Epidemiology of Environmental Mycobacterial disease in tuberculosis low incidence countries

Dirk Wagner

24e symposium tuberculose de Münchenwiler 19 mars 2015
24th symposium on tuberculosis in Münchenwiler March 19 2015
ARE THESE PROMISES THAT YOU CAN KEEP WHEN YOU DEAL WITH MYCOBACTERIA?
THE MOST IMPORTANT TAKE-HOME MESSAGE

MYCOBACTERIA, EXCEPT THOSE BELONGING TO THE MTB-COMPLEX OR M. LEPROSY, ARE NAMED \textbf{NONTUBERCULOUS MYCOBACTERIA}
Epidemiology of Non-Tuberculous Mycobacterial disease in tuberculosis low incidence countries

Dirk Wagner

24e symposium tuberculose de Münchenwiler 19 mars 2015
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To set the stage

• How become people infected with NTM?
  ▪ Where are NTM in the environment?
  ▪ Are they ingested?
  ▪ Are they inhaled?
NTM-factors and the environment

- growth at low pH
  - High numbers in acidic, brown water swamps and boreal (peat) soils
- humic and fulvic acid growth stimulation
  - Growth in drinking water distribution systems and household plumbing
- temperature resistance
  - Survive in hot springs and in buildings and home hot water systems
- hydrophobicity
  - capable of biofilm formation, occur in drinking water systems
  - high impermeability to antibiotics


Ingestion of NTM

• Children
  ▪ Main disease manifestation: cervical lymphadenitis
  ▪ Gastric aspirates:
    ▪ Uganda: prevalence of NTM in sputum samples or gastric aspirates: 3.7% - 4.6% \(^1\)
      - M. fortuitum (63.5%), M. szulgai (14.3%), M. gordonae (9.5%), M. intracellulare (4.7%), M. scrofulaceum (3.2%), M. lentiflavum (3.2%), and M. peregrinum (1.6%)
    ▪ Ethiopia: prevalence of NTM in sputum samples or gastric aspirates: 10% \(^2\)

• NTM-isolation from gastric aspirates in children evaluated for TB (Canada):
  ▪ Toronto 1999-2011, 285 pts, age 10mths -12.5 yrs, 785 gastric aspirates:
  ▪ 12 NTM-isolates (1.5%, MAC, M. xenopi, M. gordonae, M. fortuitum, M. Simiae), 11 untreated

⇒ Mostly no clinical relevance of NTM isolations from gastric aspirates (not been studied)

⇒ Gastric aspirates are not recommended for diagnosis of NTM pulmonary disease


Ingestion of NTM

• Adults
  ▪ HIV – patients with disseminated disease (and no pulmonary predisposition) or abdominal NTM-IRIS

⇒ GI tract often the route of infection
To set the stage

• How become people infected with NTM?
  - Where are NTM in the environment?
  - Are they ingested? YES
  - Are they inhaled?
To set the stage

• How become people infected with NTM?
  ▪ Where are NTM in the environment?
  ▪ Are they ingested? YES
  ▪ Are they inhaled?
BLAST results for all showerhead swab libraries, pooled at the genus-level and grouped by municipality of origin.

<table>
<thead>
<tr>
<th>Region</th>
<th>Sample ID</th>
<th>% of Total</th>
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Feazel L M et al., PNAS 2009;106:16393-16399
7/17 pts (41%) with NTM-PD from whom isolates were obtained were infected with an NTM strain having the same DNA fingerprint as at least 1 NTM isolate from their household plumbing

- **MAC, M. malmoense, M. szulgai, M. chelonae, M. gordonae, M. scrofulaceum, M. terrae, M. trivale**

If MAC is found in household water, most (73%) are M. chimaera

- **M. intracellulare** is absent from household water
To set the stage

• How become people infected with NTM?
  ▪ Where are NTM in the environment?
  ▪ Are they ingested? YES
  ▪ Are they inhaled? Probably YES
### NTM - disease - manifestations

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of cases</th>
<th>Rate a</th>
<th>No. of cases</th>
<th>Rate a</th>
<th>No. of cases</th>
<th>Rate a</th>
<th>No. of cases</th>
<th>Rate a</th>
<th>No. of cases</th>
<th>Rate a</th>
<th>No. of cases</th>
<th>Rate a</th>
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<td>M. abscessus</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>407</strong></td>
<td><strong>5.6</strong></td>
<td><strong>63</strong></td>
<td><strong>0.9</strong></td>
<td><strong>25</strong></td>
<td><strong>0.3</strong></td>
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<td><strong>0.3</strong></td>
<td><strong>10</strong></td>
<td><strong>0.1</strong></td>
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</table>

a Rate is annualized per 100,000 population and was calculated if the numerator was ≥5.
What influences NTM PD manifestation?

