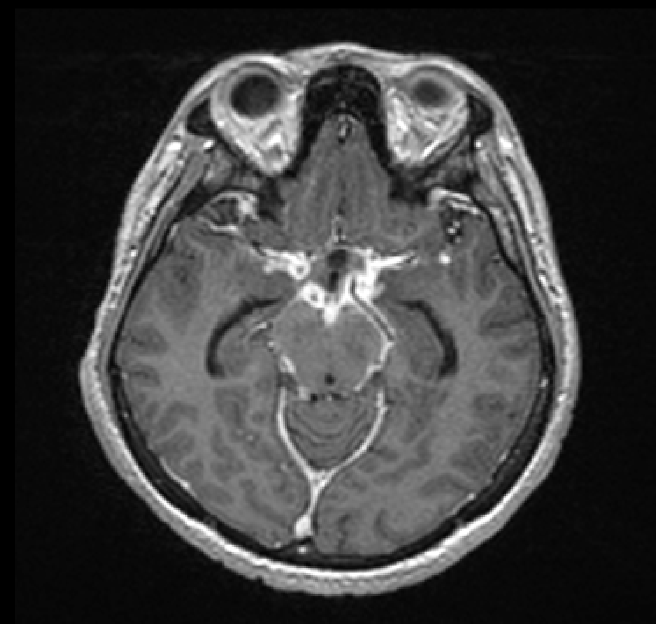
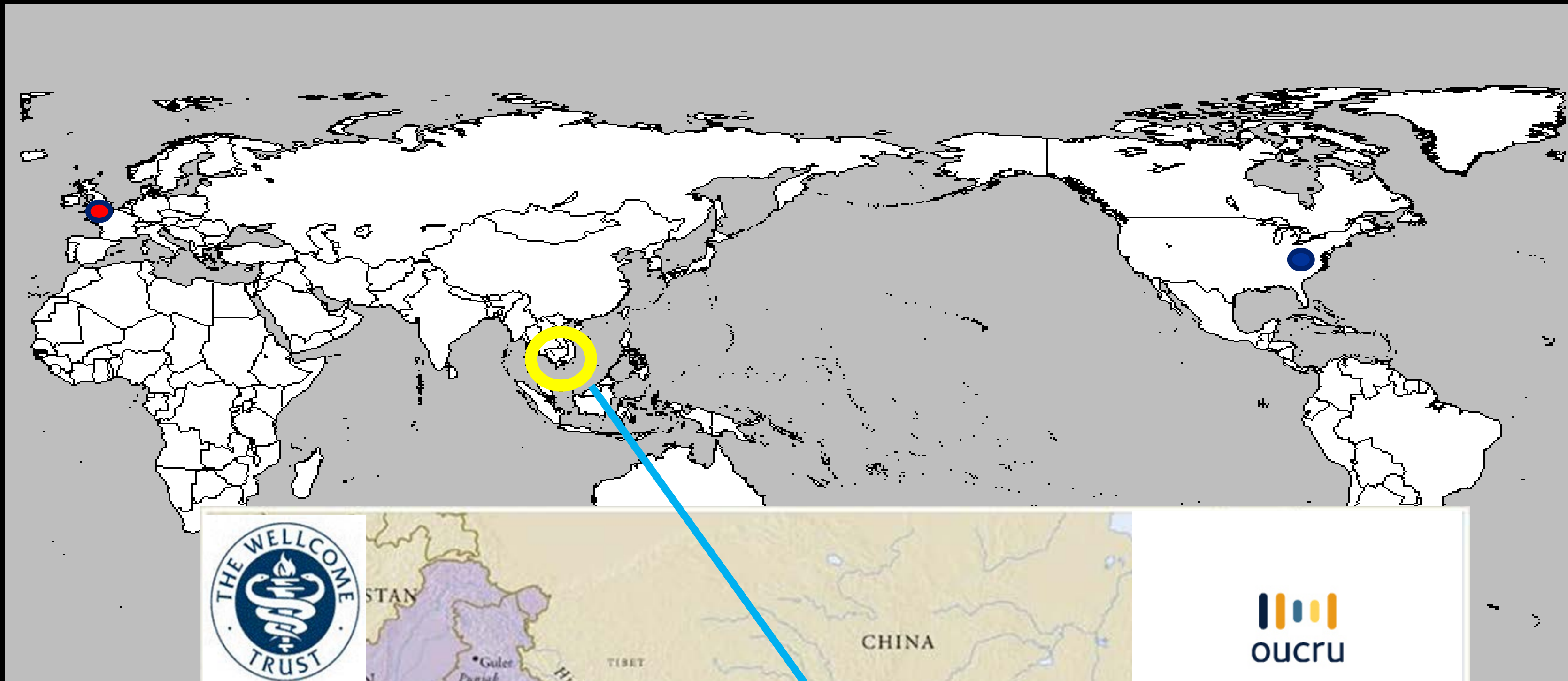
TB meningitis: the clinical research agenda



Guy Thwaites
Director, Oxford University Clinical Research Unit
Wellcome Trust Major Overseas Programme
Viet Nam



