TUBERCULOSIS INFECTION AMONG CHILDREN IN GREENLAND -USE OF NEW TB-DIAGNOSTIC AND PROSPECTS FOR NOVEL TB-VACCINES

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OUTLINE OF PRESENTATION

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TB in Greenland: Historical and present situation

PhD-presentation

- Objectives
- Material and methods
- Results
- Implications
- Future research

Prospects for novel TB vaccine

TB IN GREENLAND, HISTORICAL PERSPECTIVE

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PREVALENCE OF INFECTION

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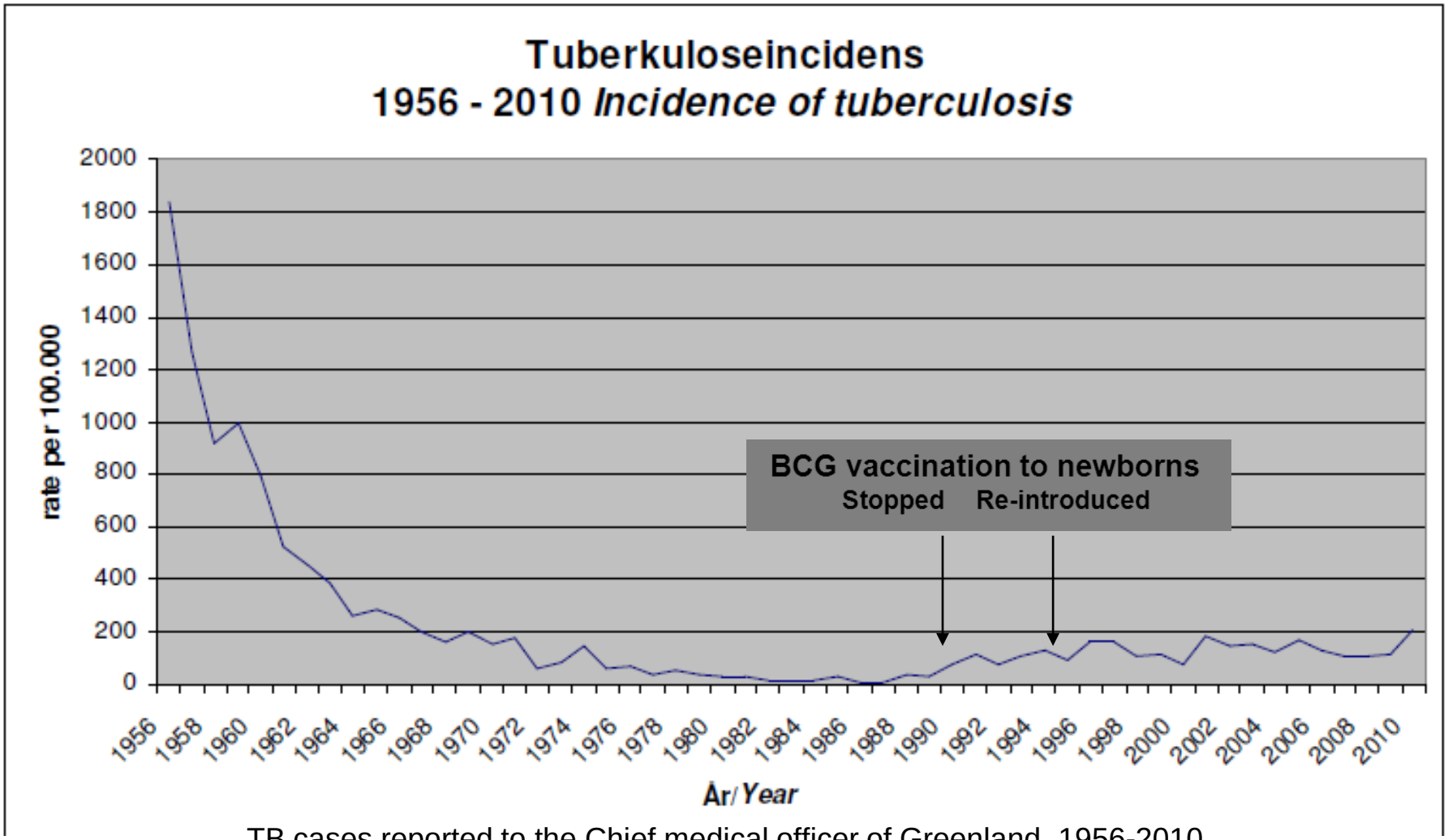
CROSS SECTIONAL TUBERCULIN SKIN TEST SURVEY CHILDREN, SOUTHERN GREENLAND, 1933

- 866 Participants, ½-20 years of age (50% of relevant population)

- ½-6 years: 43% TST positive
- 7-13 years: 86% TST positive
- 14-19 years: 100% TST positive

Ref.: Bertelsen, A. Grønlandsk medicinsk Statistik og Nosografi I–IV, Medd. om Grønland CXVII, 1943.

