FLUID



-CEREBRAL SPINAL FLUID

-LYMPH ASPIRATE



-GASTRIC FLUID

-BIOPSY SAMPLES

-BLOOD

-STOOL

-URINE

-BONE MARROW

SAMPLE PROCESSING AND VOLUMES MAY GREATLY AFFECT DIAGNOSTIC ACCURACY

EVALUATIONS OFTEN INCLUDE 'EXTRAPULMONARY TB' AS SINGLE ENTITY

Table 1. Summary of studies (n = 8) published before 7 March 2012 in which the diagnostic accuracy of Xpert® MTB/RIF for extrapulmonary TB was assessed.

Study (year)	Country	TB gold standard diagnoses (n)	TB not diagnosed (n)	Main sample types testing positive for TB (n)	Gold standard for TB diagnosis	Xpert sensitivity, % (95% CI)	Xpert specificity, % (95% CI)	Ref.
Index study								
Tortoli *et al.* (2012)	Italy	268	1206	Tissue biopsies/fine-needle aspirates (94); pleural fluid (18); gastric aspirates (61); pus (55); CSF (14); urine (16); peritoneal/ synovial/pericardial fluid (10)	Culture (solid and liquid) or suggestive radiology/ histology with documented positive response to TB treatment	81.3 (76.2–85.8)	99.8 (99.4–100)	[5]
Other studies								
Armand *et al.* (2011)	France	32	NA	LNs (16); pleural (7); bone (5)	Culture (solid and liquid media)	53.1 (34.7–70.9)		[6]
Causse *et al.* (2011)	Spain	41	299	Tissue biopsies (18); CSF (6); gastric aspirates (8); pleural fluid (4); purulent	Culture			[7]
Friedrich *et al.* (2011)	South Africa	20	5			25.0 (8.7–49.1)	100 (47.8–100)	[8]
Hillemann *et al.* (2011)	Germany	45			Culture (solid and liquid media)	77.3 (60.5–87.1)	98.2 (96.0–98.9)	[9]
Ligthelm *et al.* (2011)				Fine-needle aspiration LN biopsy	Composite standard: positive cytology + AFB and/or culture of MTB	96.6 (86.6–100)	88.9 (69.6–100) (note: only 18 samples)	[10]
Moure *et al.* (2011)	Spain	108	41	All smear-negative. Pleural fluid (26); LNs (34); abscess aspirates (17); tissues (12)	Culture (solid and liquid media)	58.3 (48.5–67.8)	100 (91.4–100)	[11]
Vadwai *et al.* (2011)	India	283	250	Tissue biopsies (105); pus (98); body fluids (24)	Composite of smear, culture, clinical, radiology and histology	80.6 (75.5–85.0)	99.6 (97.8–100)	[12]

Only studies with at least 20 gold standard diagnoses of extrapulmonary TB were included.
AFB: Acid-fast bacilli; CSF: Cerebrospinal fluid; LN: Lymph node; MTB: *Mycobacterium tuberculosis*; NA: Not available.

OFTEN MISLEADING AND DOES NOT ALLOW ROBUST EVAULATION OF DIFFERENT SAMPLE TYPES/FORMS

Stephen D Lawn*[1,2] and Alimuddin I Zumla[3,4]

Expert Rev. Anti Infect. Ther. 10(6), (2012)

Common Case Categorisations Used

DEFINATE- culture/smear confirmed (Often + PCR/histology)

