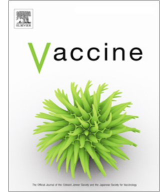
Vaccine 34 (2016) 3787–3795

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Influential factors inducing suboptimal humoral response to vector-based influenza immunisation in Thoroughbred foals

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A R T I C L E I N F O

Article history:
Received 1 March 2016
Received in revised form 9 May 2016
Accepted 27 May 2016
Available online 10 June 2016

Keywords:
Horse
Equine influenza
Vaccination
Age
Maternally-derived antibody
Canarypox-based vaccine

A B S T R A C T

Context: Numerous equine influenza (EI) epizooties are reported worldwide. EI vaccination is the most efficient methods of prevention. However, not all horses develop protective immunity after immunisation, increasing the risk of infection and transmission.
Objectives: This field study aimed to understand the poor response to primary EI vaccination.
Study design: The EI antibody response was measured in 174 Thoroughbred foals set in 3 stud farms (SF#1 to SF#3) over a 2 years period. All foals were immunised with a commercial recombinant canarypox-based EI vaccine. Sera were tested by single radial haemolysis against the A/equine/Jouars/4/06 EIV strain (H3N8) at the time of the first vaccination (V1), 2 weeks and 3 months after the second immunisation (V2), 2 days and 3 months after the third immunisation (V3).
Results: The frequency of poor-responders (no detectable antibody titres) was surprisingly elevated after V2 (56.8%), increased to 81.7% at V2 + 3 months and reached 98.6% at V3. The frequency of poor-responder was still 19.2%, 3 months after V3. Two independent influential factors were identified. The short (V2 + 2 weeks) and mid-term (V2 + 3 months, V3 + 3 months) antibody levels were positively correlated to the age at V1 (*p*-value = 0.003, 0.031 and 0.0038, respectively). Presence of maternally-derived antibodies (MDA) at V1 was negatively correlated with antibody levels after V3 only (*p*-value = 0.0056). Given that SF#1 antibody response was below clinical protective levels at all-time points studied, the annual boost immunisation (V4) was brought forward by 7.0 ± 1.1 months. V1 was delayed by 7 weeks the following year, which significantly increased short- and mid-term antibody titres (*p*-value = 9.9e−07 and 2.31e−07, respectively).
Conclusion: The age and MDA at first immunisation with the canarypox-based IE vaccine play an independent role in the establishment of antibody levels. This study also highlights the benefit provided by serological surveillance to evaluate herd immunity and to implement corrective management/vaccination measures.

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1. Introduction

Equine influenza (EI) is considered one of the most important equine respiratory pathogen due to its high morbidity, contagious nature and potential economic losses associated with its epidemics [1]. Several countries around the world have experienced major epizooties in the past such as South Africa (1986 and 2003), India

Abbreviations: EI, equine influenza; EIV, equine influenza virus; HA, hemagglutinin; MDA, maternally-derived antibodies; SRH, single radial haemolysis; SF, stud farm; TT, tetanus toxoid.

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http://dx.doi.org/10.1016/j.vaccine.2016.05.068
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(1987), Hong Kong (1992) and more recently Australia (2007) [2–6].

Vaccination against equine influenza virus (EIV) remains to this day one of the most effective methods to prevent or limit the impact of EI outbreaks [7,8]. Equine influenza vaccines are available commercially since the 1960s and are widely used worldwide. The effectiveness of EI vaccination to provide clinical and virological protection has been demonstrated repeatedly and the correlates of protection are well defined [9,10]. However, not all horses develop protective immunity after EI immunisation.

Suboptimal response to vaccination is a well-recognised phenomenon in which part of the vaccinated population fails to mount an adequate immune response and therefore remains susceptible to disease [11,12]. These horses, called low/poor vaccine responders, are partially protected and may develop a subclinical form of the disease. They can shed large quantities of infectious virus over significant periods of time [10] and can contribute to the spread of the disease [5,13,14]. Analysis of post-race samples indicated that up to 7.5% of Thoroughbred horses had no detectable levels of SRH antibodies, despite mandatory EI vaccination [15]. It is possible that the catastrophic outbreak of EI in Australia in 2007, during which over 76,000 horses were infected, was started by the importation of such a horse. Partial protection due to low vaccine response will not only reduce the overall herd immunity and lead to the spread of disease but also favour influenza virus antigenic drift that could lead to vaccine breakdown in the mid-to long-term [16].

Causes of poor response to EI immunisation remain largely unknown but are likely to be of diverse origins, including the host genetic background, the vaccine design, management conditions, health at the time of immunisation etc. This prospective observational cohort study aimed to evaluate the frequency of poor responder to EI vaccination in Thoroughbred foals. The specific objective was to measure the single radial haemolysis (SRH) antibody response, a correlate of protection against EI, during the primary field EI vaccination. All foals were immunised with a commercial EI-tetanus toxoid (TT) vaccine. Our results highlight an independent impact of age and maternally-derived antibodies (MDA) levels at the time of first immunisation against EI on short and mid-term antibody levels in Thoroughbred foals.

