Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Evaluation of a polyvalent foot-and-mouth disease virus vaccine containing A Saudi-95 against field challenge on large-scale dairy farms in Saudi Arabia with the emerging A/ASIA/G-VII viral lineage

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ARTICLE INFO

Article history:
Received 20 July 2017
Received in revised form 8 September 2017
Accepted 12 October 2017
Available online xxxx

Keywords:
Foot-and-mouth disease
Vaccines
Correlates of protection
Vaccine evaluation

ABSTRACT

In 2015, foot-and-mouth disease (FMD) viruses of the A/ASIA/G-VII lineage emerged from the Indian subcontinent to cause outbreaks in the Middle and Near East. A factor which has been proposed to have contributed to the rapid spread of this lineage is the poor *in vitro* vaccine-match of field isolates to vaccine strains that are commonly used in the region. This study used data from outbreaks on four large-scale dairy farms using routine vaccination in Saudi Arabia, to evaluate the impact of vaccination and learn how to manage outbreaks more effectively in this setting. This evaluation also included an assessment of vaccine-induced neutralisation titres to the vaccine and field strains on a related farm with no history of FMD that employed an identical vaccination schedule. The incidence risk among exposed groups ranged from 2.6 to 20.1% and was significantly higher among youngstock (18.7%) compared to adults (7.4%). Evidence was found that local isolation of individual sick animals was more effective than whole group isolation and that subclinical infection and undetected circulation may occur on large-scale farms in Saudi Arabia, although both of these points require further evaluation. On the unaffected farm, the mean reciprocal titres for the vaccine and field strains were all above the cut-off supposed to correlate with clinical protection based on evidence from challenge studies. An estimate of vaccination effectiveness was not possible on the affected farms, but the incidence of FMD provides a more realistic estimation of the expected vaccine performance than *in vivo* studies or r_1 value as it is based on field conditions and natural exposure. This study shows that analysis of field data from FMD outbreaks are a useful addition to more conventional challenge and *in vitro* based evaluations of vaccines and suggests further work is necessary to validate correlates of protection in field conditions.

1. Introduction

Foot-and-mouth disease (FMD) is a viral disease of cattle that has negative impacts for farmers in endemic countries including direct production losses and indirect losses related to implementing control measures [1]. Vaccination is one of the major tools for FMD control to mitigate the impact of clinical disease, or to reduce and eventually eliminate virus circulation as outlined in the Progressive Control Pathway for FMD control [2]. Farmers and governments dedicate large amounts of resources to purchasing and administering FMD vaccines; either for routine prophylaxis or reactively in response to an increase in exposure risk. There are a variety of documented problems with currently available FMD vaccines including antigenic mismatch between the vaccine and field strains, their relatively short shelf life, reliance on the cold chain, and a short duration of action [3,4]. Despite these constraints, vaccines have been used successful for FMD control, especially when used alongside other zoo-sanitary measures [5].

FMD vaccines are usually evaluated either by performing challenge studies in containment facilities or by demonstrating seroconversion to antibody levels that correlate with protection in susceptible species [6]. However, these approaches have important limitations including: small sample size; use of artificial exposure methods with uncertain relevance to challenge under field

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https://doi.org/10.1016/j.vaccine.2017.10.029
0264-410X/

conditions; only considering protection after a single dose of vaccine; challenge occurring at a fixed time point after vaccination so not accounting for waning immunity over time and typically only challenging a certain age and breed demographic. To address the issue of antigenic matching between the vaccine and field strains, heterologous challenge studies can be performed but have similar constraints to the homologous tests. There are various *in vitro* serological assays that can be used to predict cross protection. The test outlined by the OIE [6] compares post-vaccination titres to the homologous vaccine and heterologous field strain to generate a relationship coefficient (r_1 value). Although commonly performed, this test suffers from technical variability [3] and it is unclear what level of protection is expected in field conditions for a particular r_1 value. Other tests that have been developed including measuring IgG subtypes and antibody avidity that may improve the predicted cross-protection, though these are less frequently used and further validation is needed [7]. These combined limitations highlight the importance of performing field studies alongside *in vitro* and *in vivo* experiments to evaluate vaccines, although the results of such field studies are infrequently reported in the literature.

In 2015, viruses from serotype A (topotype ASIA, genotype G-VII, referred to as A/ASIA/G-VII), previously limited to the Indian sub-continent, emerged in Saudi Arabia, Turkey, Armenia and Iran [10]. Outbreaks due to this lineage continue to pose a risk in these countries and beyond. The results of *in vitro* vaccine matching performed at FAO World Reference Laboratory for FMD (WRLFMD) at The Pirbright Institute, UK have demonstrated a poor antigenic match to all commercially available vaccine strains, particularly those derived from the A/ASIA/Iran-05 viral lineage that are commonly used in the region [8]. However, these results need to be interpreted cautiously since previous studies have shown that high-potency serotype A vaccines may still provide clinical protection even when the vaccine-matching data is indicative of a poor match [9]. In this context, a recent heterologous challenge study with a multivalent vaccine containing A Iran-05 A Saudi-95; the latter being a vaccine strain more genetically closely related to A/ASIA/G-VII provided evidence of weak vaccine-induced protection, albeit below internationally recognised standards [8]. Furthermore, large-scale dairy farms in Saudi Arabia using regular vaccination with vaccines containing the A Saudi-95 strain have reported outbreaks of A/ASIA/G-VII [10].

