



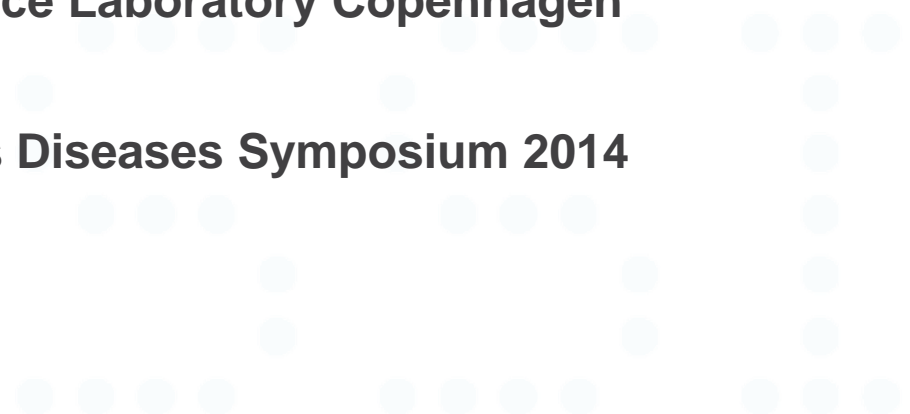
DANISH GUIDELINES FOR PREVENTION AND TREATMENT OF TB IN CHILDREN

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**International Reference Laboratory of Mycobacteriology /
WHO TB Supranational Reference Laboratory Copenhagen**

7th Danish Paediatric Infectious Diseases Symposium 2014



Quick vote:

1. Do you diagnose and/or treat children with TB in Denmark?
2. Do you use the Danish guidelines for prevention and treatment of TB in children?

[Link til svar](https://da.surveymonkey.com/analyze/nmS_2Fu24tykn_2FCegzBtou_2Bc_2BIQrCWJVThJ5_2FyA1Uspr0_3D)

https://da.surveymonkey.com/analyze/nmS_2Fu24tykn_2FCegzBtou_2Bc_2BIQrCWJVThJ5_2FyA1Uspr0_3D

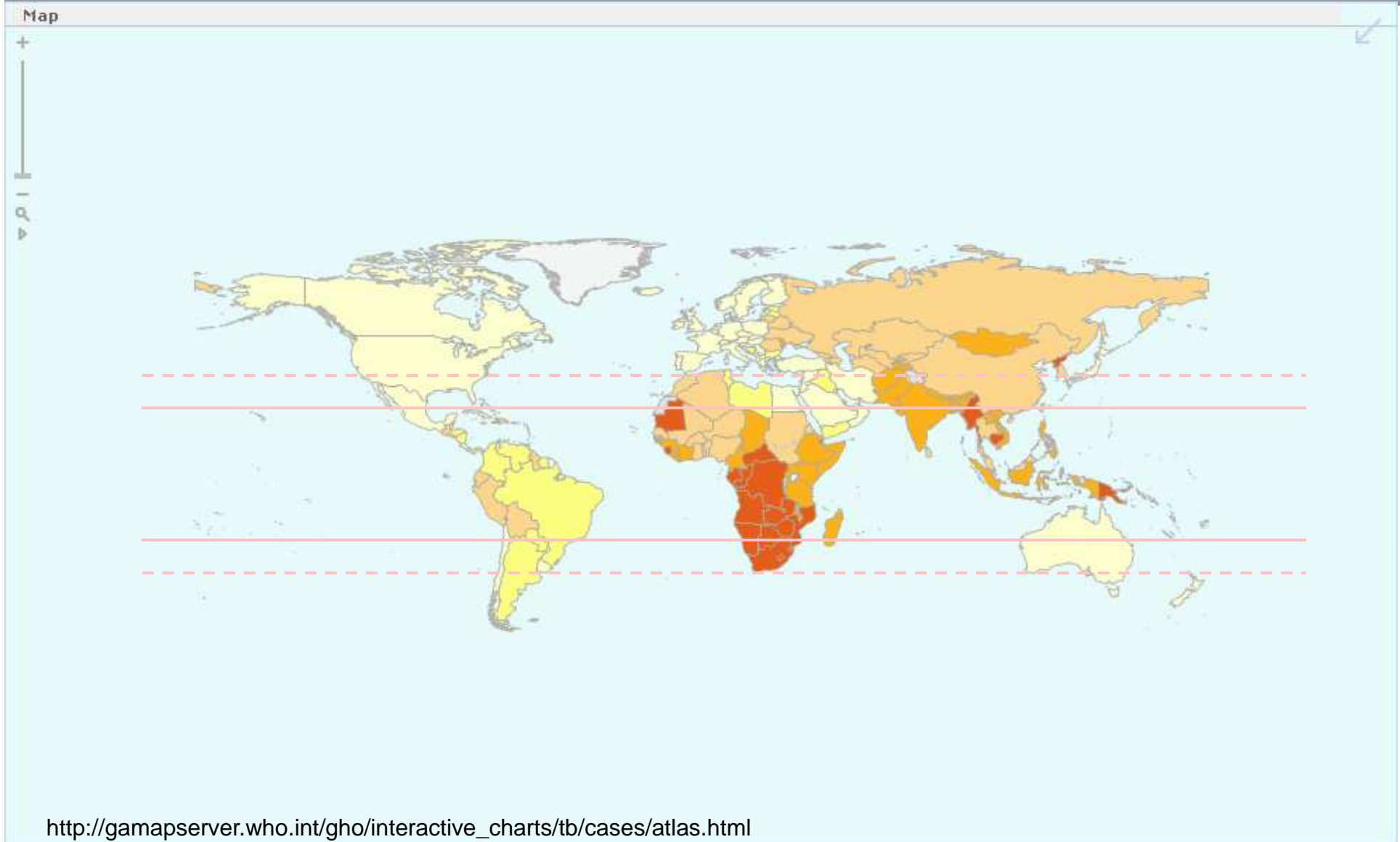


AGENDA

- ❖ TB situation, Denmark vs. world
- ❖ TB among children in DK?
- ❖ “Danish guidelines” for prevention and treatment of TB in children?
- ❖ European/other guidelines?
- ❖ Diagnostics in DK