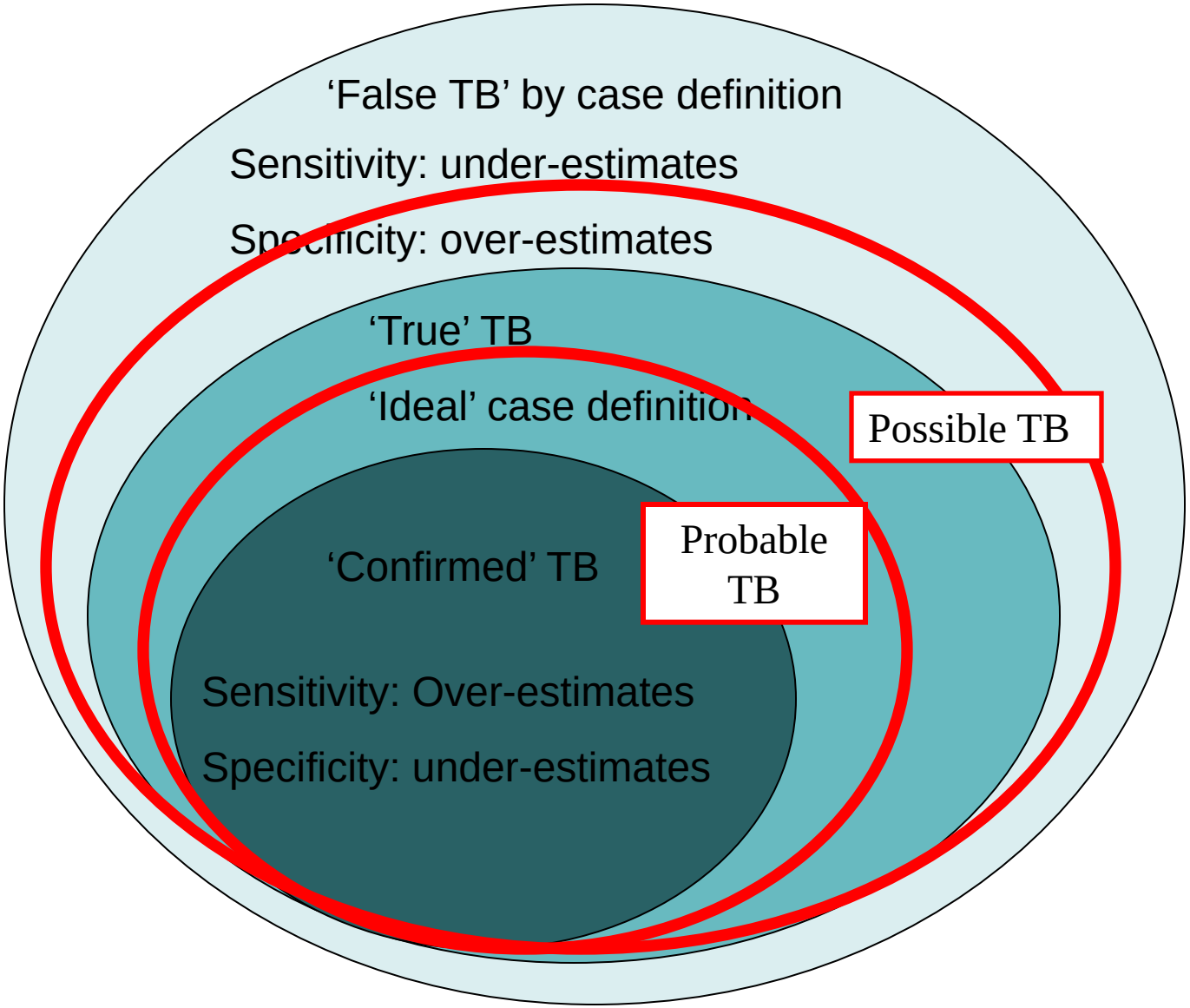
PROBABLE- no microbiological confirmation but fits tight case definition.

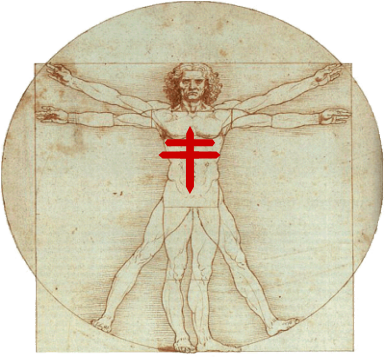
POSSIBLE – Fits only broad case definition but no alternative diagnosis

NOT TB- alternative confirmed diagnosis/recovery without TB treatment

- Definitions vary between studies- comparibility/generalisability of findings difficult to interpret

CASE DEFINITIONS AND OVER/UNDER ESTIMATION





CONSENSUS CASE DEFINITIONS ALLOW COMPARIBILITY OF STUDIES-

EXAMPLE OF TBM

Tuberculous meningitis: a uniform case definition for use in clinical research

Suzaan Marais, Guy Thwaites, Johan F Schoeman, M Estée Török, Usha K Misra, Kameshwar Prasad, Peter R Donald, Robert J Wilkinson, Ben J Marais

