

# **The Challenge of Correlates of Immunity**

**Jerrold J. Ellner, M.D.**

**Boston University**

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# Biomarkers in TB

- **Present Challenges**
- **The Need**
- **Current Status**
- **Way Forward**

# The Challenges

- **Mechanisms of protection unknown and may differ for infection/re-infection v. progression/reactivation**
- **Best correlates may not represent protective mechanisms**
- **Natural innate and adaptive immunity may differ from vaccine-induced immunity**

# The Challenges

- Correlates may be undiscovered immune mechanisms or non-immunologic
- Protection is expressed *locally* following *bacterial challenge*

# Randomized Controlled Trial of *Mycobacterium vaccae* Immunotherapy in Non-Human Immunodeficiency Virus-Infected Ugandan Adults with Newly Diagnosed Pulmonary Tuberculosis

John L. Johnson,<sup>1</sup> R. Moses Kamya,<sup>2</sup>  
Alphonse Okwera,<sup>3</sup> Anita M. Loughlin,<sup>1,4</sup> Sam Nyole,<sup>3</sup>  
David L. Horn,<sup>1</sup> Robert S. Wallis,<sup>1</sup> Christina S. Hirsch,<sup>1</sup>  
Kathy Wolski,<sup>1,4</sup> John Foulds,<sup>4</sup> Roy D. Mugerwa,<sup>2</sup>  
and Jerrold J. Ellner,<sup>1,4</sup> for the Uganda-Case Western  
Reserve University Research Collaboration

<sup>1</sup>Department of Medicine, Division of Infectious Diseases, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio; <sup>2</sup>Department of Medicine, Mulago Hospital and Makerere University, and <sup>3</sup>National Tuberculosis and Leprosy Control Programme, Kampala, Uganda; <sup>4</sup>Biomedical Research Consulting, Cabin John, Maryland

Adjunctive immunotherapy with heat-killed *Mycobacterium vaccae* was studied in a randomized, placebo-controlled trial of 120 non-human immunodeficiency virus-infected adults with newly diagnosed pulmonary tuberculosis. Patients were randomized to a single dose of

**“There are no biomarkers for disease progression because the systemic immune response is similar in people who develop disease and in those with effective disease containment”**

**Russell, et al. Nature 2009**

**Candidate markers that characterize the potential of a latent focus to reactivate:**

- $\text{INF}\gamma$  production**
- mRNA IL-4/IL-4 $\delta$ 2**
- mRNA IL-8, IL-12, FOX-P3**

