MYCOBACTERIUM BOVIS: NEW APPROACHES TO AN ANCIENT PLAGUE.

CURRENT CATTLE VACCINE DESIGNS AND PRELIMINARY DATA FROM A NOVEL SUBUNIT VACCINE

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OUTLINE

• CURRENT STATUS
• BCG REFRESHER
• CURRENT VACCINES
• NEW SUBUNIT VACCINE: OVERVIEW & PRELIMINARY RESULTS
• FUTURE DIRECTIONS
M. BOVIS—ALIVE AND WELL IN THE US

• **As of 2017**
  - 43 Dairy, 87 Beef, 2 mixed herds (+)
  - 10 Deer herds and 1 Bison herd (+)
  - >1 of every 4 states is (+)

• **In the news:**

**Officials warn hunters of bovine tuberculosis in wild deer**

By Associated Press

Posted: 9:34 AM October 11, 2018

Bovine TB Detected in Large Alcona County Beef Cattle Herd

Michigan officials say bovine tuberculosis recently was confirmed in a large beef herd in Alcona County.

Oct. 9, 2018, 7:20 p.m.
A BRIEF SUMMARY OF BCG

- **Attenuated strain of M. bovis, lacking the RD1 gene**
- **Most administered vaccine worldwide**
  - **Not currently being used in cattle**
- **Problems**
  - **Highly variable protection**
  - **Cross reactivity with the DTH test**
# NEW VACCINE APPROACHES

**Table 2**  New TB vaccines tested in cattle

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Vaccine</th>
<th>Protection against TB compared to BCG</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified BCG</td>
<td>BCG overexpressing Ag85B</td>
<td>+</td>
<td>[51•]</td>
</tr>
<tr>
<td></td>
<td>BCG Δ zmp1</td>
<td>NT</td>
<td>[63]</td>
</tr>
<tr>
<td>Attenuated <em>M. tuberculosis</em> strain</td>
<td><em>M. tuberculosis</em> ΔRD1 ΔpanCD</td>
<td>-</td>
<td>[64]</td>
</tr>
<tr>
<td>Attenuated <em>M. bovis</em> strain</td>
<td>UV-irradiated <em>M. bovis</em></td>
<td>+</td>
<td>[59]</td>
</tr>
<tr>
<td></td>
<td><em>M. bovis</em> Δ leuD</td>
<td>NT*</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td><em>M. bovis</em> Δ RD1</td>
<td>=</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td><em>M. bovis</em> Δ mce2</td>
<td>+</td>
<td>[66]</td>
</tr>
<tr>
<td>DNA vaccine</td>
<td>Mycobacterial DNA</td>
<td>=</td>
<td>[67, 68]</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial DNA + BCG</td>
<td>+</td>
<td>[44, 69, 70]</td>
</tr>
<tr>
<td>Adjuvanted protein vaccine</td>
<td>Protein + BCG</td>
<td>+</td>
<td>[45, 71]</td>
</tr>
<tr>
<td></td>
<td>Protein + BCG</td>
<td>=</td>
<td>[72]</td>
</tr>
<tr>
<td>Virus-vector vaccine</td>
<td>BCG + recombinant adenovirus or vaccinia virus expressing mycobacterial protein</td>
<td>+</td>
<td>[46••, 72]</td>
</tr>
</tbody>
</table>

NT Not tested against TB challenge or compared with BCG

* Significant protection against TB, but not tested against BCG

+ Significantly better than BCG

= Equivalent protection to BCG

- No protection against TB
CHALLENGES STILL PRESENT

- **Nothing affords majority protection**
- **Many still are (+) for the DTH**
- **Many variables yet to be worked out**
  - Age of cattle? Boosters? Duration of immunity? Route of administration?
A DIFFERENT APPROACH

• New subunit vaccine
  • Attenuated *Mannheimia haemolytica* expressing and secreting immunodominant *Mycobacterium bovis* antigens Ag85B & Tb10.4 as a fusion protein
    • MH-bTB
VACCINE UNIQUENESS

- *M. haemolytica* is a common nasal inhabitant and respiratory pathogen in cattle
- Replication competent → Colonizes mucosa
- Bacteria secrete 2 *M. bovis* immunodominant proteins
- Delivered at the point of entry for *M. bovis*

→ Repeated antigen presentation

- Should additionally provide protection against *Mannheimia*
VACCINE DYNAMICS
STUDY GROUPS

- 4 GROUPS OF CATTLE (N=12 IN EACH GROUP, TOTAL N=48)
  - Unvaccinated Controls
  - BCG Vaccinated (s.c.)
  - Mh-bTB Vaccinated
  - BCG & Mh-bTB Vaccinated
# Of Cattle Culture positive for *M. haemolytica* by group

<table>
<thead>
<tr>
<th></th>
<th>09/18/17 (pre-vaccination)</th>
<th>09/28/17 (AT-vaccination)</th>
<th>10/4/17 (6 days)</th>
<th>10/23/17 (25 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-vax</td>
<td>0/12</td>
<td>0/12</td>
<td>0/12</td>
<td>0/11</td>
</tr>
<tr>
<td>Mh-bTB</td>
<td>0/12</td>
<td>0/13</td>
<td><strong>9/13</strong></td>
<td>1/12</td>
</tr>
<tr>
<td>BCG</td>
<td>0/12</td>
<td>0/12</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td>Dual</td>
<td>0/13</td>
<td>0/12</td>
<td><strong>9/13</strong></td>
<td>1/12</td>
</tr>
</tbody>
</table>
PRELIMINARY RESULTS – IFNγ DATA

- This is suggestive of a successful challenge
PRELIMINARY RESULTS-DTH SKIN TEST

Reactor zone

Bovine PPD (mm Δ skin thickness)

Avian PPD (mm Δ skin thickness)

CCT results

Non-vaccinates
Dual Vaccinates
Mh-bTB only
BCG only
PRELIMINARY RESULTS- *M. BOVIS* CULTURE POSITIVITY

**Tracheal Bronchial Lymph Node Culture**

<table>
<thead>
<tr>
<th>Group</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11/11 positive</td>
</tr>
<tr>
<td>Mh-bTB</td>
<td>12/12 positive</td>
</tr>
<tr>
<td>BCG</td>
<td>10/12 positive, 2/12 negative</td>
</tr>
<tr>
<td>BCG + Mh-bTB</td>
<td>11/12 positive, 1/12 negative</td>
</tr>
</tbody>
</table>
PRELIMINARY RESULTS

- **MH-bTB** had no positive effect compared to **controls**
- **BCG & (BGG + MH-bTB)** provided significant reduction in disease pathology
  - Dual vaccinates did not outperform BCG alone
FUTURE DIRECTIONS

• **Prime/boost**

• **Secrete more/different antigens**

• **Vaccinate neonatal calves**
THANK YOU
 SOURCES  