ESTIMATED TB INCIDENCE 2011, WHO

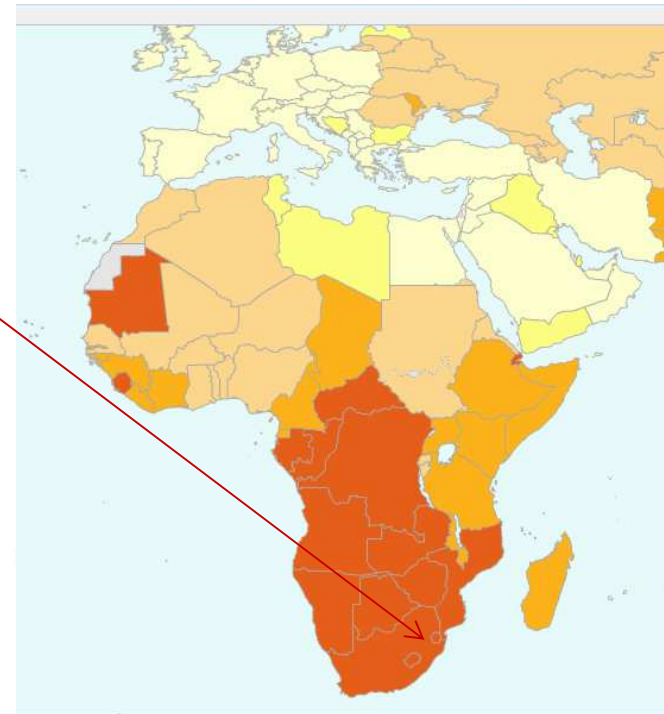


WORLD'S HIGHEST INCIDENCES / 100,000



Top 10

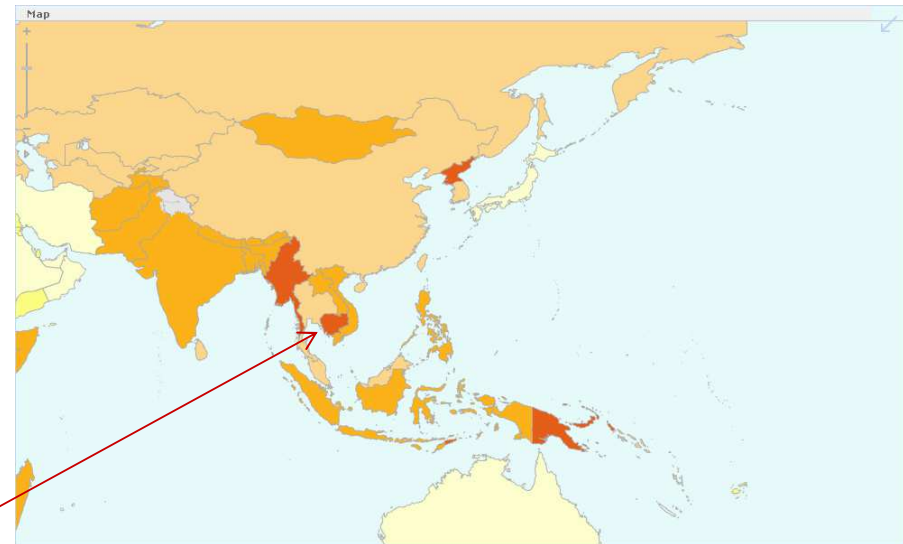
1.	Swaziland	1,327
2.	South Africa	993
3.	Namibia	723
4.	Sierra Leone	723
5.	Lesotho	632
6.	Djibouti	620
7.	Zimbabwe	603
8.	Mozambique	548
9.	Gabon	450
10.	Zambia	444



ASIA'S HIGHEST INCIDENCES / 100,000



1.	Swaziland	1,327
2.	South Africa	993
3.	Namibia	723
4.	Sierra Leone	723
5.	Lesotho	632
6.	Djibouti	620
7.	Zimbabwe	603
8.	Mozambique	548
9.	Gabon	450
10.	Zambia	444
11.	Cambodia	424



AMERICAS' HIGHEST INCIDENCES / 100,000



> 100 / 100,000

❖ Haiti	222
❖ Bolivia	131
❖ Guyana	110
❖ Peru	101



EUROPE'S HIGHEST INCIDENCES / 100,000



> 100 / 100,000

❖ Tajikistan	193
❖ Moldova	161
❖ Kazakhstan	129
❖ Kyrgyzstan	128
❖ Azerbaijan	113
❖ Romania	101
❖ Uzbekistan	101



- ❖ The burden of TB is highest in Asia and Africa¹
- ❖ 95% new cases and 98% deaths occur in developing nations
- ❖ 22 high burden countries account for over 80% of the world's TB cases.



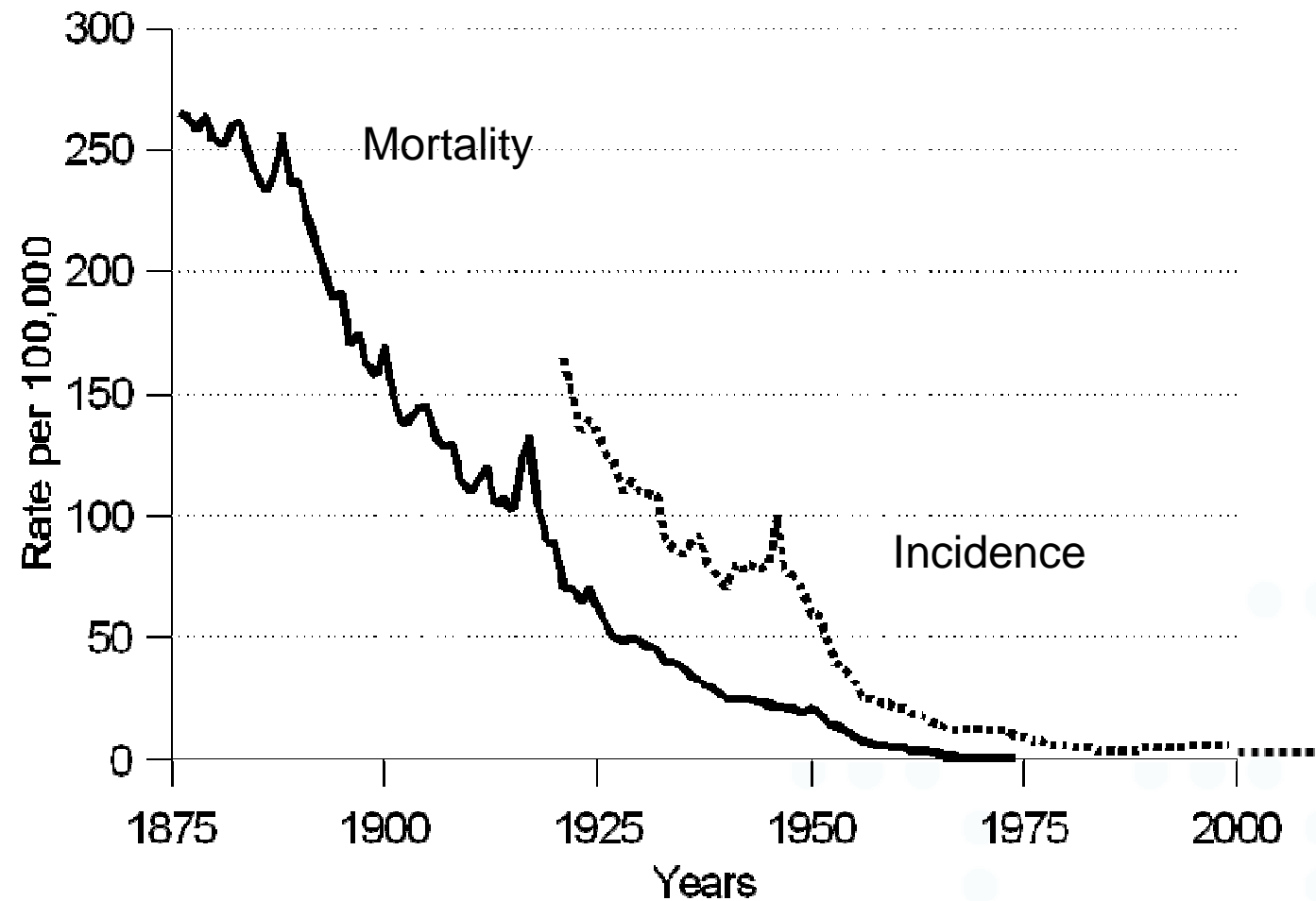
¹ http://www.who.int/tb/publications/global_report/2009/en/

- ❖ Worldwide, only 4.4% of estimated TB cases occurred in the European Region²



² <http://www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/tuberculosis/publications/2013/tuberculosis-surveillance-and-monitoring-in-europe-2013>

PULMONARY TB DK 138 YRS



Emerging Infectious Diseases 2002; 8:679-684.

TB PRESENT – UNSOLVED PROBLEMS IN DK

- ❖ Limited geography
- ❖ Good infrastructure
- ❖ TB-research since 1800 century
- ❖ 135 yrs. collection of TB data
- ❖ Centralized diagnostics since 1920 with state of art facilities
- ❖ Easy and free access to antibiotics

Despite this, significant unsolved TB problems in DK. TB is not under sufficient control.