# Whole Blood Killing as Correlate?

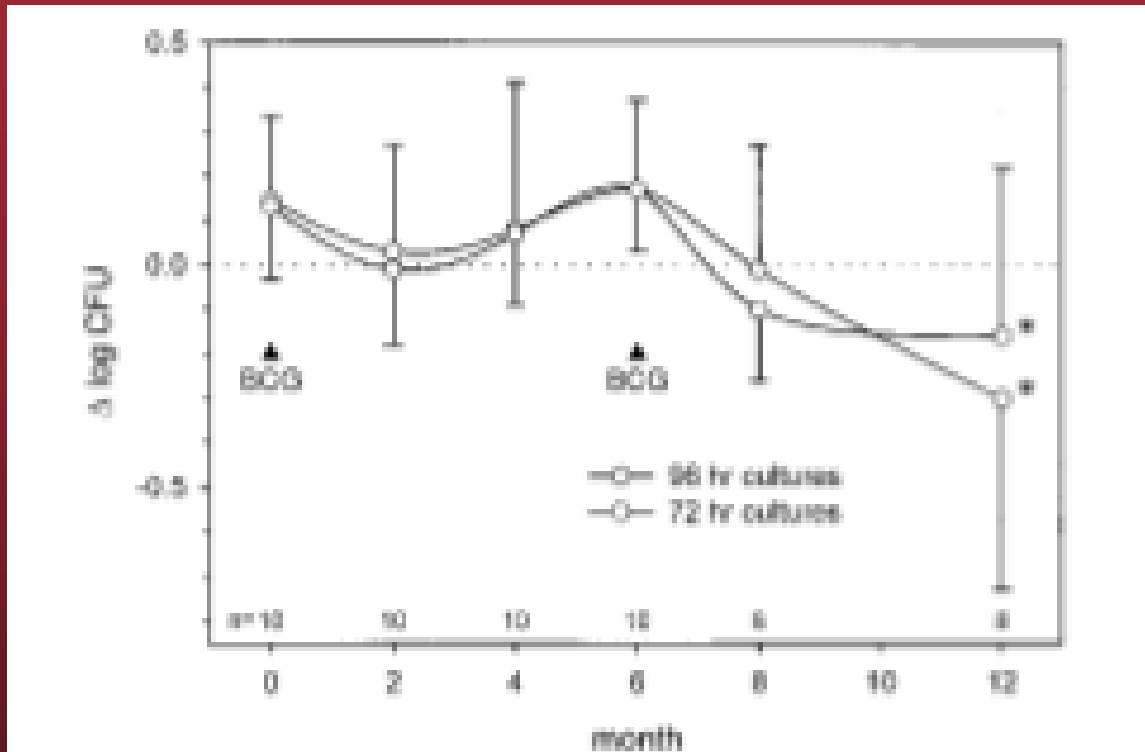
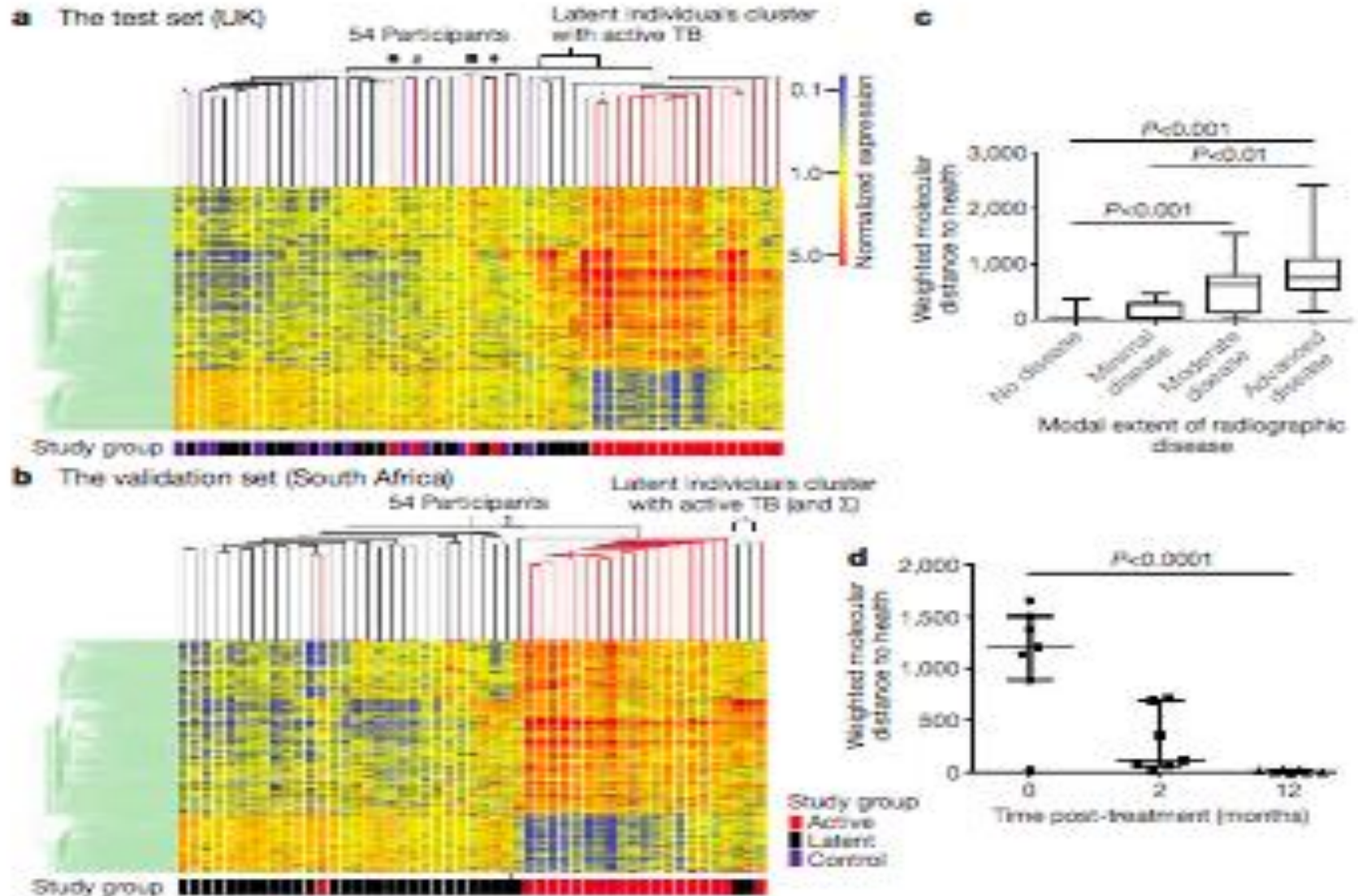