- Presence of NTM in the environment
  - Changing environment
- Bacterial virulence
- Host predisposition
  - Changing host factors
- Detection methods
  - Changing availability of detection methods
- Awareness of the disease and it’s diagnosis
  - Treatment decisions
What influences NTM PD manifestation?

- **Presence of NTM in the environment**
  - Changing environment
- **Bacterial virulence**
- **Host predisposition**
  - Changing host factors
- **Detection methods**
  - Changing availability of detection methods
- **Awareness of the disease and its diagnosis**
  - Treatment decisions
# NTM-distribution in respiratory specimen

**M. kansasii:**
- 1-5% in most continents
- 20% in South America

<table>
<thead>
<tr>
<th>Continent</th>
<th>Number of labs</th>
<th>Number of patients with NTM isolated</th>
<th>Distribution of NTM</th>
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</thead>
<tbody>
<tr>
<td>Europe</td>
<td>43</td>
<td>6804</td>
<td><img src="image1" alt="Pie chart" /></td>
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<tr>
<td>North America</td>
<td>4</td>
<td>4913</td>
<td><img src="image2" alt="Pie chart" /></td>
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<tr>
<td>South America</td>
<td>3</td>
<td>393</td>
<td><img src="image3" alt="Pie chart" /></td>
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<tr>
<td>Australia (Queensland)</td>
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<td>453</td>
<td><img src="image4" alt="Pie chart" /></td>
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<td>Asia</td>
<td>3</td>
<td>1974</td>
<td><img src="image5" alt="Pie chart" /></td>
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<td>South Africa</td>
<td>2</td>
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<td><img src="image6" alt="Pie chart" /></td>
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<td>TOTAL</td>
<td>56</td>
<td>20183</td>
<td><img src="image7" alt="Pie chart" /></td>
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### NTM-distribution in respiratory specimen

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<th>Continent</th>
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<th>Number of patients with NTM isolated</th>
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<td>MAC</td>
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<td>M. xenopi</td>
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<td>other SGM</td>
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#### Rapid growers:
- 31% in Asia: Japan 7%, Taiwan 50%
- 7% in South Africa

<table>
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<tr>
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<th>Number of labs</th>
<th>Number of patients with NTM isolated</th>
<th>Australia (Queensland) 1</th>
<th>453</th>
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<tbody>
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<td>Europe</td>
<td>43</td>
<td>6804</td>
<td>8%</td>
<td>71%</td>
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<tr>
<td>North America</td>
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<td>South America</td>
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<td>393</td>
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<td>50%</td>
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<td>5646</td>
<td>3%</td>
<td>47%</td>
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TOTAL | 56 | 20183
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<th>Number of MAC isolates (% of all NTM)</th>
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<td>2500 (36.9)</td>
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<td>322 (71.1)</td>
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</tr>
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<td>Asia</td>
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<td>1062 (53.8)</td>
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<td>South Africa</td>
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<td>2849 (50.5)</td>
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<tr>
<td>TOTAL</td>
<td>56</td>
<td>6572 (45.7)</td>
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Different places – different NTM

Major differences

- **M. kansasii**
- **M. xenopi**
- **M. malmoense**
- rapid growers

Hoefsloot Eur Respir J. 2013 Dec;42(6):1604-13
Different places - different risk of NTM-PD

5% sample of all Medicare Part B beneficiaries > 65 yrs enrolled from 1997 to 2007.
Different places - different risk of NTM-PD

TABLE 1. SUMMARY OF ALL SIGNIFICANT CLUSTERS IDENTIFIED BY SATSCAN OF PULMONARY NONTUBERCULOUS MyCOBACTERIAL DISEASE AMONG U.S. MEDICARE BENEFICIARIES 65 YEARS OF AGE AND OLDER