Living area in CPH near "Vor frelser Kirke"

PILOT PROJECT SPUTUM SCREENING CPH

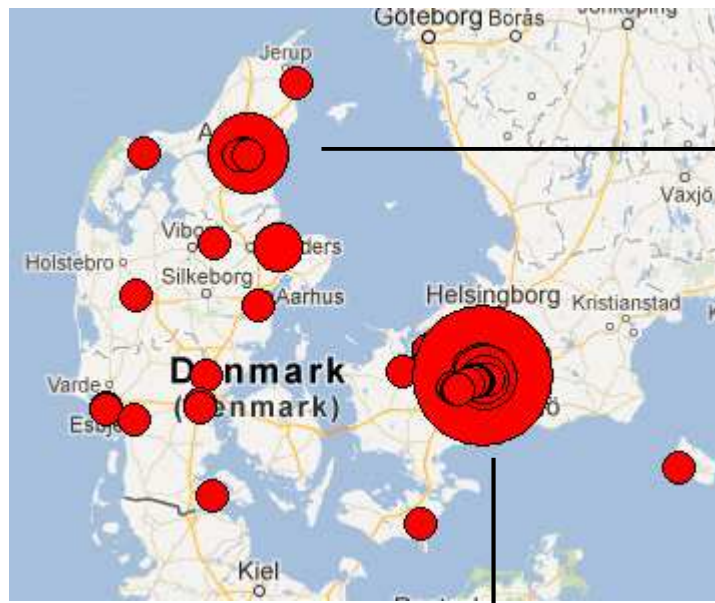
- ❖ 10 shelters / meeting places for “socially deprived persons”, inner CPH
- ❖ 1075 “users” volunteered sputum for culture
- ❖ 35 persons MT culture pos.
 - Most Danish-born or Greenlandic-born

3,3 % users had TB



STATENS
SERUM
INSTITUT

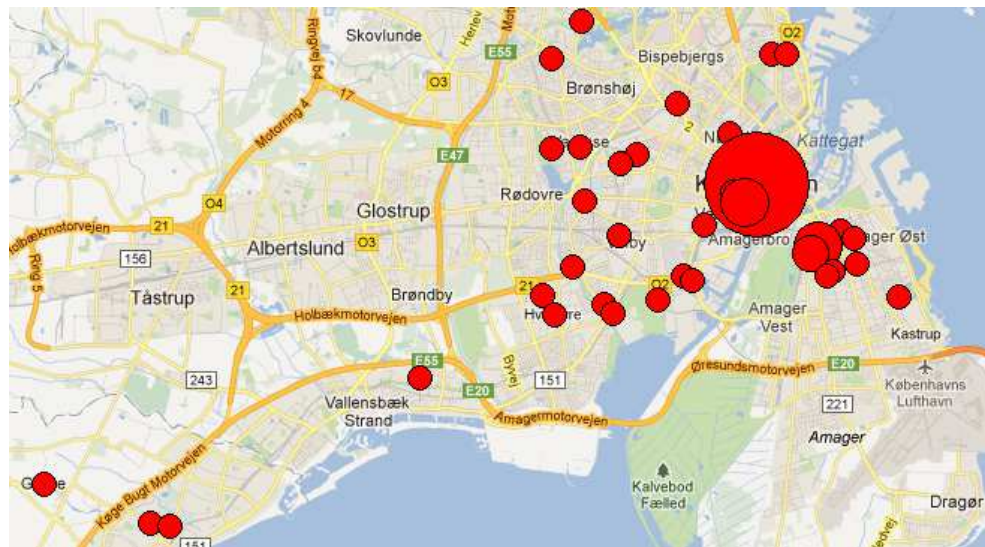
-
- C-2
- N = 7,000



A



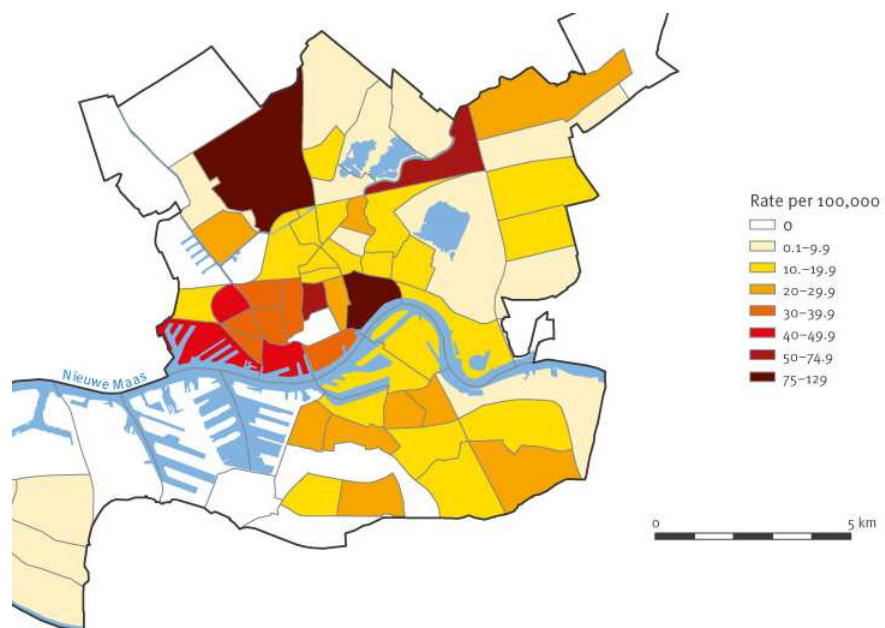
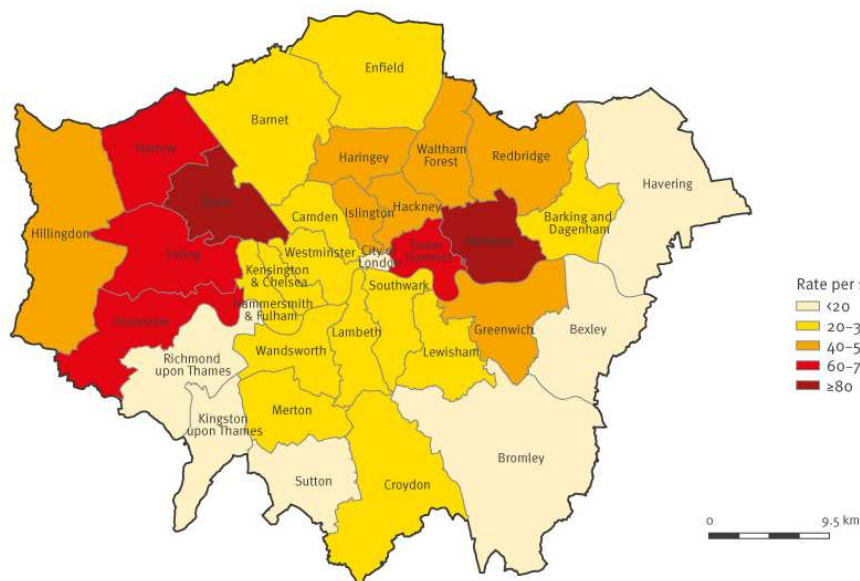
B



C

Figure S2. Cases with *Mycobacterium tuberculosis* “C2/1112-15” genotype among Greenlanders in Denmark during 20 years, from 1992 through 2011, by geographical location. Many cases are located in central Copenhagen, as indicated by the largest circles in Figures 3A+C, and located in the city of Aalborg, as indicated by the largest circle in Figure 3B. The sizes of the circles are proportional to the number of cases observed.