FIG. 2. Effect of BCG vaccination and boosting on growth of *M. bovis* BCG in whole blood cultures of 72- and 96-h duration. Data

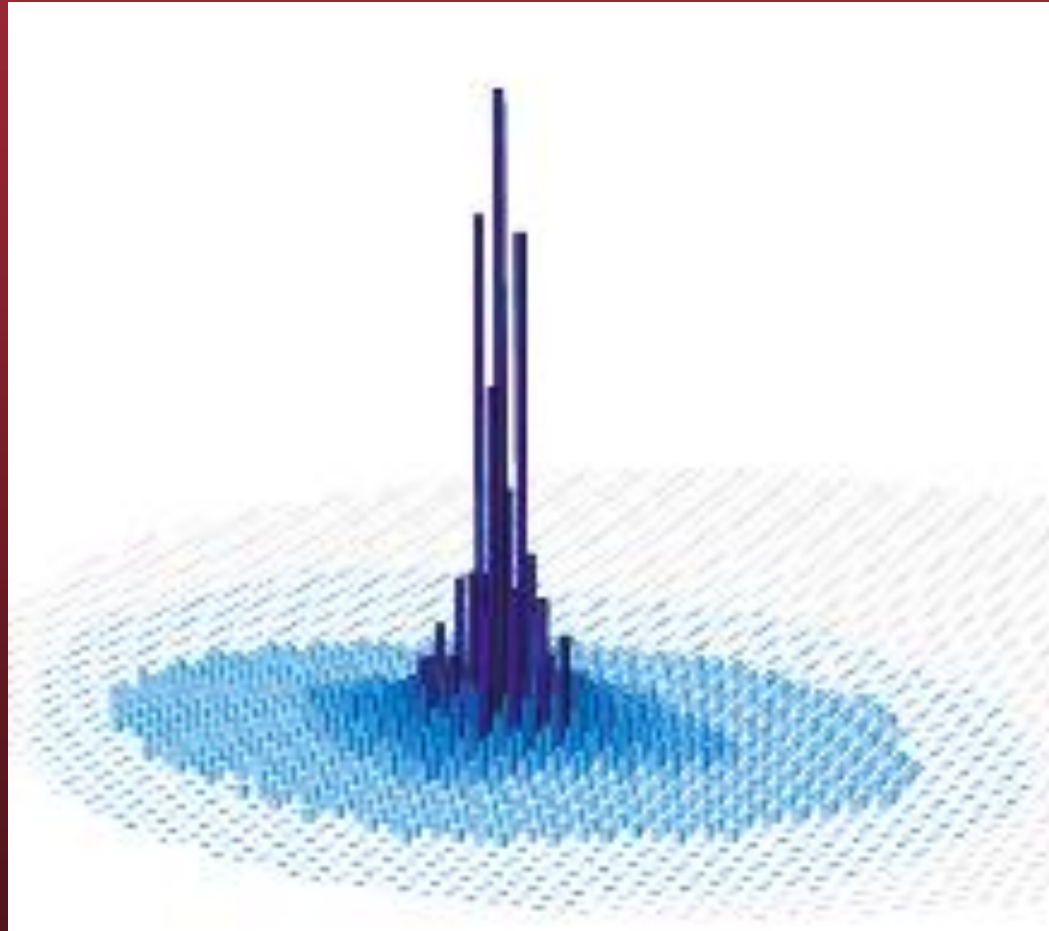
# Discovery

- **Multiplexed cytokines – TNF $\alpha$ , IL-12(p40) and IL-17 following TB10.4 stimulation**
- **Proteomics - serum amyloid, transthyretin, CRP and neopterin**
- **Genomics - lactoferrin, CD64 and the RAS-associated GTPase 33A**

