New insights in possum-TB transmission

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Outline

- TB transmission in possums
  - What do we actually know?
- Testing a new model of artificial challenge
  - To better emulate ‘natural’ TB in possums
  - To better estimate how long TB possums live
- Summary: Why does it matter?
  - Identifies natural transmission is via skin
  - Implications for declaring TB freedom

TB transmission in possums
What do we actually know?

- TB widely regarded as a respiratory disease –possums usually die of lung congestion
- Historical presumption that transmission route was via aerosol droplets
  - Proven to occur
  - Plausible given sharing of air space in dens
- But direct infection of lungs is too lethal

Rapid lethality of lung infection

- Possums infected with just a few bacilli all died within 2-3 months, *Ramsey et al. 2008*
  - with little spread beyond lungs.
- Yet wild possum with detectable already well-developed TB lived for another 3-4 months: *Ramsey and Cowan 2003, Norton and Corner 2003.*
- And wild possums often have ‘peripheral’ lesions in ‘armpits’ and ‘groin’

[From Michelle Cooke presentation ~2007]

Why do possums sometimes only have lesions in peripheral lymph nodes and not the lung?

[From Michelle Cooke presentation ~2007]

Distribution of macroscopic lesions (n = 117 TB possums):

- Most common sites for lesions:
  superficial lymph nodes (75% of TB possums)
  respiratory tract (69% of TB possums)

Distribution of microscopic lesions:

- Most common sites for lesions:
  superficial lymph nodes (93% of TB possums)
  respiratory tract (79% of TB possums)
  p=0.005

[From Michelle Cooke presentation ~2007]

Single-site lesions (n=17)

- 14 (82%) were in superficial lymph nodes; 7 of those 14 (50%) were in the left superficial lymph node
- 1 was in the mesenteric lymph node
- Only 2 were in the lung

Single-site lesions considered indicative of the route of infection (Francis 1958)

=> Most infection via skin/paws?

Testing a new model of artificial challenge

- ‘Percutaneous interdigital injection’

=> Aims to mimic lesion distribution in wild possums: (predominance of lesions in axillary and inguinal nodes)

Successful induction of superficial node lesions

‘Artificial‘ lesion

Natural lesion

Percutaneous Challenge Trial

- 18 possums injected with 500cfu, in front paw, necropsied at 8 weeks
- 17 had typical TB lesions in superficial axillary nodes
  - No head lesions, 1 mesenteric, 1 with kidney lesions , 5 liver , 5 lung.

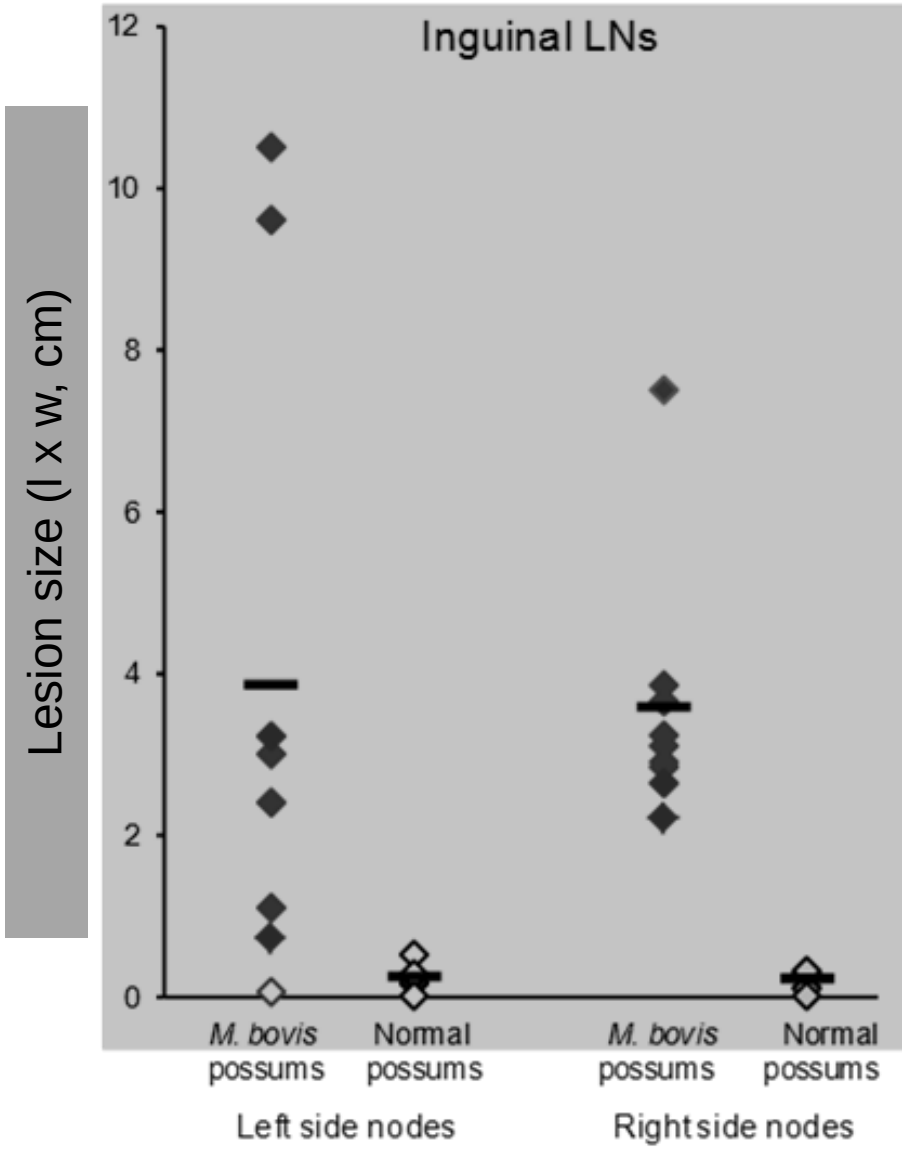
=> similar to natural lesion distribution but still too 'strong'

Subsequent trials

- Still get lesions in most possums even with just 5 cfu
- Slightly slower but still almost always produces detectable lesions at 7 weeks p.i.