TUBERCULOSIS INCIDENCE 1956-2010



TB cases reported to the Chief medical officer of Greenland. 1956-2010
Courtesy of the Chief Medical Officer in Greenland, annual report 2011

NOTIFIED NUMBER OF TUBERCULOSIS CASES

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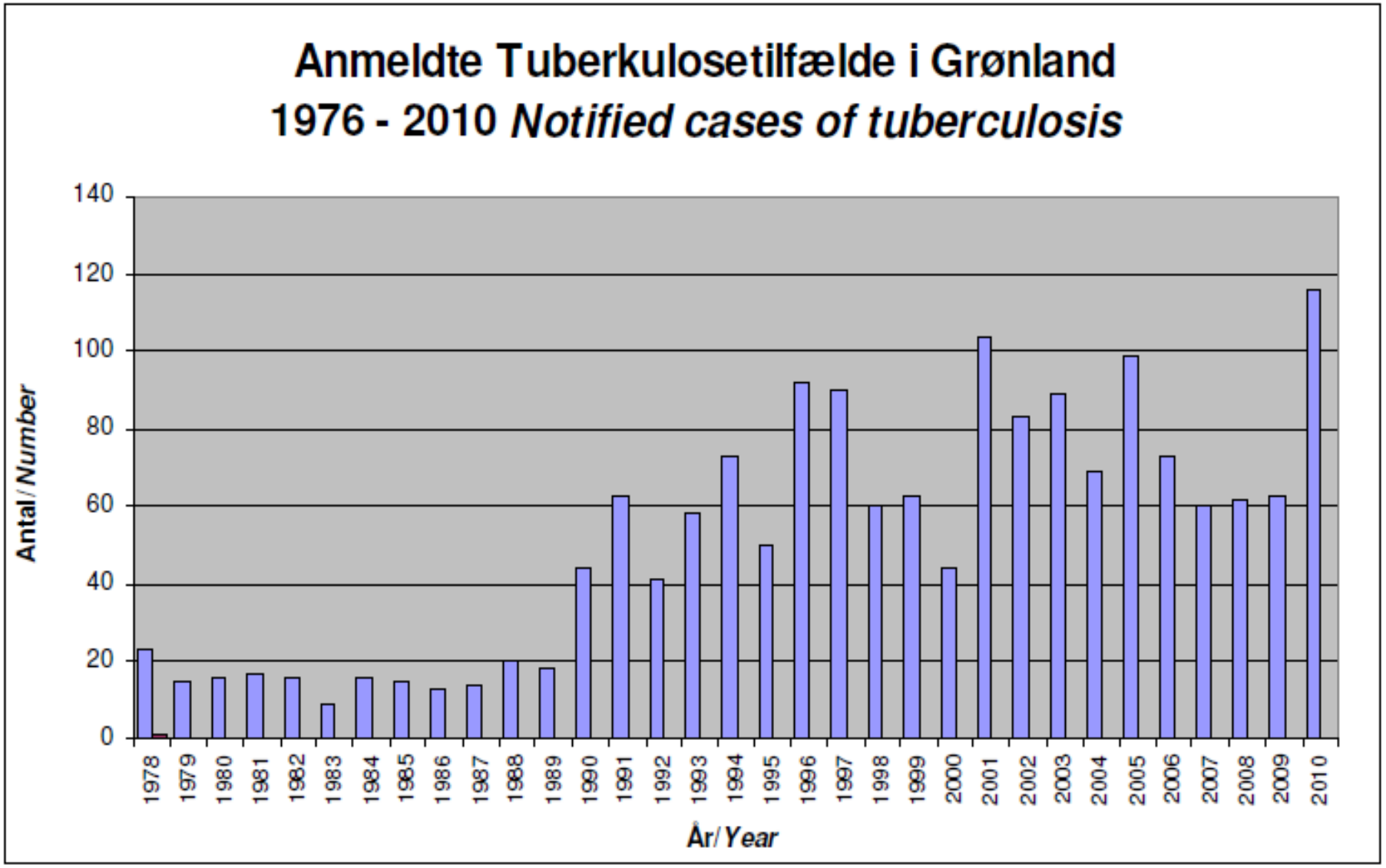

TB cases reported to the Chief medical officer of Greenland1976-2010
Courtesy of the Chief Medical Officer in Greenland, annual report 2011