E.G. IN LONDON AND ROTTERDAM



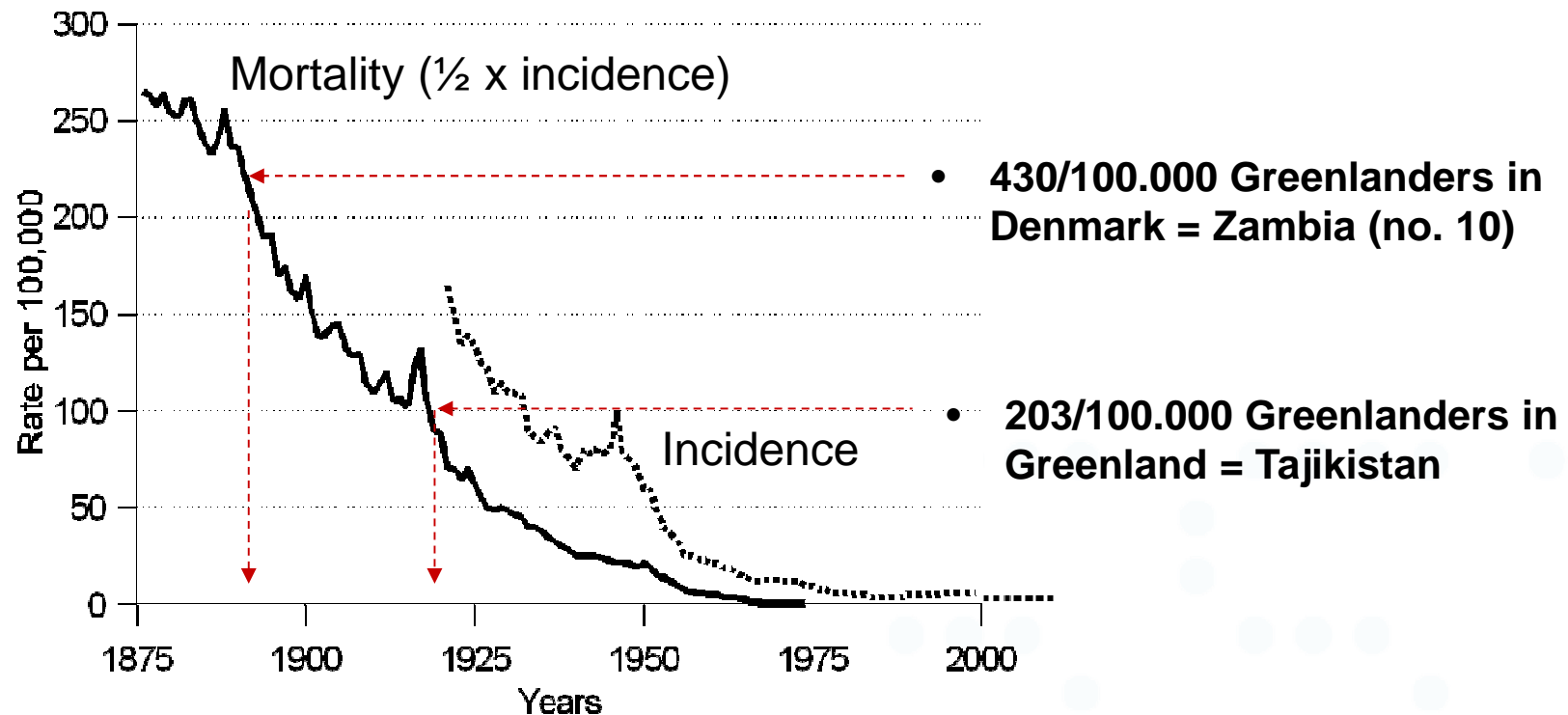
Source: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20726>

tll@ssi.dk

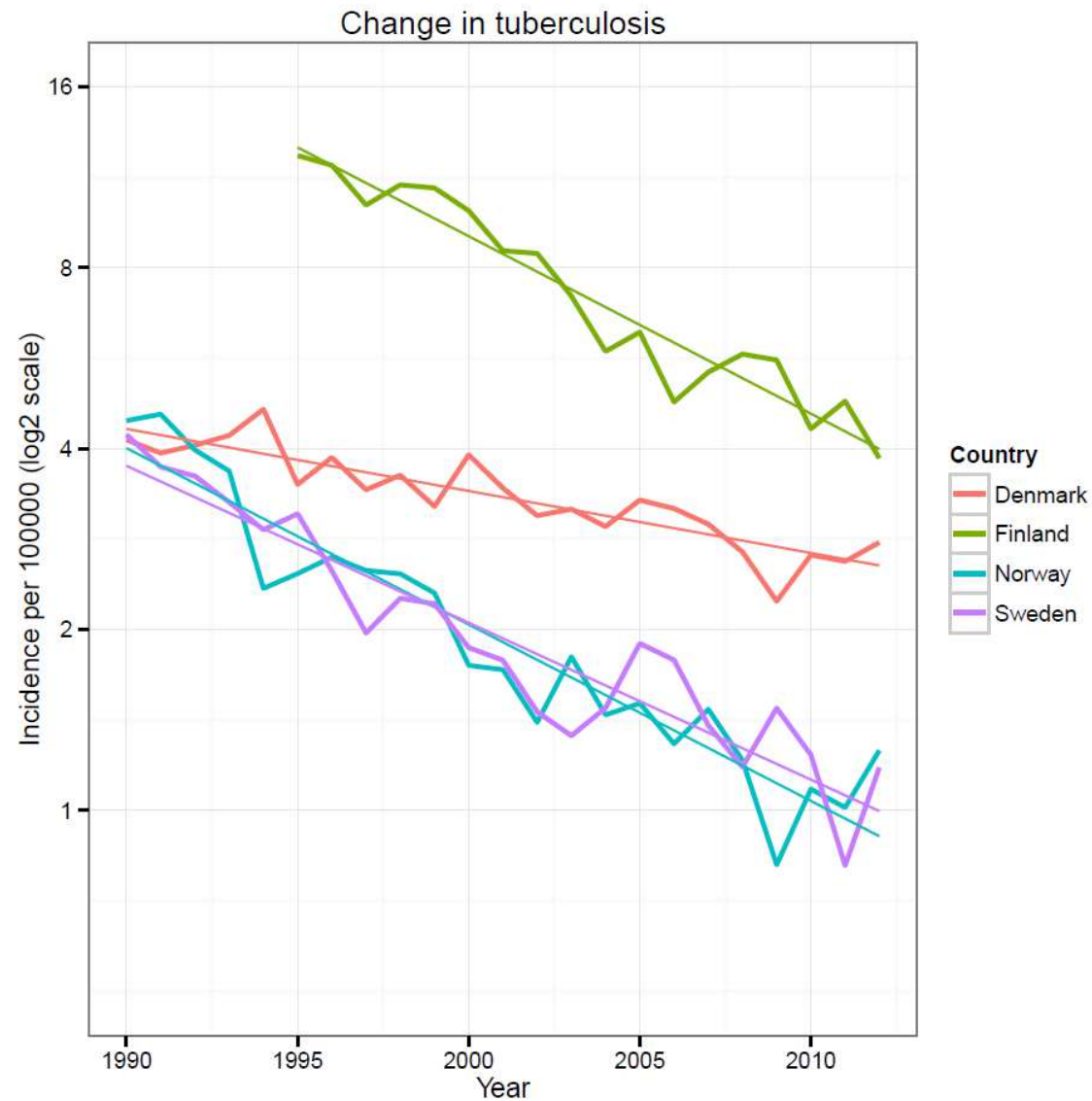
PRESENT TB – HISTORICAL PERSPECTIVE!

Who have a high risk?

- 3% Risik groups in Denmark = South African gold miners?