<table>
<thead>
<tr>
<th>Cluster Type</th>
<th>Centroid County and State</th>
<th>No. of Counties (Radius, km)</th>
<th>Relative Risk</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Highlands, FL</td>
<td>24 (159.4)</td>
<td>1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Santa Barbara, CA</td>
<td>18 (344.5)</td>
<td>2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Montgomery, PA</td>
<td>5 (42.2)</td>
<td>2.2</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>New York, NY</td>
<td>1 (0)</td>
<td>2.7</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Milwaukee, WI</td>
<td>1 (0)</td>
<td>3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Kalawao, HI</td>
<td>3 (114.8)</td>
<td>3.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Plaquemines, LA</td>
<td>3 (70.2)</td>
<td>6.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low risk</td>
<td>Washington, RI</td>
<td>16 (106.7)</td>
<td>0.5</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Iosco, MI</td>
<td>93 (351.4)</td>
<td>0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Roane, WV</td>
<td>208 (268.5)</td>
<td>0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Polk, MN</td>
<td>247 (689.7)</td>
<td>0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Cayuga, NY</td>
<td>95 (289.0)</td>
<td>0.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- California, Florida, Hawaii, Louisiana, New York, Oklahoma, Pennsylvania, Wisconsin
High risk places for NTM-PD

- greater **population densities**, higher **education** and **income** levels
- greater levels of **precipitation**, mean minimal and maximal temperatures, mean daily potential **evapotranspiration**, and **lower elevation**

⇒ **surface and atmospheric water sources and levels** contribute to an increased risk for NTM exposure and therefore to the higher prevalence of disease

---

**TABLE 3. MULTIVARIATE LOGISTIC REGRESSION MODEL OF ENVIRONMENTAL AND SOCIOECONOMIC FACTORS SIGNIFICANTLY ASSOCIATED WITH HIGH-RISK COUNTIES FOR PULMONARY NONTUBERCULOUS MYCOBACTERIAL DISEASE AMONG U.S. MEDICARE BENEFICIARIES 65 YEARS OF AGE AND GREATER**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population per square mile, per 100-person increase</td>
<td>1.4 (1.1–1.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Median household income, per $1,000 increase</td>
<td>1.4 (1.1–1.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Proportion of area as surface water, per 10% increase</td>
<td>4.6 (1.5–14.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean daily potential evapotranspiration, per 0.1-mm increase</td>
<td>4.0 (1.6–10.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Copper soil levels, per 1-ppm increase</td>
<td>1.2 (1.0–1.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Sodium soil levels, per 0.1-ppm increase</td>
<td>1.9 (1.2–2.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Manganese levels, per 100-ppm increase</td>
<td>0.7 (0.4–1.0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adjemian et al. AJRCCM 2012 186:553–558
Association with natural disasters?

Figure 1 – Number of NTM-positive cultures in Louisiana from 1997 to 2013 in relation to major hurricanes plotted by year. The names and years of occurrence of three major hurricanes that struck the state of Louisiana are also shown. NTM = nontuberculous mycobacteria.
What influences NTM PD manifestation?

- Presence of NTM in the environment
  - Changing environment
- Bacterial virulence
- Host predisposition
  - Changing host factors
- Detection methods
  - Changing availability of detection methods
- Awareness of the disease and its diagnosis
Changing epidemiology of MAC

- Queensland, Australia:

![Bar chart showing changing epidemiology of MAC in Queensland, Australia from 1999 to 2005.](chart.png)
M. kansasii – constant association

- with coal mines / toxic metals:
  - **South Africa 1993-96:**
    - Of miners with NTM isolates... *M. kansasii* and *M. scrofulaceum* accounted for 202 (68%) and 41 (14%) isolates respectively.
  - **Tschech republic (347 km²) 1968-1995:**
    - mining of black coal, metallurgical plants and ironworks
    - 961 cases, 12/100,000 inhabitants
      - mine employees at the time of contraction: 52.2%
      - other workers in heavy industry 14.6%
    - 1971-1995:
      - 538/1231 (43.7%) samples of industrial (scrapings and untreated) water *M. kansasii* was isolated
      - No *M. kansasii* in soil samples (93) / small rodents (187)
  - **Slovakia 1979-1993**
    - Miners accounted for 20 out of 51 patients

M. kansasii – decreasing over time

• The Netherlands

1956-64

n = 237
(patient isolates)

2008

n = 735
(laboratory isolates)