TUBERCULOSIS NOTIFICATION, WHO 2006

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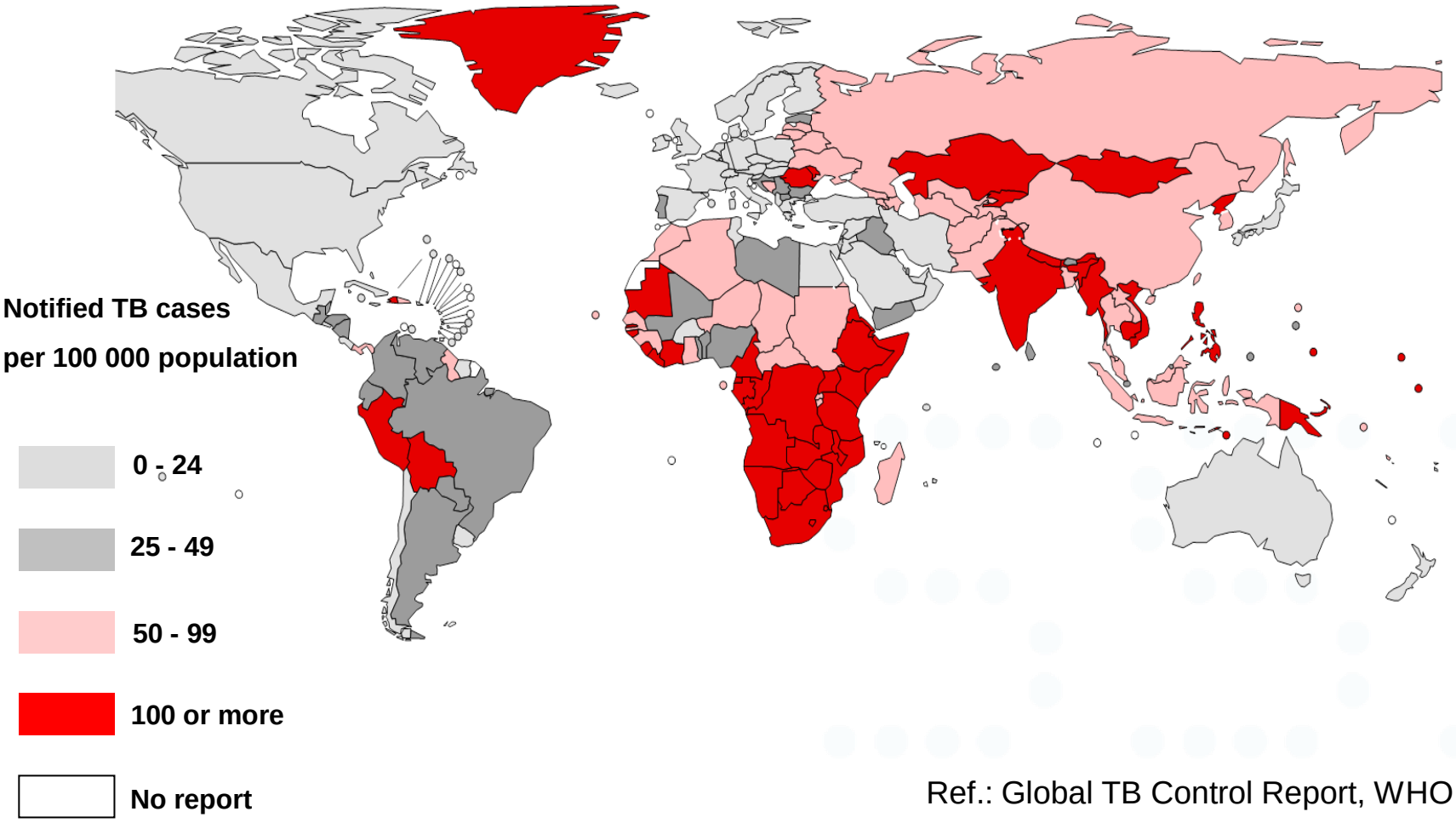
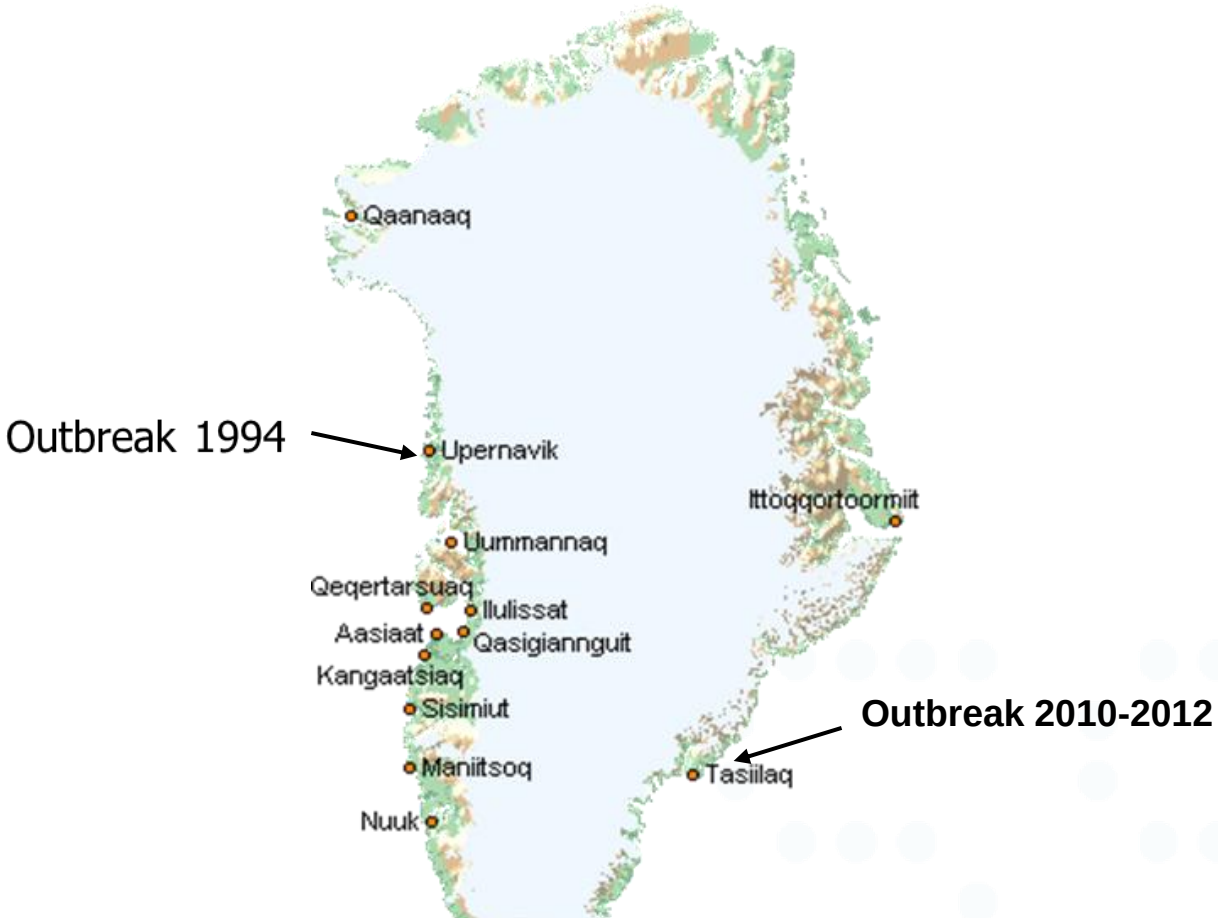


Ref.: Global TB Control Report, WHO 2006

OUTBREAK MAP



Is the current rise in TB incidence due to ongoing tuberculosis transmission or simply to reactivation of decade-old infections?