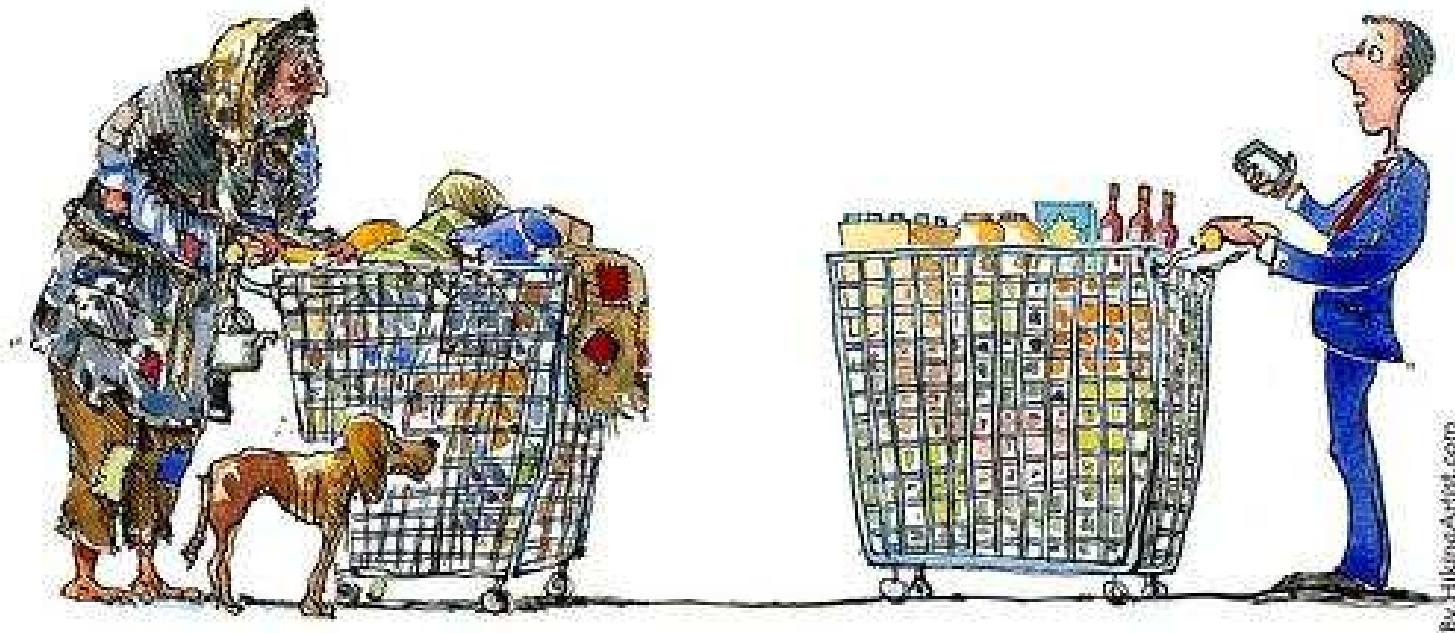


CHANGES INCIDENCE NORDIC COUNTRIES



Thanks: ESN@ssi.dk

SOCIAL DETERMINANTS TB EUROPE





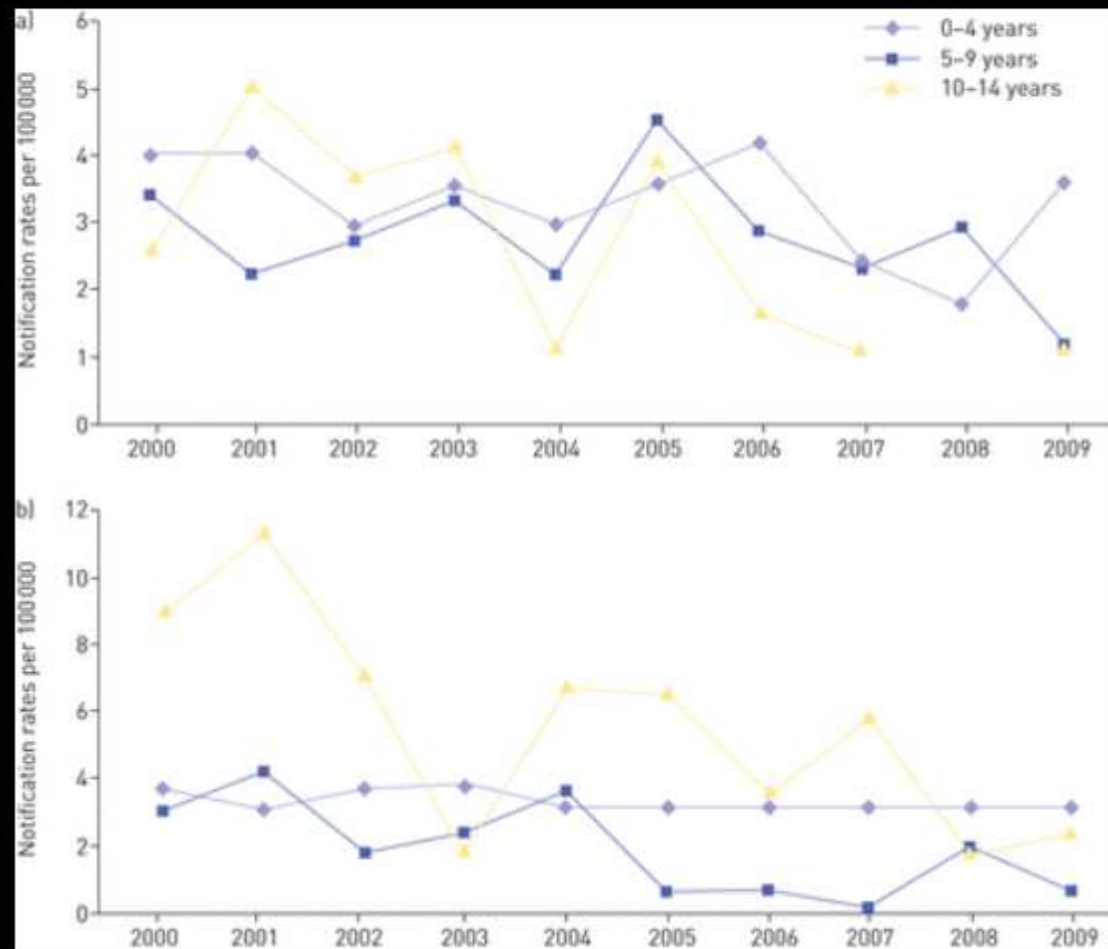
PROTECT



them from
TUBERCULOSIS

**Keep them away from sick people
Insist on plenty of rest
Train them in health habits
Consult the doctor regularly**

A review of paediatric tuberculosis in Denmark: 10-year trend, 2000–2009

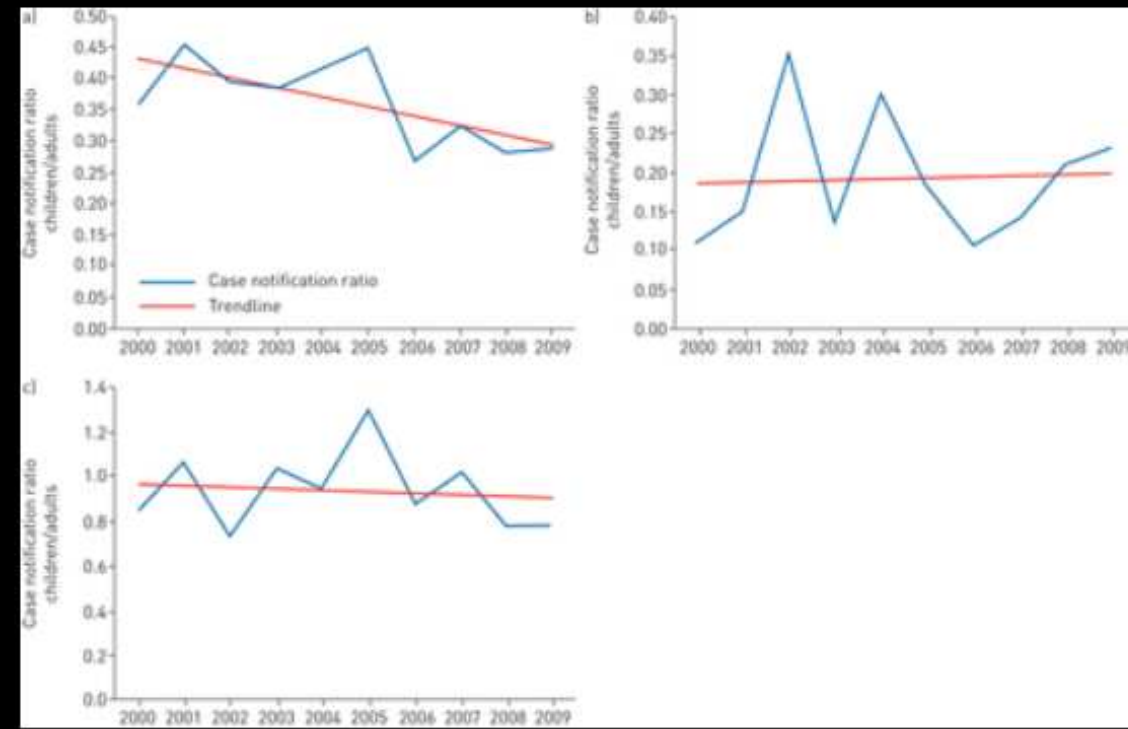


N=323
All cases <15 yrs
7.6% all cases DK

Top = males

Bottom =
females

A review of paediatric tuberculosis in Denmark: 10-year trend, 2000–2009



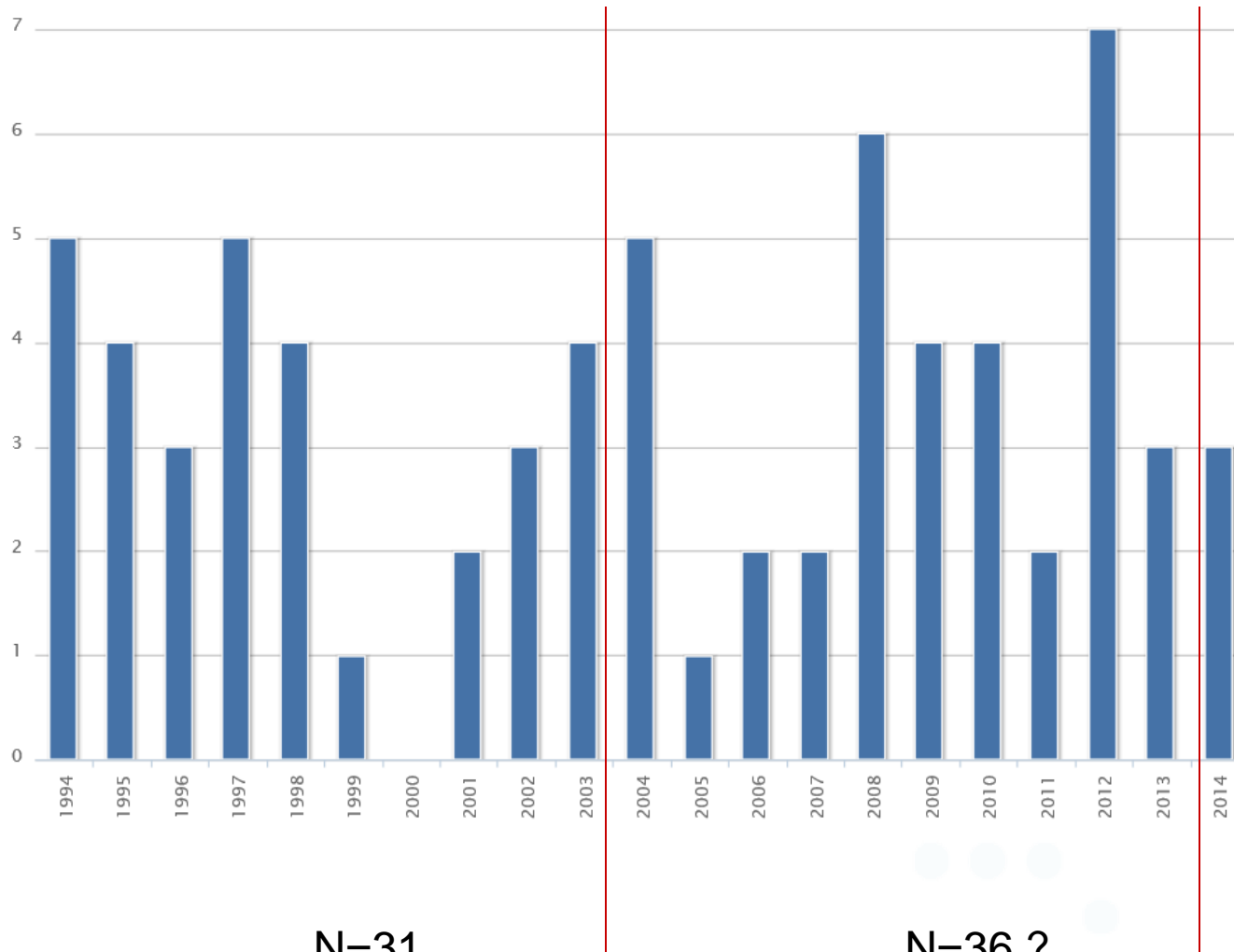
N=323

Trends in **ratio** of notification rates in Denmark 2000-2009:

a) children to adults

b) DK children to DK adults

c) immigrant children to immigrant adults



Danish-born
TB cases 1-4
yrs. old

1994-2014

Source: SSI

N=31

N=36 ?

A review of paediatric tuberculosis in Denmark: 10-year trend, 2000–2009

Table 1– Characteristics of tuberculosis cases in 323 children in Denmark

	Danes	Immigrants	Chi-squared
Subjects	66 (20.4)	257 (79.6)	
Sex			
Male	40 (60.6)	110 (42.8)	0.0097
Female	26 (39.4)	147 (57.2)	
Age years			
0–4	31 (46.9)	78 (30.3)	0.0003