M. avium complex
M. xenopi
M. scrofulaceum
fast growing NTM
M. kansasii
other

M. xenopi – decreasing over time

- Borstel, Germany

![Pie charts showing the distribution of Mycobacterium species in Borstel, Germany, from 1992-96 and 2008. In 1992-96, M. avium complex was the most common, followed by M. xenopi and M. gordonae. In 2008, M. xenopi became the dominant species.](chart.png)

- n = 10,651 (all laboratory isolates)
- n = 966 (only respiratory isolates)

Rapid growers – increasing over time

- The Netherlands

1956-64
- n = 237 (patient isolates)

2008
- n = 735 (laboratory isolates)

- M. avium complex
- M. xenopi
- M. scrofulaceum
- fast growing NTM
- M. kansasii
- other

Rapid growers – increasing over time

- Queensland, Australia:

![Bar chart showing the increase in no. isolates of various Mycobacteria species from 1999 to 2005.](chart)

Thompson et al. 2010 Changing Epidemiology of Pulmonary Nontuberculous Mycobacteria Infections. EID 16 (10), 1576-1583.
What influences NTM PD manifestation?

• Presence of NTM in the environment
  ▪ Changing environment

• Host predisposition
  ▪ Changing host factors

• Bacterial virulence

• Detection methods
  ▪ Changing availability of detection methods

• Awareness of the disease and it’s diagnosis
Frequency of disease manifestations

• How are NTM-disease-manifestations influenced by changing protective immunity?
  ▪ BCG vaccination status
  ▪ local TBC epidemiology (cross – protection)
  ▪ immunosuppression
    ✪ systemic
      – HIV infection,
      – haematological malignancies,
      – inheritable disorders of immunity
      – immunosuppressive drug use including TNF-\(\alpha\) \(^1,2\) inhibitor therapy or systemic or inhalative \(^3\) corticoid therapy !!
    ✪ local
      – pre-existent pulmonary disease

Pulmonary NTM disease: Host risk factors

- Pulmonary conditions
  - Silicosis (OR=5.0)
  - Pneumoconiosis (OR=9.8)
  - COPD (OR=15.7)
  - Bronchiectasis (OR=187.5)
  - Previous TB (OR=9.6-178.3)
  - Asthma (OR=7.8)
  - Cystic Fibrosis
- Increasing age
- Diabetes mellitus
- Alcohol abuse
- Smoking
The COPD epidemic

- 20% among 896 urban South Africans >40 years of age (BOLD study)
- 10% among 410 civil servant in Nigeria, aged 30-70 yrs
- 16% among 372 biomass fuel exposed in Malawi, mean age 42 yrs
- 8% in India among persons >40 years of age (meta-analysis)
- 3% in China, or up to 8% in the 60-69 yrs age group

⇒ COPD is becoming more prevalent in developing countries
⇒ Increasing number of people at risk for pulmonary NTM disease

Slide from J v Ingen

Yin P, et al. BMC Publ Health 2011
### Table 1

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk, Odds Ratio, or Relative Prevalence</th>
<th>Disease or Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental: individual exposures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soil exposure</td>
<td>5.9&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Indoor swimming pool use (in the past 4 mo)</td>
<td>5.9 (1.3, 26.1)&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Infection</td>
</tr>
<tr>
<td>Swimming pool use at least once per month (indoor or outdoor, over the past 5 y)</td>
<td>0.15 (0.04–0.67)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td><strong>Host factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer (neoplasms of larynx, trachea, and bronchus)</td>
<td>3.4&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>COPD</td>
<td>2–10&lt;sup&gt;7,10,27&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>44–187.5&lt;sup&gt;12,23&lt;/sup&gt;</td>
<td>Disease (coding)&lt;sup&gt;7&lt;/sup&gt; Disease (validated microbiological surrogate)&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thoracic skeletal abnormalities</td>
<td>5.4&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Low body weight</td>
<td>9.09&lt;sup&gt;4,19&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.5&lt;sup&gt;7&lt;/sup&gt;, 1.9&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Immunomodulatory drugs/anti-TNF agents</td>
<td>OR = infinity&lt;sup&gt;19&lt;/sup&gt; Anti-TNF agents 2.2&lt;sup&gt;76&lt;/sup&gt; Others 1.6–2.9&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Steroid use</td>
<td>8&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5.3&lt;sup&gt;27&lt;/sup&gt;, 1.5&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td><strong>Environmental: climatic and population factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of area as surface water</td>
<td>4.6&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Mean daily potential evapotranspiration</td>
<td>4.0&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Copper soil levels, per 1 ppm increase</td>
<td>1.2 (1.0, 1.2)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Sodium soil levels, per 0.1 ppm increase</td>
<td>1.9 (1.2, 2.9)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Manganese soil levels, per 100 ppm increase</td>
<td>0.7 (0.4, 1.0)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Increased average topsoil depth</td>
<td>0.87 (Mycobacterium intracellulare)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
<tr>
<td>Soil bulk density</td>
<td>1.8 (Mycobacterium kansasi)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Disease</td>
</tr>
</tbody>
</table>
What influences NTM PD manifestation?