THE WELLCOME TRUST
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CHINA
TIBET
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Punjab Hills
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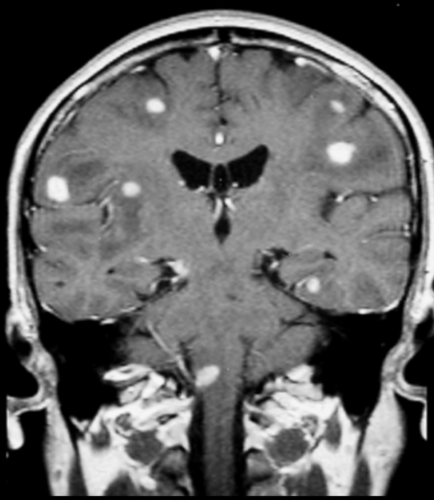
RAJASTHAN
Mewar
WEST BENGAL
Calcutta
Ajanta
Mumbai (Bombay)
INDIA
KALINGA
BANGLADESH
BURMA (MYANMAR)
Rangoon (Yangon)
THAILAND
Sukhothai
Ayutthaya
Bangkok
VIETNAM
South China Sea
PHILIPPINES
Ocean
Bay of Bengal
MALAYSIA
Borneo
Sulawesi
Sumatra
Java Sea
INDONESIA
Dieng Plateau
Bali
300 600 miles
0 300 600 kilometers

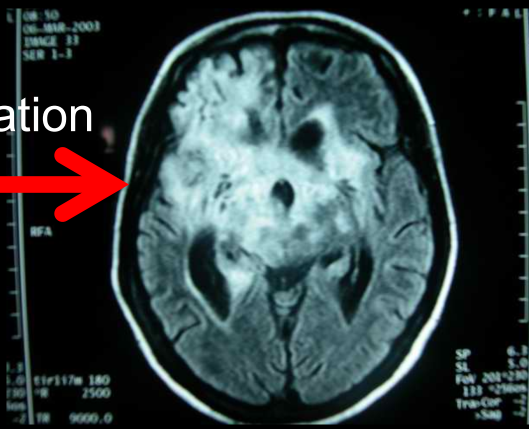
TB meningitis: pathogenesis

Bacteremia



↑Inflammation

↑bacteria

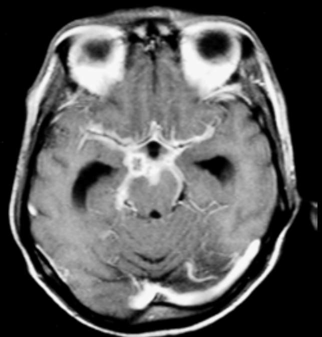


DEATH (25%)

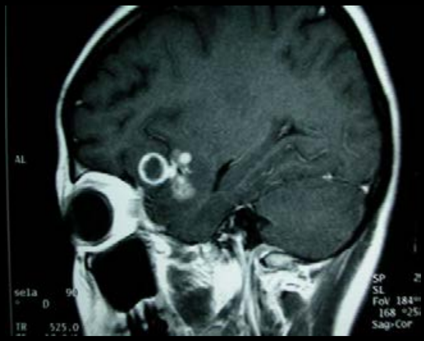
Arnold Rich
1893-1968

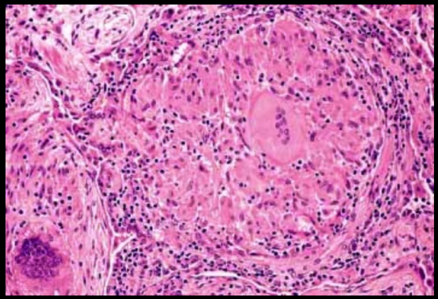
Bull John Hopkins Hosp. 1933;52:5-37.

