



Presentation at BVA Congress
24 – 26 September 2009
Cardiff, UK

PLEASE NOTE:

While this presentation may be quoted from it cannot be reprinted in full without the permission of the author and the BVA

Working for public and animal health



TB vaccines for cattle and badgers

Glyn Hewinson

**Head, TB Research Group
Veterinary Laboratories Agency - Weybridge**

r.g.hewinson@vla.defra.gsi.gov.uk



Why vaccines?

- Need to address disease in both livestock and wildlife
- Vaccines potentially valuable route to reduce TB transmission
 - Badger vaccines – reduce disease pressure in wildlife
 - Cattle vaccines – reduce risk of disease spread from wildlife and cattle
- Fit with wider EU animal Health strategy – move from slaughter to wider vaccine use
- But... Recognise potential limitations
 - Not a silver bullet – way of reducing risk
 - Another tool in the box – use with other measures
 - Practical and legal difficulties



Cattle vaccines – Legal issues



Impact on Trade

- EU Directive 64/432/EEC – OTF status
 - dependent on negative skin tests
 - **Live trade in vaccinated animals would be prohibited**
- Regulation (EC) No 853/2004 - hygiene rules for food
 - raw milk must come from OTF herds
 - milk from skin test positive animals cannot enter the food chain
 - **Couldn't use vaccine for dairy cattle**

Prohibition of use

- EU Directive 78/52/EEC - requirement to prohibit "anti-tuberculosis vaccination" in eradication plans

Amendments required to allow *any* cattle vaccination

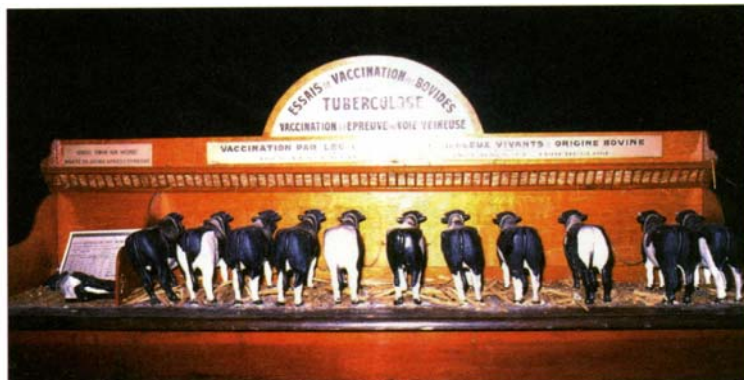
BCG



- Live, attenuated *M. bovis*
- Attenuated in cattle since 1912
- Used in humans since 1927
- Safe in a wide range of species
- Cheap
- Recommended by WHO
- Variable efficacy in humans and cattle (0-80%) and compromises tuberculin skin testing

5

BCG



Maquette schématisant le premier essai de prémuniton antituberculeux du bétail par le BCG, entreprise à Lille en 1912.

6

Genome-driven TB vaccine development (mid 1990s →)

most people mount an immune response to infection and don't get disease

Hypothesis: maybe it will help if we prime this response prior to infection?

“subunit”

identify genes encoding prominent antigens

- deliver as DNA vaccines
- deliver as recombinant proteins with adjuvant
- deliver as recombinant viral vaccines

“whole cell”

- BCG (attenuated *M. bovis*) over expressing selected antigens
- BCG with altered immunogenicity (cytokines, CD8[↑])
- alternatively attenuated *M. tuberculosis*/*M. bovis*

Small animal models (mice, guinea pigs)

BCG reduces initial bacterial replication and spread of infection
→ prolonged survival

- best of the subunit vaccines were \leq BCG
- evidence of improved protection from BCG prime + subunit boost

Clinical trials of new TB vaccines prime-boost

(Global Plan: \$2bn 2006-15)

(1) boost existing BCG with	MVA85 (Phase II/III)	<i>recombinant virus</i>
	Ad35 (Phase II)	
	Mtb72 (Phase I/II)	<i>protein/adjuvant</i>
	Hybrid-1 (Phase I)	
	HyVac4 (Phase I)	
(2) replace BCG with improved prime	BCG-antigen [↑] -CD8 [↑] attenuated <i>Mtb</i>	

Cattle: intratracheal challenge model

(all animals develop progressive disease)

BCG reduces initial bacterial replication and spread of infection
→ reduced pathology score

- neonatal BCG more effective than adult BCG
- best protection obtained with BCG prime
+ boost with recombinant adenovirus

DIVA test

BCG primes for tuberculin reactivity, so vaccination based on BCG
would need to be accompanied by a DIVA test