- Presence of NTM in the environment
  - Changing environment
- Host predisposition
  - Changing host factors
- **Bacterial virulence**
- Detection methods
  - Changing availability of detection methods
- Awareness of the disease and its diagnosis
Clinical relevance of common NTM species in pulmonary isolates.

Is clinical relevance a question of the virulence of different isolates? Is the clinical relevance different in different geographic regions?
NTM pulmonary disease and survival


- M. gordonae
- rapid growers
- other slow growers
- MAC
- M. malmoense
- M. xenopi
What influences NTM PD manifestation?

- Presence of NTM in the environment
  - Changing environment
- Host predisposition
  - Changing host factors
- Bacterial virulence
- Detection methods
  - Changing availability of detection methods
- Awareness of the disease and its diagnosis
NTM species evolution

- Over 140 NTM-species until now
  - PCR based techniques with major impact
  - Increased distribution of NTM-identification kits

<table>
<thead>
<tr>
<th>Type</th>
<th>Commonly used assays/targets</th>
<th>Discriminatory power</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single species DNA Probes</td>
<td>AccuProbe (GenProbe)</td>
<td>Low, species-specific</td>
<td>Low discriminatory power, cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4 species)</td>
<td></td>
</tr>
<tr>
<td>Line probe assays</td>
<td>GenoType® Mycobacterium CM/AS</td>
<td>Medium (30 species)</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>(Hain Lifescience)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inno-LiPA Mycobacteria v2</td>
<td>Medium (16 species)</td>
<td>Cost, low discriminatory power</td>
</tr>
<tr>
<td></td>
<td>(Innogenetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR product restriction</td>
<td>hsp65, rpoB</td>
<td>Medium-High</td>
<td>Manually processed, error prone</td>
</tr>
<tr>
<td>analysis (PRA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene sequence analysis</td>
<td>16S, 16S-23S ITS, hsp65, rpoB, secA1</td>
<td>Very high (all species)</td>
<td>Requires access to sequencers, slow</td>
</tr>
</tbody>
</table>

What influences NTM PD manifestation?

- Is the frequency of NTM-disease manifestation rising?
NTM-isolates (the Netherlands)

Number of Isolates

<table>
<thead>
<tr>
<th>Year</th>
<th>MTBc</th>
<th>NTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>1100</td>
<td>400</td>
</tr>
<tr>
<td>2003</td>
<td>1000</td>
<td>450</td>
</tr>
<tr>
<td>2004</td>
<td>900</td>
<td>400</td>
</tr>
<tr>
<td>2005</td>
<td>800</td>
<td>450</td>
</tr>
<tr>
<td>2006</td>
<td>750</td>
<td>500</td>
</tr>
<tr>
<td>2007</td>
<td>700</td>
<td>550</td>
</tr>
<tr>
<td>2008</td>
<td>650</td>
<td>600</td>
</tr>
<tr>
<td>2009</td>
<td>600</td>
<td>650</td>
</tr>
</tbody>
</table>

Arend et al. 2009 Curr Opin Pulm Med. 15:201-8
van Ingen, pers. commun.
Pulmonary NTM-disease incidence (US)

Southern California and Colorado:

TABLE 4. AVERAGE ANNUAL AGE-ADJUSTED* PERIOD PREVALENCE BY SITE AND SEX, FOUR INTEGRATED HEALTH CARE DELIVERY SYSTEMS, 2004-2006

<table>
<thead>
<tr>
<th></th>
<th>Men Cases per 100,000 Person Years</th>
<th>Women Cases per 100,000 Person Years</th>
<th>Overall Cases per 100,000 Person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser Permanente</td>
<td>5.2</td>
<td>8.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Southern California</td>
<td>2.7</td>
<td>3.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Group Health</td>
<td>3.4</td>
<td>2.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Kaiser Permanente</td>
<td>1.1</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Colorado</td>
<td>1.1</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Geisinger</td>
<td>3.4</td>
<td>3.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Combined</td>
<td>4.4</td>
<td>6.5</td>
<td>5.5</td>
</tr>
</tbody>
</table>


Oregon:
- prevalence of 4.3/100,000 in the general population, with probable cases included: 5.6/100,000
- among those at least 50 years old 10.2/100,000
Annual prevalence of pulmonary nontuberculous mycobacteria cases among a sample of U.S. Medicare Part B enrollees by sex from 1997 to 2007.