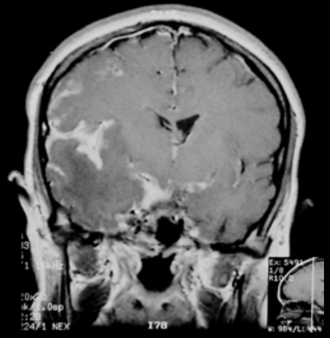
TB meningitis: pathology

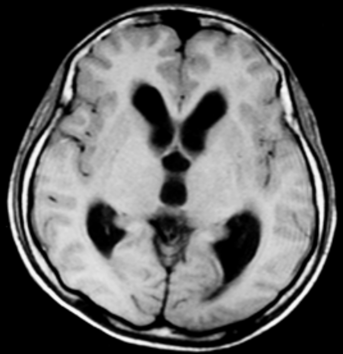


- Basal meningitis
- Hydrocephalus
- Infarcts
- Tuberculomas



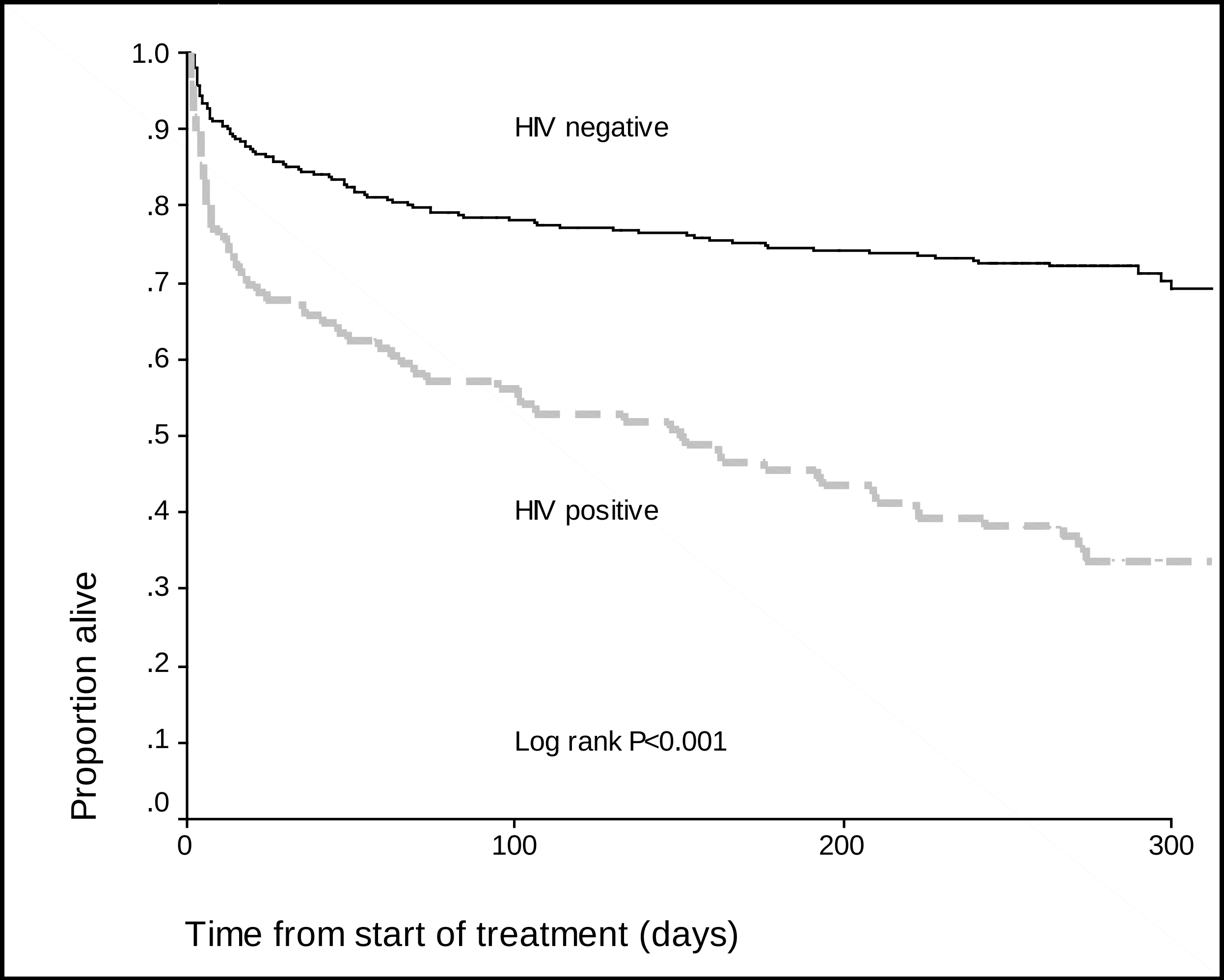






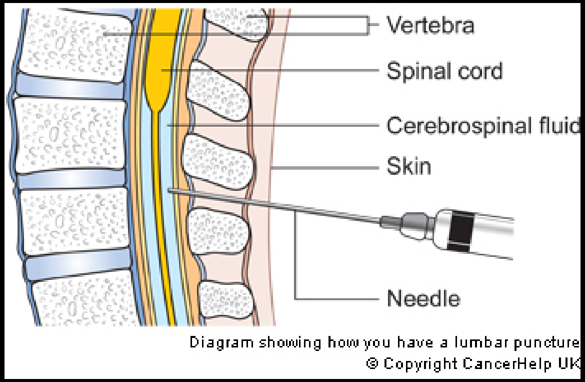
Why study TB meningitis?

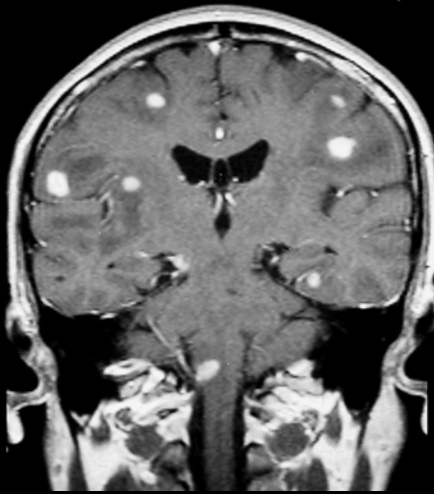
Conservative estimate: 100,000 cases each year



Why study TB meningitis?
The human model

- In hospital care (1-2 months)
- Serial cerebrospinal fluid (CSF) samples
- Serial brain imaging with CT and MRI
- High ‘event’ frequency





TBM is a medical emergency

Treatment before the onset of coma is the greatest benefit a physician can give a patient with TBM

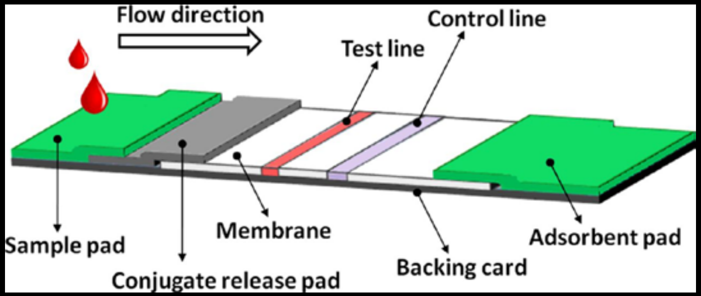
The problem: rapid diagnosis

Clinical algorithms

CSF ZN stain, microscopy, culture

GeneXpert

Can we get to this?



Key research questions

- Is GeneXpert ULTRA more sensitive than current GeneXpert for TBM diagnosis?

- How will we rapidly detect drug resistant bacteria?

- Will NGS technologies (e.g.MinION) allow rapid bacterial detection and drug resistance?