The aim of this study was to evaluate the response of routine vaccination using a polyvalent vaccine containing the A Saudi-95 strain against the A/ASIA/G-VII lineage. Data will be presented from FMD outbreaks that occurred on four large-scale dairy farms located in Saudi Arabia that were regularly using such a vaccine. As part of this investigation, sera from a different farm that did not have clinical disease but which used an identical vaccination regimen were analysed to establish titres generated using routine vaccination. Variables associated with antibody levels at the individual animal level were investigated. Data from these outbreaks will be used to improve our understanding of FMD in this type of large scale production system.

2. Materials and methods

2.1. Farm backgrounds

All dairy farms were located in a central region of Saudi Arabia. All cattle were Holstein Friesian and loose housed in dry-lots according to age and lactation status with access to outside loafing areas. Lactating cows were milked four times daily and all breeding was done by artificial insemination. Both youngstock and adults were located on the same units but managed separately so considered separately. Electronic individual animal records were kept according to a unique ear tag identification including disease events. Replacement stock were either sourced from the same farm or introduced from a limited number of other farms in the same area. All bull calves were sold by around 14 days of age.

2.2. FMD history and vaccination

Data from FMD outbreaks on four different farms were used for this study. The outbreaks occurred between 3rd September 2015 and 3rd April 2017 and were the first reported outbreaks of FMD A/ASIA/G-VII in Saudi Arabia. Upon suspicion of an outbreak, farms notified the relevant national authorities and samples were submitted to the WRLFMD for confirmation, RNA sequencing and strain characterisation (vaccine matching). Farms instigated varying degrees of internal isolation depending on the facilities available. The date and unique identification number of animals with FMD were recorded manually and entered onto the farm management software. Animals were recorded as a case of FMD if the animal was seen salivating with any of the following clinical signs: mouth lesions, feet lesions, teat lesions, fever, reduced feed intake, and lameness. All recording was done by farm staff supervised by veterinary surgeons employed by the farms.

All farms in the study regularly used a polyvalent, killed, aqueous adjuvanted (aluminium hydroxide and saponin), NSP purified FMDV vaccine (Aftovaxpur, Merial Animal Health). The vaccine contained the following FMD virus strains: O Manisa, O-3039, A Iran-05, A Saudi-95, Asia-1 Shamir and SAT-2. A four dose primary course was given to youngstock at a target of four, five, six and seven months of age. This schedule was based on the recommendations outlined by Kitching and Salt [11], although an additional dose was included in the primary course due to reported breakdowns in young animals despite this schedule. Vaccines were given at the same time each month so that animals received their first dose between 3.5 and 4.5 months of age. Thereafter, animals were vaccinated every 105 days by being incorporated into the whole herd vaccination programme. Reactive vaccination was utilised to varying degrees either in response to FMD cases occurring on the farm or a perceived increase risk from suspected FMD in the area. Due to issues of vaccine availability and unawareness of the causal strain, this occasionally involved using a different polyvalent, oil-adjuvanted, NSP purified vaccine to that regularly used (Decivac, MSD) containing a single strain of serotype A in the A Iran-05 lineage (A-TUR-06). All vaccines were administered according to the manufacturer's recommendations.

2.3. Serological sampling

In order to assess the antibody titres generated from this vaccine, a fifth farm was purposively selected that had no recent history of clinical FMD but used the same vaccine type (Aftovaxpur) and schedule. The last reported FMD outbreak on this farm was in 2008 before any of the animals currently on the farm were born. Animals may have been introduced from other farms, but were not included in the sampling. To ensure even age representation, an age-stratified sampling scheme was used. A target of 15 cattle were randomly selected for sampling from each of the following age groups: 6–12 months, 1–2 years, 2–3 years, 3–4 years, >4 years. A single group with animals of the appropriate age group was selected for sampling. Individuals were selected within each group based on the order they arrived in the handling facility. For the animals in the 6–12 month age strata, the farm had already sent samples to the WRLFMD on their own accord to monitor post-vaccination titres. Therefore, these samples were used rather that implementing re-sampling. The samples were taken between October 2014 and January 2015. All other animals were sampled

Please cite this article in press as: Lyons NA et al. Evaluation of a polyvalent foot-and-mouth disease virus vaccine containing A Saudi-95 against field challenge on large-scale dairy farms in Saudi Arabia with the emerging A/ASIA/G-VII viral lineage. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.10.029