PHD PRESENTATION: OBJECTIVES

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- To measure the extent of tuberculosis transmission to children in Greenland and to estimate the annual risk of infection.
- To evaluate to which extent the estimated annual risk of infection is altered by, BCG vaccination status, demographic variable, and use of diagnostic screening tool.
- To examine potential risk factors for tuberculosis infection among children in Greenland

MATERIAL AND METHODS

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Design:
Cross-sectional surveys, enrollment 2005 (East Greenland), 2006 (South Greenland), 2007 (West Greenland)

Study population:
All school-age children (6-16 years)

Diagnosis:
TST and IGRA (Quantiferon TB Gold In tube)

Tuberculosis infection:
TST+ **and** IGRA+, to optimize specificity
TST results evaluated using Greenlandic TST guidelines

MATERIAL AND METHODS

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Assesment of general health of child (including TB information) and information on parental education:
Self-administered questionnaire.

Information on ethnicity:
Civil Registration System

Information on BCG vaccination status:
Childhood vaccination records

STUDY PARTICIPANTS

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Total population 6-16 year
N=2,880

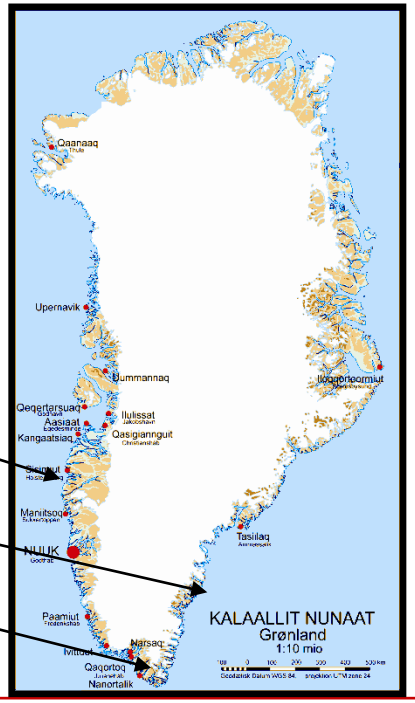
Participants
N=2,218 (77%)
Mean age 11 years

Not available
N=662 (13%)

South Greenland
N=1,198
Participation rate 85%

East Greenland
N=451
Participation rate 96%

West Greenland
N=569
Participation rate 57%



TUBERCULOSIS DIAGNOSTICS: TUBERCULIN SKIN TEST BY MANTOUX TECHNIQUE

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Bolette Søborg, bot@ssi.dk

TUBERCULOSIS DIAGNOSTICS
INTERFERON GAMMA RELEASE ASSAY (IGRA)

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FIELDWORK

CHILDREN WAITING TO PARTICIPATE, EAST GREENLAND

RESULTS

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- **Test concordance:**

  TST and IGRA showed good test agreement in these school children (concordance= 94%, kappa= 0.8)

- **Tuberculosis infected**:

  8.4% of the children were considered tuberculosis infected.