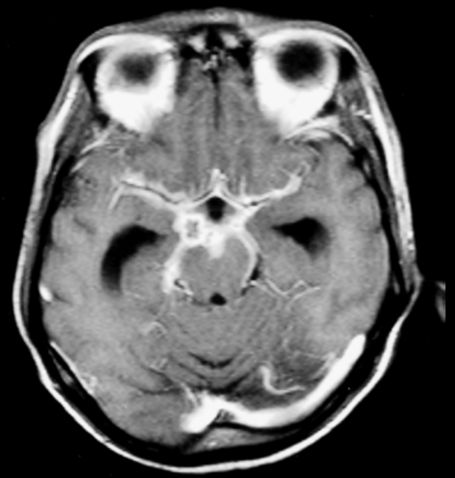
- Are there novel host/bacterial biomarkers?

TBM treatment

Enhance bacterial killing

Control intra-cerebral inflammation

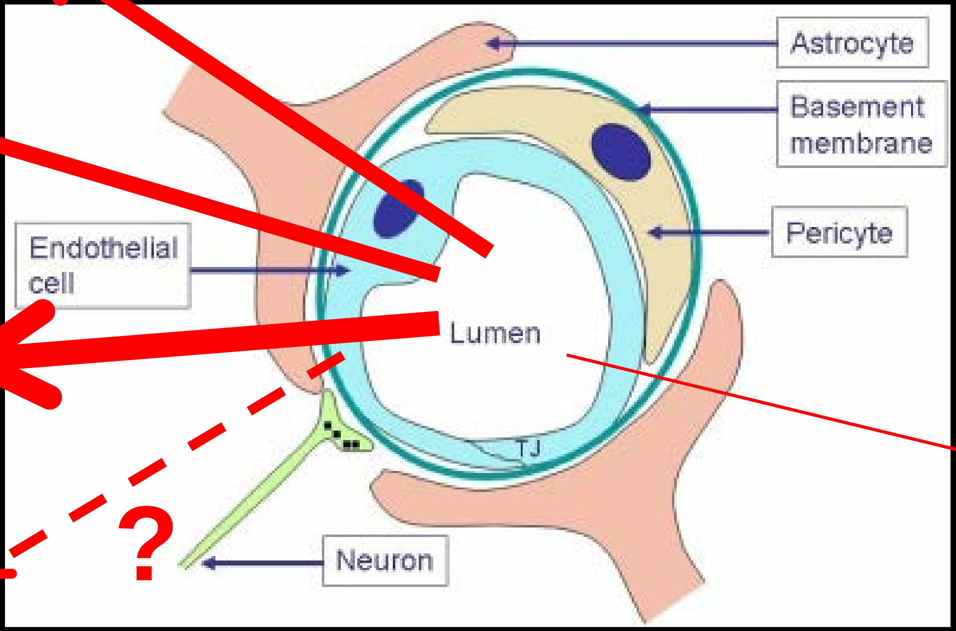
Intra-cerebral drug penetration



Levofloxacin
Moxifloxacin

INH

PZA



New agents
e.g. bedaquiline
delaminid

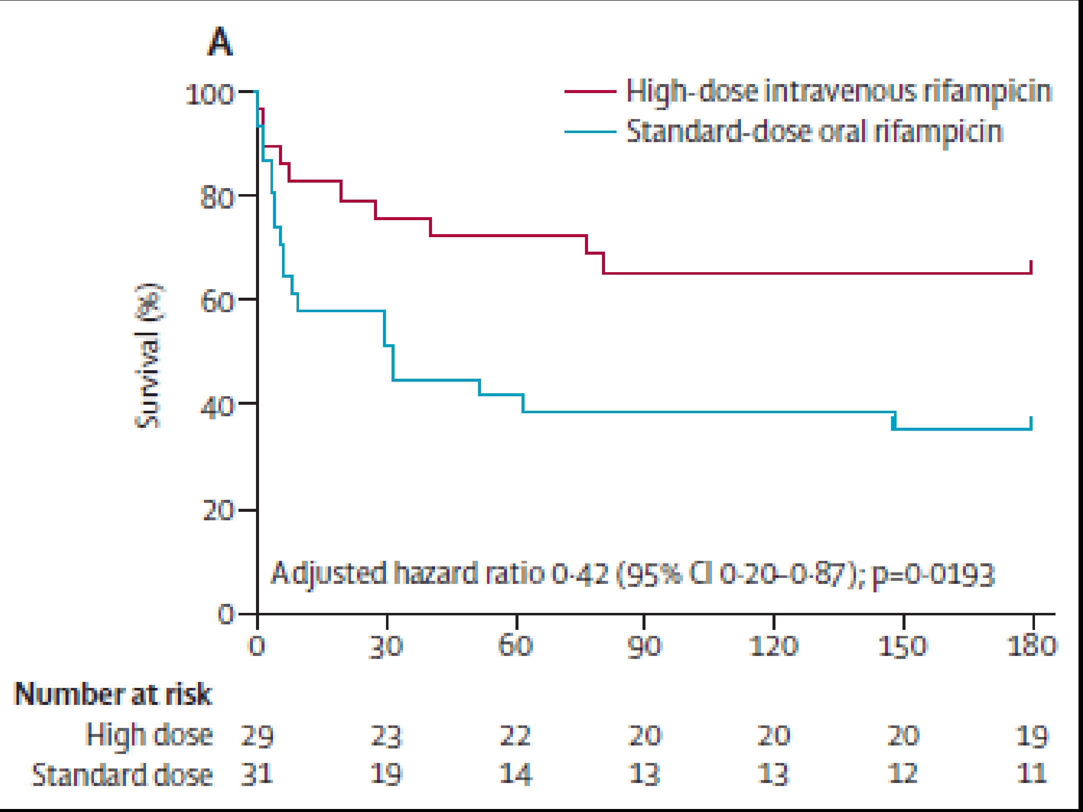
Rifampin
ETH
SM

Blood-brain barrier

Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

Rovina Ruslami*, A Rizal Ganiem*, Sofiati Dian, Lika Apriani, Tri Hanggono Achmad, Andre J van der Ven, George Borm, Rob E Aarnoutse, Reinout van Crevel

