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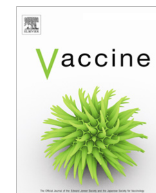

Protection in sheep against heterologous challenge with serotype Asia-1 foot-and-mouth disease virus using high potency vaccine

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ABSTRACT

Foot-and-mouth disease virus (FMDV) serotype Asia-1 is prevalent in countries considered high risk for incursion into Australia, and has recently been responsible for a number of outbreaks in India, Bangladesh, Pakistan and Turkey. *In vitro* vaccine matching has shown a number of contemporary FMDV Asia-1 strains vary antigenically to the Asia-1 Shamir vaccine strain, which could result in poor protection with use of this vaccine. Therefore it was important to test the ability of the Asia-1 Shamir vaccine to protect sheep from challenge with a recent, heterologous strain at different days post-vaccination (dpv), including in an emergency vaccination scenario (challenge 4 or 7 dpv). Sheep (5 per group) were challenged with the Asia-1/PAK/19/2014 isolate by intra-nasopharyngeal instillation 21 (V21), 7 (V7) or 4 (V4) dpv with high-potency (>6 PD_{50}) Asia-1 Shamir vaccine. An additional five sheep were mock-vaccinated with adjuvant only (antigen-free preparation) 4 days prior to challenge (A4), and five unvaccinated (UV) control sheep were also challenged. All V21, V7 and V4 sheep were protected from clinical FMD. Eighty percent of V21 sheep and 40% of V7 sheep had sterile immunity, however all V4 sheep became systemically infected. Vaccination reduced excretion of virus in nasal and oral secretions but had no effect on the development of persistent infection. All A4 sheep and UV control sheep developed clinical FMD. The high-potency Asia-1 Shamir vaccine will protect against disease should an outbreak of contemporary Asia-1 viruses occur. Intranasopharyngeal instillation is an effective challenge method for use in vaccine efficacy studies in sheep.

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1. Introduction

Foot-and-mouth disease (FMD) is an economically significant disease affecting cloven-hoofed animals. The disease is characterised by fever, lameness and the appearance of vesicular lesions on the mouth, tongue, nose, feet and teats. A large component of the world's FMD-susceptible livestock are sheep, and these animals have had an important role in a number of outbreaks, including in the UK in 2001, and in the global spread of the disease [1–4]. The clinical signs of FMD in sheep vary with the challenge strain, but commonly are mild or inapparent. This can facilitate the spread of infection through movement of misdiagnosed animals or animals with no clinical signs, and can give the impression that a vaccination campaign has been successful when in reality virus is circulating in the population. Furthermore, sheep, like other ruminants, can become persistently infected with FMD virus (FMDV), albeit for a short duration (<2 years) [5,6].

The causative agent of FMD is FMDV, a small, positive-sense RNA virus in the Genus *Aphthovirus*, Family *Picornaviridae*. There are seven serotypes of FMDV (O, A, C, Asia-1, SAT 1, SAT 2 and SAT 3) and infection or vaccination with one serotype does not confer protection against the other serotypes [7,8]. Within each serotype there are also distinct genetic lineages [9] and the emergence of antigenic variants can reduce the ability of vaccines to protect against heterologous strains of the same serotype [10,11].

In addition to serotypes O and A, Asia-1 is prevalent in countries in South Asia and the Middle East, considered high risk to Australia. Serotype Asia-1 was first identified in 1954 in Pakistan, though several outbreaks went uncharacterised from undivided India in the 1940s [12]. The outbreaks due to FMDV Asia-1 occur throughout the year in certain pockets of India. At least four distinct genetic lineages (A, B, C and D) have been described by various studies [12–16]. However, outbreaks of this serotype in South East

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Asia are rare. In the early 2000s there was a geographical spread of this serotype into eastern Asia [17] with outbreaks recorded in Myanmar, Thailand and Vietnam. In 2008, a novel Asia-1 virus, referred to as group VII or Sindh-08 lineage, was identified in Pakistan [18] and this subsequently spread to Iran, Afghanistan and Turkey, becoming the dominant strain in West Eurasia (reviewed by [19]. *In vitro* vaccine matching studies with Asia-1/Shamir vaccine strain indicated that viruses belonging to this lineage have a poor match (relative homology value $r1 < 0.3$) [18]. Additionally, outbreaks due to this strain have been reported in areas where animals were vaccinated with multivalent FMD vaccines incorporating Asia-1/Shamir. A retrospective field study showed vaccination with Asia-1/Shamir did not provide adequate protection for cattle infected with Sindh-08 viruses in Turkey [20]. In contrast, in a potency test, cattle vaccinated with a high-potency (>6 protective dose $(PD)_{50}$) Asia-1/Shamir vaccine were protected against clinical FMD when challenged with an Asia-1/Sindh-08 lineage field virus from Turkey (Asia-1/TUR/49/2011; with $r1 = 0.20$), 21 days post vaccination (dpv) [21].

Little or no information is available on the pathogenesis of Asia-1/Sindh-08 in sheep and there have been no studies to date on the ability of emergency vaccination to provide protection against viruses of this lineage in sheep. High-potency FMD vaccines have been shown to be effective in protecting animals challenged as early as 4 dpv [22–26], reducing the titre and duration of FMDV excretion, limiting the possibility of transmission and potentially minimising the duration and intensity of an outbreak. The current study examined the ability of single vaccination with high-potency Asia-1/Shamir vaccine to afford protection in sheep, and prevent the development of persistent infection, following heterologous challenge with an Asia-1/Sind-08 lineage virus, at different times post vaccination.