5–9	22 (33.3)	58 (22.6)	
10–14	13 (19.7)	121 (47.1)	
Risk factor			
HIV/AIDS		1	
Household exposure	26 (39.3)	95 (36.9)	0.7161
Non-household exposure	29 (43.9)	51 (19.8)	0.0048
Unknown/other	11 (16.6)	110 (42.8)	0.0046
Disease site			
Pulmonary	54 (81.8)	189 (73.5)*	0.1647
Milliary	1 (1.5)	3 (1.2)	0.8197
Pleural	2 (3)	8 (3.1)	0.9725
Lymphatic	3 (4.5)	35 (13.6)	0.0413
Meningitis	5 (7.3)	5 (1.9)	0.0185
Spine		4 (1.5)	
Bone			
Gastrointestinal		7 (2.7)	
Genito-urinary			
Disseminated			
Cutaneous		4 (1.5)	
Others	1 (1.5)	2 (0.7)	
Disease verification			
Culture positive	28 (42.4)	133 (51.7)	0.1765
Smear positive	1 (1.5)	1 (0.4)	
NAA positive	3 (4.5)		
Clinical symptoms	3 (4.5)	4 (1.5)	0.1369
TST	11 (16.6)	20 (8.0)	0.0393
IGRA		1 (0.4)	
Chest radiography	20 (30.3)	89 (34.6)	0.5072
Histology		7 (2.7)	
None available		2 (0.7)	

N=323

Distribution:

- ≈ 80% cases were immigrants
- Males, 61% Danes vs. 43% immigrants
- Known contact, 84% Danes vs. 57% Immigrants
- Pulm. TB, 82% Danes vs. 74% immigrants
- Lymph. TB, 14% immigrants vs. 5% Danes

Diagnostic basis:

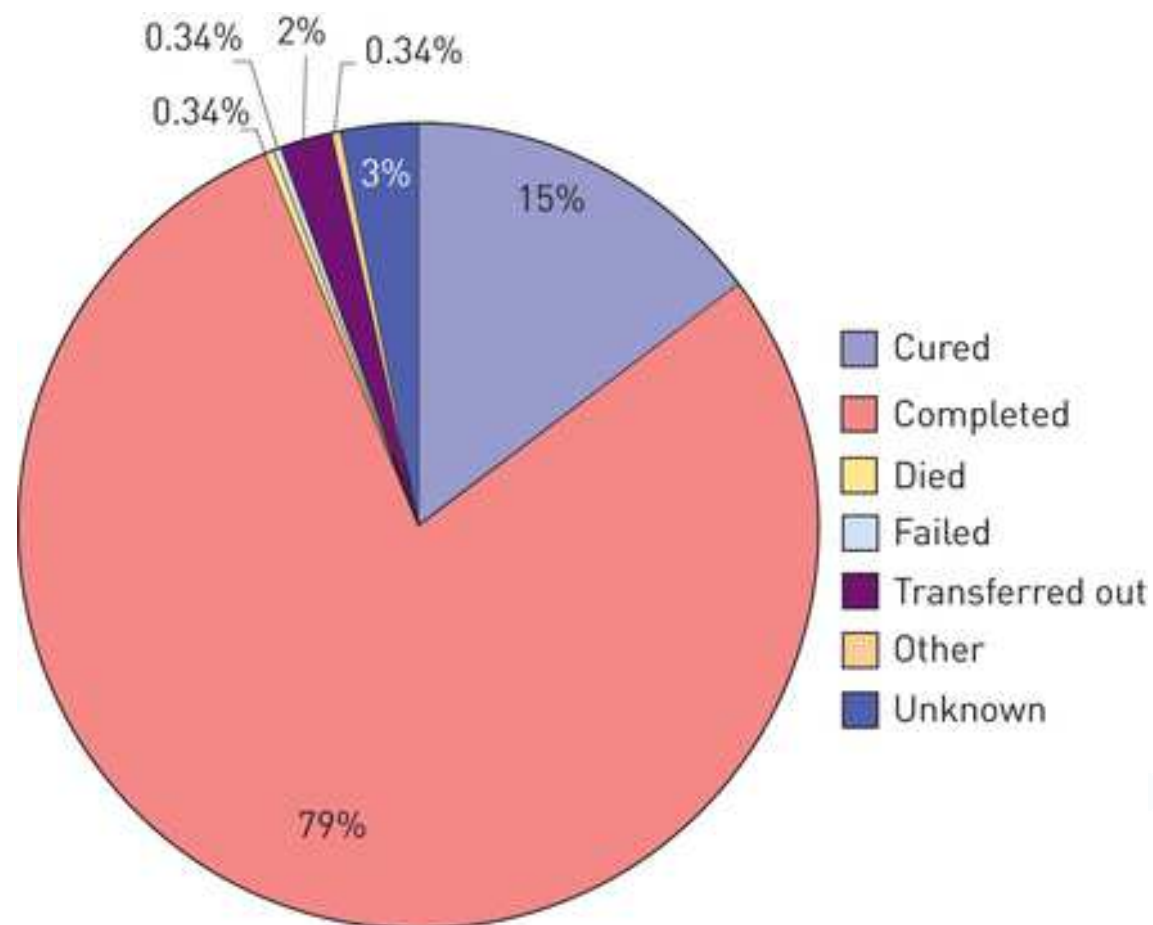
- 42% Danes vs. 52% immigrants culture positive
- 30% vs 35% chest X-ray
- 16% vs. 8% TST