# 393 Transcript Signature for Active TB

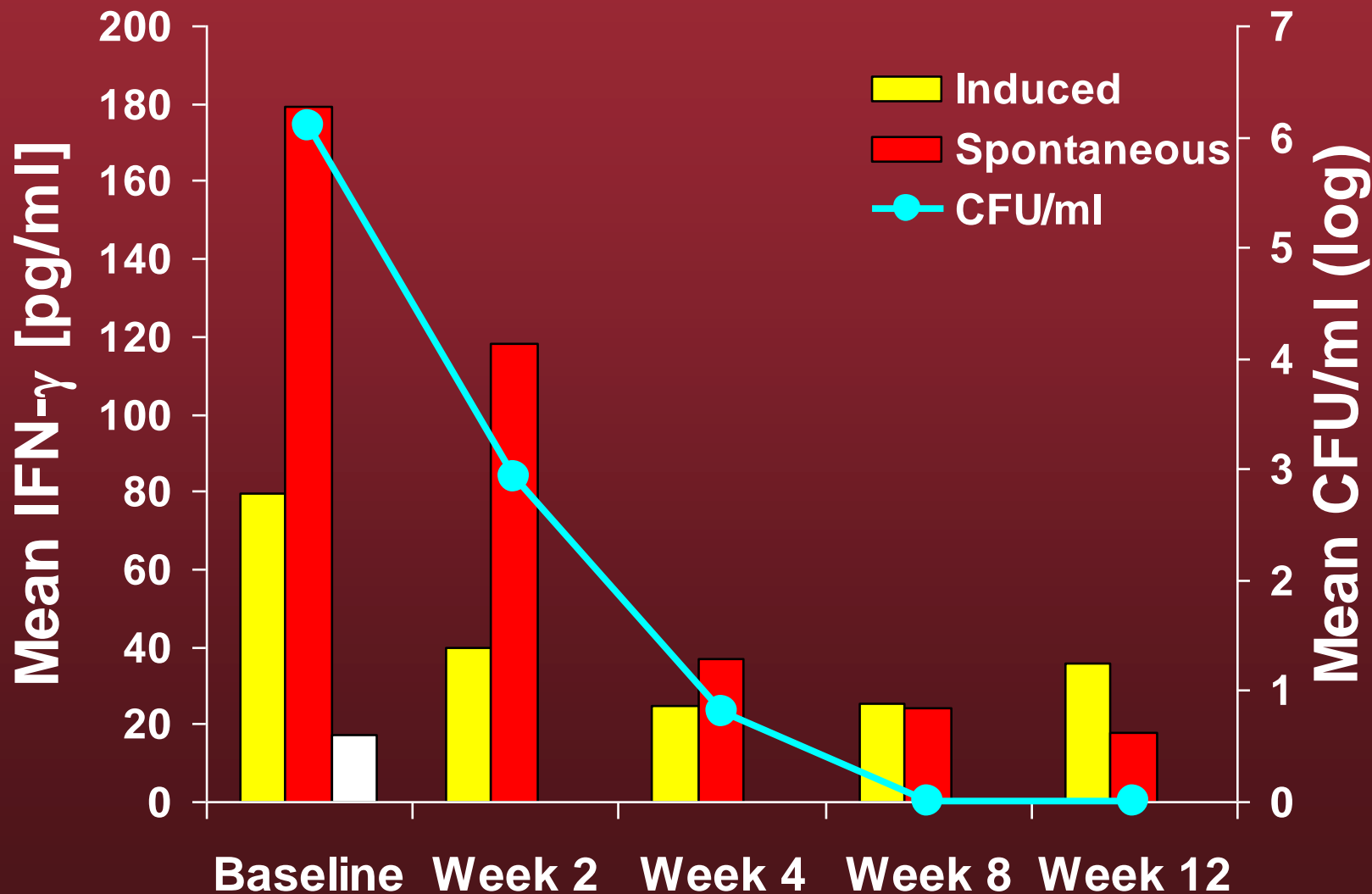


# The Immunoproteome of MTB



*PNAS* 2010; 1078:14703-8

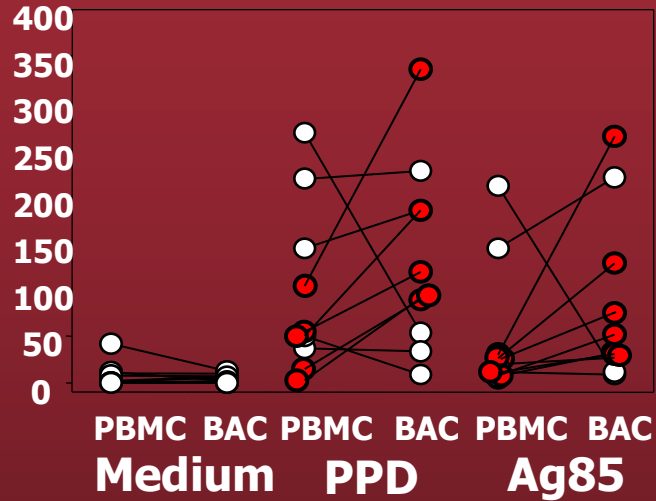
# IFN $\gamma$ Levels and MTB Load in Sputum during