- **The annual risk of tuberculosis infection:**

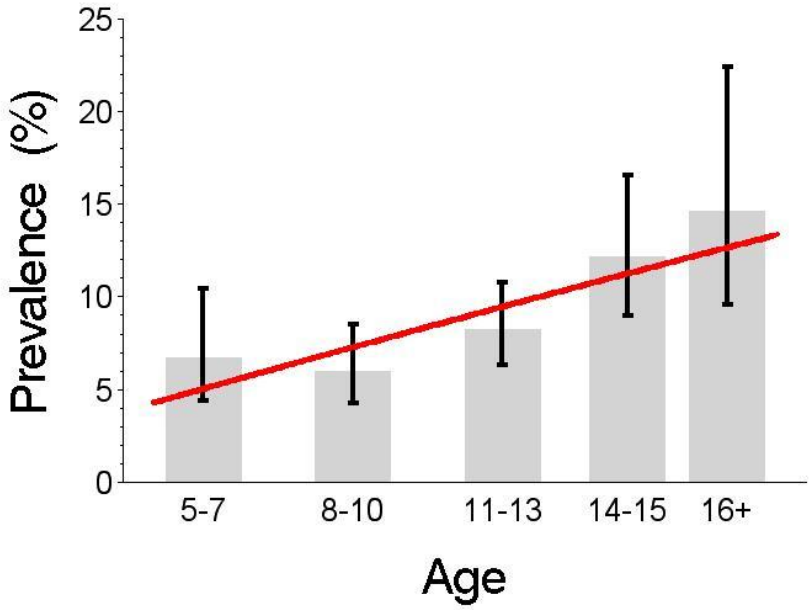
  Total: 0.80%

  varied with survey location

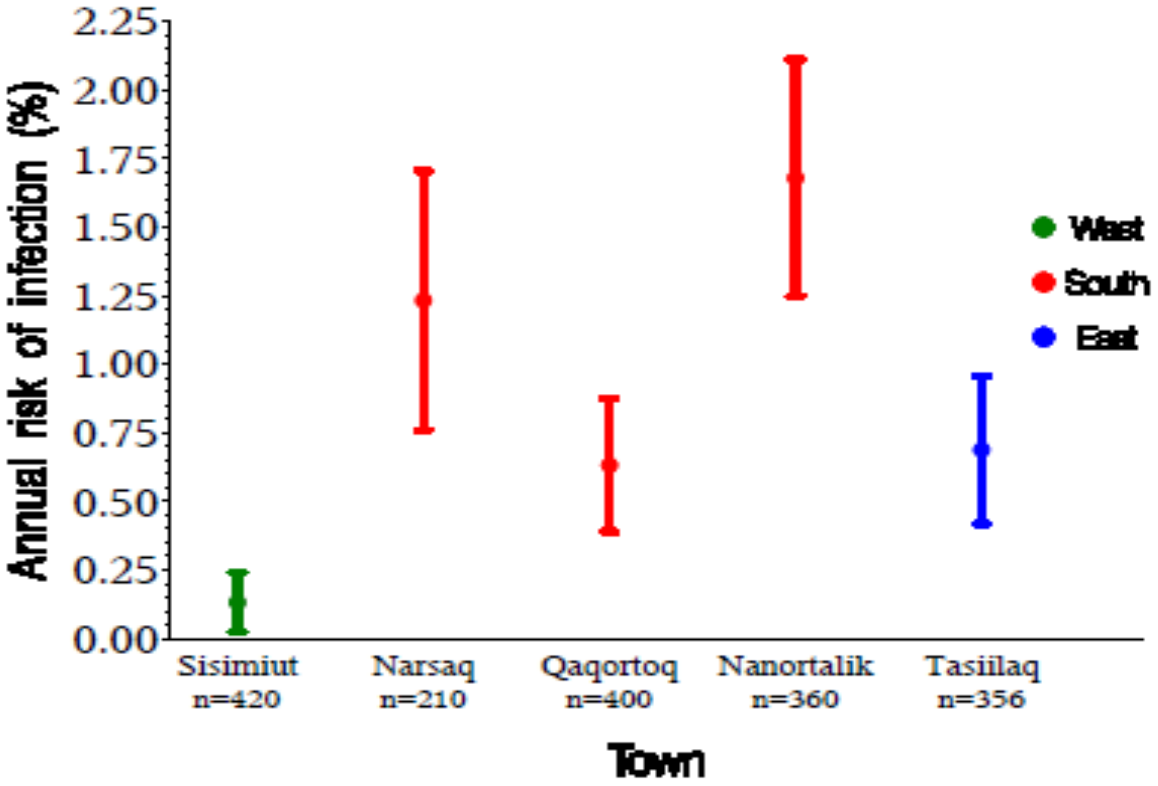
  and ethnicity: Inuit children (0.87%) vs.

  Danish or mixed children (0.02%)

MAJOR RESULTS: PREVALENCE OF INFECTION BY AGE



MAJOR RESULTS: ANNUAL RISK OF INFECTION



Tuberculosis infection was associated with

- Inuit ethnicity
- Region of residence.
- Narrow age gap to next older sibling
- Tuberculosis infection in a sibling (OR =14.2)

Among children with TB contact(s) tuberculosis infection was also associated with

- Household crowding
- Low maternal education

CONCLUSIONS

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- High rate of present ongoing tuberculosis transmission to children in Greenland
- Problem seen almost exclusively among Inuit children and more in some locations than other
- The IGRA showed excellent performance among school-age children
- Documents a strong clustering of infection among siblings, indicating a source of infection within the immediate family

STRENGTHS AND LIMITATIONS

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- **Strengths:**

  Large population-based sample (app. 25% of the entire population), stringent criteria for infection, information retrieved from national registers minimizing information bias

- **Weaknesses**:

  Underestimation of BCG vaccination status due to lack of registration, selection bias due to non participation by sick children.

- **Contribution**:

  Documents a high rate of ongoing tuberculosis transmission in Greenland and validates the IGRA as a useful diagnostic tool among school-age children

PUBLIC HEALTH IMPLICATIONS OF THE PHD STUDIES

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Based on our study findings, the Home Rule Government of Greenland allocated 15 M Danish kroner for TB intervention and initiated a revision of the existing Greenlandic TB programme

The money will primarily be used to

- Screen schoolchildren with the IGRA
- Conduct biannual population-based chest x-ray screenings in South Greenland
- Intensify contact tracing
- Launch TB information campaigns

TB INFORMATION MATERIAL

Bolette Søborg, bot@ssi.dk

FUTURE PERSPECTIVES

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However, despite the initiated efforts more needs to be done

- TB Outbreak in East Greenland 2010-2012 (ongoing)

Future research:

- Are host factors/ immune composition among Inuits causing an increased suseptibility to tuberculosis infection

- TB vaccine development research done in Arctic populations

IMMUNE RECOGNITION OF M. TUBERCULOSIS AMONG GREENLANDERS

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Overall aim

The project will evaluate antigen recognition to Mycobacterium tuberculosis (Mtb) in Greenland with the ultimate objective of determining if a progressive emergence of immune reactivity towards Mtb antigens can be established.

The study is especially valuable because Greenlanders have little cross reactivity to non-tuberculous mycobacteria, permitting clarity in understanding immune response to Mtb antigens, which are critical for the development of future tuberculosis vaccines.