60 Indonesian Adults. Oral rifampicin (450mg) vs IV 600mg for 1st 2 weeks



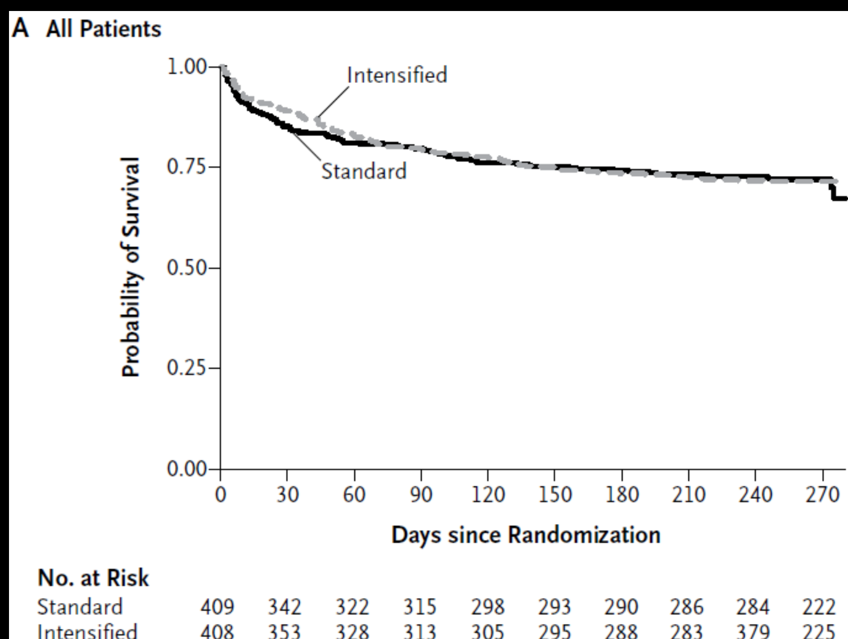
Lancet Infect Dis. 2013 Jan;13(1):27-35.

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

A. Dorothee Heemskerk, M.D., Nguyen D. Bang, Ph.D., Nguyen T.H. Mai, Ph.D., Tran T.H. Chau, Ph.D., Nguyen H. Phu, Ph.D., Pham P. Loc, M.D., Nguyen V.V. Chau, Ph.D., Tran T. Hien, Ph.D., Nguyen H. Dung, Ph.D., Nguyen T.N. Lan, Ph.D., Nguyen H. Lan, M.D., Nguyen N. Lan, M.D., Le T. Phong, M.D., Nguyen N. Vien, M.D., Nguyen Q. Hien, M.D., Nguyen T.B. Yen, M.D., Dang T.M. Ha, Ph.D., Jeremy N. Day, F.R.C.P., Maxine Caws, Ph.D., Laura Merson, B.S., Tran T.V. Thinh, M.D, Marcel Wolbers, Ph.D., Guy E. Thwaites, F.R.C.P., and Jeremy J. Farrar, F.R.C.P.

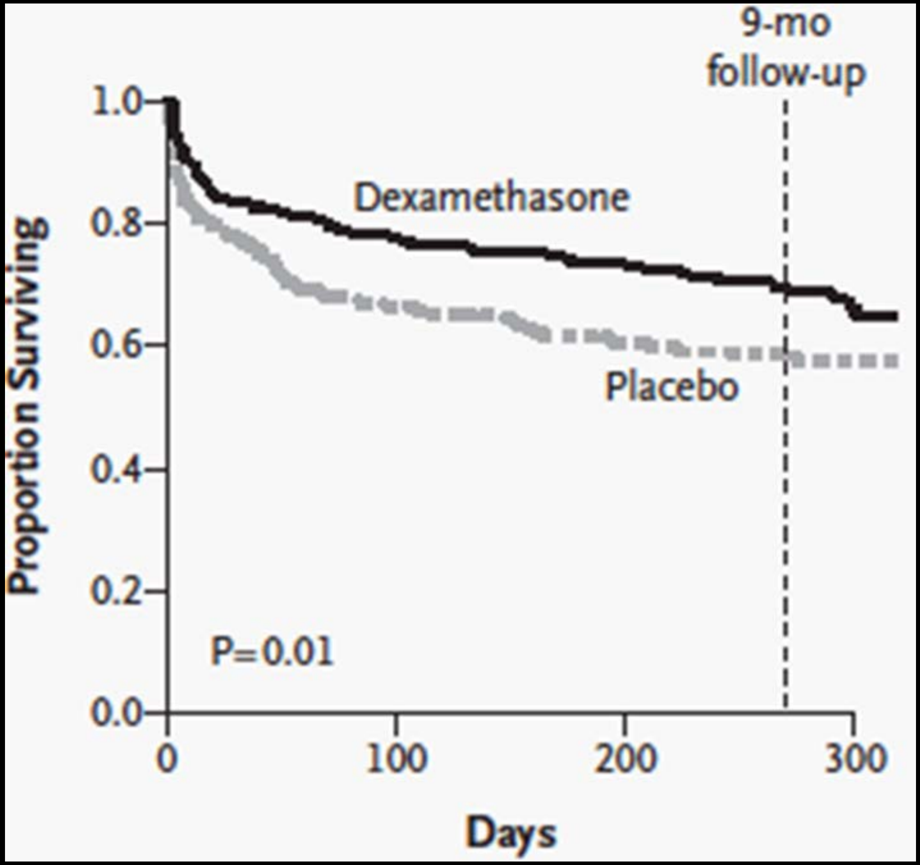
817 Vietnamese adults. Standard regimen vs rifampicin 15mg/kg + levofloxacin (1g/day)
For 1st 2 months