Treatment



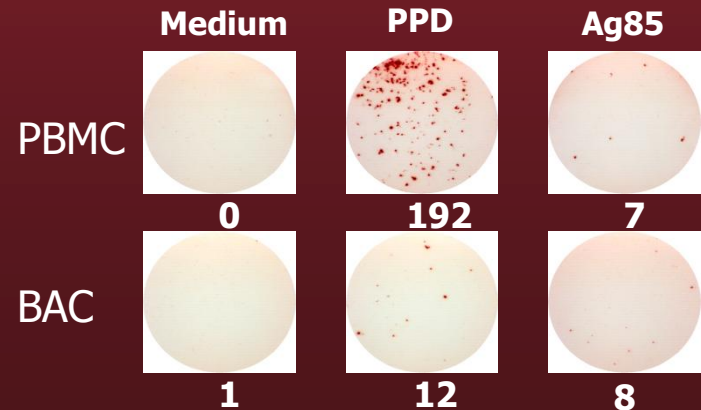
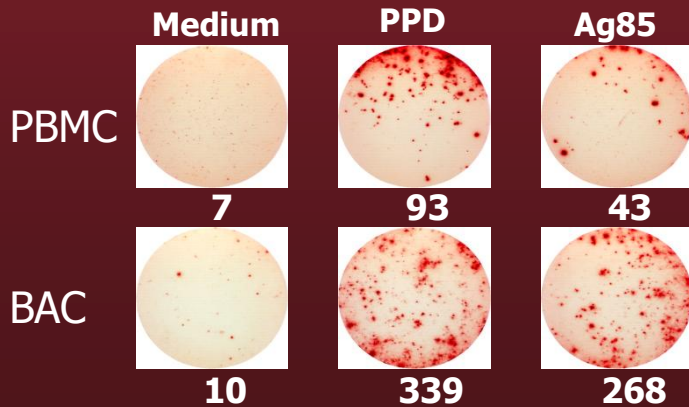
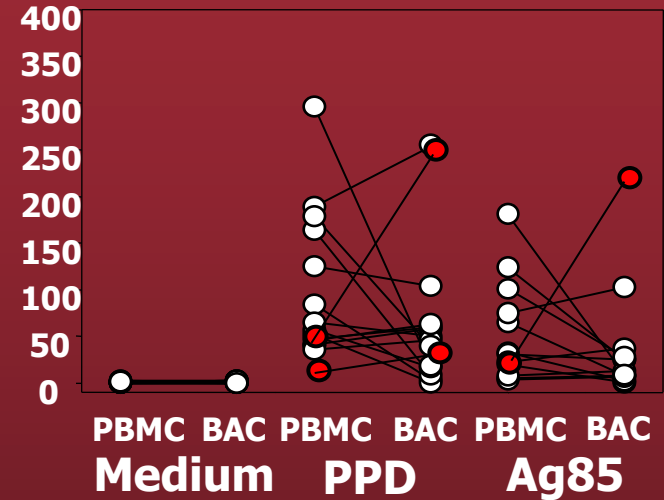
# Compartmentalization of *M.tb* Specific IFN- $\gamma$ -Producing Cells in the Lungs of Healthy Subjects