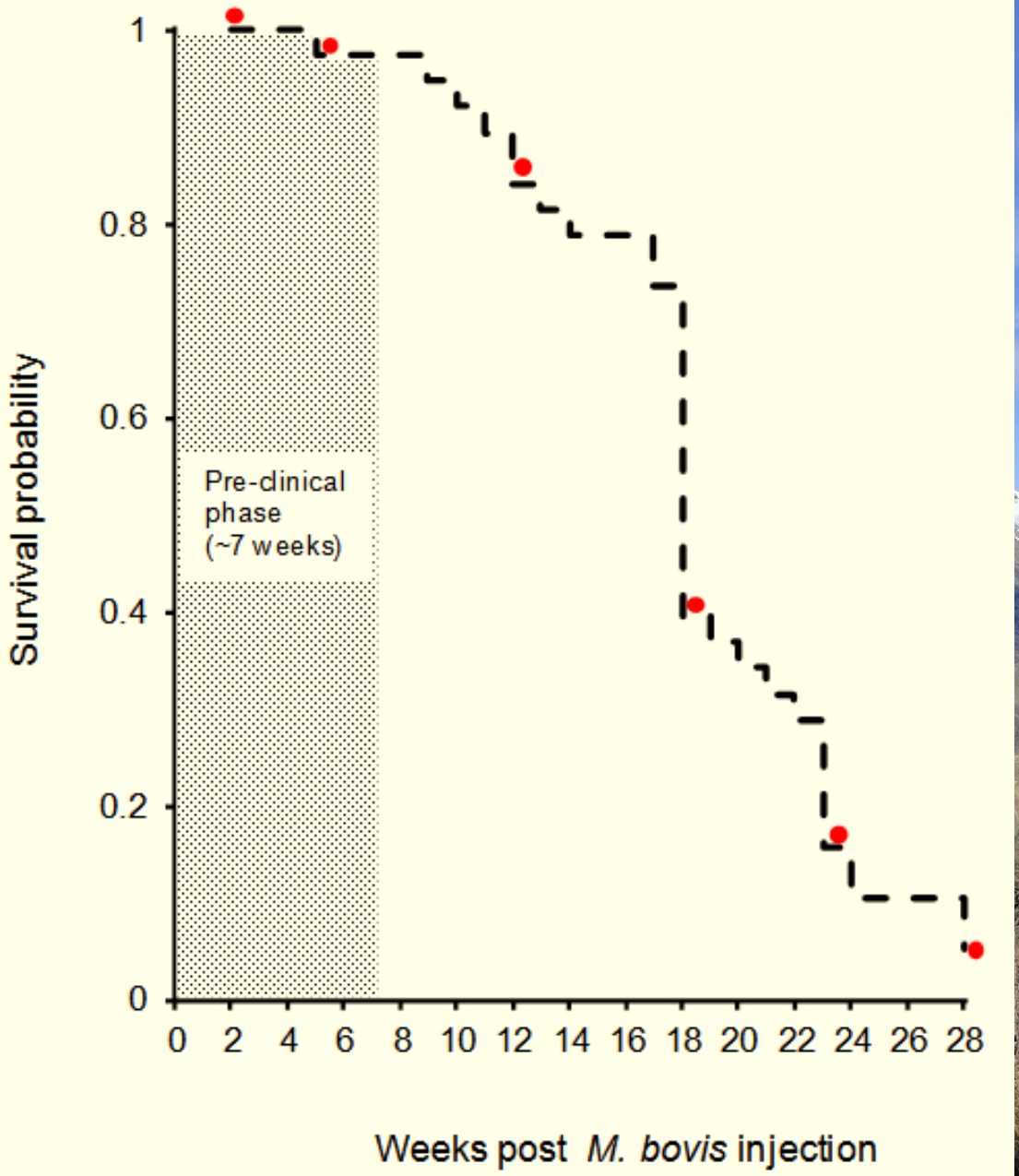
=> 'Sub clinical' (non detectable) phase of ~ 7 weeks

  - cf ~15 weeks previously estimated



How quickly do possum die of TB?

- No realistic previous estimates
  - Because time of infection in wild possums not known
- 38 possums injected with 20 cfu in each of two paws
  - released back to wild with ‘time-since-death’ radio-collars
  - Monitored for 28 weeks



Mortality rate

- 36/38 dead at 28 weeks
- Median survival = 18 weeks
  - Most dead within 6 months

⇒ Lower survival than previously assumed

*but maybe dose still too high

Summary: Transmission

- Percutaneous injection into paws accurately emulates natural infection
- Very few bacilli needed to cause TB with this route

⇒ natural route of transmission is mostly via the skin of the legs/paws? Fighting?

⇒ low force of infection may make it easy for vaccines to prevent TB

Summary: Why does mortality rate matter?

If TB possums survive only a few months

⇒ Must be 2+ transmission events each yr

⇒ Unlikely that mating or mother-offspring interactions are main transmission mechanisms

If mortality rate higher than assumed,

- the time to eradication predicted by current models may be too long

⇒ higher rate will allow faster declaration of TB freedom