N Engl J Med. Jan 2016;374:124-134.

Controlling intracerebral inflammation: adjunctive dexamethasone

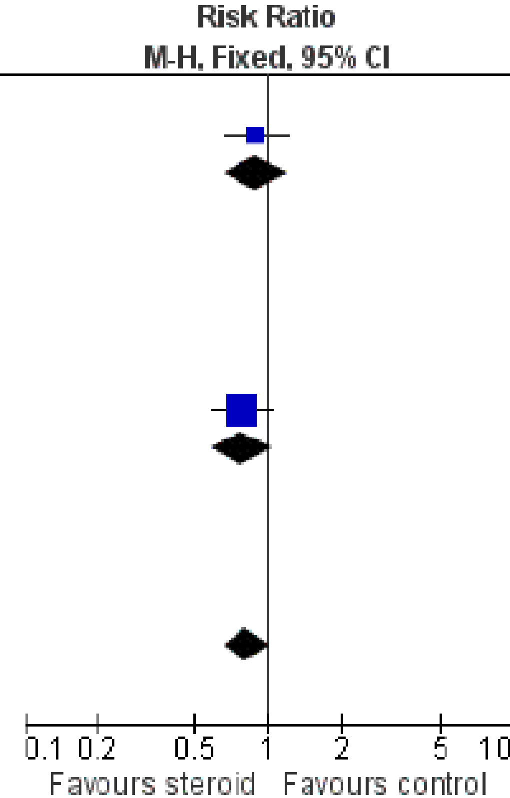
545 Vietnamese adults. 6-8 week dexamethasone vs placebo



N Engl J Med. 2004;351(17):1741-51

Adjunctive steroids and HIV-associated TBM?

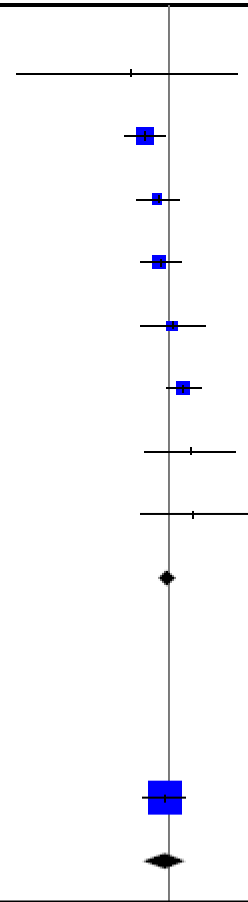
Study or Subgroup	Corticosteroid Events	Corticosteroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 HIV-positive						
Thwaites 2004	27	44	37	54	32.3%	0.90 [0.67, 1.20]
Subtotal (95% CI)		**44**		**54**	**32.3%**	**0.90 [0.67, 1.20]**
Total events	27		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
3.1.2 HIV-negative						
Thwaites 2004	57	227	67	209	67.7%	0.78 [0.58, 1.06]
Subtotal (95% CI)		**227**		**209**	**67.7%**	**0.78 [0.58, 1.06]**
Total events	57		67			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						
Total (95% CI)		**271**		**263**	**100.0%**	**0.82 [0.66, 1.02]**
Total events	84		104			
Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						



Prasad K, Singh MB, Ryan H.
Corticosteroids for managing tuberculous meningitis.
Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD002244.