IFN- $\gamma$  ELISPOTS per 10<sup>5</sup> cells

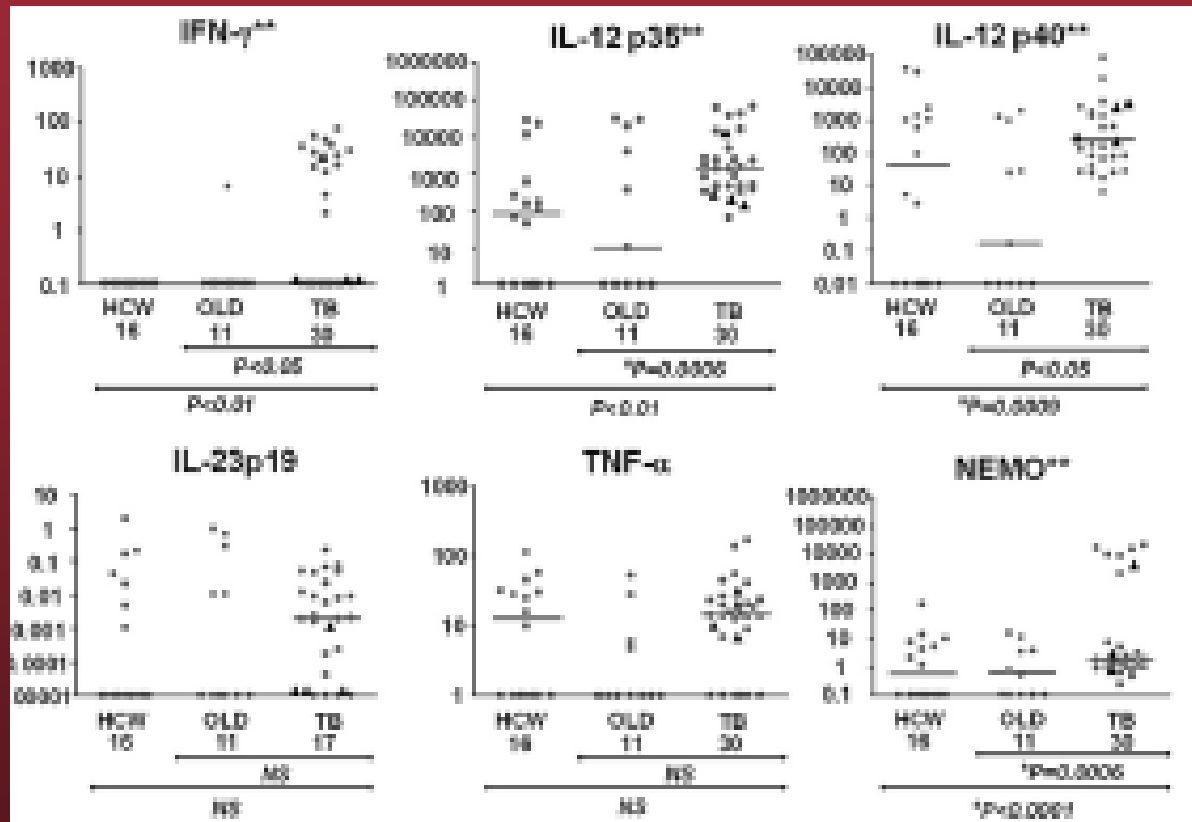
## Healthy Household Contact



## Healthy Community Control



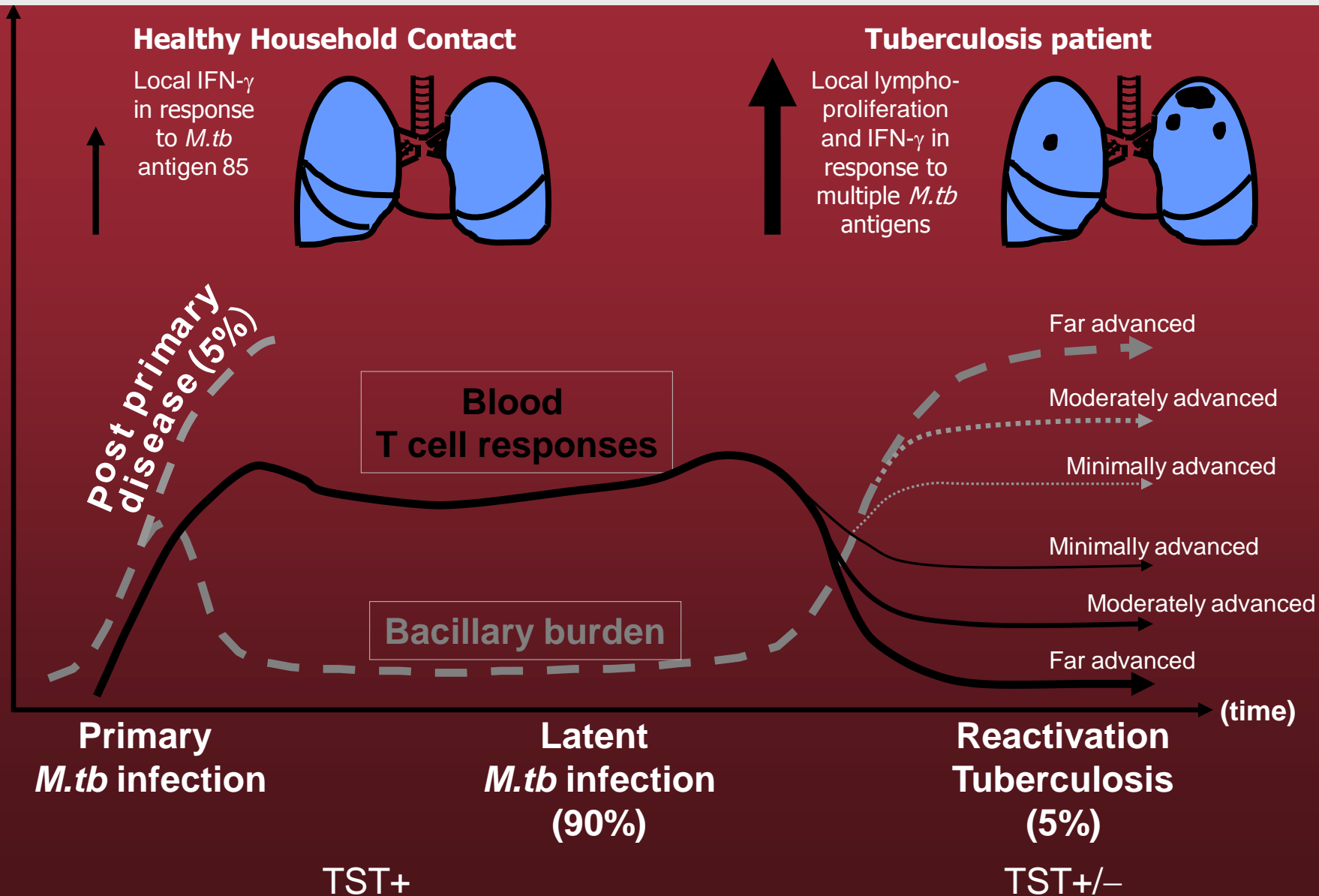
# mRNA Expression in Sputum



# Immune Response to *M.tuberculosis* in the Pleural Space

- **Compartmentalization – concomitant of intense immune response that self-cures**
- **Increase in CD4<sup>+</sup> and CD8<sup>+</sup>**
- **Increase in cytokines (IFN $\gamma$ , TNF $\alpha$ , IL-10) and pro-apoptotic ligands (sFas, sFasL)**

# Hypothetical Model of the Natural History of *M. tuberculosis* Infection in Humans



# Way Forward

- Define correlates of natural protection in prospective cohort study of high TB prevalence populations
- Define correlates of vaccine-induced protection in vaccine trials
- Don't forget protection against MTB infection!!!
- Don't forget local markers???