A review of paediatric tuberculosis in Denmark: 10-year trend, 2000–2009

Table 2– Yield of *Mycobacterium tuberculosis* in smear, nucleic acid amplification (NAA) test and culture using various specimens in all notified cases for whom samples were obtained

Type of specimen	Specimens n	Smear positive for AFB	Positive by NAA test for <i>M. tuberculosis</i> n/N [#] (%)	Culture positive for <i>M. tuberculosis</i>
Sputum	90	26 (28.8)	27/53 (50.9)	44 (48.8)
BAL	3		1/3 (33.3)	3 (100)
Tracheal aspirates	33	3 (9)	3/19 (15.7)	6 (18.1)
Gastric fluid	237	29 (12.2)	45/155 (29)	101 (42.6)
Tissue biopsy	35	6 (17.1)	10/27 (37)	22 (62.8)
Pleura fluid	10		2/7 (28.5)	3 (30)
Cerebrospinal fluid	16		3/11 (27.2)	7 (43.7)
Pus	21	10 (47.6)	9/12 (75)	19 (90.4)
Stool	4			2 (50)

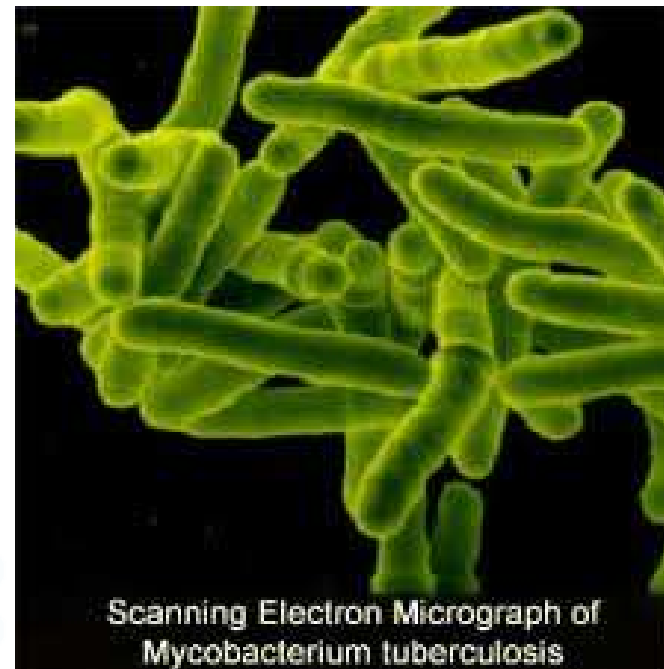
- Data are presented as n (%), unless otherwise stated. AFB: Acid-fast bacilli; BAL: bronchoalveolar lavage. [#]: N=number of NAA tests performed at clinician's request.



Treatment outcomes, pulmonary
& extrapulmonary notified
childhood TB, 2001-2009, DK

CHARACTERISTICS PAED TB

- ❖ Children generally less infectious than adult cases
- ❖ Low priority on national TB control programmes
- ❖ epidemiological patterns described for adult and paediatric TB do not necessarily overlap
 - This suggests different epidemic characteristics, case finding and prevention strategies
- ❖ In Europe, only 16.9% of paediatric cases were bacteriologically confirmed



Source: Marais BJ et al. Paediatric tuberculosis in Europe: lessons from Denmark and inclusive strategies to consider. ERJ 2014;43(3):678-684



“if you obey
all the rules,
you miss all
the fun.”
– *katharine hepburn*



"TUBERKULOSEBEKÆMPELSE I DANMARK ET NATIONALT TUBERKULOSEPROGRAM"

Danish Guidelines

4 lines, page 26 (of 62);

Children usually tolerate the treatment well

The dose should be tailored to the child's weight

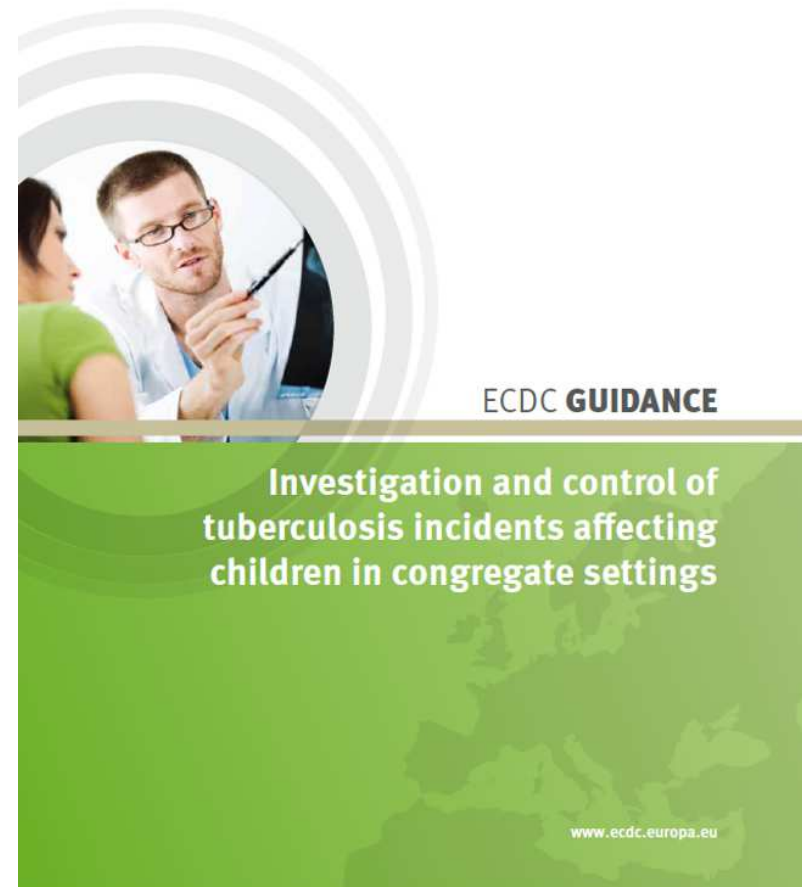
Previously, there have been concerns about the use of Ethambutol in young children due to risk of visual impairment, but this concern lapsed, as the risk of serious side effects is so small that it is outweighed by the treatment effect



PREVENTION AND CONTROL

- ❖ Young children who are exposed to people with infectious TB have an increased risk of developing TB disease if infected
- ❖ Most children will progress to develop TB disease within one year after being infected
- ❖ As such, childhood TB is an indicator of ongoing transmission within a community