PROSPECTS FOR NOVEL TB-VACCINES

Curtesy of Søren Hoff, MD, PhD
Dept. of Infectious Disease Immunology
Statens Serum Institut

CURRENT TB VACCINE: BACILLUS CALMETTE–GUÉRIN

- Live attenuated M. Bovis strain
- Introduced in 1921
- 100 million doses/year
- Used worldwide

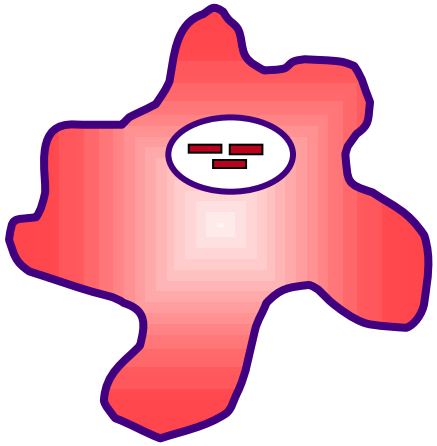
Protects children against

- Miliary TB
- TB meningitis

However there are several problems

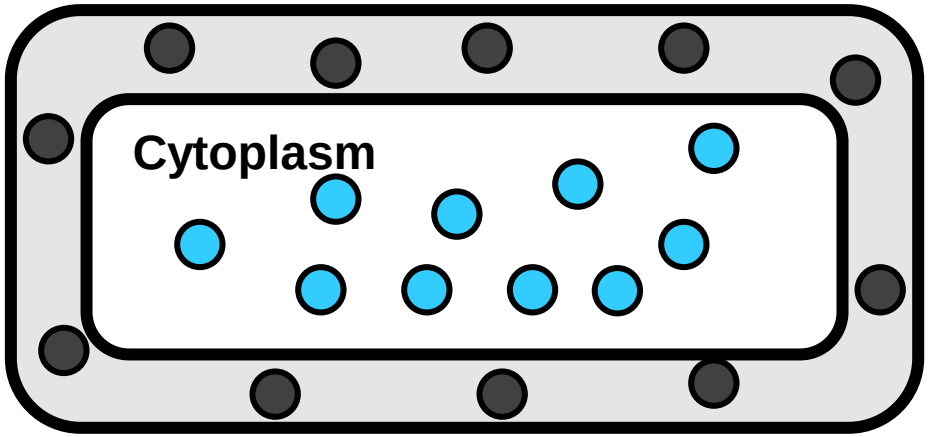
- Disseminated BCG infection in HIV children
- Waning efficacy after 10 years