While vaccine efficacy trial methodology is well established for cattle, there is no standard method to challenge sheep in FMD vaccine trials. Historically challenge has been by coronary band injection or direct contact with infected sheep or pigs, however both methods have inadequacies. Reproducible methods that closely simulate natural infection are preferable. In recent work performed in collaboration with Plum Island Animal Disease Center, we established a simulated-natural system of direct inoculation of the nasopharynx [27] referred to as intra-nasopharyngeal (INP) instillation. This model allows control of virus challenge while mimicking natural infection, targeting the known sites of primary FMDV infection [27,28].

2. Material and methods

2.1. Ethics statement

This study was approved by the Australian Animal Health Laboratory's Animal Ethics Committee (AEC 1746) and the Canadian Centre for Human and Animal Health Animal Care Committee (AUD# C-15-002) and performed in strict accordance with the recommendations of the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and the Canadian Council for Animal Care Guidelines.

2.2. Animals and vaccine groups

Male Rideau Arcott-Ile de France cross-bred sheep of 6–12 months age, weighing approximately 40 kg, were obtained from a registered supplier in Canada. All animals were housed in the BSL3 animal facility at the National Centre for Foreign Animal Diseases (NCFAD), Winnipeg, Canada. Sheep were randomly divided into five challenge groups with five animals in each group and one vaccine only group with three sheep. Sheep were vaccinated with one full sheep dose (1 ml) of high potency (>6 protective dose $(PD)_{50}$) FMDV Asia-1/Shamir double-oil emulsion vaccine, formulated by Merial Animal Health, Pirbright, UK, and administered intramuscularly in the neck region above the left shoulder.

Group V21 ($n = 5$) was vaccinated and challenged 21 days post-vaccination (dpv). Group V7 ($n = 5$) was vaccinated and challenged 7 dpv. Group V4 ($n = 5$) was vaccinated and challenged 4 dpv. Group A4 ($n = 5$) was mock-vaccinated with an antigen-free "adjuvant only" preparation and was challenged 4 dpv. Group UV ($n = 5$) was unvaccinated controls and was challenged on the same day as the vaccinated sheep. Group VO ($n = 3$) was vaccinated along with V21 group but not challenged.

2.3. Challenge virus

The challenge virus, Asia-1/PAK/19/2014, was isolated from cattle in Pakistan during 2014. The r1 value in a virus neutralisation test (VNT) vaccine matching assay was 0.18 against Asia/Shamir/89 (WRL, Pirbright). After initial isolation on baby hamster kidney cells, the virus was passaged once in cattle. Inoculum prepared from lesion material was titrated in two cattle by tongue titration ([29]) and the cattle infectious dose (CID_{50}) was calculated to be $\sim 10^{6.3}$/ml.

2.4. Challenge method

Sheep were challenged with $10^{4.5}$ CID_{50} FMDV Asia-1/PAK/19/2014 by INP instillation, as described previously [27]. Briefly, animals were sedated with xylazine hydrochloride (0.2 mg/kg) and placed in sternal recumbency. Inoculum (2 ml) was deposited into the nasopharynx by use of a flexible, 14 gauge, lubricated silicone catheter (#CATH HS D2, 2.66×500 mm, PRO-VET) inserted through one nostril. Prior to instillation, the length of the catheter was measured to match the distance from the external nares to the medial canthus of the eye to ensure deposition of inoculum in the nasopharynx. In a 5 ml syringe, 2 ml of virus and 2 ml of air was drawn up so that upon administration the air pushed the virus suspension fully out of the tubing. After INP instillation the catheter was carefully withdrawn and the sheep were held for 1–2 min before sedation was reversed with Antisedan® (atipamezole hydrochloride; 0.05 mg/kg).

2.5. Monitoring and sample collection

The sheep were monitored for the development of clinical signs such as pyrexia, lameness and development of vesicles. Rectal temperatures and clinical scores were recorded daily up to 10 days post challenge (dpc). Sheep showing elevated temperatures (>40 °C) were considered pyrexic. Clinical scores were calculated as follows: per foot, a score of 1 if a lesion developed in one location (CB, interdigital cleft or heel pad) and a score of 2 if lesions developed in two or more locations; 1 for oral (tongue, gums or dental pad) lesions, 1 if visibly lame/slow to rise. The maximum score was 10.

Clinical samples were collected at regular intervals for 35 days post challenge. Clotted blood for serology and RT-qPCR was collected prior to vaccination, then daily between 0 and 10 dpc, 14, 21, 28 and 35 dpc, at which point the experiment was terminated. Small sterile cotton buds were used to collect nasal and saliva secretions (in duplicates) at the same time points as mentioned above. The swabs placed in tubes containing 500 µl of phosphate buffered saline for RT-qPCR or 500 µl of Dulbecco's modified Eagle's medium (DMEM) containing 0.04 M HEPES and antibiotics (catalog no. 15240062; Gibco) for virus isolation. Oro-pharyngeal

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