Adjemian et al. AJRCCM 2012 186:553–558
Pulmonary NTM-disease (Germany): associated hospitalizations

B

- Rate per 100 000 population

Year

2005 2006 2007 2008 2009 2010 2011

- All
- Male
- Female

Temporal trends in disease incidence

Temporal trends in percentage of mycobacterial disease caused by NTM

### Table 1: Major studies reporting prevalence of NTM pulmonary disease

<table>
<thead>
<tr>
<th>Study/Lead author</th>
<th>Dates</th>
<th>Location</th>
<th>Study population</th>
<th>Measure</th>
<th>Prevalence—start of study period (per 100,000 person-years)</th>
<th>Prevalence—end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marras&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1997–2003</td>
<td>Ontario, Canada</td>
<td>Population-based</td>
<td>Isolation</td>
<td>9.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Winthrop&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2005–2006</td>
<td>Oregon, USA</td>
<td>Population-based</td>
<td>Disease</td>
<td>n/a</td>
<td>8.6</td>
</tr>
<tr>
<td>Winthrop&lt;sup&gt;54&lt;/sup&gt;</td>
<td>2000–2008</td>
<td>Northern California</td>
<td>Integrated health system</td>
<td>Disease</td>
<td>n/a</td>
<td>4.1</td>
</tr>
<tr>
<td>Prevots&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2004–2006</td>
<td>California, Colorado, Pennsylvania, and Washington</td>
<td>Integrated health system in four US states</td>
<td>Disease</td>
<td>n/a</td>
<td>5.5</td>
</tr>
<tr>
<td>Adjemian&lt;sup&gt;14&lt;/sup&gt;</td>
<td>1997–2007</td>
<td>USA</td>
<td>Medicare beneficiaries*</td>
<td>Disease</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>Moore&lt;sup&gt;30&lt;/sup&gt;</td>
<td>1995–2006</td>
<td>England, Wales, and Northern Ireland</td>
<td>Population-based</td>
<td>Isolation</td>
<td>0.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Lai&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2000–2008</td>
<td>Taiwan</td>
<td>University hospital</td>
<td>Disease</td>
<td>1.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Thomson&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1999, 2005</td>
<td>Queensland, Australia</td>
<td>Population-based</td>
<td>Disease</td>
<td>2.2</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*Study population limited to patients ≥ 65 years of age.
NTM-PD in US, EU5 & JAPAN

NTMPD US, EU5 & Japan Patient Records Research Study

Conducted by Clarity Pharma Research

• US: Q4 2011-Q1 2012
• EU5 & Japan: Q3 2013
• **Methods:**

NTMPD patients diagnosed annually was estimated by a 2-round Delphi method independently by 6 experts, that included anonymous feed-back of the 1\(^{st}\) round groups estimates.

The panel was asked:

• To estimate the annual NTMPD prevalence rate for each of the five countries and the most likely annual prevalence range;

• To provide comments/rationale for each estimate.
### Regional Differences of Annual NTMPD