Tuberculous meningitis causes substantial mortality and morbidity in children and adults. More research is urgently needed to better understand the pathogenesis of disease and to improve its clinical management and outcome. A major stumbling block is the absence of standardised diagnostic criteria. The different case definitions used in various studies makes comparison of research findings difficult, prevents the best use of existing data, and limits the management of disease. To address this problem, a 3-day tuberculous meningitis workshop took place in Cape Town, South Africa, and was attended by 41 international participants experienced in the research or management of tuberculous meningitis. During the meeting, diagnostic criteria were assessed and discussed, after which a writing committee was appointed to finalise a consensus case definition for tuberculous meningitis for use in future clinical research. We present the consensus case definition together with the rationale behind the recommendations. This case definition is applicable irrespective of the patient's age, HIV infection status, or the resources available in the research setting. Consistent use of the proposed case definition will aid comparison of studies, improve scientific communication, and ultimately improve care.

Published Online
September 6, 2010
DOI:10.1016/S1473-3099(10)70138-9

Department of Medicine, GF Jooste Hospital, Manenberg, South Africa (S Marais MBChB, Prof R J Wilkinson FRCP); **Clinical Infectious Diseases Research Initiative, Institute of Infectious Diseases and Molecular Medicine, and Department of Medicine, University of Cape Town, South Africa** (S Marais, R J Wilkinson); **Imperial College, London, UK**

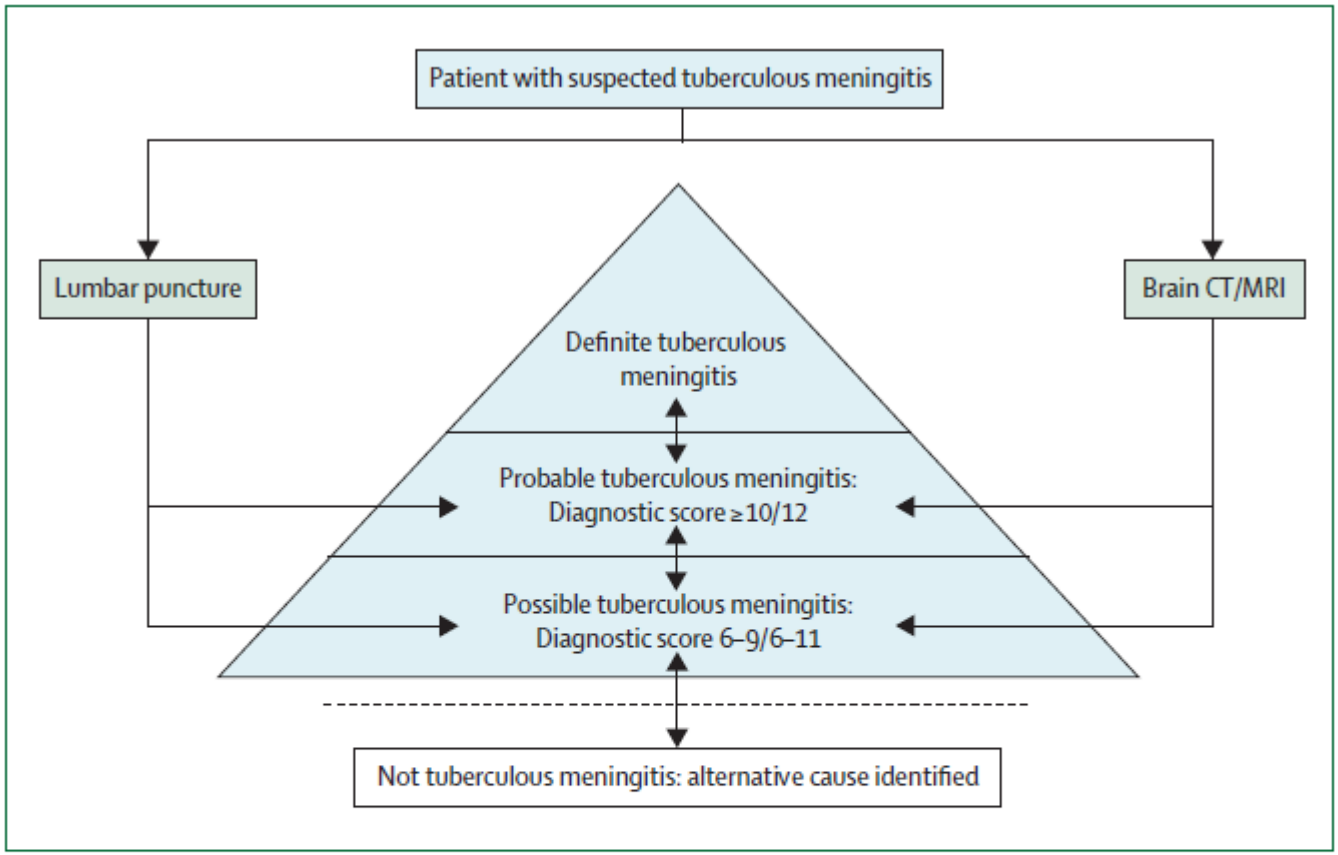
www.thelancet.com/infection **Published online September 6, 2010 DOI:10.1016/S1473-3099(10)70138-9**