NEW APPROACH TO TB VACCINE DEVELOPMENT

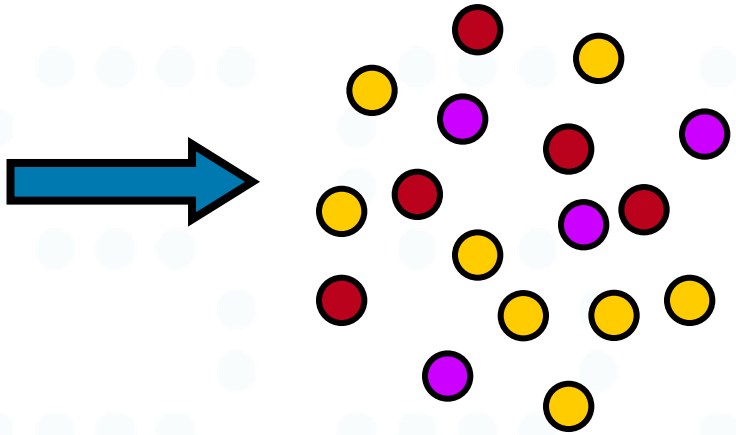


Mtb secretes antigens while encapsulated

Makrophage



Cell wall



SECRETED M. TUBERCULOSIS ANTIGENS

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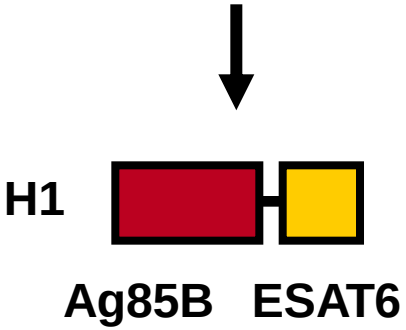
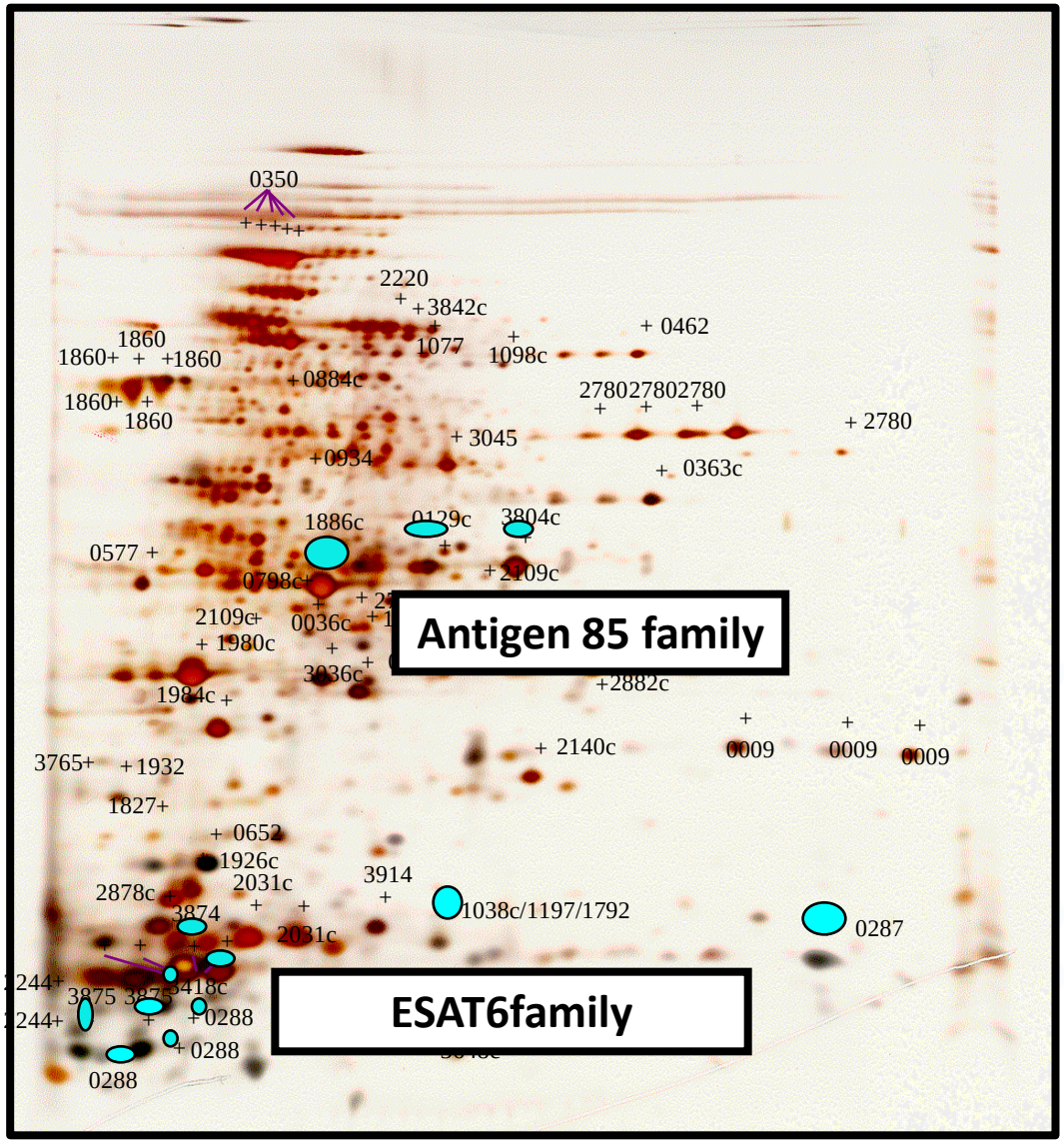
>300 different proteins discovered at SSI





SSI TB VACCINE STRATEGY

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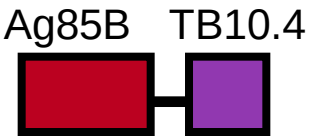
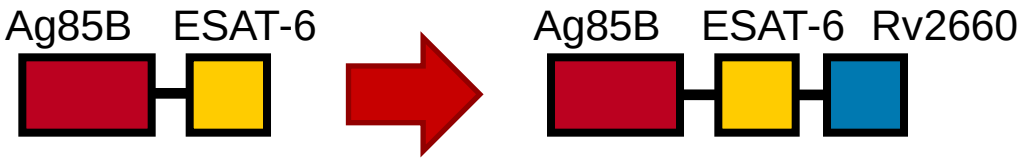
H4



Boost an existing BCG-induced immunity

- Infants – children
- BCG vaccinated

H1 → H56



Prevent acute TB disease as well as re-activation of existing latent infection

- Adolescents and young adults (BCG vaccinated)
- With and Without latent infection

SSI TB VACCINES IN CLINICAL TRIALS

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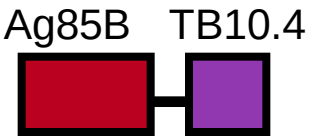
H4



IC31

Sanofi Pasteur

AERAS

Phase I / II

H1

IC31

Intercell

(KLK peptide +ODN1a)

CAF01

SSI

(Cationic liposomes + TDB)

TBVAC EDCTP

SSI

Phase IIa / Phase I

H56

IC31

Intercell

(KLK peptide +ODN1a)