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Annual NTMPD prevalence by region (Pop/100.000)</th>
<th>Estimated number of NTMPD patients</th>
<th>Annual NTMPD prevalence by region (Pop/100.000)</th>
<th>Estimated number of NTMPD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRANCE</td>
<td>Parisian</td>
<td>13.6</td>
<td>1609 (42%)</td>
<td>Madrid</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Northwest</td>
<td>7.6</td>
<td>963 (25%)</td>
<td>South</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>Southeast</td>
<td>4.1</td>
<td>638 (16%)</td>
<td>East</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>Northeast</td>
<td>3.7</td>
<td>534 (14%)</td>
<td>Central</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Southwest</td>
<td>1.3</td>
<td>112 (3%)</td>
<td>North</td>
<td>3.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6.0</td>
<td>3856</td>
<td>Total</td>
<td>5.9</td>
</tr>
<tr>
<td>GERMANY</td>
<td>East</td>
<td>8.2</td>
<td>1656 (31%)</td>
<td>England</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>7.1</td>
<td>1976 (37%)</td>
<td>Scotland</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>North</td>
<td>6.3</td>
<td>597 (11%)</td>
<td>N. Ireland</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>South</td>
<td>3.9</td>
<td>1143 (21%)</td>
<td>Wales</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6.5</td>
<td>5372</td>
<td>Total</td>
<td>6.5</td>
</tr>
<tr>
<td>ITALY</td>
<td>Central</td>
<td>10.4</td>
<td>1221 (33%)</td>
<td>Central</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>North</td>
<td>3.8</td>
<td>1003 (27%)</td>
<td>South</td>
<td>7.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6.1</td>
<td>3713</td>
<td>Total</td>
<td>6.1</td>
</tr>
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</table>

Wagner et al ERS 2014, P1065
Comparison of Treatment Practices for Nontuberculous Mycobacterial Pulmonary Disease in Japan, Europe, and the United States

• Methods
Representative samples of physicians from Japan, 5 countries in Europe (EU5: United Kingdom, France, Germany, Italy, and Spain), and the United States extracted treatment information from records of patients with a confirmed diagnosis of nontuberculous mycobacterial pulmonary disease (NTM-PD).
Results

• In the EU5 and Japan, a total of 619 qualified physicians with NTM-PD patients provided a total of 1,429 patient cases.

• In the US study, 349 physicians provided 915 patient cases.

• MAC (~80%) was the predominant causative agent in all countries, followed by *Mycobacterium abscessus* (*M. abscessus*).
NTM PD severity = late diagnosis?

Figure 1. Reported disease severity, by region
More pts are treated in EU
More pts are treated with iv antibiotics in EU

• A higher percentage of patients in EU5 (68%) received treatment compared with patients in the United States (53%) and Japan (43%).

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Total (N=1,356)</th>
<th>EU5 (n=690)</th>
<th>Japan (n=179)</th>
<th>US (n=487)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antibiotics, %</td>
<td>87</td>
<td>82</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td>IV antibiotics, %</td>
<td>25</td>
<td>31</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Inhaled antibiotics, %</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Indication to treat NTM-PD differs by country

Logistic regression analysis showed that the decision to treat was most dependent on country (odds ratio = 6.2, Spain vs France) and severity of presenting symptoms (odds ratio = 1.9, severe vs mild).
• The percentage of patients with MAC disease who received treatment with the **recommended 3-drug macrolide regimen for >6 months** differed strongly by country
Conclusion

• Each NTM species has its individual epidemiology
  ▪ differs by region, countries in the region, regions in the countries
  ▪ may determine, in part, the frequency and manifestations of pulmonary NTM disease in each region
  ▪ species specific epidemiology largely understudied

• Constant and changing local epidemiologies
  ▪ reasons are largely unknown

• NTM-PD is increasing in low TB incidence countries
  ▪ multifactorial
Conclusion

• Reliable epidemiological data are missing.
  ▪ EU wide surveillance system is urgently needed

• NTMPD patients are diagnosed too late in Europe
  ▪ Physicians need to be better educated about risk factors and screening indications.

• Psychology of antibiotic treatment
  ▪ dictates treatment decisions in southern European countries

• Critical gaps in appropriate treatment practices
  ▪ need to be addressed in the future.
Thank you for your attention!
I need a cup of coffee!
NTM-NET is an international network to promote clinically oriented research in the field of nontuberculosis mycobacterial diseases around the globe by sharing and developing ideas and research protocols.
Diagnosed with NTMPD

(100%)
n=211

Results: Treatment patterns in Germany
Results: Treatment patterns in Germany

Diagnosed with NTMPD

(100%)
n=211

Diagnosing physician

- 37% PUD
- 35% IM
- 15% GM
- 13% Other
Results: Treatment patterns in Germany

Diagnosed with NTMPD

(100%) n=211

Treating physician

49% PUD
36% IM
32% ID

Diagnosing physician

37% PUD
35% IM
15% GM
13% Other
Results: Treatment patterns in Germany

Diagnosed with NTMPD (100%) n=211

MAC only (80%) n=169
M. abscessus only (14%) n=30

Treating physician
- PUD 49%
- IM 36%
- ID 32%

Diagnosing physician
- PUD 37%
- IM 35%
- GM 15%
- Other 13%
Results: Treatment patterns in Germany

