Vaccination against equine grass sickness: piloting a randomised placebo-controlled field trial of a *Clostridium botulinum* type-C toxoid

Ireland, J.L.[1], Newton, J.R.[1], Proudman, C.J.[2], Thomson, K.A.[3] and McGorum, B.C.[4]

[1]Epidemiology and Disease Surveillance, Centre for Preventive Medicine, Animal Health Trust, UK
[2]School of Veterinary Science, University of Liverpool, UK
[3]Equine Grass Sickness Fund, Moredun Foundation, UK
[4]Royal (Dick) School of Veterinary Studies, University of Edinburgh, UK

Introduction

Equine grass sickness (EGS) is a predominantly fatal neurodegenerative disease affecting grazing equids. Britain has the highest incidence worldwide and EGS continues to represent a significant welfare concern. Research suggests that EGS is a toxico-infection involving *Clostridium botulinum* (*C. botulinum*) type C. Several studies have demonstrated a protective effect of natural immunity to *C. botulinum* type C and other equine clostridial diseases are successfully prevented by vaccination, implying that it should be possible to prevent EGS by vaccination.

EGS cannot be induced experimentally; therefore a field trial represents the only available method of evaluating the effect of vaccination and testing the *C. botulinum* toxico-infection hypothesis.

Aims

To perform a pilot study of a randomised placebo-controlled field vaccine trial (RCT) of a *C. botulinum* type C toxoid vaccine for the prevention of EGS in a selected population of horses and ponies.

Objectives

To inform refining of sample size calculations and trial methodology for a proposed full-scale prospective nationwide triple-blinded RCT, specifically with regard to:

- Recruitment and retention
- Co-ordination of treatment allocation and administration
- Data collection

Methods

- Animal Test Certificate obtained from Veterinary Medicines Directorate
- Approved by Research Ethics Committees of the Animal Health Trust and University of Edinburgh

Study Design

- Placebo-controlled randomised triple-blinded study of 12 month duration
- Parallel group experimental design
- Target sample size 100 horses/ponies
- Premises with high incidence and frequency of EGS cases
- Enrolled horses/ponies under the care of owner/keeper throughout study
- Baseline and follow-up premises and animal data obtained via telephone questionnaires

Recruitment

- Convenience sample of veterinary practices referring to Dick Vet Equine Hospital, University of Edinburgh
- Eligible premises identified by participating veterinary practices
- Owners and veterinary surgeons sent comprehensive study information packs
- Informed written owner consent obtained for each horse/pony

Randomisation and Treatment Administration

- Randomisation at premises level stratified by age group using computer-generated random numbers (Figure 1)
- Equal treatment group allocation at 1:1 ratio for vaccine and placebo

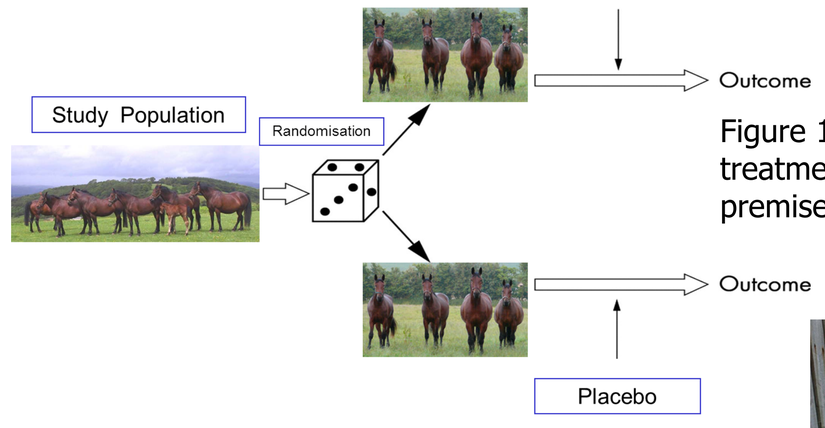
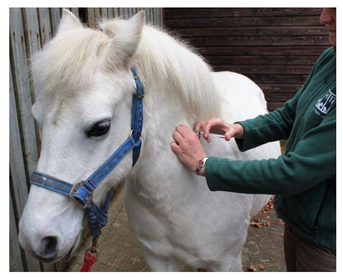


Figure 1: Illustration of random treatment group allocation at premises level



- Veterinary examination prior to each treatment
- Primary treatment course of vaccine/placebo on days 0, 21, and 42
- Booster vaccine/placebo administered day 224
- Owners record daily observations for 7 days post-treatment

Results

Study Population and Demographics

- 5 participating veterinary practices (Figure 2)
- 10 participating premises
- Median incidence of EGS at baseline 2.34 cases per 100 horse years at risk
- Median animal age on enrolment 5.5 years
- Mares/fillies 46.3%; geldings 50.5%; stallions/colts 3.1%
- Most numerous breeds: Welsh/Welsh cross (28.4%)
  Thoroughbred/TB cross (17.9%)
  Arab (10.5%)
- Age (p=0.34), gender (p=0.15) and breed (p=0.97) distributions not significantly different between vaccine and placebo groups

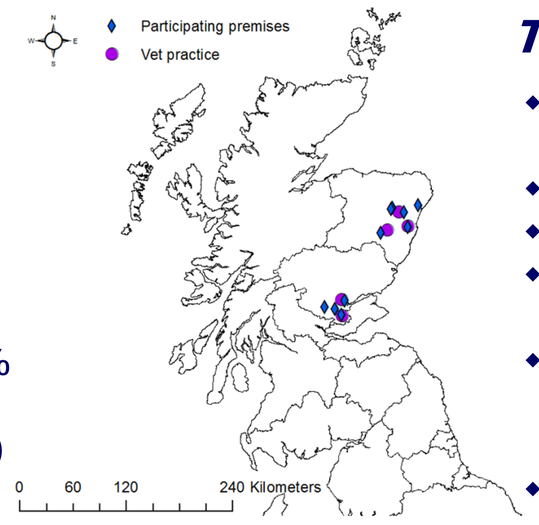


Figure 2: Point map showing distribution of recruited veterinary practices (n=5) and participating premises (n=10).

Treatment Administration and Follow-up

- 95 horses/ponies completed primary treatment course (vaccine group n=48; placebo group n=47)
- No systemic reactions reported
- Prevalence of minor inject site reactions 1.4% (n=4/285)
- Owners reported post-treatment observations easy to perform and record findings
- Veterinary surgeons reported clinical examinations easy to perform but completion of recording forms time consuming
- Retention rate to date (March 2013) 95.8%
  - 1 fatal case of EGS
  - 1 horse withdrawn for behavioural reasons
  - 1 horse sold; 1 horse gone on loan

Conclusions and Further Work

This study has provided vital information regarding the feasibility of undertaking a prospective nationwide RCT for evaluation of the efficacy of *C. botulinum* type C vaccination in the prevention of EGS. Recruitment was successfully achieved within a 5 week period, and the randomisation method utilised was straightforward and achieved successful random group allocations. Participant compliance has been excellent, and their feedback will inform modifications to study literature and standardised reporting forms. Results of this pilot study will be used to refine sample size calculations and trial methodology for a proposed future full-scale vaccine trial.

Acknowledgements

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