BMGF

AERAS

Phase I in SA

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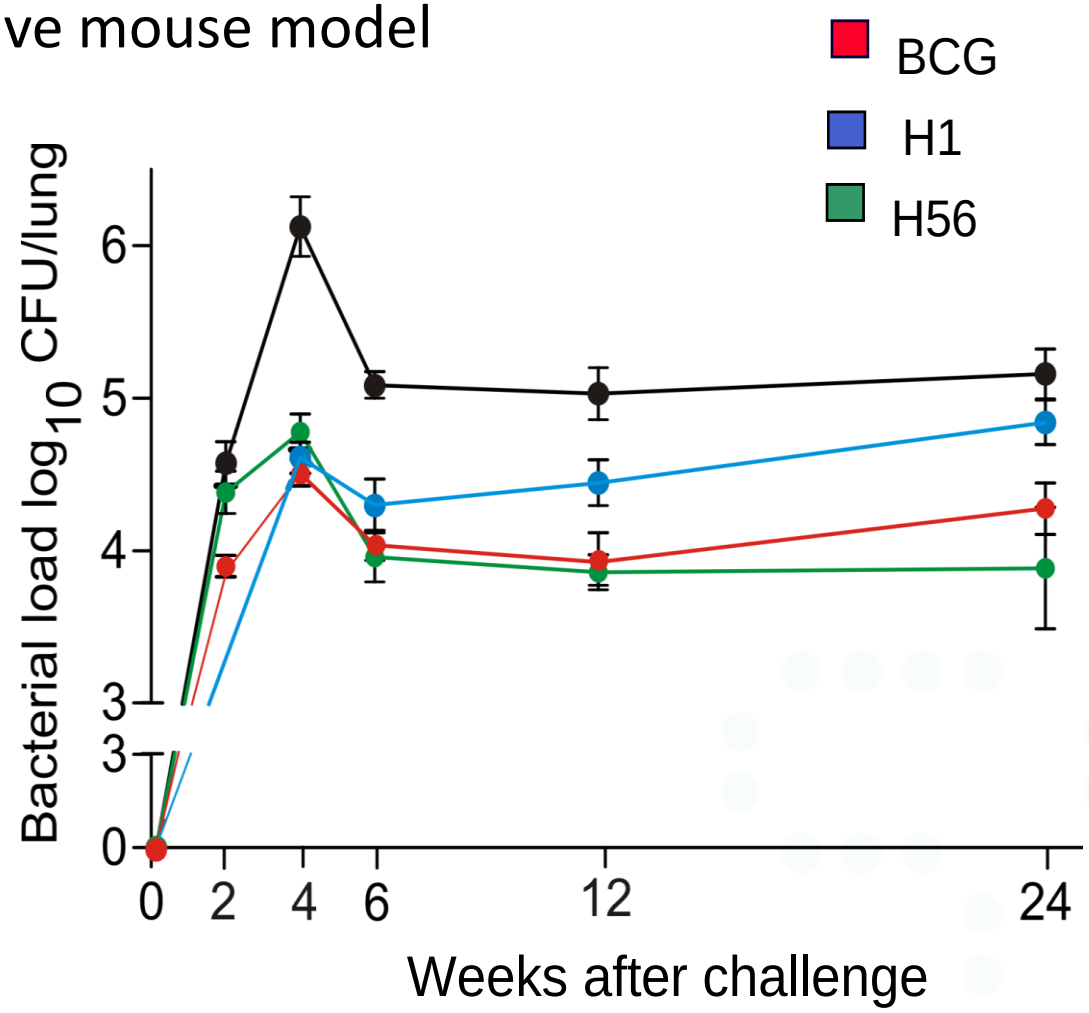
Preventive mouse model



Aagaard et al, Nat. Medicine 2011

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PHD-STUDENT SASCHA WILK MICHELSEN

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THANK YOU FOR LISTENING

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NON-HUMAN PRIMATE TRIALS

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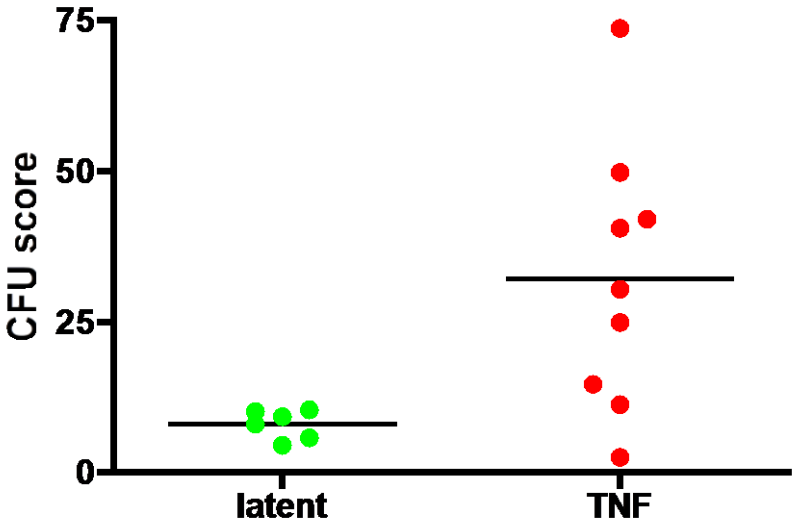
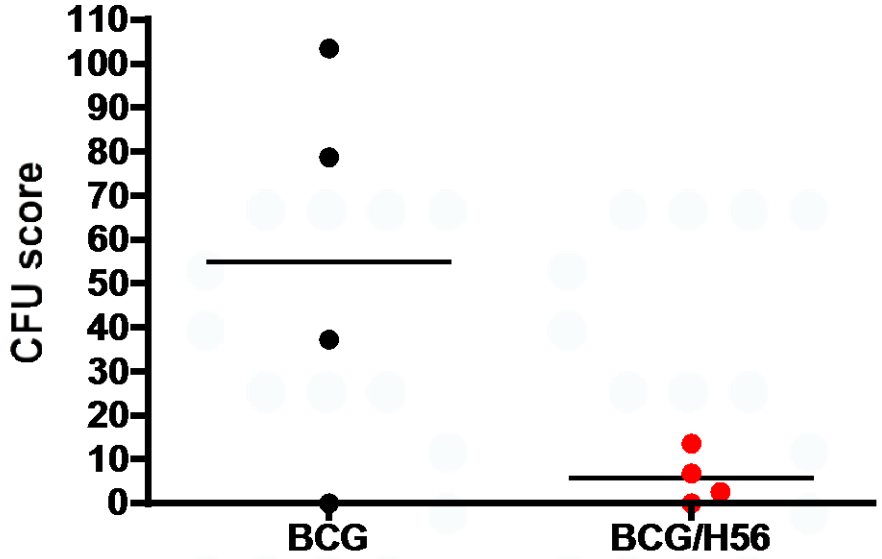
BCG
BCG/H56 → Mtb low dose challenge → Active (50%)
Mtb low dose challenge → Latent → Anti-TNF Ab To reactivate

Control monkeys



(Lin, et al **2010**)

Bacterial burden: reactivation



(Lin et al, JCI. **2012**)