Diagnosed with NTMPD
(100%)
n=211

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M. abscessus only (14%)
n=30

Severity at first presentation
- 22% Mild
- 58% Moderate
- 20% Severe

Treating physician
- 49% PUD
- 36% IM
- 32% ID

Diagnosing physician
- 37% PUD
- 35% IM
- 15% GM
- 13% Other
Diagnosed with NTMPD (100%) n=211

- NTMPD treated (63%) n=132
- NTMPD not treated (37%) n=79

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Severity at first presentation:
- Mild: 22%
- Moderate: 58%
- Severe: 20%

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- IM: 35%
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- Moderate: 58%
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- IM: 35%
- GM: 15%
- Other: 13%

Future treatment planned (45%) n=35
Diagnosed with NTMPD (100%) n=211

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  - Treated with inhaled antibiotics (8%) n=11
- NTMPD not treated (37%) n=79
- Future treatment planned (45%) n=35

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Diagnosing physician
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- IM (35%)
- GM (15%)
- Other (13%)

NTMPD treated (63%) n=132
- Treated with oral antibiotics (80%) n=106
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  - NTMPD treated (63%) n=132
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    - Treated with inhaled antibiotics (8%) n=11
  - NTMPD not treated (37%) n=79
  - Treatment regimen was changed (9%) (n=12)
  - Future treatment planned (45%) n=35
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Treated with oral antibiotics (80%) n=106
Future treatment planned (45%) n=35

Setting(s) in which prescribed *
- 71% Outpatient
- 36% Hospital inpatient

*Some patients prescribed antibiotic in both settings
Results: Treatment patterns in Germany

Diagnosed with NTMPD (100%) n=211

- NTMPD treated (63%) n=132
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  - Treated MAC patients (93%) n=123

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Treatment regimen was changed (n=12) 9%

NTMPD treated (63%) n=132
- Treated with oral antibiotics (80%) n=106
- Treated with inhaled antibiotics (8%) n=11
- Treated MAC patients (93%) n=123
- Treated MAC patients with 3-drug macrolide regimen** for ≥ 6 months (4%) n=5

NTMPD not treated (37%) n=79

Future treatment planned (45%) n=35

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- 36% Hospital inpatient

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**Either clarithromycin or azithromycin and rifamycin and ethambutol

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- (n=132)
- (n=79)
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- MAC patients treated with 3-drug macrolide regimen** for ≥ 6 months (4%) n=5

Treatment regimen was changed (9%) n=12

NTMPD treated (63%) n=132

Relative odds of treatment when other tested factors equal

*Some patients prescribed antibiotic in both settings

**Either clarithromycin or azithromycin and rifamycin and ethambutol

Results: Treatment patterns in Germany

Germany
- Spain
- Italy
- UK
- France

MAC only (80%) n=169
M. abscessus only (14%) n=30

9% Treatment regimen was changed
NTM-disease manifestations

• (Genetic) susceptibility?
  ▪ Mendelian Susceptibility to Mycobacterial Disease
    ◦ Defects in IFN-g and IL12 – pathways
    ◦ Usually disseminated diseases in early childhood
  ▪ Lady Windermere syndrome
Nodular pulmonary NTM-infection

- Prospective study of 63 pts with NTM pulmonary disease (2001-2005, USA; MAC 44 pts, *M. abscessus* 16 pts):
  - 95% female, 68% nonsmokers
  - 37% CF Transmembrane Regulator mutations (controls: 15,6%)
  - **Taller** (164,7 versus 161 cm)
  - **Leaner** (21.1 versus 28.2 BMI)
  - **Skoliosis** (51% versus 1,9%) [polymorphisms in the estrogen receptor gene overrepresented in women with adolescent idiopathic scoliosis!]
  - **Pes excavatum** (11% versus <1%)
  - **Mitral valve prolaps** (9% versus 2,4%)
  - **Bronchiectasis**: middle lobe 90%, lingula 73%

Kim et al. AJRCCM 2008: 178: 1066-1074
• Is the change of exposure to water the main factor influencing the changing NTM-epidemiology?
  ▪ Plumbing
  ▪ Shower
  ▪ Pool
  ▪ Beach
  ▪ Travel