

-----Original Message-----

From: xxxxxxxxxxxxxxxx

Sent: 30 September 2012 09:17

To: xxxxxxxxxxxxxxxx

Subject: Results of cattle vaccination study

Dear xxxxxx,

In the reference shown below it says that 39 twelve-month-old, skin-test-positive cattle were held in 10 pens for 12 months with 60 twelve-month-old, uninfected animals. Each pen held 4 infected animals and 6 uninfected animals except one pen where only 3 infected animals were held with 6 uninfected animals. Forty of the 60 uninfected animals were vaccinated with BCG at 4 to 6 weeks of age. Twenty of these vaccinated animals were subsequently boosted at 9 months of age. On slaughter and post-mortem examination after completion of the 12 months, infection was confirmed in 36 of the 39 skin-test-positive animals, and that 6 animals of the original 60 uninfected animals had lesions typical of bTB and that in a further 2 animals *M bovis* was cultured from lung-associated lymph nodes with no visible lesions. Hence there were 3 treatment groups and 3 result groups as shown below.

TREATMENT GROUPS

TG1- no treatment (20 animals)

TG2 - vaccinated (20 animals)

TG3 - vaccinated and boosted (20 animals)

RESULT GROUPS

RG1 - no change (52 animals)

RG2 - lesioned (6 animals)

RG3 - cultured with no visible lesions (2 animals)

If you can, please specify in an email to me for each of the 8 animals which became infected, the treatment group and result group for each animal.

Yours sincerely,

xxxxxxxxx,
xxxxxxxxxxxxxxxxx,
xxxxxxxxx,
xxxxxx,
xxxxx.
xxxxxxxxx

REFERENCE

A natural-transmission model of bovine tuberculosis provides novel disease insights. Short Communications. *Veterinary Record* (2012) doi:10.1136/vr.101072. AHVLA, Weybridge. Not commissioned. Externally peer reviewed. Accepted July 27, 2012.



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By E-Mail

Our Ref: ATI.072.2012.019

Date: 23 October 2012

Dear xxxxxxxx,

Provision of requested information

Thank you for your request for information about the results of a study published in the Veterinary record, which we received on 30th September 2012. Your request has been considered under the Freedom of Information Act 2000.

The information you requested is detailed below. To make reference easier, I am using the abbreviations for the groups as you defined in your request. The 8 animals you were referring to fall into the three treatment groups as follows:

- TG1- no treatment: 1 VL, 1 NVL/cu+
- TG2 – BCG vaccinated: 3 VL, 1 NVL/cu+
- TG3 – BCG vaccinated and recombinant adenovirus boost: 2 VL

I thought I would provide you with further scientific context to this experiment as the Veterinary Record format of a note does not allow much background information or discussion of results.

The original objective of this experiment was to develop a 'natural transmission model' in GB to test cattle BTB vaccines such as BCG which showed significant and demonstrable protective efficacy in our experimental challenge model of introducing *M. bovis* directly into the lung via an intratracheal/endobronchial route.

The results of this natural transmission experiment, published in the Veterinary Record paper you refer to, were clear: With the transmission rate we observed of not much more than 13 % overall, this model was not able to assess test vaccine efficacy without radically increasing the group sizes multiple times due to the low power of the study (i.e. committing what is known as a **type II error**, i.e. concluding two treatments are not significantly different when in fact the lack of significance is most likely due to insufficient data). Maintaining such group sizes would be

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unrealistic both logistically and financially. However, we recognised that we are setting ourselves a difficult target, and therefore undertook in parallel a similar, Wellcome Trust-funded, study in Ethiopia (Ameni et al., 2010)¹. Copyright laws prevent me from attaching a copy of this paper, but it can be freely downloaded from the journal's website. This study resulted in a much higher transmission rate in the non-vaccinated control animals and consequently, we could demonstrate significant protection of around 60 %, (see appendix 1).

As this study and also the many experimental challenge studies undertaken with BCG over the last 100 years have demonstrated, BCG is not 100 % effective. It was about 56 – 68 % in the study by Ameni et al. 2010. To put BCG in cattle into context: As with BCG in other species it provides a spectrum of protection:

- Some cattle will be fully protected;
- Some cattle will benefit from reduced disease;
- Some cattle will get no protection from vaccination.

In conclusion, if the experimental conditions are right, such natural transmission models can be very powerful and informative tools. We are at the moment conducting a second such experiment in Ethiopia, funded by DfID and the Bill and Melinda Gates Foundation.

Further, with the low transmission rate in our GB transmission study, one cannot conclude whether the vaccine works or does not work as the power of the study is far too low. Even if one assumes that BCG is 100 % protective, i.e. that all of the BCG vaccinates would be protected and compare this to the 2/20 that were infected in the control group, the result would not be statistically different. Thus, any conclusions drawn beyond stating that the low power precludes further conclusions, would be scientifically unsound and therefore not publishable.

Lastly, studies to date cannot provide a definite figure for vaccine efficacy when administered to cattle under field conditions in the UK and it is currently not possible to generate these data in the field because of existing EU legislation prohibiting vaccination of cattle against TB. However, small-scale field studies have been carried out recently in Ethiopia and Mexico and depending on the parameters selected; the protective effect of vaccination was between 56% and 68%.

¹ Ameni G, Vordermeier M, Aseffa A, Young DB, Hewinson RG (2010). Field evaluation of the efficacy of *Mycobacterium bovis* bacillus Calmette-Guerin against bovine tuberculosis in neonatal calves in Ethiopia. *Clin Vaccine Immunol.* 2010 Oct;17(10):1533-8. Epub 2010 Aug 18.



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If you have any queries about this letter, please contact me. I also attach an annex giving contact details should you be unhappy with the services you have received.

Yours sincerely

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XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Appendix 1: Results of natural transmission challenge study in Ethiopia. (Ameni et al., 2010)

	Gross pathology (VL) % (n)	<i>M. bovis</i> culture +ve % (n)	Spread outside head and lung regions	Condemned at meat inspection % (n)
Naïve (n=14)	86 % (12)	79 % (11)	21 % (3)	71 % (10)
BCG (n=13)	38 % (5)	31 % (4)	0 % (0)	23 % (3)
P-values (Fisher's exact test)	0.018	0.021	NS	0.021