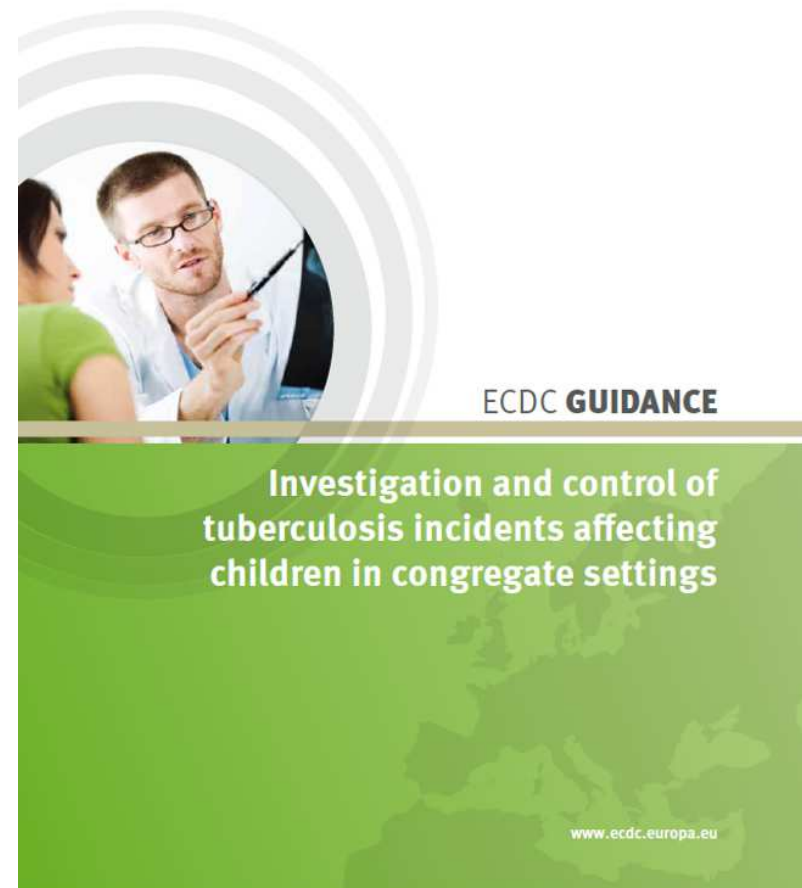
ECDC. Investigation and control of tuberculosis incidents affecting children in congregate settings. Stockholm: ECDC; 2013.



PREVENTION AND CONTROL

- ❖ The risk for children becoming infected following exposure is the highest through close contact with an infectious person
 - Household
 - congregate settings such as schools and nurseries.
- ❖ Thus, to rapidly identify the source case of infection and perform contact investigation around the case is essential for interrupting the transmission to avoid additional infected cases

ECDC. Investigation and control of tuberculosis incidents affecting children in congregate settings. Stockholm: ECDC; 2013.



EXPERT OPINIONS DIFFERENT ISSUES

Expert opinions

- **Contact investigation/ screening:**
All individuals working/attending the congregate setting should be considered. Based on an individual risk assessment, priority should be given to the contacts with the most extensive exposure to the index case (according to the stone-in-the-pond principle, see further 3.3.2) and the highest risk for progression to disease (i.e. the very young children, and immunocompromised individuals).
- **Source finding:**
All individuals working/attending the congregate setting should be considered (if a source has not been identified outside the setting). Based on an individual risk assessment, priority should be given to the individuals with closest contact and the highest risk of transmitting the disease to the index case (usually adults and adolescents).

Expert opinions

- Any health professional diagnosing TB in a person working/attending a congregate setting for children should alert the competent health authority having jurisdiction over the location of the incident, and initiate an investigation, as defined in the national legislation.

ECDC. Investigation and control of tuberculosis incidents affecting children in congregate settings. Stockholm: ECDC; 2013.

Expert opinions

Chemoprophylaxis¹:

- Chemoprophylaxis should be given to children in line with national or international guidelines. In particular young children, especially those below 2 years of age, and immunosuppressed children should be treated.
- Exclude active TB disease before initiating chemoprophylaxis.
- Take into account the results of drug susceptibility testing of the suspected source case.
- Ensure proper monitoring of side effects and best possible support to adherence in children provided chemoprophylaxis.
- Educate caregivers about relevant early symptoms and signs of TB, and the need for immediate medical evaluation if symptoms occur.
- Because of lack of evidence, no opinion is provided for the use of chemoprophylaxis when the suspected source case has MDR TB.

LTBI preventive treatment¹:

- Preventive treatment should be given to children in line with national or international recommendations. In particular young children, especially those below 2 years of age, and immunosuppressed children should be treated.
- Exclude active TB disease before initiating LTBI preventive treatment.
- Take into account the results of drug susceptibility testing of the suspected source case.
- Ensure proper monitoring of side effects and best possible support to adherence in children provided LTBI preventive treatment.
- Because of lack of evidence, no opinion is provided for LTBI preventive treatment when the suspected source case has MDR TB.
- Educate caregivers about relevant early symptoms and signs of TB, and the need for immediate medical evaluation if symptoms occur.
- Educate caregivers about the increased risk of progression to disease when immunosuppressive therapy or an immune compromising conditions is present in a person diagnosed with LTBI.

¹ Chemoprophylaxis is started as soon as possible after exposure of the child, before TST/IGRA results can prove or disprove infection. Chemoprophylaxis is discontinued as soon as infection is disproved. If LTBI however is confirmed (by TST/IGRA 8-12 weeks after exposure) and active TB excluded (by clinical and radiological examinations), it may be continued as preventive treatment. (The terms primary prophylaxis, primary prophylactic treatment and window prophylaxis are also used for the same concept of what we in this document refer to as chemoprophylaxis [16].

WHO GUIDELINES, DIAGNOSIS AND TREAT.



Tuberculosis treatment in children:

❖ <http://www.who.int/childmedicines/tuberculosis/en/>

Childhood tuberculosis

❖ <http://www.who.int/tb/challenges/children/en/>

The screenshot shows the WHO website's 'Essential medicines for children' page. The header includes the WHO logo and navigation links in multiple languages. The main content area is titled 'Tuberculosis treatment in children'. It contains a paragraph about the challenges of treatment, a section for 'Treatment guidelines' which states that dosing recommendations are based on drug-induced hepatotoxicity and previous dosing regimens, and a list of recommended drugs for first-line treatment: Isoniazid (10 mg/kg/day), Rifampicin (15 mg/kg/day), Pyrazinamide (35 mg/kg/day), and Ethambutol (20 mg/kg/day). A sidebar on the right provides contact information for the Department of Essential Medicines and Health Products.

This screenshot is a more detailed view of the same WHO page. It highlights the 'Dosing instructions for the use of currently available anti-tuberculosis medicines' section, which provides specific dosing recommendations for first-line treatment: Isoniazid (10 mg/kg/day), Rifampicin (15 mg/kg/day), Pyrazinamide (35 mg/kg/day), and Ethambutol (20 mg/kg/day). It also mentions 'Rapid Advice 2010: Treatment of tuberculosis in children'.



❖ <http://www.cdc.gov/tb/topic/populations/TBinChildren/default.htm>



❖ Microscopy:

- Ziehl Neelsen
- Auramin-rhodamine

❖ PCR / NAT, e.g.:

- ProbeTec
- Hain GenoType MTBDRplus
- Hain Genotype MTBDRsl
- Hain Gonotype Mycobacterium CM/AS
- Hain Genotype MTBC
- BD MGIT™ TBc Identification Test

❖ Culture:

- BACTEC™ MGIT™ 960 / 320 Mycobacterial Detection System
- Inoculation on selective media

❖ IGRA / MTX:

- Quantiferon
- T-spot
- Tuberculin

❖ Clinical

❖ X-rays

❖ Histology



SOME POINTS

❖ Epidemiology

- Indicator for recent transmission, represent failure to control transmission
- Reservoir for disease
- Infection control
 - Source and contact
 - Preventive treatment

❖ Disease

- Delayed case finding adults = paediatric TB

❖ Diagnostics

- In Europe, only 16.9% bact. confirmed

❖ Guidelines

- Yes please



This PA chest x-ray view is taken in a 7-month old with millary TB. There are multiple small nodules throughout the lungs bilaterally.