	Diagnostic score
Clinical criteria	(Maximum category score=6)
Symptom duration of more than 5 days	4
Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks	2
History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children <10 years of age)	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
Altered consciousness	1
CSF criteria	(Maximum category score=4)
Clear appearance	1
Cells: 10–500 per µl	1
Lymphocytic predominance (>50%)	1
Protein concentration greater than 1 g/L	1
CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2·2mmol/L	1
Cerebral imaging criteria	(Maximum category score=6)
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Pre-contrast basal hyperdensity	2
Evidence of tuberculosis elsewhere	(Maximum category score=4)
Chest radiograph suggestive of active tuberculosis: signs of tuberculosis=2; miliary tuberculosis=4	2/4
CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS	2
AFB identified or *Mycobacterium tuberculosis* cultured from another source—ie, sputum, lymph node, gastric washing, urine, blood culture	4
Positive commercial *M tuberculosis* NAAT from extra-neural specimen	4
Exclusion of alternative diagnoses	
An alternative diagnosis must be confirmed microbiologically (by stain, culture, or NAAT when appropriate), serologically (eg, syphilis), or histopathologically (eg, lymphoma). The list of alternative diagnoses that should be considered, dependent upon age, immune status, and geographical region, include: pyogenic bacterial meningitis, cryptococcal meningitis, syphilitic meningitis, viral meningo-encephalitis, cerebral malaria, parasitic or eosinophilic meningitis (*Angiostrongylus cantonesis*, *Gnathostoma spinigerum*, toxocariasis, cysticercosis), cerebral toxoplasmosis and bacterial brain abscess (space-occupying lesion on cerebral imaging)and malignancy (eg, lymphoma)	

TST=tuberculin skin test. IGRA=interferon-gamma release assay. NAAT=nucleic acid amplification test. AFB=acid-fast bacilli. The individual points for each criterion (one, two, or four points) were determined by consensus and by considering their quantified diagnostic value as defined in studies.

Table: **Diagnostic criteria for classification of definite, probable, possible, and not tuberculous meningitis**

- Clinical History
- Presentation
- Laboratory findings
- Imaging (CXR/CT/MRI)
- Alternative Dx


Patient with suspected tuberculous meningitis
Lumbar puncture
Brain CT/MRI
Definite tuberculous meningitis
Probable tuberculous meningitis: Diagnostic score ≥10/12
Possible tuberculous meningitis: Diagnostic score 6–9/6–11
Not tuberculous meningitis: alternative cause identified

Panel 2: Consensus tuberculous meningitis diagnosis

Clinical entry criteria

- Symptoms and signs of meningitis including one or more of the following: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy.

Tuberculous meningitis classification

Definite tuberculous meningitis

- Patients should fulfill criterion A or B:
  - A) Clinical entry criteria plus one or more of the following: acid-fast bacilli seen in the CSF; *Mycobacterium tuberculosis* cultured from the CSF; or a CSF positive commercial nucleic acid amplification test.
  - B) Acid-fast bacilli seen in the context of histological changes consistent with tuberculosis in the brain or spinal cord with suggestive symptoms or signs and CSF changes, or visible meningitis (on autopsy).

Probable tuberculous meningitis

- Clinical entry criteria plus a total diagnostic score of 10 or more points (when cerebral imaging is not available) or 12 or more points (when cerebral imaging is available) plus exclusion of alternative diagnoses. At least 2 points should either come from CSF or cerebral imaging criteria.

Possible tuberculous meningitis

- Clinical entry criteria plus a total diagnostic score of 6–9 points (when cerebral imaging is not available) or 6–11 points (when cerebral imaging is available) plus exclusion of alternative diagnoses. Possible tuberculosis cannot be diagnosed or excluded without doing a lumbar puncture or cerebral imaging.

