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

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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

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

Tuberculosis incidence 1956-2010

Tuberkuloseincidens
1956 - 2010 Incidence of tuberculosis

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

BCG vaccination to newborns
Stopped Re-introduced
NOTIFIED NUMBER OF TUBERCULOSIS CASES

Anmeldte Tuberkulosetilfælde i Grønland
1976 - 2010 Notified cases of tuberculosis

TB cases reported to the Chief medical officer of Greenland 1976-2010
Courtesy of the Chief Medical Officer in Greenland, annual report 2011
Is the current rise in TB incidence due to ongoing tuberculosis transmission or simply to reactivation of decade-old infections?
PHD PRESENTATION: OBJECTIVES

• 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

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
Assessment 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

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

Bolette Søborg, bot@ssi.dk
CHILDREN WAITING TO PARTICIPATE, EAST GREENLAND

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RESULTS

- **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

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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

• 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

• **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.

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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

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Illit aamma sakiallulersinnaavutit
Tuberkulose kan også ramme dig
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 susceptibility to tuberculosis infection

- TB vaccine development research done in Arctic populations

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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
Mtb secretes antigens while encapsulated

Makrophage

Cell wall

Cytoplasm
SECRETED M. TUBERCULOSIS ANTIGENS

>300 different proteins discovered at SSI

Antigen 85 family

ESAT6 family

H1
Ag85B
ESAT6
SSI TB VACCINE STRATEGY

**H4**
Ag85B  TB10.4

Boost an existing BCG-induced immunity

- Infants – children
- BCG vaccinated

**H1**
Ag85B  ESAT-6

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

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

**H56**
Ag85B  ESAT-6  Rv2660
SSI TB VACCINES IN CLINICAL TRIALS

**H4**
- Ag85B
- TB10.4
- IC31

**H1**
- Ag85B
- ESAT-6
- IC31
  - *Intercell* (KLK peptide + ODN1a)

**H56**
- Ag85B
- ESAT-6
- Rv2660c
- IC31
  - *Intercell* (KLK peptide + ODN1a)

**CAF01**
- *SSI* (Cationic liposomes + TDB)

**Sanofi Pasteur**
- AERAS

**Phase I / II**

**TBVAC EDCTP**
- AERAS

**Phase IIa / Phase I**

**BMGF**
- AERAS

**Phase I in SA**
Preventive mouse model

Aagaard et al, Nat. Medicine 2011

Weeks after challenge

Bacterial load $\log_{10}$ CFU/lung

BCG
H1
H56

Weeks after challenge
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PHD-STUDENT SASCHA WILK MICHELESEN
THANK YOU FOR LISTENING

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NON-HUMAN PRIMATE TRIALS

BCG  BCG/H56

Mtbb low dose challenge  Active  50%

Latent  Anti-TNF Ab
To reactivate

Control monkeys

Bacterial burden: reactivation

CFU score

(Lin, et al 2010)

CFU score

(Lin et al, JCI. 2012)