2. Materials and methods

2.1. Animals

2.1.1. Inclusion criteria

Thoroughbred foals receiving a primary course of EI vaccination (V1 to V3). *Year #1 (July 2013 to October 2014)*: the study was carried out in a population of 117 unvaccinated Thoroughbred foals on 3 different private stud farms (SF#1 to SF#3) in Normandy (France). The age at the time of first vaccination (V1) ranged from 119 to 259 days for the first year (159.3 ± 27.6 days; 17–37 weeks). *Year #2 (August 2014 to March 2015):* the study was carried out on 81 unvaccinated Thoroughbred foals in SF#1 and SF#2. The age at V1 ranged from 142 to 249 days (189.8 ± 22.4; 20.3–35.6 weeks). SF#3 did not join the study for Year #2. The number of foals enrolled in the study was dependent of availability in the participating stud farms. All animal work received ethical approval from the LABEO Frank Duncombe ethical advisor and owner consent were obtained.

2.2. Vaccine and immunisation schedule

The EI vaccine choice and immunisation schedule were defined by the participating Veterinary Practitioners, as part of the field management of the horse population under their care. *Year #1:* a commercial recombinant canarypox-based EI-TT vaccine (ProteqFlu-Te; Merial) was used. At the time of this study, it contains the EIV strains A/equine/Ohio/03 (H3N8; Florida Clade 1) and A/equine/Newmarket/2/93 (H3N8; European lineage) with tetanus toxoid. The commercial recombinant canarypox-based EI vaccine (ProteqFlu; Merial) was used in SF#2 at V3. *Year #2:* the recombinant canarypox-based EI-TT vaccine (ProteqFlu-Te; Merial) was used by SF#1. SF#2 used a subunit EI vaccine (Equip FT; Zoetis) that contains the EIV strains A/equine/Newmarket/77 (H7N7), A/equine/Kentucky/98 (H3N8; American lineage), A/equine/Borlange/91 (H3N8; European lineage) with tetanus toxoid. Due to this change of EI vaccine between Year#1 and Year#2, SF#2 results (year#2) were not included in the study. The vaccines were administered by deep intramuscular injection in accordance with the vaccine manufacturer's data sheet. The foals received 2 immunisations (V1 and V2), 4–6 weeks apart (30.96 ± 3.71 days for year#1 and 38.03 ± 5.21 days for year#2) and a third dose (V3), six months (177.65 ± 11.35 days for year#1 and 179.68 ± 1.71 days for year#2) after V2. SF#1 foals received a boost immunisation (V4) at 164.96 ± 31.01 days. This report follows the CONSORT 2010 guidelines (supplementary CONSORT check list and flow chart) [17,18].

2.3. Serum sample and serology

The sampling schedule was defined in collaboration with the participating Veterinary Practitioners in order to minimise the impact on usual veterinary and management procedures. *Outcome measure:* serum samples were collected at the time of the first vaccination (V1) to evaluate the presence of MDA (P1), two weeks after the second immunisation (V2) to measure the antibody response at the onset of immunity (P2), three months after V2 (P3) and 2 days after the third immunisation (V3; P4) to evaluate the immunity gap between V2 and V3, three months after V3 (P5) to identify individuals that failed to maintain their antibody response at protective levels (indicative of possible poor response to EI vaccination). Some P4 samples were missed and subsequently collected 1 week after V3. They will be referred as P4bis (P4'). The number of foals bled per sampling time points is detailed in Table 1 and the CONSORT flow diagram. Serums were stored at −20 °C until analysis. Antibodies were measured by SRH assay against the EIV strain A/equine/Jouars/4/06 (H3N8; Florida Clade 2), as previously described [19]. The A/equine/Jouars/4/06 isolate is representative of the Florida Clade 2 strains circulating in France in recent years [20]. Control antiserum from the European Directorate for the Quality of Medicines and Healthcare (EDQM) was included on each plate (A/equine/south Africa/4/03 Horse antiserum BRP reference Y0000712; acceptable range defined for the A/equine/Jouars/4/06 antigen batch used = 178.1–217.7 mm^2; average control titre = 193.4 ± 9.64; n = 65 plates/assays). The titres of SRH antibody were expressed as the area of haemolysis (mm^2). An increase of at least 25 mm^2 or 50% in the area of the zone of haemolysis was regarded as significant. A poor responder was defined as a horse that had no detectable SRH antibody response.

2.4. Statistical analysis

Statistical analyses were performed with STATGRAPHICS Centurion XVI, version 16.1.12 (StatPoint Technologies, Inc). Where appropriate based on standard deviation, analyse of variance (ANOVA) or Kruskal–Wallis Test were used to test group and/or time points significant differences (with 95% confidence intervals). Where appropriate based on normality test for group distribution, Student's t-test (S) or Wilcoxon signed rank test (W) were used to compare groups at specific time points. A two-tailed Fisher's Exact

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