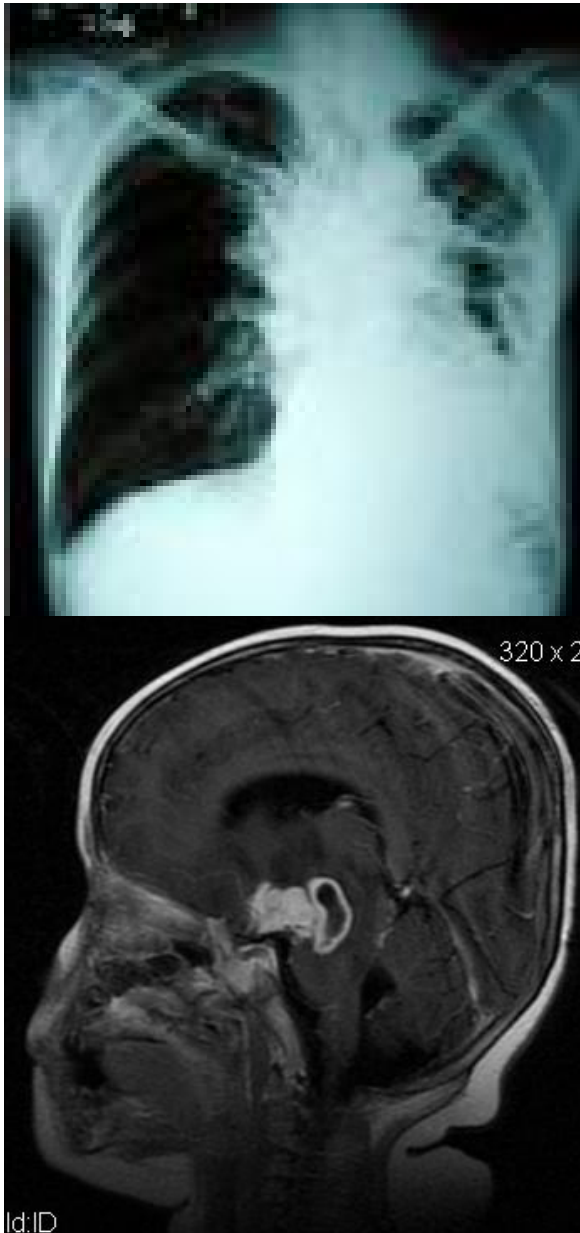
Not tuberculous meningitis

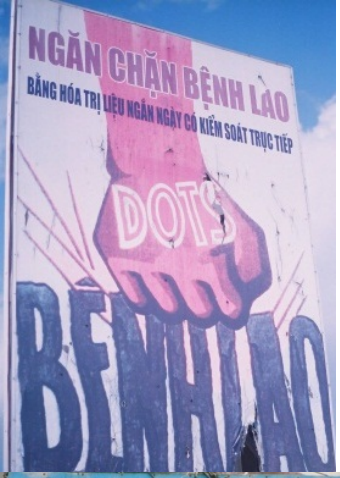
- Alternative diagnosis established, without a definitive diagnosis of tuberculous meningitis or other convincing signs of dual disease.

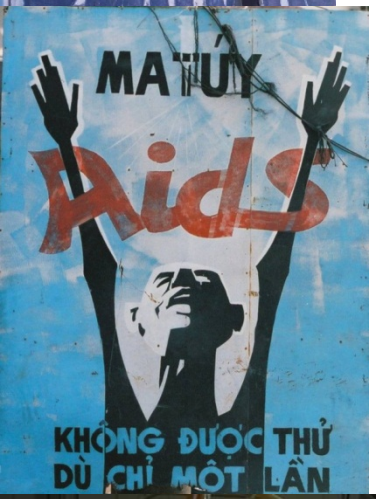
CSF=cerebrospinal fluid.

CASE DEFINITIONS:

- **May Improve standardisation and comparibility**
- **DO NOT eliminate variability**
- **Derived by expert consensus, not scientifically evaluated and always flawed**
- **Not intended to define treatment**







Other forms of Extrapulmonary TB require consensus case definition/disease categorisation

- Defined Entry criteria
- Standard sample collection and processing techniques
- Consensus case definitions
- Standardised CRFs
- Standardised analysis and reporting
- Evidence base for application/optimisation of test to xpulm samples