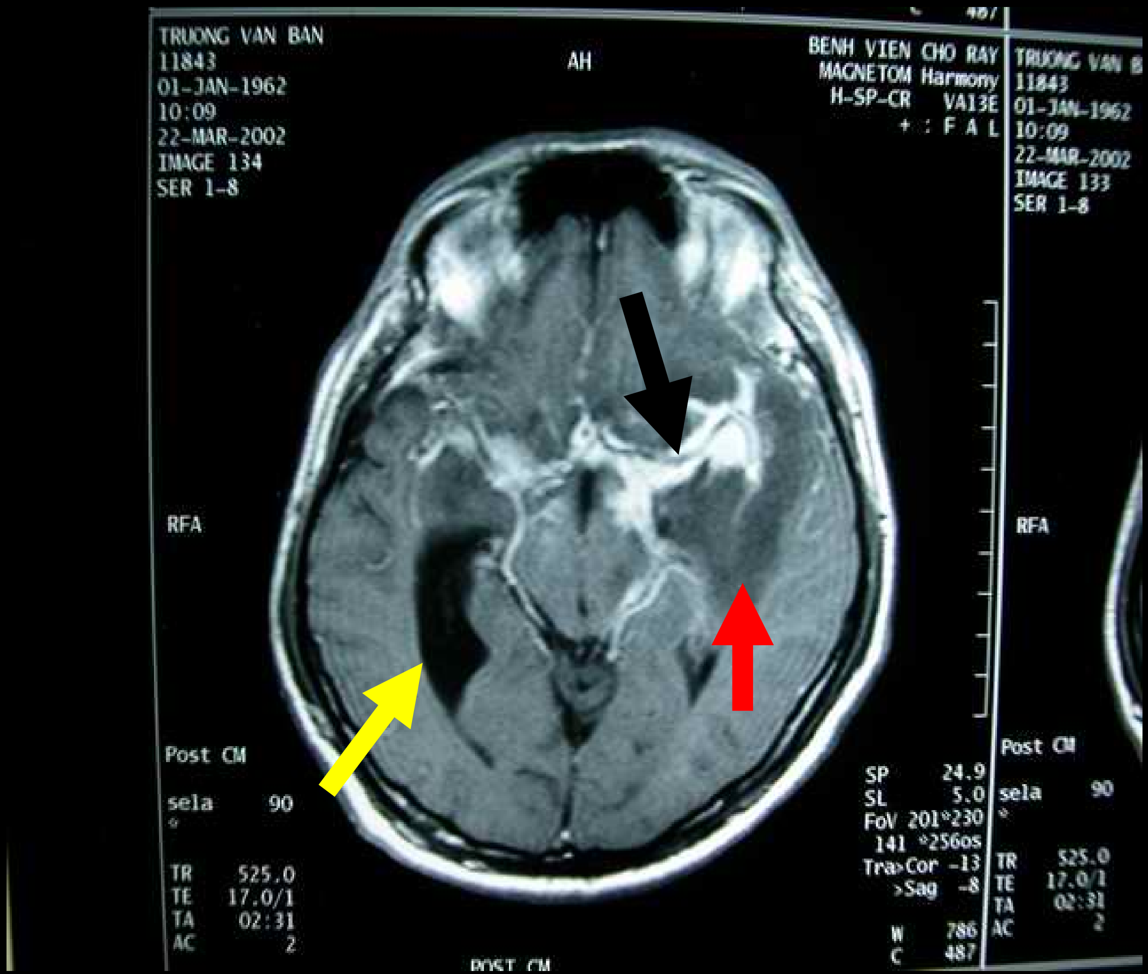
Impact on neuro-disability?

Study or subgroup	Corticosteroid n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Follow-up 2 to 24 months					
Kumarvelu 1994	0/24	1/23		1.6 %	0.32 [0.01, 7.48]
Girgis 1991	14/145	27/135		29.1 %	0.48 [0.26, 0.88]
Lardizabal 1998	10/29	14/29		14.6 %	0.71 [0.38, 1.34]
Schoeman 1997	14/70	19/71		19.7 %	0.75 [0.41, 1.37]
Malhotra 2009	11/65	5/32		7.0 %	1.08 [0.41, 2.85]
Thwaites 2004	34/274	22/271		23.0 %	1.53 [0.92, 2.54]
Prasad 2006	5/41	3/46		2.9 %	1.87 [0.48, 7.34]
Chotmongkol 1996	4/29	2/30		2.0 %	2.07 [0.41, 10.44]
Subtotal (95% CI)	**677**	**637**		**100.0 %**	**0.92 [0.71, 1.20]**
Total events: 92 (Corticosteroid), 93 (Control)					
Heterogeneity: Chi² = 11.85, df = 7 (P = 0.11); I² =41%					
Test for overall effect: Z = 0.60 (P = 0.55)					
2 Follow-up at 5 years					
Thwaites 2004	17/128	18/116		100.0 %	0.86 [0.46, 1.58]
Subtotal (95% CI)	**128**	**116**		**100.0 %**	**0.86 [0.46, 1.58]**



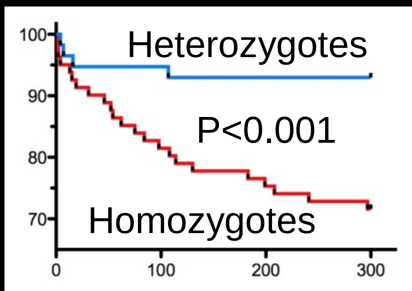
Prasad K, Singh MB, Ryan H.
Corticosteroids for managing tuberculous meningitis.
Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD002244.

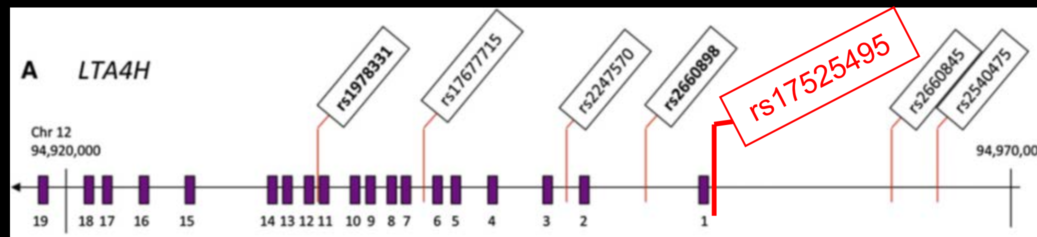
How does dexamethasone save lives?