Antigen mining

- systematic screen through genes in deletion regions
- synthetic peptide reagents, IFN γ readout
→ highly efficient and successful identification of specific diagnostic

development of a test is clearly feasible

the major issue is regulatory approval for its use

POLICY

a vaccine that is incompatible with routine tuberculin testing has low priority

DIVA problems: 1 – regulatory
2 – cost

Response

license BCG for potential use in context of trade restriction

- safety, efficacy data for licensing portfolio
- establish duration of protection from neonatal BCG
- establish duration of tuberculin positivity following neonatal BCG

search for non-sensitising vaccines

- novel adjuvants?
- subdominant antigens?
- oral vaccination?
- better understanding of protective immunity

Cattle vaccines – Legal issues



- Amendments required to give DIVA equal status to the skin test as a primary test
- Vaccine and DIVA could be *licensed* as early as 2012
 - Need to complete process before legislation can be amended
 - Consider impact of prohibition on field studies
- Could take up to 3 years to complete legal processes
 - Formal process can't start until vaccine licensed
 - Informal discussion already ongoing
- Vaccine available for use **2015**

Cattle vaccines - Practicality



- **Limited practical barriers to cattle vaccination**
 - Farmers used to the concept and practice of vaccinating their animals
 - Logistical requirements of BCG (cold chain etc) already exist for other vaccines
 - DIVA test – blood test similar to gamma, possible issue with analytical capacity
 - **Need to ensure the ideal age of vaccination is aligned with a practical approach**

Badger vaccines



Injectable

- Cage trap badgers
- Intramuscular injection

Oral

- Vaccine incorporated in bait
- Multiple baits per sett
- **Technically challenging**

- Vaccinate as many badgers as we can
 - **Vaccination of infected badgers, multiple vaccination of same badger – no negative effects expected**
 - No attempt to differentiate vaccinated/unvaccinated
 - **No attempt to differentiate infected/uninfected**
- Vaccination by *area* on annual basis
- Over a number of years >5

Badger vaccines - Legal



Injectable

- Licensing under countryside and wildlife act to use cage traps
- Licensing under protection of badgers act to trap badgers

Oral

- License under Protection of badgers act probably not required (depend on exact protocol)
- Bait must be non-meat based (animal by-product regulations)

- No prohibition against vaccinating badgers
- Would need a change in the law to make it compulsory

Badger vaccines - Practicality



Injectable

- Trapping difficult
- Injecting animal in trap

Oral

- Relatively easy
- Baits need to be placed to avoid uptake by other animals

- New skills required – training process
- Need to know where badgers are
- Difficult to monitor uptake
- Badgers not necessarily on farmers land
- Need for coordinated approach

BADGER VACCINE

- BCG is generally quite good at reducing disease in small furry animals

but

- to test impact of badger vaccine on herd breakdown
would require an experiment on the scale of the RBCT
- difficulties of experimental work with a protected species

Can we devise a progressive approach that allows us gradually to build confidence that the goals are achievable and the problems are surmountable?

License Injectable BCG for use in badgers

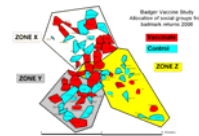
- standardised efficacy in experimental challenge model
- safety in captive badgers
- safety in wild badgers (+ monitor for indications of efficacy)



Badger Vaccine Study (BVS) 2006-10

BVS

- trap badgers (n=787) and assign to vaccine or control groups
- monitor safety (temperature, shedding, *etc*) over 48 hours (n=29)
- retrap and examine vaccination site (n=48 at 2 weeks)
- two trappings/year, collect blood, smears, *etc*
- compare immunology (IFN γ , serology) and microbiology between vaccinated and control groups
- analysis for efficacy – due 2010



Badger Vaccine Deployment Project

Policy lead

Oral BCG for Badgers

feasibility for widespread distribution

but

- stabilisation of BCG for oral delivery (NZ lipids?)
- presentation in a bait that is attractive to badgers
- delivery to cubs?
- consideration of uptake by other species – including cattle

Strategy

- development of appropriate formulation
- licensing (efficacy, safety, *etc*)
- timelines (>2014?)

PRIORITIES (most optimistic timescales)

*policy
desirability*

*science
feasibility*

oral BCG for badgers (available from 2014)

★ ★ ★

★ ★

- requires significant research input to address issues
- related to vaccine formulation and bait delivery (will disease reduction in badgers impact herd breakdown?)

injectable BCG for badgers (available from 2010)

★

★ ★ ★

- licensing portfolio being assembled for regulatory approval
- “proof of principle” but unsuitable for widespread delivery

neonatal BCG for cattle (available from 2015)

★

★ ★ ★

- licensing portfolio being assembled for regulatory approval
- emergency use in event of trade embargo?

prime-boost vaccine for cattle (available from 2015)

★

★ ★

- approval of cattle vaccine is likely to be a regulatory barrier

non-sensitising cattle vaccine (‘Mr 10 years’)

★ ★ ★

★

- dependent on innovation from fundamental research