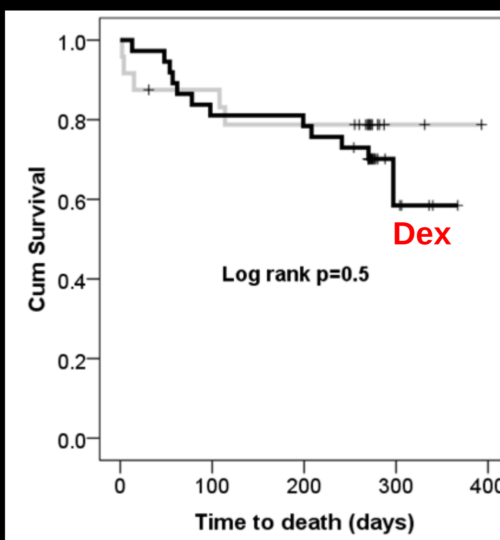
Simmons et al. J Immunol. 2007
Thwaites et al. Lancet Neurol. 2007
Green J et al. PLOS One. 2009

LTA4H Genotype determines survival and dexamethasone responsiveness

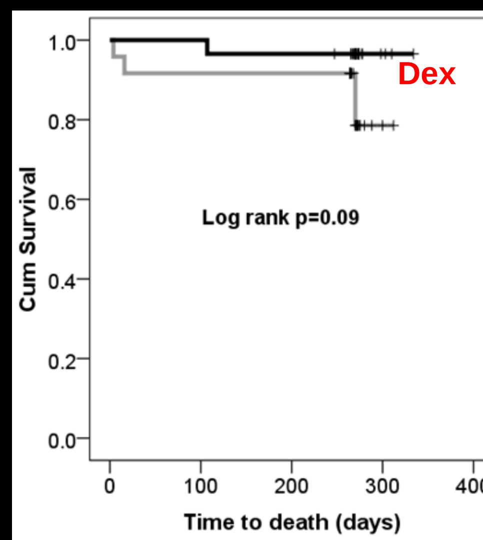




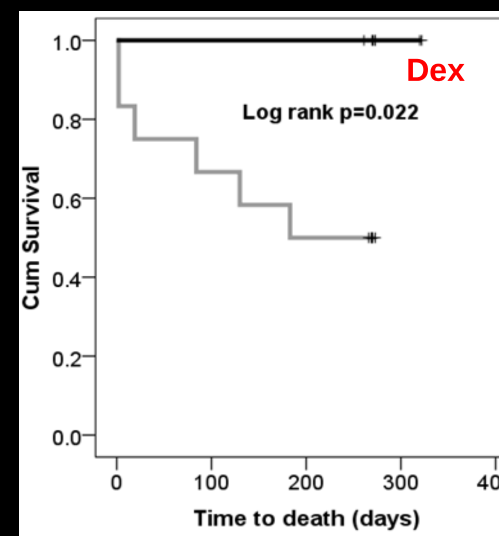
CC genotype (LTA4H low)



CT genotype



TT genotype



Survival in 182 HIV uninfected Vietnamese adults with TBM treated with or without Adjunctive dexamethasone

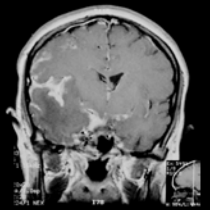
Tobin et al Cell. 2012; 148, 434–446

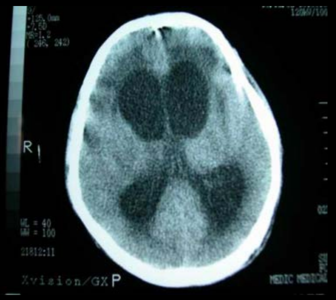
Will more directed, ‘intelligent’ host-directed therapies improve outcome?

- Aspirin
- Thalidomide
- Anti-TNF biologicals
- Interferon-gamma
- Developing list of ‘rational’ candidates

Critical care and TBM

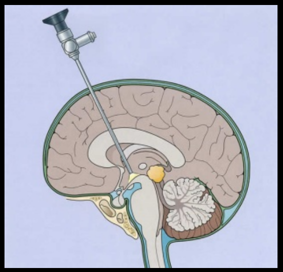
Sodium/hyponatraemia





Temperature

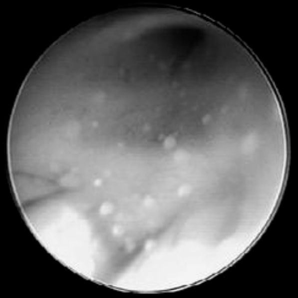
Glucose/diabetes



Mechanical Ventilation

Nutrition

Rehabilitation



Active trials (search 21/5/17)

- **Adjunctive aspirin for HIV-uninfected adults with TBM (Vietnam – complete)**
- **Optimizing Treatment to Improve TBM Outcomes in Children (TBM-KIDS) (India – recruiting)**
- **High-dose Rifampicin for the Treatment of Tuberculous Meningitis: a Dose-finding Study (ReDEFINe) (Indonesia – not recruiting)**
- **Adjunctive Corticosteroids for Tuberculous Meningitis in HIV-infected Adults (The ACT HIV Trial) (Vietnam – opens Wednesday!)**
- **Leukotriene A4 Hydrolase Stratified Trial of Adjunctive Corticosteroids for HIV-uninfected Adults With Tuberculous Meningitis (Vietnam – opens October 2017)**
- **The Relationships Between Gene Polymorphisms of LTA4H and Dexamethasone Treatment for Tuberculous Meningitis (China – not recruiting)**

Funding awaited:

- **Short intensive anti-tuberculosis and anti-thrombosis treatment for children with tuberculous meningitis (SURE trial) (Africa, Vietnam)**

Current and future clinical research priorities

Prevention

- Vaccine: Adult/HIV-infected

Diagnosis

- **High sensitivity; resistance detection**

Treatment

- PK optimised regimens; old and new drugs
- Can we improve upon corticosteroids?
- Precision/personalised anti-inflammatory therapy?
- Evidence-based critical care

Thank you